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Tumour Necrosis Factor-α Antagonists and Tuberculosis

Background

Tumour Necrosis Factor-alpha (TNF-α) is implicated in the development of immune-mediated disease, notably rheumatoid arthritis and inflammatory bowel disease.[1,2] TNF-α antagonists, which include Infliximab, Etanercept and Adalimumab, are a group of new drugs effective in the treatment of a number of immune-mediated diseases including rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, Crohn's disease, ankylosing spondylitis and psoriasis. Subsequent to the licensing of TNF-α antagonists, however, published studies showed them to be associated with a four to twenty-fold increase in risk of developing clinically active TB disease.[3-8] While establishing causality is challenging, a precautionary approach is appropriate. Recommendations to manage this risk have been published by a number of countries.[4,9-11]

In Ireland, the National TB Advisory Committee reviewed the issues and produced guidance to support clinicians and patients considering the use of TNF-α antagonists.[12]

Recommendations on initial assessment

Patients considered for TNF-α antagonists should be assessed for clinically active TB disease, and receive curative treatment if appropriate. They should also be assessed for latent TB infection (LTBI). Mantoux testing remains central to LTBI diagnosis. However, co-morbid disease and co-medication may result in anergy which complicates Mantoux interpretation. Since there is currently no robust evidence to support improved effectiveness of other approaches, testing with 2TU Mantoux should remain the standard in this scenario. While reactions over 10mm should be interpreted as indicating TB infection, the use of a 5 mm cut-off may be more useful for patients who are considered to be immunocompromised on the basis of individual risk assessment. In addition, it is recommended that the interpretation of Mantoux testing in this scenario should not usually take account of the patient's BCG history. Importantly, although a negative Mantoux test reduces the probability of LTBI, a high index of clinical suspicion for LTBI should be maintained, since the reaction to tuberculin may be complicated by anergy.

Recommendations on treatment of LTBI in this context

Patients diagnosed with LTBI should be treated: options include at least 9 months of isoniazid, which is associated with a lower risk of hepatitis; or 4 months of rifampicin +/- isoniazid, associated with a higher risk of hepatitis but offering the advantage of shorter duration which may promote compliance. Pyridoxine may also be used in combination with these regimens. Ensuring compliance is especially challenging since LTBI prophylaxis may result in additional complexity in the treatment regimen of patients already on a number of other drugs. This highlights a need for good communication between clinicians and patients; close liaison with clinicians experienced in TB treatment, and integration of care between primary and secondary care would also be helpful.

Recommendations on initiation of TNF-α antagonists

A key challenge is around the optimal timing of initiation of TNF-α antagonists for patients who require prophylactic or curative anti-tuberculous treatment, since there is currently no high-quality evidence to support specific recommendations. Initiation of TNF-α antagonists prior to commencement of treatment of clinically active TB disease or LTBI should be avoided. Where possible, it is recommended that TNF-α antagonists be postponed until prophylactic or curative treatment has been satisfactorily completed; in some cases where curative treatment is required, it is recognised that clinicians and patients may prefer to avoid TNF-α antagonists completely. However, with regard to prophylactic treatment, it is recognised that clinicians and patients may, on balancing the risks of TB and the benefits of TNF-α antagonists, prefer to initiate these agents during treatment for LTBI. Currently available evidence does not allow for a specific duration of LTBI treatment prior to initiation of TNF-α antagonists to be recommended. However, where possible, a longer duration of satisfactory LTBI treatment is suggested as good practice in managing the risk of initiation of TNF-α antagonists.

Recommendations throughout treatment

Regardless of the precautions taken to manage this risk, a high index of clinical suspicion for development of TB should be exercised during TNF-α treatment. Finally, clinicians are encouraged to report all adverse drug events associated with the use of TNF-α antagonists to the Irish Medicines Board.

References on request. The full report is available on the HPSC website at www.ndsc.ie/hpsc/A-Z/VaccinePreventable/TuberculosisTB/Guidance/.

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Malaria in Ireland, 2006

Introduction

Malaria is the most important vectorborne disease in the world, and a major problem in Africa and to a lesser degree Asia, Central and South America, the Middle East, Oceania and other tropical regions. Of approximately one million deaths from malaria annually in the world, 90% occur in Sub-Saharan Africa.

Worldwide each year, it is estimated that up to 30,000 travellers fall ill with malaria on their return from visiting countries where the disease is endemic.[1] Pregnant woman, young children and the elderly are particularly at risk. Malaria in pregnancy increases the risk of maternal death, miscarriage, stillbirth and neonatal death.

The reported incidence of malaria in Ireland has increased in recent years, due to some extent to the changing patterns of travel and immigration.

This report describes the burden of malarial illness in Ireland in 2006.

