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Microbial diseases and products that shaped world history

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For *Microbiology Australia* correspondence, see address below.

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Editorial correspondence
Prof. Ian Macreadie/Mrs Jo Macreadie
Tel: 0402 564 308 (Ian)
Email: ian.macreadie@gmail.com

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Publishing enquiries
Jenny Bennett
Email: publishing.ma@csiro.au

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Advertising enquiries
Doug Walters
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Cover image: Background: Transmission electron micrograph of recreated 1918 influenza virions (CDC image). Panels: Penicillium *inhibiting the growth of* Staphylococcus aureus *(courtesy of Prof. David Ellis); smallpox (CDC image); Louse, the typhus vector (CDC image); plague (CDC image); vaccination needles (19th Century) (courtesy of Prof. Dr İlter Uzel).*

Jon Iredell
President of ASM

Dear colleagues,

We can expect to see the beginnings of some changes in ASM over the next couple of years, as work begun by my predecessors in this role begins to take shape.

Annual national meetings in recent years are still attended by up to 700 registrants in total, with sometimes more than 300 in a single plenary. ASM Melbourne 2014 was a big success, and well attended (685 registrants, compared with 557 in Adelaide 2013 and 692 in Brisbane 2012). Sir Gustav Nossal's public lecture, reviewing the triumphs and challenges of vaccination, was standing-room only. The value of listening to exciting advances outside your own discipline/area of expertise is surely self-evident and is available most readily at a national general meeting like ours. Nevertheless, we are all subject to increased specialisation in microbiology – a focussed conference may be preferred to a general national meeting at the same or similar cost. Similarly, professional microbiologists in hospitals and industry are telling us they are less well supported to attend meetings than in previous times. The high cost of venue hire/catering and the tyranny of distance makes it difficult to cover costs at our broad general meeting but members have relatively recently voted in favour of maintaining the annual event so there are no plans to depart from this unless and until it is reconsidered.

However, there is some interest in new meetings. Some specialist areas have long separated from ASM (BacPath and the ASA, Australian Society of Antimicrobials), some have sprung up to fill a perceived gap (e.g. the MMM, Molecular Microbiology Meeting in Sydney), while some are still ideas (ASM Clinical, ASM Environmental/Ecology, ASM Genomics/Bioinformatics) that need to be worked through, but it is important that we move the Society to meet the needs of the microbiologists of Australia. We must aim to become a broad church by providing a stable support base for established meetings with their own clear identity, by fostering new ideas and helping to determine the demand for new meetings in the microbiology community, and even to support their initial piloting and development.

Some important awards are newly available in clinical microbiology. A travel award for clinical microbiologists is available (http://www.theasm.org.au/awards/asm-clinical-microbiology-travel-award/) and we are very proud to announce the creation of the first new major award for many decades, the ASM Lyn Gilbert Award, to stand alongside the ASM Frank Fenner Award and the ASM David White Award. Lyn Gilbert is a renowned Australian clinical microbiologist (and previous President of this Society), and this new award is intended to recognise major contributions in any area of diagnostic laboratory microbiology in Australia or internationally by ASM members/Fellows. The inaugural award was made in absentia to David Ellis for his contributions to clinical mycology. We hope to formally present this award for the first time at the ASM in Canberra in 2015.

Another important new initiative is the Nancy Millis mentoring breakfast with visiting speakers and students, lunchtime networking and discussion session and an evening social/mixer. The programme was formally launched with a dinner at the Royal Society attended by members of Nancy's family, close friends and colleagues and the ASM Executive. We hope to expand this in future meetings, and to include ECR development within this from 2015 on. See some of the ~90 graduate students who attended the Nancy Millis mentoring sessions in Melbourne talk about this at https://www.youtube.com/watch?v=LAdDW7fqCso.

One of the other very important changes has been to re-energise our role as an advocacy group. The creation of the role of Vice President (Communications) was an important initiative of Paul Young, and the acceptance of this challenge by Jack Wang, from the University of Queensland, has been a boon. We have seen a new website developed with our partners, ASN, and a much stronger presence in what are now standard media formats such as FaceBook (http://www.facebook.com/AustralianSocietyForMicrobiology), Twitter (@AUSSOCMIC), YouTube (http://www.youtube.com/user/AUSSOCMIC) and LinkedIn (http://www.linkedin.com/groups/Australian-Society-Microbiology-6605071). This has led to increasing engagement with membership, particularly among our younger members.

We need to continue to engage and re-engage with the membership and respond to the needs of the microbiology community as a whole. As professional and research microbiology funding contracts, the need for support from the national Society increases. The value of the state branches in education and support of early career microbiologists is greater now than ever, and those who lead these branches work hard in service of the clever country we all aspire to. We urge everyone who reads this to think about what they can do to support their colleagues in this community and to bring fresh ideas to the table at state and national level, where there is great enthusiasm for renewal and for reaching across traditional discipline boundaries. You can support the Society and your colleagues most easily by simply becoming a member.

Microbial diseases and products that shaped world history

İpek Kurtböke

University of the Sunshine Coast
Maroochydore DC
Qld 4558, Australia
Email: IKurtbok@usc.edu.au

Typhus, with its brothers and sisters: plague, cholera, typhoid, dysentery, has decided more campaigns than Caesar, Hannibal, Napoleon and all the inspector generals of history. Hans Zinsser 1935[1,2]

The 25 April 2015 will commemorate the 100th anniversary of the Gallipoli landing honouring the memories of those who lost their lives at the shores of Gallipoli: **The legendary ANZACs and the Mustafa Kemal's Soldiers**. Heroic battles fought in a dignified fashion later in the peace times brought the three nations together and paved the way towards establishment of ever lasting friendships with deep respect for each other (Figure 1). To be part of the remembrance we have decided to produce a special issue bringing together contributions from Australia, New Zealand and Turkey.

Figure 1. Turkish soldier with an ANZAC prisoner.

I would like to thank the current and past presidents of the three Microbiological Societies: Prof. Paul Young (Australia), Prof. Steve Flint (New Zealand) and Prof. Nezahat Gürler (Turkey), and the Editor, Prof. Ian Macreadie together with the Editorial Board members of *Microbiology Australia* for their support from concept to the production of this issue.

Epidemics played a significant role in the outcomes of most conflicts resulting either in defeat or victory for either parties and subsequently shaped the World's history[2]. Examples include the Yellow fever (in Haiti) and Typhus (in Russia) that sealed the fate of Napoleon's army[2]. Microbial products also came to the aid of the mankind in the 20th Century and even Churchill's life was saved by then a new sulphonamide when he had pneumonia on his return from Cairo after meeting with Roosevelt[3]. This special issue will present examples of such infectious diseases and microbially derived drugs/therapeutic agents with historical importance for Australia, New Zealand and Turkey. Prof. Ian Gust will review one of those miracle drugs: the **penicillin** that saved millions of lives and resulted in the eradication of many infectious agents. Without Australian scientist Howard Florey and his co-workers such a miracle could not have eventuated. Similarly, achievements of Florence Nightingale who established the guidelines of modern sanitary practices and played a significant role in saving the lives of wounded soldiers during the Crimean War will be reviewed by Prof. B. Gürler.

Overviews of the historical developments of the discipline of microbiology and their respective Microbiology societies will be provided by Prof. Paul Young for Australia, Emeritus Prof. Tagg, Dr Austin, Dr Maguire (first PhD graduate of University of Otago) and Dr Smith (who sadly passed away in 2007) for New Zealand and Prof. N. Gürler for Turkey.

Infectious diseases with devastating effects throughout the centuries of human history will be overviewed: (i) Smallpox by Prof. Sadi Yenen, incredible efforts of late Prof. Frank Fenner towards global eradication of the disease by Dr George and Prof. Rawlinson; (ii) Malaria by Dr Taki and Prof. Smooker; (iii) Plague by Prof. Whitehall; and (iv) tuberculosis by Prof. Çavuşoğlu.

