ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF GLASGOW

SCHOLARSHIP REPORT

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Please use typeface when completing this form.

SECTION 1 | PERSONAL AND AWARD DETAILS			
Title	Mr	**PID**	
Surname	Hefford	**Forename(s)**	Philip Michael
Scholarship/award awarded	Medical Elective 2019	**Amount awarded**	£1000

SECTION 2 | PROJECT/VISIT DETAILS	
Name/Title	Emerging Infectious Diseases – Responding to Outbreaks and Managing Tropical Diseases
Location	Instituto de Medicina Tropical & Hospital das Clinicas, Universidade de São Paulo, São Paulo, Brazil Av. Dr. Enéas de Carvalho Aguiar, 470 - Jardim America, São Paulo - SP, 05403-000, Brazil
Aims and objectives	As might be expected, my initial aims and objectives at the time of application to the RCPSG Elective Award were always subject to the circumstances of the emergent public health threats within Brazil during the time of my visit. Between the initial period of planning and actual arrival to São Paulo; The Zika Epidemic had all but died out, Yellow Fever had escalated, and a novel opportunity to study the clinical burden and baseline prevalence of sexually transmitted enteric infections amongst key populations had presented itself. Under the guidance of my supervisor Professor Aluisio Segurado, and other members of the Infectious Disease team – namely Dr Taniela Bes, Dr Gwenda Hughes (from Scotland incidentally), Professor Costa and Dr Ho – I felt confident I would meet the learning objectives for the elective I had created for myself; to learn more about: • Logistics behind managing infectious disease outbreaks • Clinical research during emerging public health threats • Immunisation implementation & monitoring (with special reference to Yellow Fever) • Microbial pathogenesis & management • Ecological drivers behind disease emergence • Portuguese language at level A1

Summary

Include methodology, results and conclusions if applicable

Introduction

Most of my placement consisted of outpatient Infectious Disease (ID) clinics, ward rounds and time spent on the ID Intensive Care Unit which became the referral site for Yellow Fever Virus (YFV) cases in the state of São Paulo. Throughout this report, I will discuss how my elective experience enabled me to learn about cutting-edge medicine with regards to a Haemorrhagic Virus that has historically had a mortality rate and disease profile to rival Ebola.

The other part of my elective was research orientated at the *Instituto de Medicina Tropical de Universidade de São Paulo* (IMT-USP), with the aim to develop a study protocol for researching the baseline prevalence of sexually transmitted enteric infections (STEIs) in key population groups – men who have sex with men (MSM) who are HIV positive, or MSM who are receiving Pre-exposure Prophylaxis (PrEP). A series of recent outbreaks amongst the MSM community, most notably the recent 2017 global outbreak of Hepatitis A, has raised the profile of HIV related STEIs in MSM.

Throughout this report I will highlight two specific clinical cases, discuss the status of my study protocol and give an account of the Yellow Fever epidemic including its' epidemiology and recent advances in care.

Case 1: HIV and TB – A Potent Reminder

HIV, TB and Malaria are considered the 'big three' infectious diseases of global burden. My medical education is from the city of Leicester, which has a notable TB burden for the UK. After London and the entirety of Scotland, the Midlands rank 3rd for TB mortality with Leicestershire specifically having a prevalence of 37.3 per 100,000 [1,2]. The state of São Paulo wins though, with a prevalence of 49.5 per 100,000. This fact was mirrored in the myriad of ways the pathogen *Mycobacterium tuberculosis* would manifest itself in patients attending the TB Ambulatory Clinics. I highlight here one case in a HIV positive patient who ended up requiring intensive care:

A 55-year-old female presents to the Emergency Unit with Acute Respiratory Distress Syndrome, haemoptysis, pyrexia and confusion. She is known to be HIV+ve but non-compliant to her Highly Active Anti-Retroviral Therapy medications (HAART). She is homeless and a known cocaine user. No further history can be obtained.

The differential diagnosis at this point is wide but the team were most concerned about tuberculosis, infectious abscess or *pneumocystis jirovecii* as a cause of her respiratory distress whilst her confusion could be explained by drug abuse, hypoxia, HIV dementia, TB or Cryptococcal meningitis or Toxoplasma infection to name a few possibilities.

Investigations showed a CD4+ T Cell Count of <50 (Ideally >350 cells/mm^3) and positive acid-fast bacilli after bronchoalveolar lavage. However, what astonished the Infectious Disease team was the CT Chest Radiography (Figure 1), showing the largest cavitating lesion that I and many of the ID ITU team had ever seen. This scan result was in keeping with a diagnosis of Tuberculosis.

