A One Health Approach To Tackle Toxoplasmosis

4 April 2018
Royal Society of Edinburgh
9.30am-3.30pm

REPORT

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1. Introduction

Toxoplasmosis is a serious disease with global impact, now recognised as one of the most important food-borne diseases worldwide and a major cause of production loss in livestock. The “One Health Approach to Tackle Toxoplasmosis” workshop brought together practitioners and stakeholders from a wide range of different groups including public health, veterinary, environment, water, farming and food sectors along with policy makers and social scientists.

Toxoplasma gondii really lends itself to a one health approach to tackle the disease caused by the parasite as there is only one species that occurs across the world, the parasite can infect nearly all warm blooded animals including people and there is a lot we now understand about the parasite genome, lifecycle transmission routes and disease epidemiology. There is much to be gained from working together across different disciplines to share knowledge and discuss new integrated approaches to prevention and control.

Thirty invited participants took part in the event which was held at the Royal Society of Edinburgh on 4th April 2018. Delegate feedback was highly positive with participants appreciating the opportunity to discuss Toxoplasma from a One Health approach with others from a wide range of different backgrounds, disciplines and perspectives.

The morning session consisted of a set of talks from a series of experts from different perspectives, bringing all participants up-to-date with the state-of-the-art in the clinical, public health, veterinary, food and environment sectors along with academic research targeting new approaches to developing drugs and vaccines. The afternoon comprised breakout discussion groups tackling key questions about future steps.

Throughout the day there was extensive discussion which highlighted areas where further information or research is necessary and which actions are the most important to tackle the issue of toxoplasmosis. This report summarises the discussions and makes recommendations for future actions to help promote a One Health approach to tackle toxoplasmosis.

The workshop was followed by a panel discussion at the Edinburgh International Science Festival in the evening, which was a sold out event, indicating the interest of the general public in parasites.

‘I think education of clinical staff would be most useful. They have all heard of Toxoplasma but it is way down their list of differential diagnosis’

2. Main recommendations

From the workshop discussions four main areas for future action were identified:

1. More evidence is required to fully understand the disease burden (in both human and animal health) and the relative importance of the main transmission routes.
2. Improved education is a priority, particularly of targeted risk groups where interventions will have the greatest impact.
3. Better tools are needed to tackle toxoplasmosis including vaccines, diagnostics and therapeutics that are effective against all life cycle stages.
4. A One Health approach to tackle toxoplasmosis is highly recommended and there is much to be learned and gained from being inclusive of all perspectives and disciplines.
5. Continue to host One Health approach meetings to bring the Toxoplasma community together across different disciplines. This will help to progress activities to tackle toxoplasmosis with the aim of creating a UK network and use this as a platform to collaborate in Europe and other countries worldwide to compare best practice in tackling toxoplasmosis.
3. A One Health approach to tackle toxoplasmosis

Aim

This workshop is an interdisciplinary platform to discuss the current impact of toxoplasmosis in the UK and how we might prioritise areas for prevention and control strategies.

Several questions are driving the need for this event:

1. What is the risk and impact of Toxoplasma infection in the UK?
2. Should we initiate a diagnostic screening programme for pregnant women?
3. What methods do we currently have to tackle toxoplasmosis, how effective are these and where are the knowledge gaps?
4. How important is a One Health approach to tackling toxoplasmosis?