Influenza with its different emerging forms (e.g. bird flu, swine flu) can still be deadly today. Prof. Mackenzie, Dr Kelso and Prof. Hampson will provide an overview on the disease. Assoc. Prof. Wilson, Dr Summers and Prof. Baker will discuss the effect of the

1918–1919 pandemic and the persisting lessons gained for pandemic control. Prof. Flint, Prof. Harper and Assoc. Prof. Wilson will tell us NZ Army's efforts in dealing with dysentery on the 'Fringes of Hell'. Similarly, Prof. Ahmet Başustaoğlu and Mr Sadık Emre Karakuş will provide information on the deaths related to infectious diseases in the WWI and Turkish War of Independence as well as the incredible efforts of then under-resourced Turkish medical personnel to fight against Typhus during these wars. Readers might note that Turkish articles will cover both the Ottoman Empire (1299–1923) and the Republican era (29 October 1923 onwards) of Turkey. Following the 1918 defeat of the Ottoman Empire, the Turkish War of Independence took place on the Anatolian plain ultimately resulting in the declaration of The Republic of Turkey under the leadership of Mustafa Kemal (29 October 1923). Following the establishment of the Republic, Turkey underwent a significant number of reforms for secularism and modernisation. One of these reforms included adaptation of surnames[4]. Distinguished medical expert of that era Emeritus Professor Tevfik Salim adapted the surname 'Sağlam' after the reforms (see Başustaoğlu and Karakuş and Karakuş and Başustaoğlu articles). Similarly Mustafa Kemal was given the surname 'Atatürk' by the Turkish Parliament (1934). Some of the Turkish articles will also cover instances of Ottoman script that was replaced by the Latin alphabet following the reforms.

Current global trends such as the (i) mobilisation of people, (ii) environmental changes such as temperature increase resulting in the subsequent vector expansions, or (iii) co-infection with HIV are resulting in transmission and re-emergence of long forgotten diseases (e.g. *Leishmania*)[5]. Although we have overwhelming information on the past and current infectious agents, yet to emerge infectious agents may manifest differently (e.g. first encounter with the Ebola virus). However, with the lessons learned from past epidemics and armed with the latest molecular advances and bioinformatics tools, we can now develop combat strategies against the global challenge of emerging and re-emerging infections such as tuberculosis.

My arrival in Australia coincided with the 75th Anniversary of the Gallipoli landing in 1990. The same year surviving veterans paid a pilgrimage to the shores of Gallipoli where they lost many of their mates. I had the honour of meeting few of them on their return at the ANZAC Parade (1991, Perth, Western Australia). **LEST WE FORGET** and foster collaboration between Australia, New Zealand and Turkey and take microbiology to new horizons for discovery of new and potent microbial products as arsenals against emerging and yet to emerge infectious diseases.

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Biography

Dr Kurtböke is a graduate of Middle East Technical University in Ankara, Turkey (BSc, 1982) and University of Liverpool, UK (PhD, 1990). She has been working in the field of biodiscovery and has been an active member of the international actinomycete research community since 1982 including conducting postgraduate studies at the University of Milan in Italy (1983–1986). She currently teaches in the fields of applied, industrial and environmental microbiology and biotechnology at the University of the Sunshine Coast, Queensland, Australia. She is also an active member of the World Federation of Culture Collections including serving as the Vice-President of the Federation from 2009 to 2012.

A brief history of Australian microbiology

Paul R Young

Australian Infectious Diseases Research Centre
School of Chemistry and Molecular Biosciences
University of Queensland
Brisbane, Qld 4072, Australia
Email: p.young@uq.edu.au

Acquired over a long period of time, Australia has an enviable record of involvement in the discipline of microbiology and continues to punch above its weight in terms of research output and translational outcomes. A comprehensive review of those involved, the characters and institutions, their achievements, successes and failures is far beyond the scope of this short article. So instead, a snapshot of a few of the interesting highlights from one person's perspective will be provided. I apologise in advance for any omission of your favourite story, character or advance in the field of microbiology that flavours your own view of this enthralling area of Australia's scientific legacy.

The Australian population's engagement with microbes and their consequences obviously started well before European settlement. As with many long-established cultures across the world from the ancient Egyptians who used honey as an antiseptic and henna as a treatment for leprosy and smallpox, to the Chinese who have used medicinal herbs for millennia, the Australian Aboriginal population had their bush medicine. An extensive array of treatments and cures for a wide range of diseases were honed over thousands of years. Unfortunately, much of this traditional knowledge has been lost with the fragmentation of their oral history following European settlement. But we do know of some of these treatments. Tea tree oil obtained by boiling the leaves of the paper-bark tree was incorporated in a tea for throat infections while eucalyptus oil from gum leaves was used for fevers and chills, a remedy that is still in use today to ameliorate the symptoms of a cold. The bright orange desert mushroom was sucked to cure a sore mouth and as a treatment for babies with oral thrush, and a tea brewed by boiling Emubush leaves was used to cleanse cuts and sores and as a mouth wash. Extracts of this plant have now been shown to have antibiotic properties. The fruit of the kangaroo apple was used as a poultice because of its anti-inflammatory properties and this plant has now been shown to contain the steroid, solasodine, important in the production of cortisone. There are many more examples of Aboriginal bush medicine treatments for microbial control that have now been documented but almost certainly many more are lost to us forever.

But our 'modern' concept of the science of microbiology did begin with European settlement. In these early years it was based largely around the consequences of the introduction into a continent that had been isolated up until that time, of new plant and animal species, as well as the settlers themselves, and their respective infectious diseases. So much of this early history was in applied microbiology, driven by the pressing need to diagnose and control these diseases. Indeed the first microbiology laboratory in Australia was a privately owned venture, the Macleay Laboratory, opened in 1874 and located on the harbour in Sydney. Its primary role was water testing, a reflection of the problems of over-crowding and sanitation that the colony had faced for many years.

However, the practise of microbiology, or bacteriology as it was then known, had been in full swing much earlier than this through efforts to control diseases such as scarlet fever, typhoid, cholera and smallpox that were all too common in the fledgling colony. Remarkably, it was only 5 years after Edward Jenner published his studies on cowpox vaccination as a preventative for smallpox (1798) that the Sydney colony's assistant surgeon Mr John Savage attempted to vaccinate orphans with his own experimental 'Cow Pock' preparation. Although this was initially unsuccessful, within a year a viable source of cowpox within the colony was established. The vaccine was subsequently maintained by inoculating unvaccinated individuals and passing the 'lymph' from arm-to-arm. Delivery of the vaccine took on many innovative forms. In 1818, the state and church came together with the Governor of the day directing that clergymen perform the inoculations at baptisms. One surgeon reported in 1841 that in order to maintain the supply of the vaccine, he conducted the necessary serial passage in residents of the 'Female Factory', a convict establishment located in the area of modern-day Parramatta. In the same year, a surprisingly forward thinking Governor Gipps proclaimed free vaccination for the residents of Sydney, but with a clever twist. A shilling was initially charged for the vaccine, but this was refunded when the vaccinated child was subsequently presented, complete with scab signifying successful inoculation and providing a resource for further inoculations. While these measures reduced the impact of smallpox infections, occasional outbreaks continued to occur resulting in the establishment in the 1880s of public health authorities dedicated to

its control. At the same time a cowpox vaccine factory was established in Royal Park, Victoria by a veterinarian using the original bovine host as the production vessel. Across the world, the practice of arm-to-arm transfer in humans that had dominated for nearly a century as the means by which the vaccine was maintained was being phased out by the late 1800s. It is significant to note that some 60–70 years later, one of Australia's premier virologists, Sir Frank Fenner led the WHO Smallpox Eradication program, and was the one who was able to officially announce on the 8th May, 1980, the removal from the planet of this centuries old scourge as a naturally transmitted disease.

