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Autochthonous falciparum malaria possibly transmitted by luggage-carried vector in Paris, France, February 2013

S Gallien (sebastien.gallien@sls.aphp.fr)[1], F Taieb[1], S Hamane[2], N De Castro[1], J M Molina[1]
1. Department of Infectious and Tropical Diseases, Paris Diderot University, Paris 7, Saint-Louis Hospital, Paris, France
2. Department of Parasitology, Paris Diderot University, Paris 7, Saint-Louis Hospital, Paris, France

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We report a case of autochthonous falciparum malaria in a patient in Paris, France, in February 2013 who reported no recent travel to malaria-endemic countries. The parasite, *Plasmodium falciparum*, was possibly transmitted by an infective Anopheles mosquito carried in baggage from a malaria-endemic area.

Case report

A man in his early 40s living in the outskirts of Paris, France, was admitted to our hospital's infectious disease department in February 2013 with fever and malaise. He reported a two-week course of fever, muscle stiffness, sweating episodes and headaches. He had also had a chronic cutaneous scalp lesion for 10 years: a biopsy two years ago demonstrated a discoid lupus erythematosus. This lesion was stable and had been never treated.

At admission, his temperature was 38.1 °C, and his blood pressure and heart rate were normal. Physical examination showed a slight spleen enlargement and the previously identified indurated scaly plaque on the scalp with alopecia. Laboratory analysis revealed a white blood cell count of 2,830/mL (norm: 4,000–10,000/mL), with 1,710/mL polymorphonuclear cells (norm: 1,700–8,000/mL). His haemoglobin level was 13.7 g/dL (norm: 13–17 g/dL) and the platelet count was low, at 116,000/mL (norm: 150,000–450,000). Blood and urine cultures were sterile. Human immunodeficiency virus (HIV) serology was negative. Unexpectedly, microscopy of a blood smear showed a few trophozoites of *Plasmodium* parasites (parasitaemia <0.01%). A diagnosis of falciparum malaria was confirmed by microscopic examination (blood smear observation, thick and thin films) and an antigenic test (BinaxNOW Malaria, Inverness Medical Innovations, Scarborough, ME, United States). He was treated with atovaquone-proguanil according to the World Health Organization (WHO) guidelines (i.e. 1000 mg atovaquone plus 400 mg proguanil once a day for three days) [1] and his symptoms resolved within two days.

He had no history of travel to malaria-endemic areas since he arrived in France in 2007 and he reported having not been in any airport since then. He lived in a migrant workers' hostel in the outskirts of Paris and also worked in this area, in locations that were more than 20 km from the nearest airport. He had no history of blood transfusion, tissue or organ transplantation, intravenous drug use, or fever in the previous six years.

He reported that a month before hospitalisation, he had shared his hostel room for two days with a friend who had just arrived from a malaria-endemic country in West Africa and who then left France for another country,. This man, who seemed healthy, travelled with luggage that had been opened for the first time since his arrival in France in presence of the patient during his stay in the hostel. No other hostel residents reported any febrile episodes during the six months since the luggage was opened.

We strongly suspected carriage of infective *Anopheles* mosquitoes in the man's baggage to be responsible for this case of malaria, even though no entomological study was performed to identify the source of the parasite. We reported this case as autochthonous malaria to the French Health Department for National Health Surveillance.

Background

The WHO defines autochthonous malaria as that acquired locally by a mosquito bite [2,3].

In areas where malaria is not endemic, the most frequent subclass of autochthonous malaria is referred to 'airport malaria', where the parasite is transmitted by airplane-carried indigenous infective *Anopheles* to people usually living and/or working around airport areas [4].

Rarely, autochthonous malaria has been reported in people who had not entered an airport recently and had never travelled to malaria-endemic areas, but for

whom transmission was suspected to arise from an infective vector brought after second transport through cars or luggage from the aircraft to the site of transmission [5].

Discussion

Luggage has occasionally been suspected of harbouring indigenous infective *Anopheles* from an endemic area, possibly causing infections when opened at arrival, as previously reported in Europe: in France (1995), Italy (1989) and Germany (1999) [5-7].

For our patient, other possible hypotheses of the origin of the parasite were ruled out by careful questioning of the patient. Misdiagnosis was excluded by extensive microbiological testing for other pathogens and confirmation of falciparum malaria by microscopic and antigen detection. The patient's condition also quickly resolved with atovaquone-proguanil, with no relapse after six months of follow-up.

Firstly, the infection was not acquired abroad. The patient originated from a malaria-endemic country, but had not been there for six years, nor had he travelled to other endemic areas during this period. In addition, both microscopic examination and antigenic testing were consistent with falciparum malaria, excluding long-lasting or relapsing malaria due to other *Plasmodium* species such as *ovale, vivax* or *malariae*.

Transmission not due to mosquitoes – e.g. through blood transfusion or tissue or organ transplantation – was also excluded, given the patient's medical history.

Secondly, we hypothesised that the case was acquired locally. First-generation local transmission by local mosquitoes that is epidemiologically linked to a proven imported malaria case is unlikely. Although 13 *Anopheles* species have been reported in metropolitan France, anopheline malaria vectors have not been found resting or breeding in and around Parisian airports [8]. Moreover, the timing of both the presumed transmission and the clinical infection was during the coolest period of the year in France (i.e. winter), thus excluding the hypothesis that a potential autochthonous anopheline vector could have been infected by a gametocyte carrier in the Paris area. No entomological study was carried out in the hostel after reporting of the case.

We suppose, but cannot definitively conclude, that this patient was infected by an infective *Anopheles* vector imported into the country. In this scenario, malaria transmission among airport employees or residents living near airports serving airplanes from malaria-endemic countries, and also in people living at some distance from the airport after secondary transport of the vectors by cars of airline employees, would be unlikely.

Finally, we hypothesise that the infective mosquito vector was brought in the luggage of the man travelling from a malaria-endemic country and that the mosquito bit the patient in their shared room, assuming that the vectors inside the luggage had escaped the WHO-recommended disinsection procedures for aircraft (assuming the recommended disinsection procedures had been performed) [4].

We note that the mode of transmission of all reported cases of autochthonous falciparum malaria in France were also not proven [5,9,10].

In clinical practice, locally acquired luggage malaria should be suspected in patients with fever of unknown origin who have been in close contact with people who have just returned from malaria-endemic areas.

Conflict of interest

None declared.

Authors' contributions

SG, FT, NDC and JMM took part in the clinical management of the patient. SH made the parasitological diagnosis and contributed to the epidemiological investigation. SG wrote the manuscript, which was reviewed by all the authors. All authors read and approved the final manuscript.

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Plasmodium knowlesi infection imported to Germany, January 2013

H Orth[1], B O Jensen[1], M C Holtfreter[1], S J Kocheril[1], S Mallach[1], C MacKenzie[2], I Müller-Stöver[1], B Henrich[2], M Imwong[3], N J White[4], D Häussinger[1], J Richter (Joachim.Richter@med.uni-duesseldorf.de)[1]

1. Department of Gastroenterology, Hepatology and Infectious Diseases, Heinrich-Heine-University, Düsseldorf, Germany
2. Department of Medical Microbiology and Hospital Hygiene, Heinrich-Heine University, Düsseldorf, Germany
3. Department of Molecular Tropical Medicine and Genetics, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
4. Mahidol-Oxford Tropical Medicine Research Unit; Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

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Plasmodium knowlesi **was known as a plasmodium of macaques until *P. knowlesi* transmission to humans was recognised in Borneo and later throughout South-East Asia. We describe here a case of a *P. knowlesi* infection imported to Germany from Thailand. The patient had not taken antimalarial chemoprophylaxis and suffered from daily fever attacks. Microscopy revealed trophozoites and gametocytes resembling *P. malariae*. *P. knowlesi* malaria was confirmed by PCR.**

In January 2013, a 55 year-old German woman presented to her practitioner because of fever, nausea and vomiting ten days after a holiday in Thailand. She had not taken antimalarial chemoprophylaxis. She was referred to hospital, where laboratory abnormalities included a decreased platelet count (27,000x10^9/L), elevated aspartate aminotransferase (AST) (237 U/L; normal value (nv): ‹35 U/L), alanine aminotransferase (ALT) (277 U/L; nv: ‹45 U/L), gamma-glutamyltransferase (gamma-GT) (480 U/L; nv: ‹55 U/L), lactate dehydrogenase (LDH) (419 U/L; nv: ‹248 U/L) and C-reactive protein (CRP) levels (102 mg/L; nv: ‹5 mg/L). Red blood cell count, white blood cell count (7.360x10^9/L), electrolytes, urea, creatinine and CK were normal. Electrocardiography showed no abnormalities except for sinus tachycardia with a heart rate of 105 beats per minute Suspecting a bacterial infection, empirical antibiotic treatment with piperacillin and tazobactam was initiated. However, the patient continued to suffer from daily fever attacks. The serum creatinine rose to 3.45 mg/dL, while she became oliguric. The procalcitonine level rose to 3.71 ng/mL, interleukin-6 to 66.8 pg/mL, haematocrit fell to 29.7%, and microscopy of stained blood films revealed malaria parasites, but the hospital's microbiologist reported that he felt unable to identify a specific *Plasmodium* species.