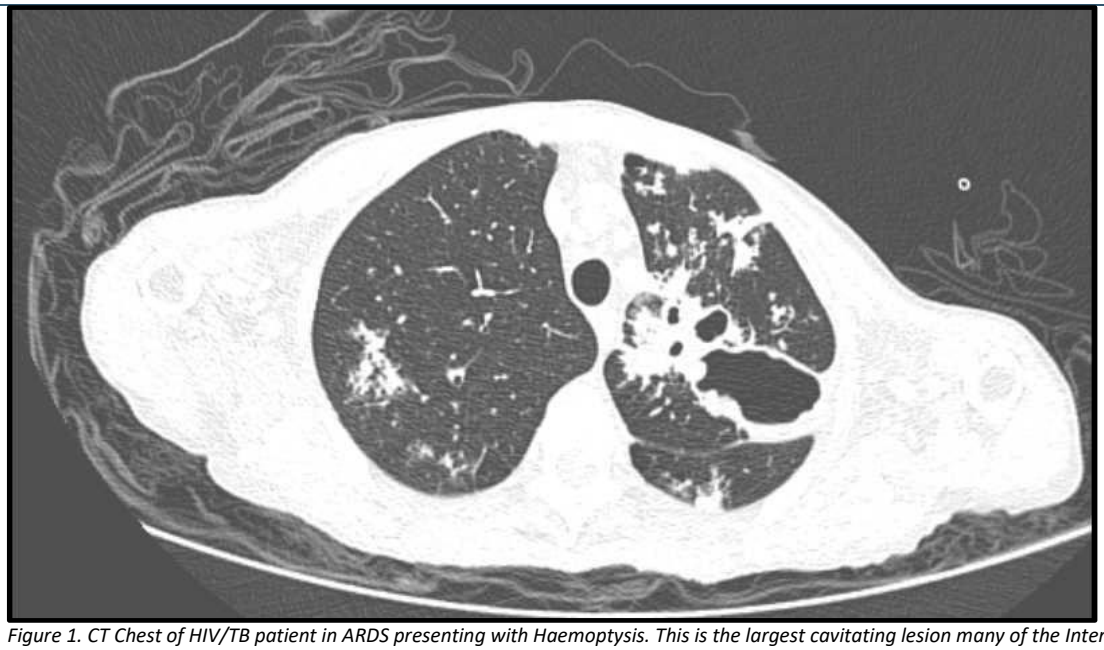

Figure 1. CT Chest of HIV/TB patient in ARDS presenting with Haemoptysis. This is the largest cavitating lesion many of the Intensive Care Infectious Disease team (USP) had seen in their careers. CT scan taken on Wednesday 27th February, 2019. Patient consent obtained.

The patient's CT head scan was equally remarkable (Figure 2), showing a diffuse cortical atrophy which, the team suspect, may be a result of long-term poorly controlled HIV infection; HIV Dementia.