Arguably one of the most remarkable microbiological stories of Australia's early history surrounds none other than the esteemed Louis Pasteur. It involved political intrigue, scientific jealousy, protracted fights over funding, the rabbit plague and somewhat surprisingly, Australian Federation and the origins of Australians' taste for beer! It all started in 1859 with a British-borne pastoralist in Geelong, Victoria by the name of Thomas Austin, who released 24 rabbits, 72 partridges and five hares in an attempt to bring a touch of his native England to his property. Within 20 years the rabbit population had exploded, reaching plague proportions in Victoria, New South Wales and South Australia. The numbers were estimated to be in excess of a billion and by 1887 had become a significant threat to the rural economy. With the repeated failure of large-scale eradication campaigns, the NSW premier Sir Henry Parkes proposed an international competition for a microbiological solution – the prize was £25,000 (equivalent to about $10 million in today's currency). There were over 1,500 entries from around the world and in order to decide on a preferred approach that met the needs of all the Australian colonists, Sir Henry formed a Rabbit Commission, a judging panel onto which he invited representatives from each of the Australian colonies and New Zealand. It is widely suspected that this was the model on which he later formed his constitutional convention on Federation.

On the other side of the world, Louis Pasteur had fallen on difficult financial times as a result of changing politics and loss of patronage. A lack of funds meant that his dream of an Institut Pasteur in Paris was on hold. But after his wife pointed out to him an advertisement of the rabbit plague competition in a Parisian paper, he saw his rescue. Pasteur had earlier conducted experiments on chicken cholera, which he had shown efficiently dispatched rabbits and was convinced that he would win the competition. He instructed his nephew, Adrien Loir to conduct confirmatory field trials over the Christmas of 1887 and with the success of those experiments was sent to Australia leading a three-man Pasteur team to claim the prize. The team was sent with funds to cover their expenses for six weeks in the colony, however on arrival in Melbourne they struck a number of problems. There was resistance in NSW to the introduction into the country of what was then thought to be an exotic agent (perhaps a forerunner of our strict quarantine ethos) and the terms of the competition required field-testing of the proposed approaches for up to 12 months. Loir feared that he would have to return to Paris empty-handed. But it transpired that a local brewer, Thomas Aitken was at that very time, preparing to sail for Denmark to learn from the Carlsberg company the secrets of the new techniques of yeast cultivation and fermentation, recently introduced by Pasteur himself. On hearing that Pasteur's nephew was in town, Aitken offered Loir £250 to teach his staff the Pasteur technology. With this, Loir had enough funds to head to Sydney for the extended period. The result of the happy coincidence of Loir landing in Melbourne was Victoria Bitter and a shift in Australian beer tastes from ale to lager. The quarantine question was answered by Parkes who set up the Pasteur team on Rodd Island in the middle of Sydney Harbour.

However, despite trials showing that chicken cholera was effective in killing rabbits the prize was never awarded and instead, it was decided that rabbit fencing was the answer. Many of the judges on the Commission had their own agendas – two were importers of the barbed wire that would become the back-bone of the fencing approach, one was the president of the poultry farmers association fearful of the effects of chicken cholera and two of the judges were past students of Pasteur's arch rival in Europe, Robert Koch. Rabbits remain a problem in outback Australia to this day, despite two later attempts to eradicate them with microbiological approaches; myxoma virus in the 1950s from a team led by Frank Fenner and the CSIRO's 1990s effort with rabbit hemorrhagic disease (rabbit calicivirus disease, RCD). Despite the fact that he did not succeed in his original objective, the ever-resourceful Loir still managed to leave a considerable impact from his time in Sydney. During the deliberations of the Commission he conducted research for the Queensland delegation on what was referred to at the time as 'Cumberland disease' of livestock. He determined that it was in fact anthrax and as Pasteur had already developed an anthrax vaccine Loir proposed that the Parkes government support a vaccine trial. The trial was successful and the vaccine was rolled out to the graziers at a handsome profit. In order to generate sufficient doses the Rodd Island laboratories were expanded and a Pasteur Institute of Australia was established. The profits from the vaccine amounted to more than the original prize for the rabbit competition and so Pasteur was able to finish his Paris Institute. A little known fact is that because of Loir's efforts, the Sydney based Pasteur Institute was actually the first in the world, operating before the Paris headquarters opened in 1888. It was moved to Double Bay in 1896 but only survived for another 2 years, with the anthrax vaccine manufacture eventually being taken over by another Sydney based group.

The serious issues of livestock and crop diseases were not unique to NSW and to address these problems in Queensland, the Stock Institute was established in Brisbane in 1893. The role of the first Director was actually offered to Adrien Loir in an attempt to lure him back to Australia. However despite his wish to take up the post, his wife refused to return and so he had to reluctantly decline, instead travelling to the French colony of Tunis in North Africa where he established another Pasteur Institute which is still in operation today. The Brisbane Stock Institute became the Bacteriological Institute in 1899. Tropical diseases such as malaria and dengue afflicted the far north and in 1910 the Institute for Tropical Medicine was established in Townsville – the first medical research institute in the country.

During the early part of the 20th Century, government and universities played integral and connected roles in the development of microbiology in Australia. Microbiological research was conducted in universities with departments usually working closely with hospitals, contributing directly to diagnostic laboratory activities. The University of Melbourne medical school taught bacteriology in the early 1890s, and provided the diagnostic services for The Royal Melbourne Hospital. This activity arose out of the intersection of teaching and research in medicine, veterinary science, science and dentistry with a separate microbiology focus not being a feature of this dynamic until many years later. Unlike the University of Sydney, where there was no centralised teaching of microbiology, both the University of Queensland and the University of Melbourne established Departments of Microbiology from which students in medicine, science and dentistry were taught. The universities of Adelaide and Western Australia formalised their research and teaching in microbiology somewhat later, 1920 for medical students in Adelaide and 1923 for agriculture students in Western Australia – and for medicine and science students in 1956. The University of Tasmania introduced microbiology into the Faculty of Agricultural Science in 1962.

By the 1950s, there was a growing number of Australian microbiologists who were teaching and conducting research in microbiology, primarily arising from the increased activities of both teaching institutions and government agencies. For some time, this group had been meeting at the Congresses organised each year by the Australian and New Zealand Association for the Advancement of Science (ANZAAS), a body founded in 1888. With the growth of the discipline, the perceived need for a more focused grouping and the example of the biochemists who had recently formed their own society, discussions were held among a group of microbiologists at the 1958 Adelaide meeting about the possibility of a society dedicated to microbiology. The meeting was chaired by Eric French and the outcome of deliberations was that an association of microbiologists in Australia would be formed. A working group developed a proposal which was presented within a week of that first meeting and it was resolved to establish a learned society that would be dedicated to the science of microbiology, to the fostering of knowledge, the exchange of ideas and the promotion of the discipline. A constitution was drafted, state branches inaugurated and in the following year, in May 1959, the first General Meeting of the Australian Society for Microbiology was held in Melbourne. The office bearers who were elected in that first iteration of the Society Executive were a star grouping – Sir Macfarlane Burnet was elected President, Sydney Rubbo Vice President, Jack Harris Honorary Secretary and Nancy Atkinson Honorary Treasurer. The ASM was born. It was not until 1976 that the Society became incorporated, a move that accompanied a broadening of membership to embrace all practicing microbiologists and a new professionalism. The Society is undergoing new challenges in the modern era of discipline specialisation but I am certain that these challenges will be embraced and treated as opportunities to further grow its role as Australia's peak body in microbiology.

There is so much more that could be written about the history of microbiology in Australia, our many celebrated researchers and practitioners, our Nobel prize winners, our key role in the development of the first antibiotics, the development of new vaccines, antiviral therapies, microbial discovery – the list of achievements and milestones is very long indeed. The science of microbiology in Australia is in a remarkably healthy state and we are in exciting times.

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Biography

Paul Young is Professor of Virology and Head of the School of Chemistry and Molecular Biosciences, The University of Queensland and is the Immediate-Past President of the ASM. He is the current President of the Asia-Pacific Society for Medical Virology. His research interests are focused on understanding the molecular basis of dengue virus induced pathogenesis, improved diagnostics as well as vaccine and therapeutic control strategies for the flaviviruses, dengue virus and West Nile virus and also respiratory syncytial virus. His laboratory is also investigating the current invasion of the koala genome by a novel retrovirus and what this can tell us about cancer induction and viral evolution.

Early developments in New Zealand microbiology




John Tagg, Frank Austin, Terry Maguire and Sandy Smith

Email: john.tagg@otago.ac.nz

The inception of microbiology in New Zealand was, as elsewhere, strongly linked to the investigation of infectious diseases in humans. However, since the country's economy has always been firmly based on primary industries, the need to maintain animal and plant health was also a powerful early influence.