Materials and Methods

Malaria has been notifiable in Ireland since 1948. The case definition adopted since 2004 is based on the EU case definition.[2] Since 2001, enhanced surveillance data, e.g. country of infection, reason for travel and use of chemoprophylaxis, are provided to HPSC where available. Notification and enhanced surveillance data are maintained in the CIDR (Computerised Infectious Disease Reporting) system. The data used in this report are based on information retrieved from the CIDR database (as of October 2nd 2007) on malaria cases in 2006. Census data from 2006 (CSO) were used to calculate incidence rates.

Results

Incidence in Ireland

In 2006, 96 cases of malaria were notified (figure 1). This is an increase of 118% on the number reported in 2005, and equates to a crude annual incidence rate of 2.3 per 100,000 (95% C.I. 1.8-2.7).

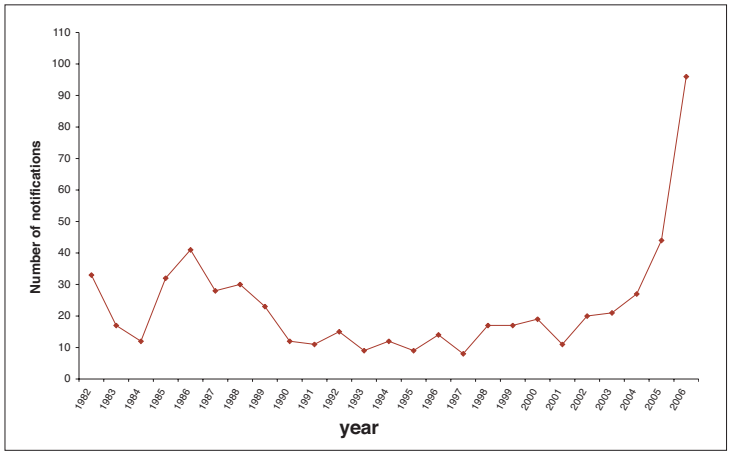

Figure 1. Number of malaria notifications, Ireland 1982-2006

Regional distribution

Cases were distributed across the country, with almost half reported in the HSE East (n=45). A further 17 cases were reported in the HSE North East, nine in the HSE South, seven in the HSE West, six in the HSE North West, five in the HSE Midlands, four in the HSE South East and three in the HSE Mid-West.

Species of *Plasmodium*

As in previous years, the most common species reported was *Plasmodium falciparum*, accounting for 83% of all cases notified (n=80). There were also four *P. vivax*, six *P. ovale*, one *P. malariae* and five cases where the species was not specified. This is similar to the species distribution reported by the United Kingdom and in Europe for cases of imported malaria.[3 4]

Age and sex distribution

Fifty-eight cases were male, 36 were female, and for two cases sex was unknown/unspecified (figure 2). Cases ranged in age from 10 months to 63 years. Notably there were 26 paediatric cases (27%) and 39 males (41% of all cases) in the 20-44 years age range.

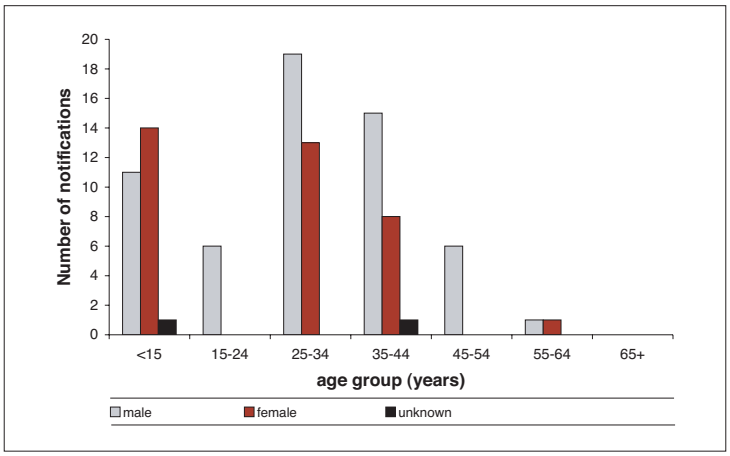

Figure 2. Age-sex distribution of malaria notifications, Ireland 2006

Severity of illness

Information on patient type was available for half of patients (n=48), with 44 cases reported as hospital in-patients, one as a hospital out-patient, two as GP patients, and one patient type was reported as 'other'. No deaths from malaria were reported in 2006.

Country of infection

Country of infection was recorded for 77 cases. The majority were exposed in Sub-Saharan Africa; a small but increasing number of cases were associated with exposure in Asia (table 1).