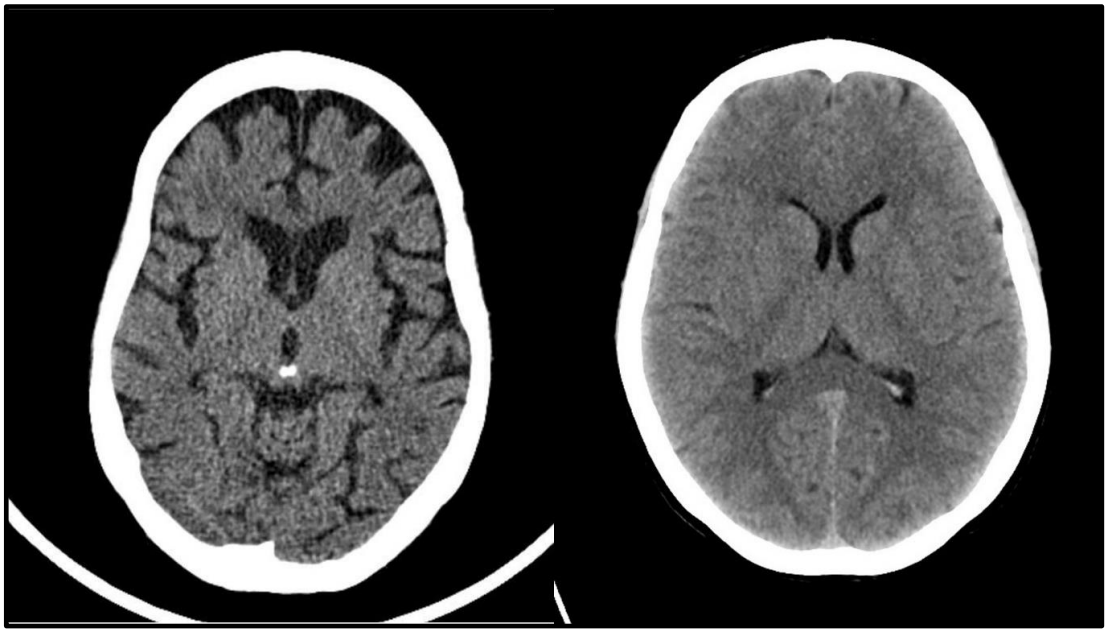

Figure 2. The CT head scan to the left, belonging to our HIV/TB patient in São Paulo, shows diffuse cortical atrophy which is likely a source of her confused presentation. HIV related pathology - resulting in dementia - is a probable cause. The CT scan to the right is of a normal, healthy brain for comparison.

Although we often see cases of HIV/TB co-infection in large UK cities, I include this case due to the stark severity of the pathology. Assisting in this patient's care also served as a potent reminder that the global challenge of tackling at least two of 'the big 3' (HIV, TB and Malaria) still has a long way to go. While I am personally fascinated by exotic diseases, these more common and equally devastating maladies should continue to demand our attention. In facing this challenge as a global health community, we must navigate through complex social, environmental and political factors. As Peter Piot, the founder of UNAIDS and co-discoverer of Ebola wrote in his recent autobiographical work, there is "no time to lose" in working to mitigate the spread and consequences of HIV/AIDS [3].

Case 2: Full Blown *Weil's Syndrome*

A male in his 40's presented to an Emergency Unit, 45 minutes' drive south of our Hospital. He had several episodes of haemoptysis, pyrexia, myalgia, confusion and features of acute kidney injury. Vital signs showed tachycardia, pyrexia, hypotensive shock and a severely low oxygen saturation of 69%!

Dr Ho (*Figure 3A*) is the head of the ID Intensive Care Unit at USP. Leptospirosis is notoriously difficult to culture, however, once serology and PCR confirmed infection – manifesting as the most severe Weil's Syndrome in this instance – Dr Ho ordered her team to accept the case and have the patient escorted from the Emergency Unit to her ITU. Weil's Syndrome is a zoonotic leptospirosis infection (typically found in rat urine) which progresses towards the triad of acute kidney injury, jaundice (from fulminant hepatitis) and haemorrhage.

Dr Ho is well versed in treating patients with Extra Corporeal Mechanical Oxygenation (ECMO) for a range of pathogens which severely compromise pulmonary function. Her team established venous-venous ECMO for this patient swiftly, enabling him to reach an oxygen saturation of at least 99%.