Programme

9.30-10.00 Registration and Coffee
10.00-10.05 Welcome and Introduction
10.05-10.20 *Host-pathogen interactions and vaccines*  
Professor Craig Roberts, University of Strathclyde
10.20-10.35 *Current treatments and drug development*  
Dr Lilach Sheiner, University of Glasgow
10.35-11.05 *Clinical overview of congenital toxoplasmosis*  
Professor Rima McLeod, University of Chicago
11.05-11.20 *Incidence, diagnosis and impact of toxoplasmosis in England and Wales*  
Dr Stephen Hadfield, Toxoplasma Reference Lab, Wales
11.20-11.35 *Incidence, diagnosis and impact of toxoplasmosis in Scotland*  
Dr Roger Evans, Scottish Toxoplasma Reference Lab, Inverness
11.35-12.00 *Impact of foodborne toxoplasmosis*  
Professor Joke van der Giessen, National Institute for Public Health and the Environment, The Netherlands
12.00-12.15 *Toxoplasma in the environment*  
Dr Beth Wells, Moredun Research Institute, Edinburgh
12.15-12.30 *Veterinary impact of toxoplasmosis*  
Dr Frank Katzer, Moredun Research Institute, Edinburgh
12.30-13.30 Lunch
13.30-14.45 Breakout discussion groups
14.45-15.20 Reporting back and whole group discussion
15.20-15.30 Summary and actions going forward

‘The meeting was interesting with the presentation of very contrasting views which really opened up lively and useful discussion and it would be good to build on this and have an annual event’
4. Background and motivation for workshop

It is estimated that up to a third of the world’s population is infected with *Toxoplasma*. Many of those infected are unaware of the infection, as it was thought that *Toxoplasma* presents no major complication in immunocompetent individuals. However, this is now under scrutiny as there is increasing evidence that infection may provoke chemical and immunological imbalances that could lead to debilitating conditions, such as Parkinson’s Disease, Schizophrenia and others that affect the central nervous system (Ngo *et al.*, 2017). In addition, there have been several recent reports from South and Central America that there are virulent strains of *Toxoplasma* that can cause severe disease (blindness and in some cases death) of immunocompetent individuals (McLeod *et al.*, 2012; Dubey *et al.*, 2012).

There is no doubt that *Toxoplasma* infection is a major concern for individuals with compromised immune systems, such as those undergoing chemotherapy or HIV-AIDS, as persistent infections can reactivate, causing fulminant disease (Basavaraju *et al.*, 2016). Importantly, *Toxoplasma* presents a serious risk during pregnancy as it can cause harm to the fetus (Elbez-Rubinstein *et al.*, 2009). The parasite may infect and cross the placenta and infection during the first trimester can result in spontaneous abortion, whereas infection in the latter stages can cause severe abnormalities in the foetus and stillbirth. Screening for *Toxoplasma* during pregnancy is mandatory in some countries, but not in Scotland or the UK.

It is thought that the most common route of infection is through the consumption of undercooked meat containing *T. gondii* tissue cysts from grazing farm animals or wild game. A recent study from the Netherlands looking at the impact of food borne pathogens by measuring DALYS (Disability Adjusted Life Years) showed that *Toxoplasma* is one of the most important food borne pathogens worldwide (EFSA, 2018).

Not only is *Toxoplasma* a risk factor for public health but the parasite can cause abortion in sheep and goats and is recognised as a major cause of reproductive loss in the UK and many other countries across the world. A vaccine for veterinary use is available but this is a live vaccine and has a short shelf life. There is currently no safe vaccine for human use (Innes *et al.*, 2019).

Considering that *Toxoplasma* has a very close relationship with both livestock rearing for food consumption and human disease, we proposed to host this workshop with the purpose to bring together practitioners and stakeholders from a wide range of different groups including: those involved in veterinary, medical, environmental and public health along with those involved in the farming and food industries and researchers with expertise in *Toxoplasma*, midwives, who are the first point of contact for pregnant mothers and policy makers to help make recommendations for policy and future research.

Within the workshop there was space to share experience, concerns and discuss issues such as the need for diagnostic screening tests during pregnancy and to raise awareness and increase understanding of the impact of *Toxoplasma gondii* in public, veterinary and environmental health. Current infectious disease screening policies have not yet endorsed a recommendation for screening for *T. gondii* infection during pregnancy due to insufficient evidence (2016 policy report, UK National screening committe). The scope of this workshop will explore what evidence can be presented to further assess this current situation.