With a diagnosis of malaria and acute renal failure, the patient was referred to our Tropical and Infectious Diseases service. Rapid immunochromatography test (Malaria now Binax, United States) showed a negative result for *P. falciparum*-specific histidine-rich protein-2 but was positive for pan-plasmodial aldolase. In stained thin and thick blood films, plasmodia resembling *P. malariae* were present with 0.2% trophozoite parasitaemia and numerous gametocytes. *P. knowlesi* malaria was suspected because of the disease severity and the patient's recent stay in Khao Sok National Park in southern Thailand. A multiplex real-time PCR for the species *P. falciparum*, *P. ovale*, *P. vivax* and *P. malariae* detected in addition the presence of plasmodial DNA on genus level. The sequence of the amplified genus-specific DNA was homologous with the species *P. knowlesi*. Infection by this parasite was confirmed by a specific PCR in the Faculty of Tropical Medicine, Mahidol University Bangkok, Thailand. DNA was extracted from a dry blood spot using QIAamp blood mini kit (Qiagen, Germany). *Plasmodium spp*. infection were tested using three PCR protocols based on 18sRNA [1-2], mitochondrial DNA [3], the linker region of dihydrofolate reductase and thymidylate synthase [4]. Monoinfection of *P. knowlesi* was confirmed by all three techniques. Direct sequencing from PCR products were also performed and showed more than 98% identity to reference *P. knowlesi*.

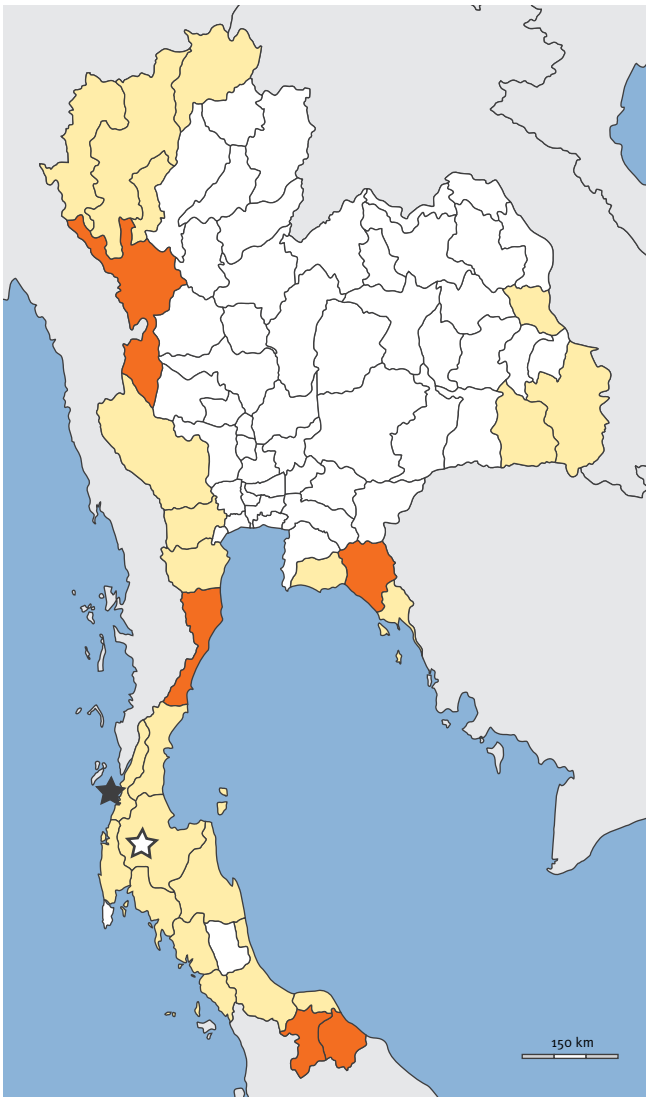
Intravenous treatment with artesunate (2.4 mg/kg) was started on Day 3 after admission and switched to oral treatment with artemether/lumefantrine the following day. The patient recovered promptly and malaria parasites cleared within two days. With intravenous isotonic saline administration, urine output was restored and serum creatinine fell to 1.3 mg/dL on Day 4.

Discussion

P. knowlesi was first described in 1931 as a plasmodium of long tailed and pig-tailed macaques and one year later was shown to be transmissible to humans [5]. A naturally acquired human infection was reported 1965 in a citizen of the United States returning from Malaysia [6]. Thereafter, human *P. knowlesi* infections were reported only occasionally until 2004, when a study by Singh et al. revealed that *P. knowlesi* accounted for more than 50% of endemic human

Figure

Presumable geographical site of acquisition of *Plasmodium knowlesi* infections, Thailand, 2010 and 2013



Orange: Provinces with *P. knowlesi* transmission [3];
yellow: provinces with stable malaria transmission;
black star: presumable site of infection of a French tourist [9];
white star: presumable site of infection of our patient.

malaria cases in Kapit division of the Malaysian state of Sarawak, located on the island of Borneo [7].

With increasing awareness of this pathogen, *P. knowlesi* has been diagnosed frequently in human malaria cases on the island of Borneo, and has also been reported from Indonesia, the Malay peninsula, Myanmar, the Philippines, Singapore, Thailand and Vietnam [8].

As a cause for imported malaria, *P. knowlesi* has been identified only occasionally: only five cases of *P. knowlesi* malaria imported to Europe have been published so far. The first case was a Swedish traveller to Malaysian Borneo in 2006, the second a Finnish traveller to peninsular Malaysia in 2007, the third was a Spanish traveller in 2009 who had spent six month in several south east Asian countries including Indonesia, Malaysia, Thailand and Vietnam, and the fourth was a French tourist who presumably acquired the infection on the island of Kho Phayam (Thailand) in 2010 [9-12] (Figure). The most recent case was reported in August 2013 and occurred in a German traveller with human immunodeficiency virus (HIV) co-infection who presumably acquired the infection in Ranong province in Thailand [13].

The retrospective analysis of blood samples from Thailand suggests that the prevalence of *P. knowlesi* infections has not changed significantly over time during the period from 1996 to 2008 [3]. Therefore, it is most likely that the increasing number of cases recognised is due to the awareness of the possibility of human *P. knowlesi* malaria and to the application of diagnostic molecular biology techniques to differentiate this parasite from other malaria parasites.

The prevalence of *P. knowlesi* infections in Thailand (1%) is very low compared with the highly endemic Kapit division (50%) in Borneo, Malaysia Thailand [3,7]. Therefore, large numbers of imported cases from Thailand are not to be expected in the near future. However, changing tourism patterns like the trend towards eco-tourism might increase the risk of infection with *P. knowlesi* even in low prevalence countries. In the present case for instance, the infection was most likely acquired during a stay in the forested Khao Sok National Park inhabited by the natural monkey host.

It is important to recognise *P. knowlesi* infections, especially in the late stage when the parasites resemble *P. malariae*, because *P. knowlesi* infections can sometimes be associated with complications and may be fatal. A study on 107 patients reported severe malaria in 6.5% of *P. knowlesi* infections, among these three cases presenting with acute renal impairment. Whereas these severe *P. knowlesi* cases reported were associated with hyperparasitaemia, acute kidney failure occurred in our case despite a low parasitaemia of 0.2% [14]. Because of the possibility of a severe course of *P. knowlesi* infections, physicians must be increasingly aware of this possibility and contact specialised centres as soon as possible to ensure early appropriate diagnosis and timely treatment.

Conflict of interest

None declared.

Authors' contributions

HM O and JR treated the patient and wrote the paper. MC H, C MkC, B H and M I did the parasitological and molecular investigations and contributed to writing the manuscript. BEO J, SJ K, S M, I MS, and D H managed the patient and contributed to the manuscript. All authors participated in writing the manuscript and approved the final version.