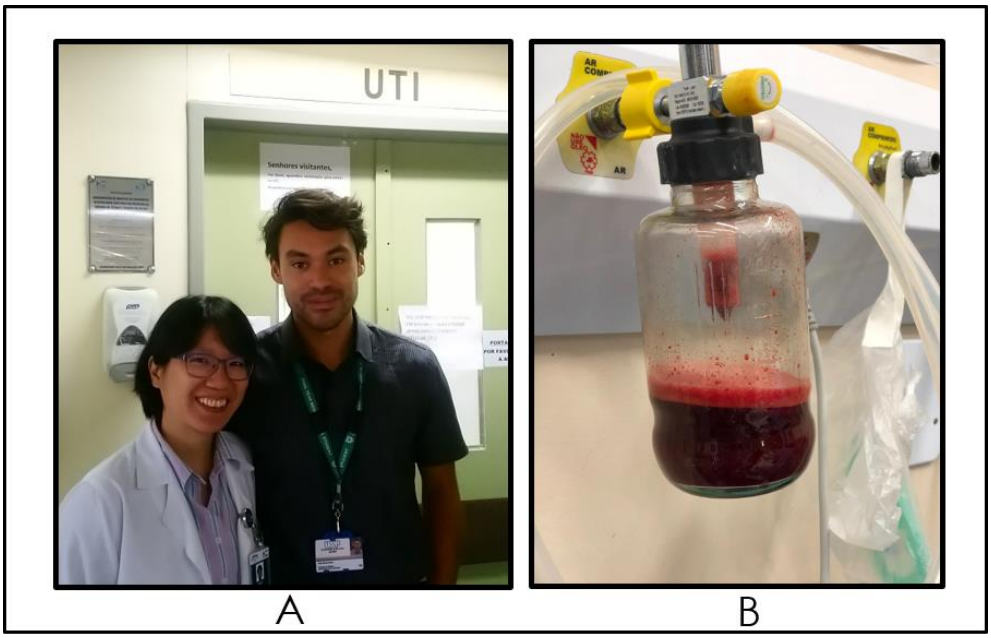

Figure 3. A - With Dr Ho outside of her Intensive Treatment Unit (UTI in Brazilian Portuguese) in the Infectious Disease Wing at Hospital das Clinicas, Universidade de São Paulo. B - Pulmonary Aspirate after suctioning our patient who had massive pulmonary haemorrhage, as a result of developing Weil's Syndrome from leptospirosis infection.

Dr Ho is inspiring in many ways – for her vast knowledge across the Infectious Disease spectrum, her clinical acumen, her willingness to teach, and her deep level of personal integrity. I was particularly impressed at her composure when leading the treatment of this man's pulmonary haemorrhage (*Figure 3B*), reversing his hypoxia and administering life-saving antibiotics – (typically a penicillin, but they had run out and so gave ceftriaxone which is just as good). Although leptospirosis infection is possible throughout Europe, most cases occur throughout the tropics and throughout periods of heavy rains in regions of poor sanitation and hygiene. From this case, I learned how difficult leptospirosis can be to diagnose microbiologically; how tricky it can be to differentiate clinically from more common infections; and how effective a combination of symptomatic treatment, antibiotics and ECMO can be at treating its' most severe manifestation of Weil's Syndrome.

Other Tropical Medicine Wonders

To briefly touch on a few more experiences; I palpated the largest spleen I have ever done courtesy of Schistosomiasis; heard numerous stories of the fall and rise of Chagas (*Trypanosoma cruzi*), witnessed the opisthonus of *Clostridium tetani* and saw in person the brutality of *Mycobacterium abscessus* (*Figure 4*).

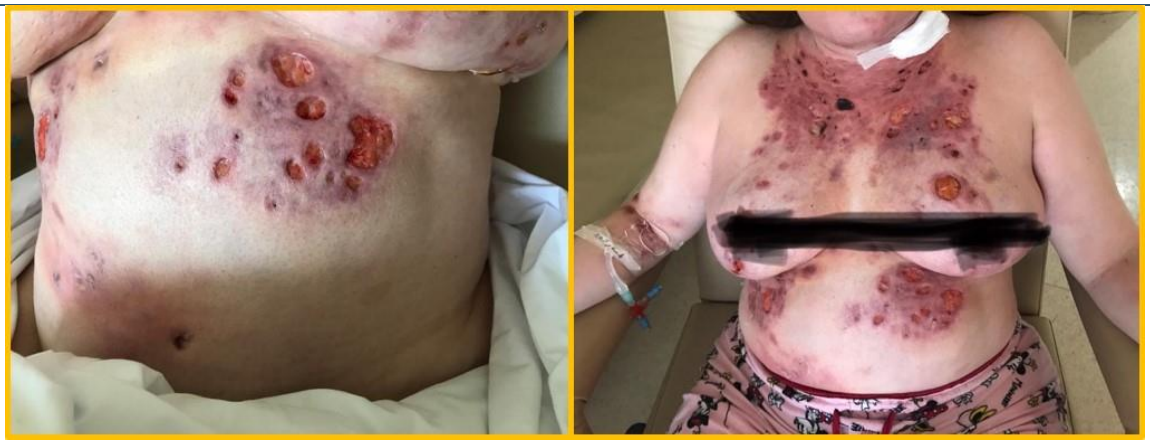

Figure 4. Mycobacterium abscessus – A 44-year-old Brazilian woman had a botox injection into her cheek in 2017 for aesthetic purposes. Sadly, it inoculated a notoriously robust pathogen, leaving her with skin abscesses across her face, chest, trunk and upper thighs. The standard TB regimen of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol does not work against most non-TB mycobacterium infections – often leaving patients with limited antibiotic options. Patient consent obtained for sharing images.

Developing a Study Protocol – STEIs in MSM

I had spent several afternoons of my elective period creating a study protocol to investigate the baseline prevalence of STEIs in HIV positive MSM, and in MSM receiving PrEP. This project was suggested due to the global Hep A outbreak in MSM which impacted Brazil in 2017, and other noted sexually transmitted cases of shigella, campylobacter and giardia for example. However, the protocol is still in its infancy, and there are several hurdles to overcome which are mainly financial and logistical in nature. For example, even though our proposal of introducing shigella PCR testing in these key population groups would be a simple enough procedure, there is only one centre in São Paulo state (Casa da AIDS) that would be able do this at present, which is a large tertiary centre for HIV care and has a skewed patient population who are of generally higher socioeconomic status within the state.