Historical overview

Bacteriology was taught to medical and botany students at the University of New Zealand in the last decade of the nineteenth century. In 1905 the first research and diagnostic station for the study of animal diseases in Australia or New Zealand (Wallaceville Animal Research Centre) was established by the Department of Agriculture. Bovine mastitis was among the first problems to be investigated. Additional research centres were subsequently launched, focusing on other major infectious diseases of livestock including clostridial diseases, leptospirosis, brucellosis, salmonellosis, toxoplasmosis and facial eczema.

In the mid-1920s the two Agricultural Colleges of the University of New Zealand (Massey in Palmerston North and Canterbury at Lincoln) introduced microbiology as a subject in the agricultural science courses, and students received instruction about the role of microorganisms in plant diseases. At about the same time, the Plant Diseases Division of the Department of Scientific and Industrial Research (DSIR) broadened its field of investigation to include plant diseases caused by viruses, fungi and bacteria. The first government-supported industrial research institute, the Dairy Research Institute, was also established during this period.

During the past 80 years major expansions have occurred in the teaching of microbiology and in the government-funded employment of microbiologists. Since the early 1990s, various research centres (e.g. the DSIR, and Ministry of Agriculture and Fisheries Divisions, the Forest Research Institute and the Communicable Disease Centre) have been amalgamated and/or assigned to one of the newly-established Crown Research Institutes, such as Landcare Research, HortResearch, AgResearch, Crop & Food Research and Environmental Science & Research. All have major microbiological research interests and knowledge bases.

Medical microbiology

With the appointment of a bacteriologist to the Dunedin (Otago) Medical School in 1911, the bacteriology course for medical students was extended, and a beginning was made in investigative work on tuberculosis, bacterial meningitis, poliomyelitis, typhoid fever, diphtheria and scarlet fever, all of which were prevalent at that time.

A second medical school was established at the University of Auckland in 1968, and the University of Otago Medical School established Clinical Schools in Christchurch and Wellington. Several other universities (e.g. Canterbury, Massey and Waikato) also formed new departments specialising in various aspects of clinical microbiology. The teaching of immunology flourished at Otago, as recognised by the renaming (in 2004) of the Microbiology Department as New Zealand's sole Department of Microbiology and Immunology.

Medical microbiology research received an impetus with the establishment of the Medical Research Council (now the Health Research Council) of New Zealand in 1937. In the 1940s it was supporting research on haemolytic streptococci, phage-typing of staphylococci and leptospirosis. The Medical Research Council formed a Virus Research Unit in Dunedin (1949) to provide a diagnostic service to hospitals and to conduct research into viruses causing human

disease. Early topics included viral diagnostic serology, poliovirus immunity, arboviruses and viral hepatitis. Other projects funded in the late 1950s–1970s were concerned with bacterial plasmids, *Pseudomonas aeruginosa, Candida albicans*, dermatophytes, molecular biology of bacterial viruses, tumour virology, interferon and the biological control of mosquito vectors of dengue viruses and filaria.

During the 1980s and 1990s the Health Research Council funded projects concerned with influenza, hepatitis and papilloma viruses, virus vaccines, leprosy, streptococcal diseases, oral microbiology, gastrointestinal microbiology, kidney infections, protozoal and fungal infections and antimicrobial resistance.

More recently (2000s) research support has responded to the widespread publicity and debate surrounding the emergence of multi-drug resistant 'superbugs', the potential H5NI bird flu pandemic, invasive meningococcal disease, *Campylobacter* and *Legionella* infections, tuberculosis and rheumatic fever.

A small number of specialty research groups having a medical microbiology and/or immunology focus have been established for varying periods. As well as the Virus Research Unit at Otago, these have included portions of the Dental Research Unit in Wellington, the Disease Research Laboratory and an Oral Biology Research Unit at Otago and a Protozoology Research Unit at Massey. Immunology research has also been carried out by the Malaghan Institute in Wellington. The only other major research centre for medical microbiology is the Environment Science and Research Communicable Disease Centre at Porirua, although several hospitals (e.g. Auckland, Middlemore, Waikato and Christchurch) have been actively engaged in infectious diseases-orientated research. The oral probiotic company BLIS Technologies Ltd was launched in the year 2000 from research at Otago University.

Microbiology at universities

Otago

Sydney Champtaloup was the first Chairman (1911–1920) of 'Microbiology' (Department of Bacteriology and Public Health) at the University of Otago (then part of the University of New Zealand), followed by Charles Hercus (later Sir Charles Hercus) during 1921–1954. However, microbiology as a science discipline first really flourished during John Miles's tenure as Chairman (1955–1977)[1].

Lincoln

The BAgSc course, initiated in 1926, included the subject 'Microbiology' – a simple unit based on the relevance of microbes to plant diseases. Post-1950, while still primarily specialising in plant pathology, there has been an increasing emphasis on soil and water microbiology.

One of the early students was Royd Thorton (MAgrSc, 1948), who later became Director of the Cawthron Institute. Harvey Smith, another Masters student in the late 1940s later became Director of the Crop Research Division of DSIR. Both Smith and Thorton were prime movers in the establishment of the New Zealand Microbiological Society (NZMS) (see below).

Canterbury

Microbiology at the University of Canterbury had its origins within the Botany Department where short lecture/laboratory courses on fungi were offered in the mid-1950s. Subsequently, the first specific appointee in microbiology (the plant pathologist John Allen) pressed for a degree in general microbiology and this led to the institution in 1964 of an Honours degree in Microbiology within the Botany Department. The appointment in 1969 of a Reader in Microbiology (John Waid, who in 1974 became foundation Professor of Microbiology at Latrobe University) increased interest in soil microbiology, while additional appointments in the mid 1970s further strengthened plant pathology and soil microbiology teaching and research.

Massey

In 1958, all microbiology teaching and research at Massey University was conducted by three teaching staff employed part-time from the New Zealand Dairy Research Unit. The Department provided an introductory course in microbiology for agricultural students, a diploma course in dairy microbiology and a course in plant pathology including postgraduate studies.

In 1966 Don Bacon became the first Professor of Microbial Genetics and later Microbiology. Gradually the staff expanded and taught courses in medical microbiology, wine microbiology, mycology, protozoology, genetics, virology, immunology and cell biology. Close associations were formed with the Faculty of Veterinary Science. At its height in the mid 1990s, the Department of Microbiology and Genetics had around 40 academic and support staff. However, with the demise of the Departmental structure at Massey, microbiology disappeared as a distinct entity, and all microbiology teaching and research became broadly contained within the Institute of Molecular BioSciences.

Waikato

Microbiology began at Waikato with the appointments of Hugh Morgan (1973) and Chris Harfoot (1975) within the school of Biological Sciences. Students now graduate with a BSc often combining microbiology with genetics or biochemistry. Microbiological research was given a great boost by the establishment around 1980 of the Thermophile Research Unit.

Auckland

When the decision was taken to establish a Medical School at the University of Auckland (circa 1962), Dick Matthews, a plant

Figure 1. Joc Neill, first President of NZMS.

virologist, was appointed Professor of Microbiology in a Cell Biology Department which focused on research and postgraduate teaching. In the late 1970s a second attempt to initiate Microbiology centered upon the establishment of a Chair in Microbiology within the Pathology Department. However, the appointment of cellular immunologist, Jim Watson, to the position, led to a spin-out Department of Immunology (subsequently changed to Molecular Medicine) being formed and the concept of a department focused on the core discipline of microbiology was not achieved.

The founding of the NZMS

By the 1950's the various microbiologists in universities, hospitals, government-supported research centres and industry all worked in small isolated groups and only rarely met. The only opportunities for joint discussions were at Section meetings of the infrequent Science Congresses organised by the Royal Society of New Zealand (RSNZ) and the Australian and New Zealand Association for the Advancement of Science (ANZAAS). It was during the 1954 RSNZ Science Congress in Auckland that Royd Thornton and Harvey Smith of the Plant Diseases Division of the DSIR convened a meeting to consider the formation of a microbiological society. Provisional rules were minuted and in May 1956 the inaugural meeting of the Society was held at Victoria University college in Wellington. This pre-dates the May 1959 launch of the Australian Society for Microbiology[2].