‘Until we have some idea of the number of clinically symptomatic cases per year we cannot really define the problem and therefore we need better diagnostic and surveillance data about *T. gondii*, this may be helped by making the disease notifiable’
5. Speaker talk summaries

Toxoplasma gondii host-pathogen interactions and vaccine prospects
Professor Craig Roberts, University of Strathclyde

Toxoplasma gondii infects approximately 30% of the world’s population and is responsible for ocular disease, neurological disease, congenital disease and abortion in humans. There is now compelling evidence that T. gondii infection is associated with the development of schizophrenia in humans and potentially increases the risk of other psychoneurological diseases. Current chemotherapeutic options are far from ideal as they control, but do not eliminate infection and are often poorly tolerated. No vaccines exist for humans despite the fact that literature indicates a natural infection provides good protection against future challenge. Recent advances provide new hope for the development of an effective vaccine for humans. Firstly, the sequencing of the 3 major lineages and a number of atypical strains provide an almost complete supragenome. Secondly, predictive algorithms for MHC 1-binding peptides provide a means to mine this supragenome and with the aforementioned facilitate a bioinformatics-informed approach to epitope identification. Thirdly, novel vaccine delivery systems and adjuvants show promise in inducing potent appropriate immune responses. Fourthly, In vivo Imaging Systems (IVIS) allow the efficacy of vaccines to be accurately assessed at early stages of infection. Finally, human MHC 1 (HLA) transgenic mice provide the means to test candidate vaccines for human use. Progress towards a vaccine for human toxoplasmosis will be discussed.

T. gondii Current treatments and drug development
Dr Lilach Sheiner, University of Glasgow

While typically asymptomatic, Toxoplasmosis could be life threatening. This is mainly the case for people with weakened (or no) immune system such as AIDS patients. Likewise, when a woman is first infected during pregnancy her baby is in danger. Drug treatments are largely suboptimal: upon infection during pregnancy Pyrimethamine and sulfadiazine are the routinely used drugs in this case but both have undesired side effects that could be as mild as nausea but as severe as suppression of the bone marrow that helps produce blood cells and toxicity in the liver. Furthermore, one of the main Daramprim (Pyrimethamine) manufacturer in the US, Turing Pharmaceuticals, raised the price from $13.50 to over $300 a tablet. In addition, a main problem is that Toxoplasma infection is highly prevalent and that the parasite remains dormant in people over a long time, thus when people become immunocompromised the parasite re-emerges. To date there is no treatment that can clear the dormant form.

Clinical overview of congenital toxoplasmosis
Professor Rima McLeod, University of Chicago

Rima McLeod, MD is a Professor of Ophthalmology & Visual Science and Pediatrics, and Medical Director of Toxoplasmosis Center at the University of Chicago. She is internationally recognized for her expertise and extensive research in toxoplasmosis. She specializes in the comprehensive care of congenital toxoplasmosis and other Toxoplasma gondii infections.

In the laboratory, Dr McLeod leads investigative studies designed to ultimately develop more effective screening, detection and treatment strategies for toxoplasmosis. Her research examines multiple aspects of this disease, including genetic factors, immune response, and vulnerable populations—specifically, pregnant women and newborns. Dr McLeod’s toxoplasmosis research is funded by the National Institutes of Health.
The Public Health Wales Toxoplasma Reference Unit provides a specialist confirmatory testing service to clinical laboratories throughout England and Wales, as well as providing advice on clinical case management and infection risk-reduction. The unit receives approximately 12,000 samples per year. Serological testing is performed using the Sabin-Feldman Dye Test, enzyme immunoassays for IgM and IgG avidity, and IgM and IgA immunosorbant agglutination assays. Real-time PCR is performed for detection of Toxoplasma DNA in a range of clinical samples including amniotic fluid, cerebrospinal fluid and ocular fluids. The unit also performs enhanced surveillance with Public Health England to assess the incidence of toxoplasmosis in England and Wales, with approximately 350 confirmed cases detected each year. In addition, the Unit also analyses parasite DNA extracted from clinical samples using genotyping methods allowing molecular surveillance of genetic lineages causing disease in England and Wales.