Regardless, it is somewhere to make a start. A successful study here can generate data which may help determine better health care for key populations. I continue to work on developing the study protocol remotely, from the UK, with Dr Gwenda Hughes. It is also an excellent learning opportunity for me.

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The Yellow Fever Epidemic

The Brazilian YFV epidemic has everything for a great medical story - fascinating epidemiology, newly discovered pathology, magnificent vector biology (*Figure 5*), problematic health infrastructure and novel treatment strategies. I learned a great deal. With great difficulty, I will try to keep this brief.

For three consecutive years, Brazil is the only country in the world to have suffered large scale sylvatic cycle outbreaks with ‘spillover’ events of a Haemorrhagic Virus, despite a very efficient, globally available vaccine. This clearly represents a colossal public health failure.

Figure 5. Sabethes species, one of two mosquito species (the other being *Haemagogus*) responsible for maintaining the sylvatic (jungle) cycle of YF in Brazil of the last 3 years. This beautiful photo features in the book gifted to me from USP.

In the largest outbreak of 2017-2018 in the state of São Paulo [*Figure 6, Ref 4*], the mortality rate for YFV was 63% in those patients who made it to treatment at Hospital das Clinicas. The ID team were essentially going in blind, relying on textbooks more suited to the Urban Cycles of East Africa which require a different mosquito species vector (*Aedes aegyptii*). Clinical presentations did not clearly fit, and effective symptom management often became guesswork. It was only towards the end of last year's outbreak that the team began to trial 'plasma-exchange' protocols inspired by trials of convalescent plasma therapy for Ebola Virus recent West African outbreaks [5]; but even then, it was unclear whether it had any positive clinical impact.

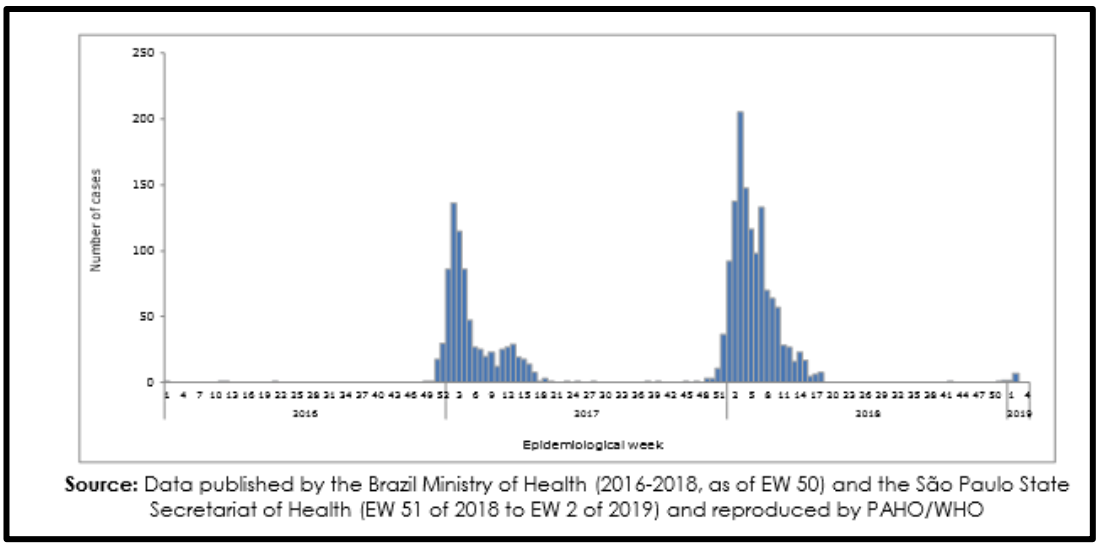

Figure 6. The late 2017-early 2018 outbreak of YFV was the biggest YFV outbreak of human concern to hit brazil since 1942 [4].

Eventually, thousands of reservoir Howler Monkeys species died out (a devastating ecological consequence of YFV) and the intermediary vectors *Haemagogus* and *Sabethes* no longer had enough opportunities to find unvaccinated humans to transmit YFV to [6]. A quiet 34 weeks passed by until cases cropped up on the southern border of São Paulo state in early 2019, in locales neighbouring the state of Parana, just before my arrival to the YFV referral centre at Universidade de Sao Paulo.