The foundation President Mr J. O. C. Neill (Figure 1) chose for his inaugural address a philosophical dissertation on the importance of microbial activities to other living organisms, the origin of life and evolution[3]. This was followed by 12 scientific papers[3], 11 having a focus on plant microbiology, clearly showing which group was principally behind establishment of the Society.

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We are indebted to Paul Mulcock, Dick Bellamy, Don Bacon, Brian Jarvis, Tim Brown, Hugh Morgan, Chris Harfoot and Tony Cole for their contributions to the booklet *The First 50 Years. A brief history of the New Zealand Microbiological Society* written by the present authors together with the late Sandy Smith to coincide with the 50th Meeting of the Society held in Dunedin in November 2005. Excerpts from that booklet are accessible on the NZMS website[4]. The present text draws heavily upon information in that publication and also the article written by Frank Austin in 1974 for the American Society for Microbiology[5]. The authors (JT, FA and TM) respectfully dedicate this present article to the memory of our colleague and friend Sandy Smith.

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Biographies

John Tagg is a Professor Emeritus in the Department of Microbiology and Immunology at the University of Otago. Currently a research consultant to the Dunedin-based company BLIS Technologies Ltd, he is a Past President and Honorary Member of the New Zealand Microbiological Society.

Frank Austin spent almost the entirety of his working career (1950–92) in the University of Otago Virus Research Unit, during which time he obtained a MSc in microbiology and PhD in virology. Frank's research interests included polio, arbo, hepatitis and influenza viruses. In 1993 he was elected an Honorary Member of NZMS.

Terry Maguire was in 1964 the first PhD to graduate in Microbiology at the University of Otago. Prior to his official retirement from the Virus Research Unit in 1997 his principal research interests were insect-transmitted viruses and hepatitis, but he subsequently continued to be involved in virus vaccine development.

Sandy Smith. A popular teacher and Head of the Department of Microbiology at Otago, Sandy's principal research contributions were in the fields of medical mycology and antibiotic resistance. Sandy passed away in August 2007.

Advancement of medical microbiology in Turkey and the Turkish Society for Microbiology

Nezahat Gürler

President, Turkish Society for Microbiology
İstanbul University
İstanbul Medical Faculty
Department of Clinical Microbiology
Çapa, İstanbul, Turkey
Email: ngurler@istanbul.edu.tr

The history of *Bacteriology* in Turkey is also regarded as the history of *Microbiology*. As in many countries, advances in microbiology and its acceptance as a proper scientific field started in the second half of the 19th Century. The earliest work in the field of microbiology in Turkey was related to branches of medical, clinical and veterinary microbiology as expertise was cross-disciplinary[1–11]. This article will provide an overview of the history of microbiology starting from the Ottoman Empire era (1299–1923) and advancing into today's Republic of Turkey (established in 29 October 1923).

Although infectious diseases were known, their causative agents were not identified until the early 20th Century. Prior to this era, the course of infectious diseases was observed and recorded; however, the therapies that followed were without any sound scientific basis. During the Ottoman Empire, the earliest studies in the field of microbiology came through vaccination. After 1840, scientific studies related to smallpox and vaccine preparation advanced rapidly and the smallpox vaccine in use was hailed a success. Investigations related to smallpox, rubella, cholera and plague were conducted from as early as the 12th Century, with syphilis, tuberculosis and leprosy also receiving attention. However, these studies were still limited to the description and recording of the cases. The first medical school and hospital date back to 1206 and 1399, in Kayseri and Bursa, respectively, and those of İstanbul (Fatih) and Edirne followed. In the 16th Century, again in İstanbul (Süleymaniye district), an independent medical school was established. The Greek (Balıklı) Hospital in İstanbul treated plague victims in 1753.

Ottoman Sultan Selim III (1784–1839) closely followed the advancements in Europe and started modernization of the practices in the Empire to combat infectious diseases. In the 18th Century when Europe was hit by a devastating smallpox epidemic, vaccination practices kept the numbers low in Turkey. This was due to the homely practice of Turkish women taking samples from lesions and drying them out in nut shells before reintroducing them into uninfected members of the community. Lady Montagu, who was a survivor of the disease and had lost her brother to it, observed this practice during her stay in Turkey in 1717. Lady Montagu who was instrumental in the adaptation of the practice in Europe (see Yenen article of this issue) vaccinated her son in March 1718. A modern smallpox vaccine laboratory was established in 1892 by Dr Hüseyin Remzi.

Upon advice from the Chief Surgeon Mustafa Behçet Efendi at the Ottoman Court, the first Medical Faculty was opened (Şehzadebaşi, İstanbul) in 1827. This was followed by the opening of another Medical Faculty in the district of Galatasaray in İstanbul (1839), to train military medical personnel, with French as the language of instruction. The first bacteriology laboratory was established in 1887 by Dr Zoeros Pasha in the district of Sirkeci in İstanbul and investigations under his direction were conducted from 1887 to 1899. Still operating today, the Foundation Hospital Gureba was established by the son of Sultan Mahmut II in 1843, followed by the opening of the St. George Hospital (Galata, İstanbul) in 1865 to treat cholera victims.

The first parasitology lectures were given by Dr Hüseyin Remzi upon his return from France where he received further training and together with his colleague Hüseyin Hüsnü published the first book in microbiology (1888). Both doctors also published later on rabies and its treatment. Bacteriology lectures were first given by Zoeros Pasha and Rıfat Muhtar Ahmet in the medical faculties as well as by Hamdi Aziz at the military medical academy. From 1847 onwards all Turkish medical microbiologists began actively working on medicine and public health after their return from overseas. In 1890, Dr Cemil (in the Republican era Dr Cemil Topuzlu), following his return from France, applied the antiseptic techniques of Lister-Alfonse in operations he conducted and Dr Celal Muhtar following his stay in Paris (1889–1892) applied quarantine restrictions during cholera epidemics. He also discovered the causative agent of *Trichophyton*, which was causing eczema-like infections on the feet, defining the *tinea pedis et mannum* published in 1892. His discovery resulted in the effective antifungal treatment of the disease on German and French soldiers of WWI.

In 1893, during the cholera outbreak in İstanbul Dr Zühtü Nazif and Dr Rıfat Hüsamettin who had also returned from France, were able to isolate the causative bacterium from human faecal samples. During the epidemic, upon the request of the Sultan, Pasteur sent Dr Chantemesse to İstanbul, and a second visit by Dr Maurice Nicolle followed. Dr Nicolle then became the director of the Bakteriyolojihane-i Osmani, which was the first bacteriology laboratory in İstanbul and conducted investigations with the support of a Turkish colleague, Zühtü Zaim. He provided bacteriology training, both theory and practice for young Turkish Military doctors, and became an important foundational scientist in Turkey for the further advancement of bacteriology by applying modern methods similar to those developed and used at the Pasteur Institute in those days. Military Doctor Refik (in the Republic era Dr Refik Güran) who worked with Dr Maurice Nicolle and colleagues Dr Ziya Seyfullah, Calligrapher Mustafa Rakım and Dr Süleyman Nuri also conducted microbiology courses which were also frequented by veterinary microbiologists. Veterinary microbiologists Adil Mustafa, Osman Nuri, Dr Kimyager Nurettin, Dr Hayim Naim, Dr Rıfat Muhtar, DrFerit İbrahim and Dr Ethem worked closely with Dr Nicolle. In particular, Adil Mustafa Şehzadebaşı who worked with Nocard in France at Alfort Veterinary School conducted investigations of importance after 1897 and was involved in the preparation of diphtheria serum. Adil Mustafa Şehzadebaşı and Dr Refik together with Dr Nicolle produced significant research work on cattle plaque. Dr Nicolle's efforts resulted in growth and development of both bacteriology and veterinary microbiology in the then Ottoman Empire including the development of therapeutic sera against diphtheria and plague. After Dr Nicolle's return to France in 1901 he was replaced by other Pasteurians: Dr Remlinger and Dr Simond.