The requirements of a diagnostic reference service for toxoplasmosis are complex. The simple identification of an acute, primary infection is not sufficient; different testing strategies are required, dictated by the clinical presentation of the patient and the status of the infection. Data from the diagnostic service provides an invaluable insight into the epidemiology of the infection. This presentation describes how these techniques and strategies have developed to meet the demands of this parasitic infection and address the needs of the different patient groups who are affected. It also describes the changing epidemiology of toxoplasmosis in Scotland over the last twenty years and its implications for public health.

Toxoplasma gondii infections cause a high disease burden in the Netherlands, with an estimated health loss of 1,900 Disability Adjusted Life Years and a cost-of-illness estimated at €44 million annually and ranks third in disease burden among all foodborne pathogens in the Netherlands. Also in Europe, comparing the disease burden with other foodborne pathogens, T. gondii ranks third after Salmonella and Campylobacter. Two major infection routes are considered for human infections. The relative contribution of both routes is still unclear. Most infections are asymptomatic or mild symptoms, but potentially leading to the development of ocular toxoplasmosis. Infection in pregnant women can lead to stillbirth and disorders in newborns. A quantitative risk assessment (QMRA) showed that beef is an important cause of meatborne toxoplasmosis in the Netherlands.
**Toxoplasma gondii in the environment**

Dr Beth Wells, Moredun Research Institute, Edinburgh

The protozoan parasite *Toxoplasma gondii* is one of the most common parasites to infect warm blooded animals worldwide, with felids being the only definitive host. Studies have confirmed that environmental contamination with *T. gondii* oocysts is widespread. Indeed the significance of toxoplasmosis has increased globally and it is now considered to cause the highest disease burden of all the food-borne pathogens. Eating raw or undercooked meat and cross infection from cat faeces are recognised ways of becoming infected with *T. gondii*. Another route is through contamination of drinking water, but very little is known about this mainly because there are no approved methods for testing water. The waterborne transmission of *T. gondii* is likely to be more important than previously thought as evidenced by large scale outbreaks of toxoplasmosis caused by contamination of drinking water with *T. gondii* oocysts. These outbreaks have been responsible for serious public health issues in pregnant women including abortions and birth defects through congenital infection, in people with weakened immune systems and more recently, ocular disease in healthy people due to the emergence of atypical strains of the parasite in countries such as Brazil.

In this project, we optimised and validated methods for the processing of water samples and developed a sensitive and specific test for the detection of *Toxoplasma gondii* DNA in water (http://www.ncbi.nlm.nih.gov/pubmed/27523933). We then validated these methods using 1427 water samples collected by Scottish Water from 147 public water supplies throughout Scotland, from both raw and final waters. Using qPCR targeting the 529bp repeat element, 8.8% of the samples analysed were positive for *T. gondii* DNA. One third of the water plants tested yielded at least one positive sample and these plants were widespread geographically throughout Scotland. This is the first study reporting the detection of *T. gondii* DNA in water supplies in Scotland where environmental contamination with the parasite is known to be widespread.

Following this work, a project is currently running at Moredun to determine if *T. gondii* DNA in water samples originates from oocysts (infective stages) and if so, to investigate if any oocysts identified are viable (infective) or not. In this study, 10 catchments were identified that yielded the highest numbers of samples positive for *T. gondii* DNA previously and microscopy methodology for screening both clean and dirty final water samples has been completed as well as clean raw water samples. All but the dirty, raw samples have now successfully been screened by microscopy. To date, no oocysts have been identified by microscopy in clean and dirty final water samples. Screening is ongoing concentrating on times where either high rainfall events or *Cryptosporidium* contamination events have occurred.