Table 1. Malaria notifications by country of exposure, Ireland 2006

Place of infection	Number of notifications	% of all cases
Sub-Saharan Africa	71	74%
Nigeria	*48*	*50%*
Other than Nigeria	23	24%
Asia	6	6%
Not reported	19	20%
Total	**96**	**100%**

Reason for travel

Reason for travel was recorded for 73 cases. The largest subgroup identified in 2006 were people who had travelled to visit family in their country of origin – over half of those for whom the information was available (n=40). The second most common reason reported for travel was holidays (n=13). This is an increase on the number of holidaymakers reported in the last two years (one in each year). New entrants made up a further 12 cases, with the remainder reported as business travellers (n=1), armed services (n=2), Irish citizen living abroad (n=1), foreign visitor ill while in Ireland (n=1), other (n=3) and not specified (n=23).

Of the 40 cases whose reason for travel was reported as 'visiting family in country of origin', 11 were born in Ireland and all 11 were less than 10 years of age, presumably representing the children of immigrants.

Use of chemoprophylaxis

Excluding new entrants (those who had recently entered the country but had spent their lives to date living in an endemic region would not be expected to be taking chemoprophylaxis), information on malaria prophylaxis was available for 57 of the remaining 84 cases. Of these, 43 took no prophylaxis, and 12 took prophylaxis but failed to continue for the required period. Only two cases reported full compliance with their prescribed course of prophylaxis.

Discussion

In 2006, the number of notified malaria cases reached 96, more than double the number of cases reported in 2005. *P. falciparum*, which causes the most severe form of malaria, was responsible for the majority of cases, and a high proportion of cases required hospitalisation. With increasing holiday travel to endemic destinations, and a growing immigrant community, it is now becoming more likely that clinicians will be presented with malarial patients. Given the potential for fatal complications in severe cases, it is important to consider malaria as a diagnosis for patients with compatible symptoms who have history of travel to an endemic country within the preceding year.

As in 2005, visiting family in country of origin was the most common reason reported for travel to an endemic area - over half of those for whom this information was available. This is similar to the situation in the United Kingdom where immigrant families (who are likely to travel more frequently to endemic countries) make up a sizeable proportion of reported cases.[5] An emerging sub-group within this category is composed of children born in Ireland visiting family in country of origin (presumably the children of immigrant parents). In comparison to their parents who may retain some immunity from previous infections (although this wanes over a number of years without repeated exposure to the parasite after they leave their country of origin), these children will be more susceptible than their parents.

In 2006, there was a sharp rise in the number of cases who reported holiday as their reason for travel, compared to 2004 and 2005. With long-haul travel becoming more accessible, and long-term travel becoming more common, it is important that all persons travelling to endemic areas seek advice appropriate to their risk.[6]

Mosquito bite avoidance and malaria prophylaxis are the cornerstones of malaria prevention in persons travelling to malaria endemic areas. As in previous years, the majority of Irish cases notified in 2006 either failed to take any prophylaxis or failed to comply fully with their prescribed course. It is important that travellers to endemic areas:

- **are aware of the risk of malaria**
- **avoid mosquito bites**
- **comply fully with prescribed prophylaxis (including continuing with the full course) and**
- **are aware that preventive measures are not 100% effective, and that they should seek treatment promptly if they suffer symptoms suggestive of malaria within a year following their return, informing their physician of their travel history.**

The guidelines of the Health Protection Agency Advisory Committee on Malaria Prevention in Travellers were revised extensively in January 2007, and include recommendations for advising travellers under many different circumstances or who have specific medical conditions.[6]

Patricia Garvey and Paul McKeown, HPSC

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Reptile-associated Salmonellosis in Residents in the South East of Ireland, 2005 - 07

Introduction

Salmonella can be spread through contaminated food, person-to-person transmission, waterborne transmission and numerous environmental and animal exposures. Reptiles serve as reservoirs of *Salmonella* and can shed *Salmonella* organisms in faecal material. Over 2,460 serotypes of *Salmonella* have been identified. Many serotypes have been associated with reptiles.[1]

In 2006, 422 cases of salmonellosis were notified in Ireland, a crude incidence rate of 10.0 per 100,000 population.[2] Sixty-five different serotypes were identified by the National Salmonella Reference Laboratory (NSRL) in 2006, of which *S. enterica* subsp. *enterica* serovar Enteritidis and *S. enterica* subsp. *enterica* serovar Typhimurium accounted for 60% of cases of human isolates.[2]

Methods

Although there is no national enhanced surveillance programme for human salmonellosis, in HSE South (South East), a surveillance questionnaire is administered to each case as part of the public health measures taken to prevent and control the disease.

Following notification in September 2007 of salmonellosis in a three-week old baby whose parents kept a pet snake, snake faeces and environmental samples from the snake's tank were obtained for salmonella testing.

All cases of salmonellosis notified to the South East from 2005 to 2007 were reviewed.