Again from 1899 onwards, Turkish doctors Dr Rıfat (in the Republican era Dr Rıfat Muhtar), Dr Refik (in the Republican era Emeritus Professor Dr Refik Güran) and others, following their return from France continued to work in the fields of bacteriology, veterinary microbiology, pharmacology and dentistry (1908–1909). From 1913 onwards, in the laboratory, vaccines against typhoid, dysentery, plague, cholera and meningitis as well as serum development against diphtheria and dysentery were developed and were later used both for soldiers and the public during WWI and the Turkish War of Independence (1919–1923) (see articles by Karakuş and Başustaoğlu and Başustaoğlu and Karakuş in this issue).

Dr Refik (Güran) became the director of the Bacteriology Laboratory following the departure of Dr Simond in 1914. He also became the director of the Faculty of Medicine which had been in existence since 1908. Dr İhsan Sami (in the Republican era Dr İhsan Garan) ve Dr Ziya (in the Republican era Dr Ziya Öktem) were his co-workers who all played significant roles in the advancement of Microbiology in Turkey. Emeritus Professor Dr Refik (Güran), who himself had survived typhus, was instrumental in the development and advancement of bacteriology and its related educational institutions in Turkey that trained significant numbers of Turkish microbiologists. He was also the author of the first book on Bacteriology in 1919, reprinted in 1928. The foundation of today's Republic of Turkey in 1923 led to higher education reform in 1933 and the Faculty of Medicine moved to its current premises in İstanbul. Many distinguished European scientists were invited to contribute to the Faculty's teaching and research programs. Emeritus Professor Dr Hugo Brown became the director of the Institute of Microbiology and Infectious Diseases in the Faculty. His Associate Professors were Dr Zühtü Berke, Dr Vefik Vassaf Aken and Dr Ziya Öktem.

Advancements in the field of microbiology (Golden Age of Microbiology) led by Robert Koch and Louis Pasteur were closely followed in Turkey (then the Ottoman Empire). Tuberculosis studies by Koch led to immediate replication of the studies for disease prevention in Turkey. During Pasteur's studies on rabies, Ottoman Sultan Abdülhamit II sent 10,000 gold coins to the Pasteur Institute to support their research activities. Pasteur's talk on rabies and its prevention at the Paris Academy of Medicine was even translated into Turkish and published in 1885. With the request of the Ottoman Government, doctors Hüseyin Remzi and Hüseyin Hüsnü, under the leadership of Zoeros Pasha, were sent to Paris to observe the preparation and administration of the rabies vaccine. After a 6 month stay in Paris, they returned in 1887 with two infected rabbits to be used for vaccine development in the first established rabies hospital of İstanbul.

In the Republican era, following Atatürk's reforms, infectious disease control became part of the holistic public health approach. This approach has been very successful in the eradication and control of many infectious diseases including malaria, smallpox, trachoma and tuberculosis (see Cavuşoğlu article in this issue). Refik Saydam, who was a military doctor during the Balkan wars and WWI and later joined Atatürk's army in 1919, became the Minister of Public Health in 1920. The distinguished Institute Hıfzısıhha was established by him in Ankara (1920) to prevent infectious diseases and since then has been one of the key microbiology institutes in Turkey. In 1933, rabies vaccine was produced at Refik Saydam Merkez Hıfzısıhha Institute in Ankara (now known as the *Public Health Institution of Turkey*).

One of the prominent scientists in the early years of the Republic was Osman Nuri Eralp (1884–1940) who worked in the fields of bacteriology and virology. His research on tuberculosis, tuberculin, cattle plague, cholera, syphilis, and milk derived infectious diseases were

among many of significance. Rıza İsmail Sezginar (1884–1963) was another important bacteriologist with significant contributions in the field of veterinary microbiology, infectious diseases and food-borne disease control. He was instrumental in the establishment of hygienic practices within the İstanbul Abattoir. Ahmet Şefik Kalaylı (1886–1976) was another scientist who reassured the public about the lack of human-cattle cross-infection and prepared a serum against the infectious agent of cattle plague.

The Republican era produced significant numbers of eminent Turkish microbiologists and since 1929 Bacteriology specialization is offered in Turkish academic institutions. Turkish Microbiology Institutions are now capable and equipped to produce world class training and research. Since the 1980s, molecular advancements have been adapted in Turkey for diagnostic purposes including reference laboratories. Every novel approach is immediately adapted and applied in Turkey in all areas of microbiology. Currently, there is an influx of overseas scientists who pursue training in Turkey in the field of microbiology.

Turkish Society for Microbiology (Türk Mikrobiyoloji Cemiyeti (TMC)) (http://www.tmc-online.org/)

Control of infectious diseases dating back to the early years of the 20th Century has been an important field of research in Turkey and gaining further momentum in the early years of the Republic of Turkey founded in 1923. The Turkish Society for Microbiology (TMC), established in 1931, is one of the oldest societies of Turkey. It has over 2000 members today and since its establishment has played a significant role in the advancement of microbiology in Turkey. TMC is an active member of many other international organizations (listed below) since 1980s and is a frequent host for international conferences, symposia and workshops including the IUMS-2008.

(1) FEMS (Federation of European Microbiological Societies)
(2) ESCMID (European Society of Clinical Microbiology and Infectious Diseases)
(3) IUMS (International Union of Microbiological Societies)
(4) WASPalM (World Association of Societies of Pathology and Laboratory Medicine)
(5) ECMM (European Confederation of Medical Mycology – until 2012)
(6) EFS (European Federation of Sexology)
(7) IFIC (International Federation of Infection Control)
(8) ELM (European Laboratory Medicine)
(9) FESCI (The Federation of the European Societies for Chemotherapy and Infections)
(10) UEMS (European Union of Medical Specialist)
(11) TMC has also links with the American Society of Microbiology (ASM).

TMC brings together scientists working in the fields of medical, veterinary, food, environmental, oral, pharmaceutical, cosmetic, molecular microbiology and biotechnology under its umbrella. It will continue to expand its interest groups and seek collaboration from other microbiology societies all around the World and continue to operate as a strong and active society in Turkey.

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Biography

Prof. Dr Nezahat Gürler graduated from the İstanbul University in 1972 majoring in Biological Sciences. She received further training in Clinical Microbiology becoming a resident specialist at the İstanbul University, Medical Faculty, Department of Clinical Microbiology. From 1980 to 1982 she was in Germany (Deutsche Akademischer Austauschdienst Fellowship) and conducted research at Göttingen, George August University, Microbiologie Institut, and Würzburg Medical Faculty, Department of Hygiene and Microbiologie. After her return to Turkey, she received her PhD (1986) and became a full professor in 1995 in the same medical faculty. Her main research interests are Clinical bacteriology, anaerobic infections, paediatric infections, paediatric febrile neutrophenia, antibiotic resistance, serotyping of Streptococcus pneumonia. She is member of the Society of Antimicrobial and Chemotherapy, Clinical Microbiology and Infectious Disease Society, AIDS Society, Paediatric Infections Society, Clinical Microbiological Society. She is currently the President of the Turkish Infectious Diseases Foundation as well as the President of the Turkish Society for Microbiology. She is also a member of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID).

The historic effect of plague

John Whitehall

School of Medicine
University of Western Sydney
Locked Bag 1797
Penrith South DC, NSW 2751,
Australia
Tel: +61 2 4620 3787
Fax: +61 2 4620 3891
Email: john.whitehall@uws.edu.au

As palaeopathology appears to have confirmed *Yersinia pestis* as the organism responsible for all three pandemics of plague (Justinian[1,2], Black Death[3] and Modern), arguments for the origin of the disasters have given way to debates on their effects. Records narrate the horrors but barely hint at historical results[4]. This article maintains each pandemic has had a lasting effect and, cumulatively, *Y. pestis* has been more influential than gun powder and could still be explosive.