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Treatment outcome of multi-drug resistant tuberculosis in the United Kingdom: retrospective-prospective cohort study from 2004 to 2007

L F Anderson (Laura.Anderson@phe.gov.uk)[1], S Tamne[1], J P Watson[2], T Cohen[3], C Mitnick[4], T Brown[5], F Drobniewski[5], I Abubakar[1,6]
1. Public Health England, Respiratory Diseases Department, TB Section, London, United Kingdom
2. Department of Respiratory Medicine, Leeds General Infirmary, Leeds, United Kingdom
3. Department of Epidemiology, Harvard School of Public Health, Boston, United States
4. Department of Global Health & Social Medicine, Harvard Medical School, United States
5. Public Health England, National Mycobacterial Reference Laboratory, Centre for Immunology and Infectious Disease, Barts and The London School of Medicine and Dentistry, London, United Kingdom
6. Research Department of Infection and Population Health, University College London, London, United Kingdom

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United Kingdom (UK) guidelines recommend at least 18 months treatment for patients with multidrug-resistant tuberculosis (MDR-TB). Prior to 2008, data on treatment outcome were only available at 12 months and therefore the proportion completing treatment was unknown. This retrospective-prospective cohort study reports on treatment outcomes for MDR-TB patients notified between 2004 and 2007 and examines factors associated with successful outcomes. 70.6% (144/204) completed treatment in 24 months or more, 6.9% (14) stopped treatment, 6.9% (14) died, 7.8% (16) were lost to follow up, 0.5% (1) relapsed and 4.4% (9) were transferred overseas. Following adjustment for age, being non-UK born, non-compliance and having co-morbidities, treatment with a fluoroquinolone (OR 3.09; 95% CI 1.21-7.88; p<0.05) or bacteriostatic drug (OR 4.23; 95% CI 1.60-11.18; p<0.05) were independently associated with successful treatment outcome. Treatment completion for MDR-TB cases remains below the World Health Organization (WHO) target. Our findings support current WHO guidelines for MDR-TB treatment. The UK should consider adopting individualised regimens based on WHO recommended drugs, taking into account drug sensitivities. Improving treatment completion rates will be key to tackling further drug resistance and transmission from untreated infectious cases.

Introduction

Multidrug-resistant TB (MDR-TB) remains a threat to the global tuberculosis (TB) control effort [1]. In the United Kingdom (UK), the annual number of culture confirmed cases of MDR-TB increased from 28 to 58 between 2000 and 2009 [2] and there were a total of eight extensively drug-resistant (XDR) cases reported (data unpublished). The prolonged treatment associated with MDR-TB and the often severe adverse effects of second-line antibiotics increases the challenges to achieve treatment completion. The rise in the number of MDR-TB cases has important implications for clinical management, social support and financing of TB control programmes [3]. Internationally, in resource rich settings, initial empirical treatment of MDR-TB patients should be based on past drug resistance results for patients with a previous TB episode, drug resistance profiles of an identified source case, or the levels of background drug resistance in the patient's country of origin [4,5]. This should be followed by individually adapted drug regimens once drug susceptibility results become available [4].

In 2008, the World Health Organization (WHO) recommended that the MDR-TB treatment regimen should ideally consist of a combination of ethambutol and pyrazinamide, an injectable agent (e.g. aminoglycosides), a fluoroquinolone and if necessary, a bacteriostatic drug should be added to give a total of at least four drugs to which resistance has not been demonstrated. Antibiotics with unknown efficacy should only be used when better options are exhausted [4]. Recently published WHO guidelines recommend the inclusion of the bacteriostatics ethionomide or prothionamide and either cycloserine or p-aminosalicylic acid in the regimen [5]. The treatment should last at least 20 months in total [5] and be supervised by directly observed therapy (DOT) [4].

In the UK, there is no recent national guidance for MDR-TB treatment [6,7]. The National Institute for Health and Clinical Excellence (NICE) guidelines published in 2011, did not specifically address the treatment of MDR-TB but suggested to consult experienced clinicians who specialise in MDR-TB treatment and care [8]. Data on the effectiveness of different drug combinations for MDR-TB are limited [5] and in the UK, it is

currently unknown which treatment regimens are most commonly used.

For cases notified in the UK in 2010, the proportion of MDR-TB cases completing treatment was 72.1% [9] which was below the WHO and UK treatment completion targets of 75% [10] and 85%, respectively, [11] but higher than the European Union (EU) target of 70% [12]. Prior to 2008, data on treatment outcome was only available at 12 months after the start of treatment and therefore it has been unclear how many cases completed treatment at 24 months. The enhanced surveillance of treatment outcome monitoring of MDR-TB cases allows treatment regimens and management to be assessed and progress towards achieving targets set by WHO [10], the EU [12] and the UK [11] to be evaluated over time.

The aims of this study were to determine the number and proportion of MDR-TB patients completing treatment who were diagnosed in the UK between 2004 and 2007, to describe the clinical characteristics of patients and to examine factors associated with a successful treatment outcome, loss to follow up and death.

Methods

All patients diagnosed with MDR-TB in England, Wales and Northern Ireland between 2004 and 2007 were included in the study. Treatment outcomes for all years were collected in 2009. Patients still on treatment at 24 months were followed up prospectively for treatment outcome on an annual basis until June 2012. All patients were followed up for a minimum of four years for relapse.

The following definitions and terms were used:
MDR-TB was defined as TB resistant to at least isoniazid and rifampicin.

Treatment regimen

Drugs used for treatment were categorised in five groups based on WHO criteria [4] (Table 2). To calculate the number of effective drugs used for treatment, in accordance with current guidelines, Group 5 agents, rifabutin (not recommended due to cross-resistance with rifampicin [4]) and drugs assumed to be ineffective due to phenotypic resistance testing methods were subtracted from the number of drugs in the initial regimen. A drug change was defined as an unexpected and unplanned addition, subtraction or substitution of a drug in the treatment regimen.

Treatment outcomes

Standard treatment outcomes routinely collected for surveillance in the UK are:

Completed treatment: Completed a full course of therapy within 12/24 months of starting treatment/notification.

Lost to follow up: Defined as failure to obtain contact with the patient before the end of treatment so that treatment outcome is not known.
Treatment stopped: Patient found to have stopped treatment (by choice) or for any other reason not mentioned below.
Still on treatment: Patient is still on treatment at 12/24 months due to

(a) initially planned e.g. in patients with TB affecting the central nervous system (CNS) or drug resistance;
(b) interruption as a result of side effects/intolerance, non-compliance, other interruption in taking treatment for two months or more;
(c) change in the treatment regimen due to intolerance/side effects, drug resistance (initial or acquired), failure to culture convert or poor clinical response.

Transferred out: Responsibility for patient's care transferred to another clinical team within the UK.
Transferred out overseas: Responsibility for patient's care transferred to another clinical team outside the UK. This treatment outcome was collected in addition to those above as part of this study.

Data collection

Demographic and clinical characteristics of patients were obtained from the Enhanced TB Surveillance system (ETS) which is the web-based TB notification system in the UK. Questionnaires were sent by mail to treating clinics to collect further information on: treatment outcome reported at 12 and 24 months, social risk factors (current or a history of alcohol or drug misuse, homelessness, imprisonment, smoking), co-morbidities (diabetes, chronic liver or renal disease, chronic hepatitis B or C positive and receiving immunosuppressive therapy), the initial drug regimen for MDR-TB, treatment start date, details of changes in treatment, duration of treatment (planned and given for those who completed treatment), DOT (defined as direct observation of ingestion of anti-TB treatment by a health professional in the community, the home or the clinic) and non-compliance (interruption of treatment for two consecutive months or more without medical approval or non-compliance reported by medical staff).

All questionnaires were returned. Previous history of TB diagnosis was self-reported and recorded in ETS; in addition, information from previous episodes diagnosed in the UK was ascertained through a search of ETS to complete missing data. Mortality data from the Office of National Statistics was searched manually for cases that were lost to follow up or had an unknown cause of death.

TB was considered to have caused or contributed to death if this was reported in ETS and/or recorded on the death certificate; ICD10 codes A15-A19 [13]. Human immunodeficiency virus (HIV) infection status was attained by record linkage as previously described [2]. Matching was not carried out on cases aged younger

Box

Treatment outcome categories, multidrug-resistant tuberculosis, United Kingdom

Treatment outcome category		
Successful	Adverse	Neutral
Treatment completed at 24 months or longer.	Treatment completed at 12 months.	The patient was transferred out overseas.
	Treatment completed at 24 months or longer but patient relapsed.	The patient died but TB was incidental to death.
	The patient died and TB caused or contributed to death or the relationship between the two was unknown. This includes patients diagnosed but not initiated on treatment prior to death.	
	Treatment stopped.	
	Lost to follow-up.	

Outcome categories were based on criteria by Ditah et al. (2007) [15].

than 15 years (10/204; 4.9%) as HIV infection in children is reported separately.

Laboratory methods

Drug susceptibility and strain typing data for cultured isolates of *Mycobacterium tuberculosis* complex were available from the UK Mycobacterial Surveillance Network (MycobNet). Drug susceptibility testing (DST) was carried out using the proportion or the resistance ratio method [14]. MDR-TB cases, notified in the UK (excluding Scotland) between 2004 and 2007, were identified by matching laboratory isolates to case reports in ETS [2], including those who subsequently developed MDR -TB during treatment. Cases of laboratory cross-contamination were excluded. Drugs with borderline resistance were considered to be resistant. The number of additional drugs to which MDR isolates were resistant was based on the resistance profile prior to the initiation of MDR-TB treatment.