**Veterinary impact of toxoplasmosis**

Dr Frank Katzer, Moredun Research Institute, Edinburgh

*Toxoplasma gondii* is capable of infecting all warm blooded animals and in most animals the infection is asymptomatic unless the animal is immunosuppressed. For example cats don’t usually show any signs of toxoplasmosis but they produce millions of oocysts during a primary infection and then they become solidly immune and they do not shed oocysts again following subsequent infections. However if cats become infected with FIV, then Toxoplasma infection will lead to fever, lymphadenopathy, encephalitis and even death. There are other animals that are very susceptible to *T. gondii* infection, such as lemurs, marsupials and sea mammals. These animals have evolved in the absence of the parasite and this has not allowed their immune system to co-evolve with the challenges of the parasite and these animals usually do not survive infection. Studies in cattle have shown that these animals have exposure to the parasite on pasture and they can have high seroprevalence figures but in experimentally infected cattle it is very difficult to find any evidence that these animals contain any viable tissue cysts. Infection in sheep is very similar to humans, where most infections are asymptomatic but if a primary infection occurs during pregnancy of a ewe, then this can lead to abortion of the foetus or the birth of a persistently infected lamb. Toxoplasmosis is the second most commonly diagnosed cause of abortion in sheep in the UK leading to significant losses for the sheep industry. Studies have shown high seroprevalence figures for *Toxoplasma* in sheep in the UK with significant exposure to parasite oocysts on pasture. However, a vaccine exists that is very efficient at protecting sheep against abortion but this vaccine is only licenced in a few countries. For the livestock industries there is an additional challenge associated with toxoplasmosis and that is that the meat of their farmed animals may contribute to the spread of the parasite to humans. For example *Toxoplasma* infected pork was considered a major source for human infection, however intensively indoor reared animals, with good rodent control and no access of cats to their feed has resulted in a drastic risk reduction. This change in farming practices has been credited with the reduction in human seroprevalence figures in continental Europe. A future consideration for policy makers and the livestock industry would be the use of the Toxoplasma vaccine in an attempt to make meat safer for human consumption which was shown to be the case for lamb and pork.
6. Breakout discussion summaries

Notes from breakout session

Q1: What is the risk and impact of Toxoplasma infection in the UK?
- Public, veterinary and environment health
- Incidence
- Genotypes and virulence
- Transmission routes

Need more up to date data on incidence and prevalence

What strains of *T. gondii* are currently circulating in Scotland and what are the threats of introducing some of the more virulent strains eg: those occurring in South and central America?

What causes some strains of *T. gondii* to be more virulent than others?

What is the relative importance of the transmission route with oocysts compared to transmission through consumption of cysts in undercooked or rare meat?

Q2: Should we initiate a diagnostic screening programme for pregnant women?
- Benefits and risks
- Learning from other countries

What is the true burden of disease and how can we assess this? Eg DALYS

What would be an appropriate screening strategy who would we target and when would they be screened?

Are our current diagnostics sensitive and specific enough to run an effective screening programme?

What would be the impact of false positive and false negative results?

Can we learn lessons from the experience in France where they have been running a screening programme for a long time now?

What is the efficacy of the treatments offered to pregnant women and the known side effects?

Are there alternative preventative approaches?

Cost-benefit analysis of a screening programme

Q3: What methods do we currently have to tackle toxoplasmosis, how effective are these and where are the knowledge gaps?
- Vaccines
- Drugs and treatments
- Diagnostics
- Education and prevention

We need an overall strategy to help advise policy as regards the application of diagnostics in veterinary, public and environmental health using similar diagnostic markers.

Do we target particular “at risk groups” such as pregnant women?

Should we develop a point of care test?

We need a diagnostic that can discriminate between acute infection vs persistent infection

We need a diagnostic that can help to determine how people became infected ie through consumption of oocysts or tissue cysts.

We need to develop therapies that can work on tissue cysts.

Vaccination: What can we learn from the successful veterinary vaccines to help in developing vaccines for humans?

Should we target vaccination of young women?

Should we target vaccination of cats?

Should we target vaccination of food animals?

Education is a real gap and there is a lot that could be done using a One Health approach to target education towards policy and public.

Q4: How important is a One Health approach to tackling toxoplasmosis?

A One Health approach is very important in this disease due to the transmission routes involving animals to people and the fact that it is the same species of parasite that causes disease in both livestock and people.