A New Treatment Protocol

This year, Dr Ho and her team were ready to trial a new protocol; the intricate details of which, alongside the case series report, are to be published within the coming months across two papers in the Lancet Infectious Diseases.

Dr Ho's team also started an open label randomised trial of Sofosbuvir (licensed for use in Hepatitis C infection, another flavivirus) and again, the results of this are pending. I can share, however, that this year the mortality rate at this tertiary YFV referral centre is currently 18-20% as opposed to last year's 63%. Dr Ho will be giving weight to the following findings in her upcoming publication:

- A successful, rigorous plasma-exchange protocol
- An appreciation for the role of YFV in stimulating endogenous release of heparin-like molecules, thereby inhibiting clotting despite an apparently normal coagulation profile [7]
- 'Yellow Fever' as a misnomer – a high bilirubin level not necessarily equating to jaundice in most cases independent of severity
- Newly described pathophysiology** including Pancreatitis and Cerebral Microhaemorrages
- Sofosbuvir as a therapeutic agent in YFV infection [8]

** There is a favoured mnemonic amongst medical students for causes of Acute Pancreatitis which I would recommend now needs reviewing – 'GET SMASHED' to change to 'Y GET SMASHED?'. I suppose this is in the spirit of promoting a healthier drinking culture.

Y – Yellow Fever
G – Gallstones
E – Ethanol
T – Trauma

S – Steroids
M – Mumps
A – Autoimmune
S – Scorpion Sting (Trinidad and Tobago)
H – Hypercalcaemia, Hyperlipidaemia, Hyperparathyroidism
E – ERCP
D – Drugs

Outbreak Mitigation

The large scale, Multiple-State outbreak of 2018 has largely been attributed to several decades' worth of poor YFV vaccine vigilance in both humans and animals alongside major ecological disturbances, however, the full reasons are far too elaborate for the remit of this elective report. Cases in 2019 have been concentrated on the southern border of the State of São Paulo and State of Parana, although in order to get there a trail of dead monkeys have been found across more central and northern regions of the State of São Paulo (Figure 6). During my time in Brazil, Rapid Support Teams consisting of ID Physicians, epidemiologists, nurses, biomedical pathologists and veterinary specialists headed towards Parana in order to characterise and mitigate the outbreak, whilst also providing effective community-wide public engagement. One key strategy employed was to set up satellite vaccination clinics, with fractionated YFV vaccine which has recently proven effective at inducing protective immune status. Simultaneously, primate species in nearby rainforests were vaccinated to reduce risk of crossover events as molecular epidemiological studies have confirmed this outbreak as a continuing Sylvatic Cycle [9]. The buzz-phrase 'One Health' tends to attract a touch of cynicism, however, early epidemiological data (to be published) suggests this approach is working to curb YFV, and it does makes very rational sense to care for ecological and animal health in a bid to protect human lives alongside the future of our planet's ecosystems. Even though I had no direct involvement in this success as a visiting medical student, it was important for me to be there and learn from specialists in the time and place where this all happened.

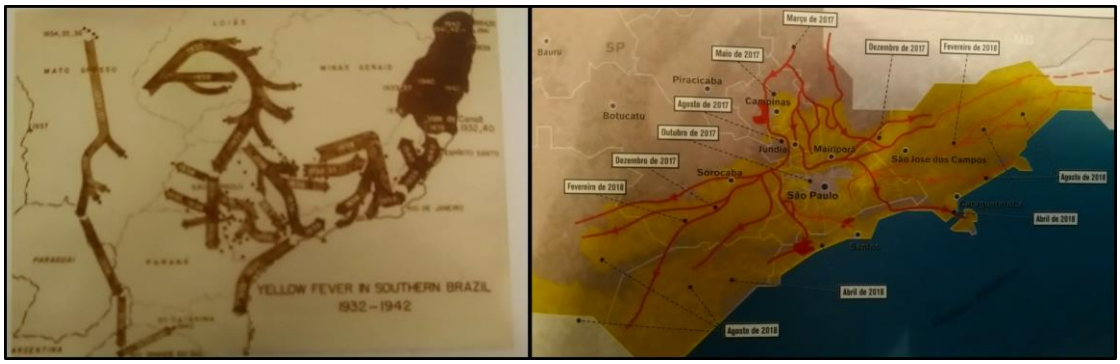

Figure 6. In the early 20th Century, a Brazilian Physician – Adolpho Lutz- described the trajectory of Brazil's YFV Sylvatic outbreaks across 1932 – 1942 (Left). The next series of large-scale outbreaks would not happen for at least 70 years, but when they did, the trajectory was remarkably similar (Right). In each instance, a trail of primate deaths (mainly Howler Monkeys) have been reported, with their territories overlapping strongly with vector mosquitoes *Sabethes spp* and *Haemagogus spp*.