Statistical analysis

The demographic and clinical characteristics of cases, drug resistance and the treatment regimen, management and outcome were described. Logistic regression modelling was used to calculate odds ratios for factors associated with a successful treatment outcome. All variables independently associated with treatment outcome in the univariate analysis ($p<0.2$) were considered in the multivariable model to evaluate the effect of drug treatment on outcome. A likelihood ratio test was used to investigate whether interactions between the different drug classes should be included in the final model. Individual co-morbidities were not considered in the multivariate analysis due to co-linearity with co-morbidity.

Ciprofloxacin is no longer recommended for use and therefore we did not include it as a variable in the model as it is no longer relevant for consideration in future treatment of MDR-TB.

Outcome categories were based on criteria by Ditah et al. (2007) [15] but were modified for the study population of drug-resistant, rather than fully sensitive TB cases (Box 1). Neutral outcomes (n=10) and patients who did not initiate treatment because they were diagnosed post mortem (n=3) were excluded from this part of the analysis.

Additional analyses using a chi-square test were undertaken to determine factors associated with the following adverse outcomes: (i) loss to follow up (included all MDR-TB cases) and (ii) death (included all patients with a known vital status at 24 months and excluded those transferred overseas or lost to follow up). Statistical analyses were carried out using Stata version 10.0.

Results

Demographic, clinical and social characteristics

There were 204 culture-confirmed cases of MDR-TB diagnosed in the UK between 2004 and 2007. Just over half of these cases resided London and the majority were 15 to 44 years old, non-UK born and of Indian subcontinent or Black African ethnicities (Table 1). Pulmonary disease was most common (70.1%, 143/204); 61.5% (88/143) of these cases, were sputum smear positive. Only 30.4% (56/184) of patients had a previous history of TB diagnosis. Of those with information recorded on social risk factors and co-morbidities, 18.6% (32/172) had at least one social risk factor and 26.7% (49/183) had a co-morbidity, of which HIV infection was most common (Table 1).

Isolates were resistant to a median of four drugs (range 2-9) and were most commonly resistant to streptomycin (53.9%, 110/204) and ethambutol (35.3%, 72/204). There were no cases of XDR-TB. High proportions were resistant to a bacteriostatic agent (22.5%, 46/204), and to at least one (42.2%, 86/204) and two or more (24.0%, 49/204) second-line drugs. Fluoroquinolone resistance was uncommon (4.4%, 9/204) and 10.3% (21/204) were resistant to all first-line drugs.

Treatment regimen and management

Among the 94.6% (193/204) patients who began treatment the planned duration was recorded for 83.9% (162/193). The duration of the intensive treatment phase was not recorded. A treatment course shorter

Table 1

Characteristics of multidrug-resistant tuberculosis cases, United Kingdom, 2004–2007 (n=204)

Characteristic	n (%)
Living in London	
Yes	104 (51.0)
Sex	
Male	103 (50.5)
Age (years)	
0-14	10 (4.9)
15-44	170 (83.3)
45-64	17 (8.3)
≥ 65	7 (3.4)
Born in UK (n=201)	
Yes	31 (15.4)
No	170 (84.6)
Ethnicity (n=201)	
White	22 (10.9)
Black African	59 (29.3)
Indian subcontinent	78 (38.8)
Other	42 (20.9)
Previous diagnosis of TB (n=184)	
Yes	56 (30.4)
No	128 (69.6)
Site of disease	
Pulmonary, sputum smear positive	88 (43.1)
Pulmonary, other	55 (27.0)
Extrapulmonary disease only	61 (29.9)
Social risk factor (n=172)[a]	
Yes	32 (18.6)
No	140 (81.4)
Homelessness	9 (5.2)
Drug abuse	9 (5.2)
Alcohol misuse	12 (7.0)
Imprisonment	5 (2.9)
Smoking	21 (12.2)
Any co-morbidity (n=183)[b]	
Yes	49 (26.7)
No	134 (73.2)
Diabetes (n=192)	10 (5.2)
Chronic renal disease (n=192)	7 (3.6)
Chronic liver disease (n=192)	3 (1.6)
Immunosuppressive therapy (n=192)	4 (2.1)
Hepatitis B/C positive (n=192)	9 (4.7)
HIV positive (n=193)	30 (15.5)
Total	**204 (100)**

[a] Patients were coded as yes if they had "yes" for any social risk factor and no if they had "no" for every social risk factor included.

[b] Patients were coded as yes if they had "yes" for any co-morbidity and no if they had "no" for every co-morbidity included. If data were missing for one or more co-morbidities, they were coded as missing.

HIV: human immunodeficiency virus; TB: tuberculosis; UK United Kingdom.

than 18 months was planned for 11.1% (18/162) of patients but 23.2% (33/142) of those completing treatment, where a treatment start and completion date was available, actually received less than 18 months. The median treatment duration for cases completing treatment was 19 months (range 3–47) and increased from 18 to 23 months between 2004 and 2007.

The most common drugs used for treatment were pyrazinamide, moxifloxacin and ethambutol (Table 2). A median number of four effective drugs (range 0-8) were used in the initial drug regimen and 19.7% (38/193) of cases were treated with fewer than four effective drugs.

Over half of patients (54.4%, 105/193) had at least one change to their treatment regimen at some point during treatment. In the majority of these cases, the reason for this was not stated. When documented, most regimen alterations were in response to side effects or drug intolerance and only rarely in response to a change in drug susceptibility (data not shown).

Only 39.9% (77/193) of all patients and 53.1% (17/32) of those with identified social risk factors were placed on DOT. Main reasons for not administering DOT, where recorded, were a lack of indicators for non-compliance 40.0% (42/105), being an inpatient 25.7% (27/105) or using a dossette box as an alternative 11.4% (12/105).

Treatment outcome

A total of 70.6% (144/204) of patients successfully completed treatment at 24 months or more. For those with unsuccessful outcomes 6.9% (14/204) had their treatment stopped, 6.4% (13/204) died where TB was recorded as a causative or contributory factor or the relationship between the two was unknown, 7.8% (16/204) were lost to follow up, 2.9% (6/204) completed treatment within 12 months and 0.5% (1/204) completed treatment but relapsed. Ten of the 204 (4,9%) patients had neutral outcomes: nine were transferred overseas and mainly referred to clinics in resource-poor countries in Asia and Africa and one died where TB was incidental to death.

Factors associated with treatment success

Results of the univariate analysis are shown in tables 3 and 4. In the multivariable analysis patients receiving a fluoroquinolone or a bacteriostatic drug were more likely to have a successful treatment outcome compared to those who did not (Table 5). Treatment with an injectable agent did not have a significant effect on treatment outcome after adjusting for treatment with a fluoroquinolone and a bacteriostatic drug. No significant interactions were detected and all other factors remained significantly associated with treatment outcome, apart from having resistance to five or more drugs. Exploratory analyses were carried out to try to explain the relationship between resistance to five or more drugs and a successful outcome. Firstly, resistance to five or more drugs was added to the model,

Table 2

Drugs used for treatment of multidrug-resistant tuberculosis cases, United Kingdom, 2004–2007 (n=193)

Treatment groups	Number of cases	%
Group 1 - First line drugs	170	88.1
Isoniazid	6	3.1
Rifampicin	6	3.1
Ethambutol	126	65.3
Pyrazinamide	155	80.3
Rifabutin	4	2.1
Group 2- Injectable agents	139	72.0
Streptomycin	37	19.2
Amikacin	76	39.4
Capreomycin	30	15.5
Kanamycin	0	0
Group 3 - Fluoroquinolones	147	76.2
Levofloxacin	6	3.1
Moxifloxacin	129	66.8
Ofloxacin	14	7.3
Ciprofloxacin	44	22.8
Injectable and fluoroquinolone	111	57.5
Group 4 - Bacteriostatic drug	151	78.2
Ethionamide	11	5.7
Prothionamide	113	58.5
Cycloserine	69	35.8
Para-aminosalicylic acid (PAS)	19	9.8
Group 5 - Agents with unclear efficacy	83	43.0
Linezolid	8	4.1
Clofazimine	2	1.0
Amoxicillin	0	0
Imipenem	0	0
Clarithromycin	78	40.4
Other	13	6.7
Augmentin	2	1.0
Azithromycin	11	5.7
Total	**193**	**100**

[a] No longer recommended for use.

following adjustment for all factors associated with a poor treatment outcome (Table 5), and remained significant. Each treatment was then added separately and only adjustment for bacteriostatic drug treatment led to loss of statistical significance.