Results

A total of 120 cases of salmonellosis were notified in the South East between 2005 and 2007. Of these, there were six episodes of salmonellosis (5%) in five individuals who had contact with reptiles. While the associations were not definitively proven, all cases had a history of direct or indirect contact with reptiles and all were infected with serovars previously associated with reptiles.[3-8]

Case reports

In each case, a medical officer spoke with the family about the risk of salmonellosis associated with reptiles. Samples of reptile faecal matter and reptile habitat were obtained for Case 5 only.

Case 1

In January 2005, an 11-year old male was admitted to hospital with bloody diarrhoea, vomiting, fever, nausea, abdominal pain and haematuria. He was hospitalised for three days and a stool sample tested positive for *S. enterica* subsp. *enterica* serovar Minnesota. He had been ill the previous month with one episode of colicky abdominal pain and blood in the urine. The boy had direct contact with a number of pets: an iguana which he bred, two Persian cats and two rabbits. The only other risk factor identified was a take-away meal of chicken nuggets eaten five days before the case was admitted to hospital. The boy's mother and sister were also ill with diarrhoea but recovered quickly and were not tested for salmonellosis.

Case 1b

Over a year later, in June 2006, Case 1 attended his GP with diarrhoea, abdominal pain and headache. A stool sample tested positive for *S. enterica* subsp. *enterica* serovar Monschaui. Apart from the ongoing contact with his animals, possible ingestion of river water during sporting activities sometime before he became ill was also identified as a risk factor.

Case 2

In March 2006, a 15-year old female was admitted overnight to hospital on two occasions with diarrhoea, but stool samples were not taken at this time. She continued to suffer from intermittent diarrhoea. In April 2006, the girl spent three days in hospital with diarrhoea, abdominal pain and fever. A stool sample taken during this time tested positive for *S. enterica* subsp. *enterica* serovar Enteritidis PT 21. The girl had direct contact with a number of pets: four fish, a dog and a terrapin which was bought on March 1st, 2006. No other risk factors for salmonellosis were identified.

Case 3

A 6-month old boy was notified in March 2006 with salmonellosis. The boy had been ill with diarrhoea and respiratory symptoms. Laboratory testing confirmed *S. enterica* subsp. *diarizonae*. Because the illness had been ongoing, it was not possible to obtain an accurate food history. The child had indirect contact with the family pets: two snakes and a tarantula. One of the snakes had died of unknown causes three weeks before notification of the case. No other risk factors were identified.

Case 4

During March 2007, a 4-month old boy became ill with bloody diarrhoea and vomiting. He attended the local out-of-hours GP service and hospital A&E. A stool sample taken at this time tested positive for *S. enterica* subsp. *enterica* serovar Pomona. The boy had indirect contact with two terrapins which were kept in a tank at home. The boy was fed exclusively on a commonly available infant formulation which was prepared using cooled boiled water.

Case 5

Case 5, a 3-week old boy was admitted to hospital for two days with diarrhoea in September 2007. Laboratory testing confirmed *S. enterica* subsp. *arizonae* with antigenic structure O41:z_4,z_{23}. The child was fed on a commonly available infant formulation in powdered form prepared using cooled boiled water and also as a ready made preparation. *Salmonella* was not isolated from two household contacts tested. Case 5 had indirect contact with a snake and had also visited a reptile farm recently. A faeces sample from the snake and a sample of the snake's bedding grew *S. enterica* subsp. *diarizonae* with antigenic structures O48:i,z and O65:z_{10} respectively. Swabs taken from the snake container grew *Salmonella enterica* serogroup O57.

Table 1 Summary of reptile-associated salmonellosis, 2005 – 2007

Case	Age	Gender	Organism isolated	Associated reptile contact
1	11 years	M	*Salmonella* Minnesota (2005) *Salmonella* Monschaui (2006)	Pet iguana
2	15 years	F	*Salmonella* Enteritidis PT21	Pet terrapin
3	6 months	M	*Salmonella enterica* subsp. *diarizonae*	Parents have pet snakes
4	4 months	M	*Salmonella* Pomona	Parents have pet terrapins
5	3 weeks	M	*Salmonella enterica* subsp *arizonae*	Parent has pet snake. Child visited reptile farm with parent

Discussion

All six episodes of salmonellosis occurred in children, with three occurring in infants less than one year of age, probably as a result of indirect reptile-contact. Four episodes resulted in illness severe enough to require hospitalisation. Keeping reptiles as pets is becoming more popular in Ireland. These recent salmonellosis cases emphasise the need for public education aimed at preventing reptile-acquired salmonellois. Pet shops, veterinarians and healthcare providers should provide this information to owners and potential owners of reptiles. The CDC has published recommendations which include washing hands with soap and water after handling reptiles or their cages and keeping reptiles out of food preparation areas. The CDC also advises that pregnant women and young children should not have reptiles as pets.[9] Similar guidelines are needed in Ireland.

References on request

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