My Elective Experience – Final Comments

This was a clinically inspiring time to be in São Paulo, Brazil. To witness the remarkable success of curbing a mortality rate of a truly tropical pathogen by 40% is an honour, and it has cemented my passion for the discipline. It was evident that lessons had been learned from all angles relating to Yellow Fever Virus in Brazil between 2018 and 2019, and it was a fascinating to be there to see the improved outcomes first hand. Unfortunately, due to the sensitive nature of the work in the epidemic, I am unable to share any clinically related photos of my own (including patients & equipment) out of respect for the upcoming Lancet publications.

On my last day at Hospital Das Clinicas - USP, I was gifted a book from the Infectious Disease team and my overarching supervisor Professor Aluisio Segurado, which documents the history of YFV in the state of São Paulo from the early 20th century until now (*Figures 7 & 8*). Given the book is written in Portuguese, I feel encouraged to learn the language and, someday soon, return to Brazil to pursue a Clinical PhD in Tropical Medicine as part of my future training. This really would be a dream come true, and right now remains an important orientating reflex for my clinical career.

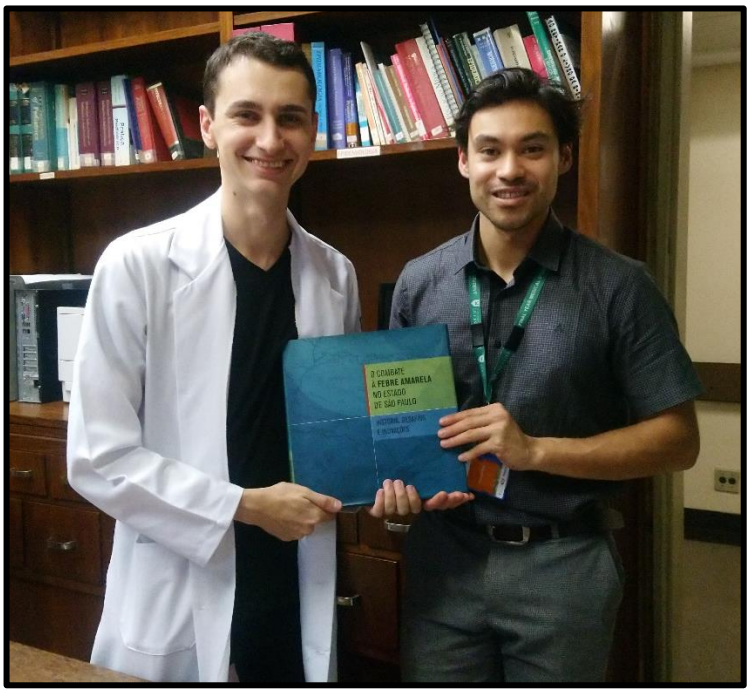

Figure 7. With Dr Gabriel, a talented and talkative Infectious Disease physician, holding 'The Fight Against Yellow Fever in the State of São Paulo' – a parting gift to me at the end of my placement at USP

Figure 8. Prof Aluisio Segurado of USP - a key figure in HIV/AIDS care throughout Brazil and in leading the Public Health responses the recent Yellow Fever Epidemics in the State of Sao Paulo

References

[1]. https://statistics.blf.org.uk/tb [accessed 2019 Mar 23]

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[7] Calvo E, Mizurini DM, Sa-Nunes A *et al.,* 2011. *J of Biol Chem* **286**(32):27998-8010

[8] De Frietas CS, Higa LM, Sacremento CQ, Ferreira AC, Reis PA, Souza TML *et al.* 2019. *PLoS Negl Trop Dis*. **13**(1):e0007072. doi: 10.1371/journal.pntd.0007072

[9] Faria NR, Pybus OG *et al.,* 2018. Genomic and epidemiological monitoring of Yellow Fever Virus Transmission Potential. *Science* **361**(6405):894-899

Learning outcomes

Detail here how the aims and objectives were met

Logistics behind managing infectious disease outbreaks

I spent time with ID physicians, epidemiologists and veterinary medics who were all involved in detailing the YFV outbreak, mass scale vaccination of animals and humans in regions of spillover risk, and public engagement with 'at risk communities' to raise awareness of vaccine availability and mosquito deterrents.