Factors associated with treatment stopped, mortality and loss to follow up

Reasons given for stopping treatment in 14 patients included 'non-compliance', resulting in the clinician's decision to discontinue treatment, 'patient's choice', 'pregnancy', 'side effects' and 'spontaneous recovery'.

Of the 14 patients who died, six died prior to starting treatment and three of these were diagnosed post mortem. Compared to cases who were known to be alive at the end of treatment, death was found to be strongly associated with having any co-morbidity ($p<0.0005$), and in particular with HIV ($p<0.0005$), diabetes ($p=0.002$) or chronic renal disease ($p=0.002$). Only being a new entrant to the UK (11/12 were in the UK ≤2 years prior to diagnosis, $p=0.030$, with six returning home) was associated with being lost to follow-up. Reasons given for completing treatment within 12 months were that 'the patient improved', 'it was the recommendation at the time' or 'it was initially planned and the patient was followed up instead'.

Discussion

The proportion of MDR-TB cases notified between 2004 and 2007 completing treatment in the UK was 70.6%. This was higher than the EU/European Economic Area (EEA) average of 30.9% [16] for 2007 MDR-TB cases and most other low incidence resource-rich countries[17-19]. This completion rate met the EU target of 70% [12] but was still below the WHO target of 75% [10] and the UK Chief Medical Officers action plan goal of 85%[11]. The treatment completion rate for MDR-TB cases in the UK has improved in recent years with 80% and 72% completing treatment for cases notified in 2009 [20] and 2010 [9], respectively.

Treatment with a fluoroquinolone or a bacteriostatic drug were statistically significantly associated with achieving treatment success, which provides further evidence to support the recent WHO recommendations to include drugs belonging to Groups 2, 3 and 4 in a treatment regimen for MDR-TB [5]. These findings have potential implications for the development of future national guidelines and the UK should consider adopting individualised regimens, based on the drug classes recommended by WHO for treatment of MDR-TB cases, taking into account DST results.

While the majority of patients appeared to have appropriate treatment according to WHO guidelines, approximately a quarter of patients had a substandard regimen with too few effective drugs or shorter treatment duration than required. DST results were not always used to ensure administration of effective individualised regimens. However, we note that DST results for most drugs other than isoniazid and rifampicin are less accurate [21] and therefore it is possible that these patients still received effective treatment.

The majority of patients, even those with social risk factors and those hospitalised, did not receive DOT although it is recommended for all MDR-TB patients [4]. Therefore greater use of DOT remains important until 85% treatment completion is achieved.

Table 3

Univariate analysis of drug resistance pattern, treatment regimen and treatment management associated with successful treatment outcome in patients diagnosed with multidrug-resistant tuberculosis, United Kingdom, 2004–2007 (n=191)

	Adverse treatment outcome (n = 47) n (%)	Successful treatment outcome (n = 144) n (%)	Unadjusted OR (95% CI)	P value
Drug resistance				
Number of drugs				0.017[a]
Resistance to 2-4 drugs at the start of treatment	42 (28.4)	106 (71.6)	1	
Resistance to 5 or more drugs at the start of treatment	5 (11.6)	38 (88.4)	3.01 (1.11-8.17)	
Group 1 - First-line drugs[b]				0.911
Susceptible	26 (24.3)	81 (75.7)	1	
Resistant	21 (25.0)	63 (75.0)	0.96 (0.50-1.87)	
Second-line drugs (Any)				0.429
Susceptible to all	19 (27.9)	49 (72.1)	1	
Resistant to at least one	28 (22.8)	95 (77.2)	1.32 (0.67-2.59)	
Group 2 - Injectable agent[c]				0.592
Susceptible	23 (26.4)	64 (73.6)	1	
Resistant	24 (23.1)	80 (76.9)	1.20 (0.62-2.32)	
Group 3 - Fluoroquinolone[d]				0.269
Susceptible	43 (23.8)	138 (76.2)	1	
Resistant	4 (40.0)	6 (60.0)	0.47 (0.13-1.73)	
Group 4 - Bacteriostatic drugs[e]				0.459
Susceptible	38 (25.9)	109 (74.1)	1	
Resistant	9 (20.5)	35 (79.5)	1.36 (0.60-3.08)	
Developed further drug resistance whilst on treatment				0.914
No	43 (24.7)	131 (75.3)	1	
Yes	4 (23.5)	13 (76.5)	1.06 (0.33-3.44)	
Initial treatment regimen				
Group 2 - Injectable agent[c]				0.010*
No	22 (36.7)	38 (63.3)	1	
Yes	25 (19.1)	106 (80.9)	2.45 (1.24-4.86)	
Group 3 – Fluoroquinolone[d]				0.000*
No	23 (44.2)	29 (55.8)	1	
Yes	24 (17.3)	115 (82.7)	3.80 (1.88-7.67)	
Ciprofloxacin				0.084
No	32 (21.6)	116 (78.4)	1	
Yes	15 (34.9)	28 (65.1)	0.51 (0.25-1.08)	
Group 4 - Bacteriostatic drugs[e]				0.000*
No	24 (50.0)	24 (50.0)	1	
Yes	23 (16.1)	120 (83.9)	5.22 (2.54-10.72)	
Treatment management				
DOT at any time during treatment				0.230
No/Unknown	32 (27.6)	84 (72.4)	1	
Yes	15 (20.0)	60 (80.0)	1.52 (0.76-3.06)	

DOT: directly observed therapy.

[a] Significance p<0.05.
[b] Group 1 oral agents Ethambutol or Pyrazinamide
[c] Group 2: Amikacin, Capreomycin, Kanamycin or Streptomycin.
[d] Group 3: Moxifloxacin, Ofloxacin, Ciprofloxacin.
[e] Group 4: Ethionamide, Prothionamide,Cycloserine, Para-aminosalicylic acid.

Table 4

Univariate analysis of demographic and clinical characteristics, social risk factors and comorbidities associated with successful treatment outcome in patients with multidrug-resistant tuberculosis, United Kingdom, 2004–2007 (n=191)

	Adverse treatment outcome (n = 47) n (%)	Successful treatment outcome (n = 144) n (%)	Unadjusted OR (95% CI)	P value
Living in London				0.288
Yes	28 (27.7)	73 (72.3)	1	
No	19 (21.1)	71 (78.9)	1.43 (0.73-2.79)	
Age				0.000[a]
0-14	1 (10.0)	9 (90.0)	2.36 (0.29-19.27)	
15-44	33 (20.8)	126 (79.2)	1	
45-64	6 (40.0)	9 (60.0)	0.39 (0.13-1.18)	
≥65	7 (100)	0 (0)	0 (0)[b]	
Sex				0.256
Male	27 (28.1)	69 (71.9)	1	
Female	20 (21.0)	75 (79.0)	1.46 (0.76-2.85)	
Born in the UK				0.026[a]
Yes	3 (10.0)	27 (90.0)	1	
No	44 (27.7)	115 (72.3)	0.29 (0.08-1.01)	
Ethnicity				0.877
White	5 (25.0)	15 (75.0)	0.84 (0.27-2.67)	
Black African	15 (28.3)	38 (71.7)	0.71 (0.31-1.60)	
Indian subcontinent	16 (21.9)	57 (78.1)	1	
Other	10 (23.8)	32 (76.2)	0.89 (0.36-2.21)	
Previous diagnosis of TB				0.532
No	28 (23.0)	94 (77.0)	1	
Yes	14 (27.4)	37 (72.6)	0.79 (0.37-1.66)	
Site of disease				0.279
Pulmonary sputum positive	23 (27.7)	60 (72.3)	1	
Pulmonary other	14 (28.0)	36 (72.0)	0.99 (0.45-2.16)	
Extrapulmonary disease only	10 (17.2)	48 (82.8)	1.84 (0.79-4.24)	
Social risk factor				0.443
No	29 (22.0)	103 (78.0)	1	
Yes	9 (29.0)	22 (71.0)	0.69 (0.29-1.66)	
Unknown	9 (32.1)	19 (67.9)	0.59 (0.24-1.45)	
Non-compliant[c]				0.019[a]
No	31 (21.1)	116 (78.9)	1	
Yes	10 (52.6)	9 (47.4)	0.24 (0.08-0.64)	
Unknown	6 (24.0)	19 (76.0)	0.85 (0.31-2.30)	
Comorbidity				0.001[a]
No/Unknown	28 (18.9)	120 (81.1)	1	
Yes	19 (44.2)	24 (55.8)	0.29 (0.14-0.61)	
Diabetes				0.014[a]
No/Unknown	41 (22.6)	140 (77.4)	1	
Yes	6 (60.0)	4 (40.0)	0.19 (0.05-0.73)	
Chronic renal disease				0.061
No/Unknown	43 (23.4)	141 (76.6)	1	
Yes	4 (57.1)	3 (42.9)	0.23 (0.05-1.06)	
Chronic liver disease				0.732
No/Unknown	46 (24.5)	142 (75.5)	1	
Yes	1 (33.3)	2 (66.7)	0.64 (0.06-7.31)	
Hepatitis B/C positive				0.408
No/Unknown	44 (24.0)	139 (76.0)	1	
Yes	3 (37.5)	5 (62.5)	0.53 (0.12-2.30)	
HIV-positive				0.048[a]
No/Unknown	37 (22.2)	130 (77.8)	1	
Yes	10 (41.7)	14 (58.3)	0.40 (0.16-0.97)	

[a] Significance p<0.05.