Y. pestis is a pleomorphic gram-negative bacillus with characteristic 'safety pin' appearance with Giemsa stain. It has a remarkable life cycle through two disparate hosts: a cool flea and a warm rodent. Temperature, however, is not merely one challenge: it is probably one of the external factors that influence gene expression in the different hosts. For survival in the hostile intestine of the flea after being swallowed in rodents' blood, bacterial genes promote enzymes that cause the bacteria to aggregate in biofilm to protect from digestion and excretion[5]. When the biofilm expands to obstruct the oesophagus, hunger causes the flea to bite voraciously and spread the bacteria in regurgitation. Other genes permit the bacteria to digest proteins and lipids contained in blood.

In the warmer mammal, the phenotype changes from passive aggregation to virulent spread, aided by proteins that oppose host clotting and immunity. At first, the small numbers of *Y. pestis* that are injected into the host find refuge in de-activated macrophages in the dermis where they multiply and develop their capacity to avoid killing by neutrophils. They then spread to lymph nodes to induce pain and swelling, known as buboes, which have characterised the disease since its earliest descriptions and lent the name 'bubonic plague'. In the lymph system, metabolism by protein digesting enzymes is downregulated in favour of those digesting polysaccharides[6]. Some bacteria escape into the blood stream, leading to a septicaemic presentation while others travel to the lung and cause an overwhelming pneumonic form in which bacteria may be exhaled in droplets.

The bacteria may cycle from flea to rodent (or other small mammal) in enzootic manner and humans may be incidental victims but, on three grand occasions, the disease has taken hold in human populations with devastating, pandemic results.

Though the last pandemic began in 1894, its bacterial offspring are still causing problems, infecting over 2,000 humans each year, in increasing numbers and in places where the disease has been absent for decades[7]. Plague is a re-emerging disease[8].

The first pandemic

The first pandemic emerged in Egypt in 541 AD during the rule of the Byzantine Emperor Justinian[9] and spread around the Mediterranean to beyond Persia in the east and Gaul in the west. It recurred in waves throughout the following two centuries before acquiescing to forces unknown. The capital of Byzantium, Constantinople, was probably ravaged in each of the 18 onslaughts.

Christian elder, John of Ephesus, returning to Constantinople from Cairo as the disease travelled north through Palestine reports there were 'corpses with their putrefied bellies swollen, their mouths open, eyes staring, and arms stretched upward, that burst open in the streets with their pus running down like water' and there were so many they 'were loaded on ships and cast in the straits or like dung on the opposite shore'. To transport the bodies 'men and women were trodden down, and in the space between them the young and infants were pressed down, trodden with the feet and trampled down like spoilt grapes'[10]. He says 'Houses and farms were abandoned. Animals forgot their domestication. . .Crops of wheat were white and standing but there was no one to reap them and store the wheat. Vineyards, whose picking season came and went, shed their leaves, since winter was severe, but kept their fruits hanging on their vines, and there was no one to pick them or press them'[11].

The slaughter was so great in this first and then the second pandemic there were similar effects. With the loss of a third to a half of populations, labour became scarce and its value increased. Loss of productivity reduced governmental revenue which resulted in increased taxation. Rising prices fuelled inflation. Traditional working relations were challenged: slavery and serfdom were weakened by the rising value of labour, but sought to be strengthened by decree. The ranks of the military were reduced: there was less money for campaigns and even for self defence. Cultures and values were threatened. Some sought to appease divinities and other

ethereal forces, while others retreated to hedonism. Associated famines, wars and earthquakes made everything worse.

Before the first pandemic, the western half of the Roman Empire had succumbed to invaders from its north. Based in the capital of the surviving eastern half, Justinian aspired to resurrect the Empire, and battles had already been won. His forces had reclaimed parts of Africa from the Vandals, and had overcome Goths in the Italian peninsular, but much warfare was needed to restore the Empire. Lombards were laying claim to the peninsular from the north, Slavs were crossing the Danube and seizing the Balkans, and Persians and then Arabs thrusted from the east.

Byzantium succumbed. It failed to resurrect the Empire in the west, permitting the development of states whose independence foreshadowed modern Europe. It also failed to repel Persia from the East, preparing both for Islam.

How much did *Y. pestis* hollow-out Byzantium? How fundamental was it to weakness that permitted historic change? Stathakopoulos concludes it was, at least, catalytic[12].

The second pandemic

The second pandemic emerged in Crimea in 1346 and spread around and inland from the Mediterranean. Its first wave was catastrophic, but its effect was compounded by recurrent outbreaks of varying severity until it, too, mysteriously relented in 1741[13–15]. Narratives are as harrowing as those of the first but variations in presentation, rate of spread and infectivity have generated debate as to whether this 'Black Death' was really *Y. pestis* and not some kind of Ebola-like virus. DNA extracted from the pulp of teeth of skeletons from medieval burial sites has, however, revealed the presence of *Y. pestis* as it has from teeth pulp from Justinian cemeteries[16].

Though its long term effects are as debated as those of the first pandemic, there is consensus the recurrent outbreaks of plague reduced agricultural manpower in Western Europe and led to the end of manorial production: serfdom gave way to mobilised wage labour. Governments were able to restrict the process in Eastern Europe but in the West there emerged an independent 'yeoman' who could be described as the fore runner of the wage earner of the Industrial Revolution'.

Less measurable but of no less historical importance may have been a weakening in the religious culture in the West. Disillusion in established Catholicism as mediator with a punishing God, and disgust with the cowardice of many of its self-serving priests, encouraged a critique that was expressed in the Reformation and the reactionary birth of Protestantism. If social philosopher Max Weber is to be believed[17], the work ethic and financial determination of Protestanism would become responsible for the spirit for capitalism that went on to transform the world.

If plague lead to the Reformation, did its momentum lead to the questioning of all religion in the Renaissance? How much did this intellectualism contribute to the conviction that plague was an objective, contagious entity that could be actively combatted rather than passively accepted? Is Dols correct in arguing plague caused more suffering under Islam because of passive acceptance of divine will[18]? The Black Death altered the mind of man as much as his working relations.

The third pandemic

The third pandemic emerged in eastern China, reaching Hong Kong from 1894. From that port *Y. pestis* spread to distant parts of the world where its offspring continue to reside within various mammals, from whence to infect several thousand humans each year. Though narratives from this pandemic are more often expressed in the colder language of a medical profession at war with a now recognisable enemy, the horrors remain even if better understood. With Alexandre Yersin unveiling the bacteria in Hong Kong in 1894 and Paul Simon incriminating the rat and its fleas in 1896, the force of public health was unleashed on rat infested slums to the bewilderment and resentment of their inmates who rejected the germ theory in commitment to ethereal origins of disease. But, slums were razed, quarantines imposed, migration opposed and the disease was at least contained in Hong Kong. In India, the enthusiasm of the colonial government abated when opposition was so great it threatened civil war[19]. Perhaps 12 million Indians joined the hundreds of thousands of Chinese victims in those early years of the third pandemic. Did their deaths affect the history of the millions who remained?

The man who would lead the revolution that overthrew the Qing dynasty and establish the Republic of China in 1912, Sun Yat Sen, graduated from the College of Medicine for the Chinese in Hong Kong in 1892 when plague was emerging in southern China. He had been schooled in Hawaii and had studied in a Christian hospital in Canton before transferring to Hong Kong and, along the way, had become committed to political reform. He objected to the restrictions of traditional Chinese culture and was inspired by the scientific method (and political freedoms) he had observed in western culture[20]. The extent the germ theory and the application of public health influenced his determination for liberation from traditional bondages is unknown but he was intimately associated with the colony that was employing them against the plague that had broken out in his home territories.

Plague erupted again in China, in 1910, when the Republic was being born. It emerged in the north, in Manchuria, where three powers were contesting for natural resources and their management[21]. Chinese citizens died of plague under their infantile government. Western powers were weak and overstretched in their efforts to contain the epidemic, but the Japanese were strong. They had

already humiliated Russia in the war of 1905 and were in China in organised, determined force, and they controlled the outbreak in their regions with military precision. Did the weakness of their opponents in the face of the plague encourage the Japanese to believe they could invade China in 1937 and the rest of Asia in 1941? One lasting effect of that invasion of China was the exhaustion and subsequent defeat of its Nationalist government (the Kuomintang of Sun Yat Sen) by the Communists. Then, under Mao, millions, died. Did the flea set those dominoes off?