Clinical research during emerging public health threats

I gained understanding of a new treatment protocol trial of plasma exchange in YFV patients, alongside an open label trial of Sofosbuvir for YFV patients during an outbreak. My time spent creating a study protocol for STEI in MSM was also useful in understanding the requirements logistically and financially for a very different nature of outbreak.

Immunisation implementation & monitoring (with special reference to Yellow Fever)

I shadowed ID physicians involved in this and discussed with surveillance scientists how they collect their data accurately and rigorously for effective monitoring of vaccine coverage. The jump to using fractionated dosing of YFV vaccine in a shortage was ultimately evidence based and successful.

Microbial pathogenesis & management

I had multiple opportunities to shadow ID physicians in ambulatory clinics, wards and in Intensive Care. Here I learned the pathogenesis and medical management for a variety of pathogens including *Trypanosoma cruzi*, *Leishmaniasis, Schistosomiasis, Paracoccidiomycosis, Mycobacterium and YFV*.

Ecological drivers behind disease emergence

Attending Dr Faria's (of Oxford University) seminar at the Institute of Tropical Medicine, USP on 'Real-Time Genomic and Epidemiological Surveillance of YFV Transmission' was the most memorable academic contribution in meeting this learning objective. Additionally, clinics in Schistosomiasis and Chagas were useful in understanding ecological drivers for disease presentation.

	Portuguese language at level A1 I spoke Portuguese as much as possible with colleagues and locals. It is safe to say I am not a natural, but surprisingly my Spanish improved vastly thanks to the high population of Colombians and Bolivians at the International Housing (site of my accommodation). I will need more time and exposure to improve my Portuguese to be a competent A1 level speaker. My Spanish, however, is firmly within A2 if not B1.
Evaluation *How has this scholarship/ award impacted on your clinical/NHS practice or equivalent?*	Receiving the RCPSG award has benefited in several ways: • Supporting a medical elective with both a clinical and research component in Tropical Medicine – a field of medicine I wish to pursue. • Strengthening my CV for future applications to Core Medical Training and Infectious Disease / Tropical Medicine specialisation. • Helping me to become more a more rounded individual, improving my skills from a clinical, research and language perspective. The experience motivated me, and I intend for the impetus to continue throughout my impending Foundation Years. • Creating connections and friendships with Brazilian ID physicians, alongside other international medics and scientists. • Provision of an orienting reflex for my clinical career – after verbal discussions over pursuing a PhD in Clinical Tropical Medicine at USP with an adjoining UK host institution.

SECTION 3 | IMAGES

Most of the clinically relevant images are embedded within the body of the report. However, it was Carnival period whilst I was in Brazil after all, and so I include here a few more light hearted snapshots.

Myself with Dr Taniela Bes – mentor and friend - en route to Carnival in Rio de Janeiro. Some well-deserved downtime!

Sambodromo. A cultural experience of pure samba celebration, unique to Brazil.

Outside IMT- USP, with colleague and incredible friend Roozbeh Tahmasebi from Iran. He is studying gastroenteric viral outbreaks in Tocantin, Northern Brazil. I already miss his wisdom and high-pitched laugh dearly.

A few members of Instituto de Medicina Tropical, who I presented to regarding my elective experiences at the end of my placement. Prof Silva Costa (green floral dress, central) - a specialist in Bone Marrow Transplant Infections - presented me with Brazilian Cocoa, in case you are wondering what is in the bag I am holding.

Celebrating the successful graduation of several Infectious Disease Residents who can now proudly call themselves 'Attending Physicians' - Our equivalent to 'Consultant'. One of the worst photos of my entire trip, and yet one of my favourites.

SECTION 4 | EXPENDITURE	
Breakdown of expenditures *Please demonstrate how the scholarship/award funding was used to support your project/visit*	Flights: £607.60 Accommodation: Free (Provided by the Hospital of University of São Paulo) Food: £210 (Avg £5 per day for 6 weeks) Inner City Travel: £90 (£15 per week) Personal Care / Phone / Toiletries: £60 Travel to Other Project Sites – namely Casa da AIDS on eight occasions - 8 x £8 Uber Rides (Average w/ Return): £64 VISA: None Required (as stay is <90 days) Leisure: £120 (£20 x 6 weeks) **Total: £1151.60** ^^ The Leicester Medical School Bursary and RCPSG Scholarship covered almost all the main expenditures for my medical elective.

SECTION 5| PUBLICATION	
Scholarship/award reports may be published in College News. Please tick here if you agree to your report being published.	☒ I give permission for my report to be published in College News *If your report is selected for publishing, the editor of College News will be in touch to discuss this with you.*