[b] Not estimable.

[c] Interruption of treatment for two consecutive months or more without medical approval or non-compliance reported by medical staff.

CI: confidence interval; HIV: human immunodeficiency virus; OR: odds ratio; TB: tuberculosis; UK: United Kingdom.

Table 5

Multivariate analysis of factors associated with successful treatment outcome (n=182)

Covariable	Adjusted OR (95% CI)	p-value
Age (years)		0.289
0-14	3.49 (0.32-38.1)	
45-64	0.46 (0.10-2.07)	
≥65	Not estimable	
Born in UK	0.45 (0.10-1.92)	0.2548
Non-compliant[a]	0.14 (0.04-0.49)	0.0079
Comorbidity	0.26 (0.09-0.71)	0.0090
Resistant to five or more drugs	2.17 (0.68-6.94)	0.1736
Group 2[b]- Use of injectable drug	1.49 (0.56-3.98)	0.4323
Group 3[c]- Use of fluoroquinolone	3.09 (1.21-7.88)	0.0191
Group 4[d]- Use of bacteriostatic drug	4.23 (1.60-11.18)	0.0036

[a] Interruption of treatment for two consecutive months or more without medical approval or non-compliance reported by medical staff.

[b] Group 2: Amikacin, Capreomycin, Kanamycin or Streptomycin.

[c] Group 3: Moxifloxacin, Ofloxacin, Ciprofloxacin.

[d] Group 4- Ethionamide, Prothionamide,Cycloserine, Para-aminosalicylic acid.

CI: confidence interval; OR: odds ratio; UK: United Kingdom.

Mortality rates of 6.4% in our study, were similar to those observed for all TB cases in the UK in the same period (6.2%, 2004-2007) (data unpublished) and to other low incidence countries[16], although higher than expected for a population where most cases are 15 to 44 years old [22]. Similarly to other studies, death was significantly associated with presence of HIV infection [23-27], chronic renal disease [28,29] and diabetes [28,30]. Treatment of HIV co-infected patients is complicated due to a high tablet burden, increased drug side effects [31] and opportunistic infections. TB patients with chronic renal disease may also experience more treatment side effects and some TB drugs can directly damage kidney function [32]. Anti-TB treatment can worsen glycaemic control in patients with diabetes [30]. These problems are intensified in MDR-TB where treatment duration is prolonged and drug options are limited.

The association between successful treatment outcome and fluoroquinolone or bacteriostatic drug use, has been shown previously [21,27,33-37]. The relative infrequency of resistance to fluoroquinolones in our study further supports their use in MDR-TB treatment. Consistent with previous reports [38,39], ciprofloxacin was not shown to be an effective agent in the univariate analysis, supporting its recent exclusion from the list of recommended TB drugs [4].

Similarly to findings in resource-rich countries, where the majority of MDR-TB cases are imported, we detected high proportions of streptomycin and ethambutol resistance [17,18,21,40]. In contrast to other studies [41-47], the treatment success of UK MDR-TB patients is not affected by the number of additional drugs to which isolates are resistant, which may reflect the local availability of alternative second line antibiotics. The association between resistance to a greater number of drugs and a successful treatment outcome was not significant following adjustment for treatment with a bacteriostatic agent. A possible explanation for this is that those with fewer treatment options are more likely to receive a bacteriostatic which leads to treatment success.

Our study has several limitations. The small sample size limited our ability to detect the effect of individual antibiotics on treatment outcome or significant interactions. The initial drug resistance profile affects the choice of antibiotic used and therefore this may have confounded associations between antibiotics used and treatment outcome.

The treatment outcomes in the UK differ from the standard WHO definitions [48], which means that it is difficult to compare outcomes directly with other countries. For example, in the absence of bacteriological or radiological data at the end of treatment we were not able to determine whether patients who completed treatment had been successfully cured. The relapse rate in the UK however is low, despite lack of evidence of cure [49,50] and during the study period only one case relapsed and was appropriately categorised as unsuccessful.

The treatment outcome classification used in the statistical analysis was based on an approach by Ditah et al. [15] which also differs from other studies. Deaths where TB is incidental to death are usually classified as an unsuccessful outcome but we chose to exclude them from the analysis as the eventual outcome, for example had the patients not died for another reason, was unclear. The UK however, has a strong vital registration system and we are therefore confident that these deaths were not caused by TB.

The partly retrospective study design prevented time to event analysis as we did not have the dates for all outcome categories. Data sources used to complete the questionnaire may not have been as accurate or complete as they would have been in an entirely prospective cohort. This may be particularly true for variables that can vary in definition such as DOT or variables relying on comprehensive notes such as changes in treatment. Future prospective studies or randomised control trials will likely provide stronger evidence for the association between individual drugs and treatment outcome, as well as allow for the investigation of the role of treatment duration on treatment completion or cure.

Public health and clinical implications

Since 2011, WHO guidelines for MDR treatment regimens recommend the inclusion of an oral bacteriostatic drug in combination with a fluoroquinolone and an injectable agent. This study, in addition to a recent meta analysis of 9,153 patients [37], supports these guidelines and therefore, provided the future MDR-TB population remains similar to our study population, we recommend that a bacteriostatic drug should be considered an important part of all MDR-TB treatment regimens in the UK, taking into account drug susceptibility. However due to side effects associated with bacteriostatic drugs their use should be managed with care.

During our study period the WHO guidelines in use did not recommend one fluoroquinolone over another but moxifloxacin was more widely used, as many clinicians believe that it may be more potent. Current WHO guidelines [5] recommend the use of later generation fluoroquinolones such as moxifloxacin and levofloxacin and these have also recently been shown to be significantly associated with successful treatment outcomes [37].

The failure to take account of drug sensitivity results appropriately as shown in our study, could reflect a lack of experience in treating MDR-TB, possibly due to its rarity in the UK. If geographical considerations prevent all cases being managed in specialist centres, outcomes may be improved by advice from clinicians in the national web-based MDR-TB advisory service hosted by the British Thoracic Society [51].

Since the majority of cases who were lost to follow up returned to their countries of origin, efforts should be made to engage with national TB programs overseas at an early stage in treatment to ensure optimised continuation of management. Alternatively, patients should be supported to complete treatment in the UK, especially if they are returning to resource-poor countries where TB treatment and, in particular, the supply of effective second line antibiotics may not be guaranteed. Referring detainees prior to deportation to a TB service dedicated to improving health in mobile populations, such as TBNet (part of the Migrant Clinicians Network, USA), has been shown to result in high treatment completion rates [52] and this option should be explored for the UK.

Conclusion

Our findings are in line with the international guidance for the use of a bacteriostatic drug in addition to an injectable agent and a fluoroquinolone for the treatment of MDR-TB. It is important to continue to monitor treatment outcomes of MDR-TB patients to improve treatment management policy. Further research should evaluate the role of DOT among MDR-TB patients in the UK. Patients should be given psychosocial support to improve treatment compliance.

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Conflict of interest

None declared.

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Incubation period for campylobacteriosis and its importance in the estimation of incidence related to travel

B J Horn (Beverley.horn@esr.cri.nz)[1], R J Lake[1]
1. Institute of Environmental Science and Research, Christchurch, New Zealand

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Differentiation between travel-related and domestic cases of infectious disease is important in managing risk. Incubation periods of cases from several outbreaks of campylobacteriosis in Canada, Europe, and the United States with defined exposure time of less than 24 hours were collated to provide information on the incubation period distribution. This distribution was consistent across the varied outbreaks considered, with 84% (702/832) of cases having an incubation period of four days or less and 1% having an incubation period of eight days or more. The incubation period distribution was incorporated into a model for the number of travel-related cases presenting with symptom onset at given dates after return to their country of residence. Using New Zealand notification data between 2006 and 2010 for cases who had undertaken foreign travel within 10 days prior to symptom onset, we found that 29.6% (67/227 cases; 95% confidence interval (CI): 28.3–30.8%) of these cases were likely to have been domestic cases. When cases with symptom onset prior to arrival were included, the probable domestic cases represented 11.8% (67/571; 95% CI: 11.2–12.3%). Consideration of incubation time distributions and consistent collection of travel start/end dates with symptom onset dates would assist attribution of cases to foreign travel.