Can we set up a One Health working group in Scotland similar to those looking at other zoonotic pathogens eg: E. coli?

We need more integrated surveillance data and a better method to quantify the impact and disease burden eg: DALYS.

To prevent toxoplasmosis we need to intervene where it will make most impact eg: in livestock and in the environment and therefore a One Health approach is the obvious way forward.

Good communication between the different health sectors (veterinary, public and environmental health) is essential.
Overall, the workshop brought together toxoplasmosis experts from different sectors and stimulated lively discussion, which was appreciated by the delegates and highlighted in the positive feedback. While many areas and issues were raised, four main points were identified as being of importance for future activities.

Firstly, more evidence is required, particularly on prevalence of infection in the UK, with most studies now being relatively old or limited in scope. Better baseline data in both human and animal health and prevalence of the parasite in water, food and the environment would be highly beneficial to inform future decision making. In order to obtain this information, there was a discussion around whether toxoplasmosis should be a notifiable disease and what might be the best way to ensure accurate recording of all cases. There was a recommendation that it would be useful to update/extend UK/Scottish epidemiological studies, e.g. extending the NHS Highlands seroprevalence in pregnant women study from 2011 (including Toxoplasma genotypes).

Secondly, all delegates agreed that improved education was important. While this could (and should) encompass general awareness raising among the public, it was considered that targeted communications towards particular risk groups would generate the most impact. For example, clinicians and general practitioners should be encouraged to consider toxoplasma in a wider variety of situations. Midwives and pregnant women were another key group. Surveying the knowledge and views of risk perceptions in pregnancy would also help inform how to deliver appropriate education and the appetite for a potential screening programme. Considering a One Health perspective, education among farmers and the food and water sector could promote better practices reducing the risk of disease transmission.

Thirdly, there was a consensus amongst participants that improved tools are required to tackle toxoplasmosis including vaccines, diagnostics and therapeutics that are effective against all life cycle stages. In addition, further work is required to provide improved evidence of the impact of toxoplasmosis on the population (in the first instance, in the UK). This would help the community understand the links between lifestyle, environment and prevalence. We already have good examples of this from other countries e.g. the action in the Netherlands relating to the prevention of food-borne toxoplasmosis.

Finally, all participants agreed a One Health approach was essential and advocated for further similar meetings, with a diversity of participants bringing together a range of different perspectives.
8. References and links

Antenatal screening for Toxoplasmosis. External review against criteria set by the UK National Screening Committee. https://legacyscreening.phe.org.uk/toxoplasmosis


Helen Bridle is an Associate Professor at Heriot-Watt University. She is currently investigating the detection of waterborne pathogens, in particular protozoan pathogens in the environment, using a variety of different techniques. Helen has been a member of the RSE Young Academy of Scotland since 2014.

Elisabeth A Innes leads a group at Moredun Research Institute in Edinburgh, looking at developing solutions to control diseases caused by protozoan parasites of livestock and combines this with her role as Director of Communication at Moredun. She was awarded an MBE in the New Years Honours in 2015 for services to scientific research and science communication and also holds Honorary Professorships from Heriot Watt University, University of Edinburgh and University of Glasgow. Elisabeth recently received an award for outstanding contribution to Knowledge Exchange at the prestigious Scottish Knowledge Exchange Awards in February 2017 and was elected as a Fellow of the Royal Society of Edinburgh in 2017.

Fiona Henriquez is Professor of Parasitology at the University of the West of Scotland. Her research interests are in drug discovery on eukaryotes pathogens and parasites of humans and fish in aquaculture and understanding host-pathogen relationships. She has worked with Toxoplasma gondii for 20 years, when she commenced a PhD focusing on T. gondii secretory proteins. Lately, she has also been working on the impact of environmental factors and microbiomes on the emergence of antimicrobial resistance. Fiona has been a member of the RSE Young Academy of Scotland since 2016.

Workshop Co-ordinators

For further information about this workshop or if you would like to be included in future events please contact:

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