Introduction

The World Tourism and Travel Council reports that international travel grew in both traveller numbers and economic value for the third consecutive year in 2012 for all regions, including Europe [1]. Therefore differentiation between travel-related and domestic cases of infectious disease is increasingly important to researchers and regulators seeking to understand the epidemiology of disease and potential preventive measures within a single country. The proportion of travel-related bacterial enteric disease cases has been estimated as approximately 20% for North America and England [2-4], while in Scandinavia and Switzerland the proportion is approximately 50% [5-7].

To classify a case as infected abroad, the exposure event should have occurred outside the country of residence. Cases that arrive in the country exhibiting symptoms and were out of the country for the entire potential incubation period can be easily categorised. For short visits abroad, it is possible that the infection was acquired domestically before leaving. Cases for which there is a period of time between arrival and symptom onset are more difficult to assign. It is possible that some cases with symptom onset after returning home were actually the result of an exposure in their home country, but with a short incubation period. Thus there is potential for over-reporting of travel-acquired illness.

The generally accepted incubation period for campylobacteriosis is two to five days, with a range of one to 10 days [8]. The assignment of a notified case as a travel-related case, or 'out-of-country' acquired infection often depends on the judgement of a doctor or public health worker with knowledge of the incubation period of the pathogen involved. For example, in a Swedish study the clinical notifications were described as infected abroad 'based on the best judgment of the notifying clinician based on patient history and knowledge of the characteristics of the pathogen in question' [5]. The United States (US) FoodNet defines a campylobacteriosis case as foreign-travel related when the patient returned from an international destination within seven days of illness onset [2]. Studies of the importance of travel with regards to acquiring campylobacteriosis using data from the United Kingdom [4,9] and Finland [10] have considered as travel-related campylobacteriosis cases those which had been abroad either five days or two weeks preceding the onset of illness.

In New Zealand, the notified rate of campylobacteriosis in 2011 was 151.9 per 100,000 population (6,692 cases) [11]. Campylobacteriosis risk factor data on notified cases is collated by Public Health Unit (PHU) staff and may include foreign travel risk factor information. This information includes symptom onset date, arrival date

back in New Zealand, and for some cases the countries visited and duration of the visits. In 2011, of those who reported the information, 7.3% reported overseas travel during the incubation period. The notification instructions list campylobacteriosis as having the generally accepted incubation period as above.

The aim of this paper is to establish the incubation period profile for campylobacteriosis from defined exposure events reported in the scientific literature, and to use this to model New Zealand notification data to improve estimation of the proportion of cases with symptom onset after arrival, which were infections acquired outside the country.

Methods

Review of incubation times

To establish a distribution for the likely incubation period for campylobacteriosis, international outbreak reports from the scientific literature located by keyword searches in PubMed 'campy* AND outbreak' and Science Direct 'campylobacter AND outbreak' were reviewed. The records were reviewed by title, abstract, and if necessary full text, to identify outbreaks of campylobacteriosis (only) which could be associated with a fixed event, and where the event started and finished within a 24 hour period. Examples included sporting and entertainment events. Outbreaks associated with contaminated drinking water or ongoing food supplies were not included, as it was not possible to define the exact exposure date for cases associated with this type of outbreak.

Reports from outbreaks with fixed exposure dates were then reviewed for information on the period between exposure event (day 0) and the onset of symptoms. This provides the incubation time in days for campylobacteriosis symptoms to appear.

For some outbreaks the time to symptom onset is given for both laboratory-confirmed and suspected (probable) cases. For the purposes of this paper, we assumed all suspected cases that occurred within the time range of the occurrence of confirmed cases were also due to the exposure associated with the outbreak.

The periods between exposure and symptom onset retrieved from the individual outbreak reports were examined graphically to compare the distribution of incubation periods for consistency across different events. We then combined the cases from the outbreaks and compiled a data set including all the cases with known period between exposure and symptom onset. This dataset was used to establish the distribution of incubation times. For the proportion of cases with given incubation periods (days), 95% confidence intervals (CI) were estimated from the 2.5th and 97.5th percentiles of 5,000 bootstrap samples taken with replacement. Analyses were conducted using the R statistical package [12].

Review of New Zealand notification data

Notification data are recorded using a web-based application (EpiSurv) available to staff at each of the 18 PHUs in New Zealand. These data are transferred to the Institute of Environmental Science and Research (ESR) Ltd., where they are collated, analysed and reported on behalf of the Ministry of Health.

Anonymised notification reports of cases of campylobacteriosis for which foreign travel was reported as a risk factor were obtained from EpiSurv for the period 2006 to 2010, following approval from the Multi-Region Ethics Committee. These records were carefully reviewed to identify a subset of the cases which reported both the date of arrival in New Zealand and the date of onset of symptoms which was either during travelling or after return to New Zealand. The time in days relative to arrival in New Zealand was calculated for each case, with the arrival date set to day zero. While there are fields for the dates of arrival to and departure from countries visited in the notification database, these fields are rarely filled in and so were not used in this study.

The incubation period distribution derived from the combined outbreak dataset was used to estimate the proportion of travel-related cases with symptoms starting on each day in the range of one to 10 days after returning to New Zealand that could be due to domestically-acquired infection. It was assumed that cases were equally likely to have been infected on any of the 10 days prior to arriving in New Zealand, and there was no difference in the distribution of the incubation period for infections acquired domestically and abroad. Given these assumptions, the estimated number of cases associated with travel abroad with onset on day d after arrival in New Zealand, C_T, can be given by,

$$C_T(d) = A\,(1 - \sum_{i=1}^{d} Proportion\ of\ cases\ with\ incubation\ period\ i).$$

The scaling factor, A, was derived from fitting the equation to the number of cases recording symptom onset one day after return to New Zealand and the proportion of cases with incubation period i was taken from the outbreak data distribution.

The number of estimated foreign travel-related cases was compared graphically to the number of notified cases associated with foreign travel to determine the number of days after arrival in New Zealand after which any consistent difference in the two estimates could be observed. From this point, the difference between the notifications and the model outputs for the remaining days up to 10 days post arrival in New Zealand was used to estimate the over-prediction of travel-acquired infections. The estimated over-prediction of travel-acquired infections were presented as the 2.5th, 50th and 97.5th percentiles of over-prediction calculated

Table

Campylobacteriosis outbreaks (n=7) with reported incubation periods for cases (n=832) and defined exposure events, 1983–2010

Exposure	Number of campylobacteriosis cases with incubation data	Country	Reference
Orienteering event with raw milk drinks available	451	Switzerland	Stalder et al. 1983 [13]
Mud ingestion during mountain bike event	225	Canada	Stuart et al. 2010 [14]
Cadets killing, cooking and eating chickens	78	Netherlands	Brouwer et al. 1979 [15]
Wedding meal	24	England	Inns et al. 2010 [16]
Farm visit including drinking unpasteurised milk	23	Wales	Evans et al. 1996 [17]
Dinner dance	20	England	Skirrow et al. 1981 [18]
Undercooked barbequed chicken	11	United States	Istre et al. 1984 [19]

from 5,000 bootstrap samples of the incubation period distribution taken with replacement.

Results

Incubation period distribution

From the PubMed (641 records) and Science Direct (85 records) searches, seven outbreaks with known distinct exposure events and number of reported cases for each incubation period (days) were identified. These are summarised in the Table. Laboratory-confirmed *Campylobacter jejuni* was reported as being associated with all the outbreaks. The three largest outbreaks each involved between 78 and 451 cases [13-15] and provided incubation periods for a total of 754 cases while four smaller outbreaks [16-19] involved 11 to 24 cases per outbreak and provided a total of 78 incubation periods.

The incubation period distribution is presented in Figure 1a for the three large outbreaks and Figure 1b for the smaller outbreaks. The incubation period distribution is displayed as the cumulative proportion of the cases in each outbreak to have an incubation period of equal to or less than the days given. The distribution curves are similar for the large and smaller outbreaks.

Figure 2 shows the distribution of incubation period for cases from all outbreaks for up to 10 days. Of the 832 cases with known exposure and symptom onset dates, only 17 (1%) recorded an incubation period of greater than seven days. Most cases, 702 (84%), had an incubation period of four days or less.

Overseas travel case attribution

A total of 945 confirmed New Zealand cases of campylobacteriosis with overseas travel as a reported risk factor over the period 2006 to 2010 were obtained from EpiSurv records. Of these, 121 (13%) did not have an exact symptom onset date and of the remaining records 253 (27%) did not have an exact arrival date in New Zealand. These cases were excluded from the analysis, resulting in 571 records (60%) where the number of days between arrival in New Zealand and symptom onset could be calculated. For 344 of these cases, symptoms had occurred prior to arrival in New Zealand, leaving 227 cases with a defined period to symptom onset of one to 10 days after arrival.

Figure 3 shows the frequency of cases' symptom onset relative to the number of days after arrival in New Zealand. Most cases (66%) record symptom onset within one to four days, but for longer periods the frequency is higher than might be expected from the distribution shown in Figure 2.

The incubation period distribution in Figure 2 was used to derive a likely frequency distribution for symptom onset following arrival in New Zealand. The scaling factor for this data, A, was derived to be 69.5 cases, which resulted in a predicted frequency of cases which acquired campylobacteriosis abroad, also shown in Figure 3.

Comparison of the predicted number of cases associated with foreign travel, with the number of cases reporting foreign travel as a risk factor in notification records (Figure 3) suggests that a proportion of the cases with symptom onset of five or more days after arrival in New Zealand could be domestic cases. Using the subset of travel-associated cases with symptom onset after return to New Zealand, this proportion with domestically-acquired campylobacteriosis is 67/227 (29.6%, 95% CI: 28.3–30.8%) of cases. A lower bound for the overestimation of all travel-associated cases, 67/571 (11.8%, 95% CI: 11.2–12.3%), can be calculated by assuming that all infections with symptom onset before arrival were acquired overseas. However, this overestimation percentage will be higher if some of the cases became infected before the start of their travels.

Figure 1

Cumulative density plots for campylobacteriosis incubation periods of up to 10 days for (a) three large campylobacteriosis outbreaks along with the distribution obtained from combining the data from four smaller outbreaks, and (b) the four smaller outbreaks, 1983–2010 (n=832 cases)

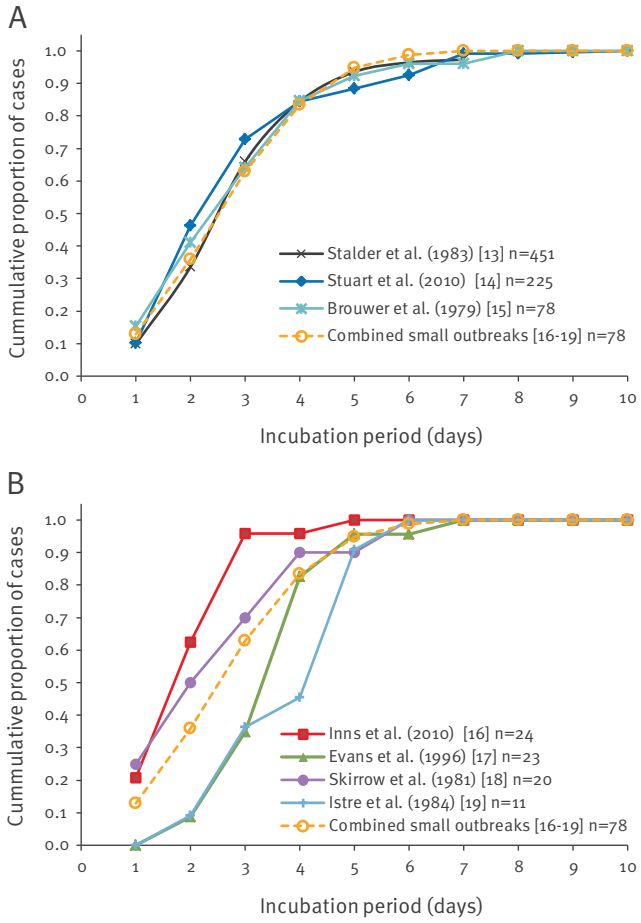
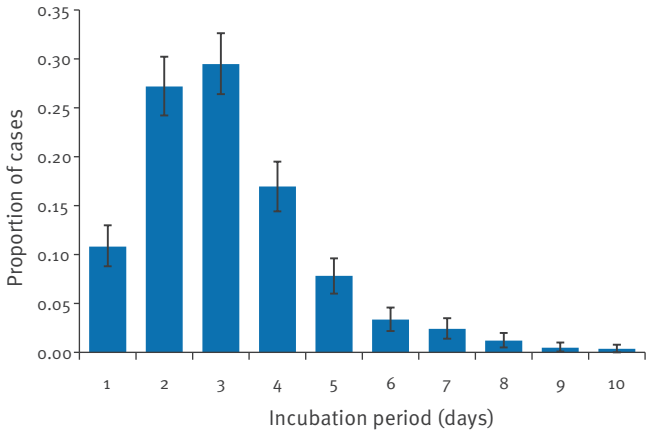


Figure 2

Distribution of the proportion of campylobacteriosis cases in function of their incubation periods among 832 cases associated with outbreaks with known exposure events



2.5th and 97.5th percentile bootstrap intervals of the proportion are plotted.

Discussion

This analysis suggests the importance of travel as a risk factor may be overestimated when only 'yes/no' answers to foreign travel in the incubation period data from notification records are considered. This is a minor adjustment for New Zealand, where travel is estimated to be a risk factor in less than 10% of notified cases of campylobacteriosis [11]. However, in Europe and North America where travel-related cases are a higher proportion of the total reported, and where out of country travel may be for shorter periods, the adjustment required to attribution estimates, based on our results, may be more significant.

The analysis depends on reported outbreak incubation period data. The three largest outbreaks considered in this study have similar distributions for incubation period, with nearly half the cases showing symptoms within two days of the exposure event and 85% of cases reporting symptoms starting in the first four days after the exposure event. The four smaller outbreaks show more variation than the larger outbreaks. The wedding meal outbreak [16] has a larger number of cases with short incubation periods (≤3 days) while the farm visit [17] and the barbeque outbreak [19] have a smaller proportion of cases showing symptoms over this time period. Such variation may be strain dependent or due to the natural variation expected from sampling smaller datasets. Combining the data from the four smaller datasets provides a distribution close to those given by the three larger datasets as shown in Figure 1a.

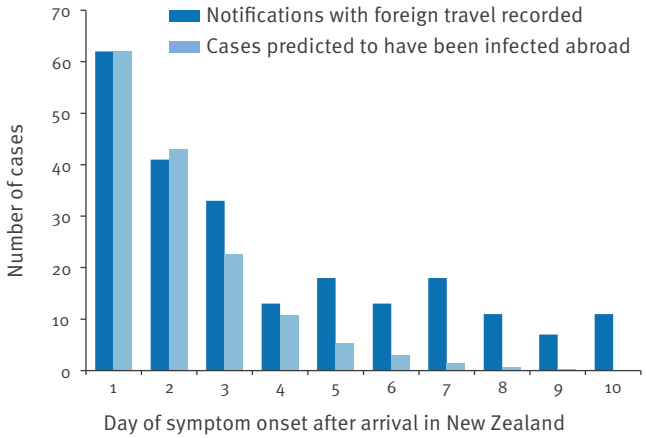
In the outbreaks considered, only 18 of the 832 cases had an incubation period of more than seven days. In the outbreak reported by Evans et al [17], all 23 primary cases had symptom onset within seven days after the farm visit. However, a number of secondary cases were observed from day seven onwards, which were family members of cases who did not take part in the farm visit. It is possible that notified or outbreak cases with incubation periods of eight to 10 days do not all result from the identified exposure, but are actually secondary cases.

In this analysis we have assumed that all strains of *Campylobacter* have the same incubation period pattern, which is supported by the consistency of the outbreak data. Studies in Switzerland and New Zealand have found differing genotypes of *Campylobacter* in domestic and travel-associated cases [7,20]. We also assume the incubation period pattern found in the various countries listed in the Table where outbreaks occurred also applies to the New Zealand population.

A recent analysis of gastrointestinal infections for Norway found that of those reported as travel-associated and with symptom onset after travel return, 94% of campylobacteriosis cases occurred within the commonly reported incubation period (≤5 days), and over 98% occurred within the maximum incubation period

Figure 3

Comparison of the predicted number of travel-related cases with a subset of the recorded numbers of cases of campylobacteriosis, with symptom onset within 10 days following return to New Zealand, 2006–2010 (subset n=227)



(≤10 days) [6]. Our analysis of outbreak data is in agreement with these results (92% of cases with an incubation period ≤5 days).

Data on arrival and symptom onset dates were essential for this type of analysis, and enabled careful filtering of the records. As was also found in the analysis of cases from Norway, data for return date and date of symptom onset were complete for only approximately 60% of New Zealand cases which may have been travel associated [6]. We concur with those authors in recommending more complete reporting of travel data, in particular date of departure and duration of travel, as exposures prior to departure may be important for very short trips (less than 4–5 days) combined with longer incubation periods. Such information should be included in the risk factor information collated as part of case investigations.

Although the adjustment for travel-associated cases examined in this paper will not identify specific cases that could be domestically acquired, it would improve estimation of the incidence of domestically-acquired infections, and hence burden of disease. We recommend a close examination of the incubation period distribution as part of future estimates of the attribution of diseases to foreign travel.

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