The future

Could the flea do it again? History shows *Y. pestis* can vary its presentation from the more indolent bubonic to the highly contagious pneumonic form. But, either way, antibiotics and insecticides are now available and science may prevail over grossest ignorance.

In 1967, I was the doctor in a refugee camp in South Vietnam after graduating the previous year with no knowledge of many things including plague. I assumed my patients with fevers, prostration and large suppurating lumps in their groins were suffering from staphylococci and wielded streptomycin, the only antibiotic we had. Plague, of course, is sensitive to that drug: No one died, no workers were infected and the contagion subsided[22].

As long as we have antibiotics to which *Y. pestis* is sensitive, and in sufficient amounts, we should not face a new Black Death. But resistance is being reported[23] and both Nature and human beings retain a capacity for rupturing medical supply in disasters and warfare.

Human beings also have an unlimited capacity for mendacity and, though most killings have been inflicted with chemicals or explosives, bacteria have been considered. There are anecdotes that plague was inflicted by catapulting corpses over 14th century city walls but spread by fomites is uncommon and fleas abandon cooling hosts. The Japanese air-force dispersed infected fleas over civilians in Manchuria in WW2 but the effects were limited[24]. In the Cold War, both US and USSR sought better ways to deliver and disperse plague as a weapon that would both demoralise and deplete their opponents. Reportedly, USSR ultimately developed strains that were resistant both to antibiotics and to certain vaccines, and factories that could produce them in tons until at least the 1990's[25]. Aware of the potential for disaster in 1970, WHO declared the effects of dropping 50 kg of aerosolised plague on a city of 5 million could be 150,000 cases of pneumonic plague with 36,000 deaths[26]. Does Russia still possess these facilities?

Could plague be inflicted in a terrorist attack? An expert committee in the US believed there was 'great concern' in 2000[27], over a year before terrorists demonstrated their ability to hi-jack airliners.

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Biography

John Whitehall is Professor of Paediatrics and Child Health at University of Western Sydney. He has worked in a number of developing countries that have inspired a deep interest in microbiology and history.

Influenza



John S Mackenzie[A,B,G], *Anne Kelso*[C] *and Alan W Hampson*[D,E,F]

[A]Faculty of Health Sciences, Curtin University, GPO Box U1987, Perth, WA 6845, Australia. Tel: +61 4 3987 5697

[B]Burnet Institute, 85 Commercial Road, Melbourne, Vic., Australia

[C]WHO Collaborating Centre for Reference and Research on Influenza (VIDRL), at the Peter Doherty Institute for Infection and Immunity, 792 Elizabeth Street, Melbourne, Vic. 3000, Australia. Tel: +61 3 9342 9310, Email: anne.kelso@influenzacentre.org

[D]School of Applied Sciences and Engineering, Federation University

[E]Influenza Specialist Group

[F]5A Lynne Street, Donvale, Vic. 3111, Australia. Tel: +61 3 9894 5049, Email: Interflu@bigpond.net.au

[G]Corresponding author. Present address: 20A Silver Street, Malvern, Vic. 3144, Australia. Email: j.mackenzie@curtin.edu.au

Influenza virus infection has probably shaped human populations for centuries, if not millennia. Novel influenza viruses formed by genetic reassortment of avian and mammalian viruses emerge sporadically and, if they have the necessary infectivity and transmissibility in humans, spread rapidly around the globe causing a pandemic. While mortality and morbidity varied widely between the pandemics of the last century, the loss of an estimated 50 million lives in the most devastating pandemic of 1918–1919 has had a lasting global impact. Here we briefly review the history and effects of influenza pandemics on the global human population and events of the time. Then we discuss some of the ways in which the experience of the 1918–1919 and later pandemics has influenced development of international influenza surveillance and global public health policy, the full impact of which will become apparent in future pandemics.

Early history of influenza

Influenza viruses evolved in aquatic birds. They remain there in a number of antigenically diverse forms as an enzootic reservoir[1] from which they occasionally cross into and become established in other species, including humans. Swine and horses are known to have been infected with avian influenza viruses and suggested as intermediate hosts for introduction to humans[1,2]. Their domestication together with that of ducks, thousands of years ago, could have provided opportunities for repeated introductions into humans.

Outbreaks of human influenza have been chronicled from the late Middle Ages in Europe and Britain, and although outbreaks as early as the 5th century in Greece have been described by some historians, most believe that descriptions predating 1520, and possibly later, should be treated with caution[3,4]. Many of these outbreaks were accompanied by high morbidity and sometimes mortality. However, it is unclear whether any of those recorded in the pre-Elizabethan period shaped world history although influenza reputedly contributed to the demise of Oliver Cromwell[2]. A possible exception to this was the suggestion that influenza was introduced to the Americas by Columbus's second voyage in 1492, and was the first of the Old World diseases to depopulate indigenous peoples in Hispaniola and beyond with many hundred thousand deaths[5]. Although this has been questioned, it seems probable that influenza contributed to the depopulation of the New World and other remote, immunologically naive communities including French Polynesia[6]. Similarly, the first recorded influenza outbreak in Australia in 1820 severely affected the indigenous population[7].

A disproportionate impact on indigenous populations in Australia[8], New Zealand[9] and elsewhere[10] persists to this day.

Pandemic influenza: the 1918–1919 pandemic

We now know that recent, and presumably previous, influenza pandemics involved viruses bearing surface antigens, haemagglutinin (H) and neuraminidase (N), to which most or all of the population lacked immunity. These surface antigen genes originate from the avian influenza gene pool, by adaptation or genetic reassortment with circulating human or animal influenzas, thus acquiring the ability to infect and be serially transmitted in humans. Spread is global and rapid, with high morbidity and often high mortality. The new pandemic virus then persists for decades as a seasonal infection by virtue of exceptional mutability.

Although numerous epidemics with significant morbidity and mortality occurred from the 16th century it is generally agreed that the first recorded outbreak meeting pandemic criteria is that of 1580 followed by those commencing in 1729, 1781, 1830 and 1889[3,4]. The pandemic of 1918–1919 was the most deadly influenza pandemic recorded with a recent estimate of 50 million or more deaths[11]. The pandemic was inextricably intertwined with World War I. It influenced the capacity to conduct hostilities[12] while its evolution may have been influenced by crowded conditions and soldiers' exposure to toxic gases[13]. Remarkably the genetic blueprint of the H1N1 pandemic virus has been determined and the virus reconstructed[14]. Nevertheless, unanswered questions remain: how and where the virus evolved and reasons for the unusual age distribution of deaths and usually three distinct waves of differing pathogenicity.

Mortality varied across countries with sparing attributed to affluence[15] and delayed introduction achieved by maritime quarantine[16]. Australia, where introduction was delayed until March 1919, had one of the lowest mortality rates, particularly in Tasmania[16]. Undoubtedly the pandemic had enormous social and economic impact in most societies but most attention was given to elucidating its cause, mode of transmission and toll, rather than to its social and cultural dimensions or consequences. It may never be possible to disentangle these from the consequences of the war. In Australia, where it stressed relations between the states, it was a catalyst for formation of the Commonwealth Department of Health[17]. There is, however, the intriguing possibility of one huge historical consequence. US president Woodrow Wilson suffered severe influenza absenting him from much of the WW1 armistice negotiations. This resulted in Britain and France imposing severe punitive conditions on Germany in the Treaty of Versailles which may have facilitated the rise to power of Adolf Hitler[18].

The virologic era

Influenza viruses were first isolated in the early 1930s, and shortly afterwards the first inactivated virus vaccines were produced and used by the allied forces in the Second World War. In 1947, a major antigenic change in the circulating Type A viruses resulted in vaccine failures. This kindled fears of another influenza pandemic like 1918–1919 and was a driver for an informal meeting of influenza experts during the 4th International Congress of Microbiology in Copenhagen in July 1947. They recommended to the Interim Commission of the World Health Organization (WHO) that an international surveillance program for influenza be initiated. Following adoption by WHO in September 1947, a World Influenza Centre was established at the National Institute for Medical Research, London, to work with regional laboratories and, later, national centres to study epidemiology and isolate new influenza strains[19]. In Australia, the Commonwealth Serum Laboratories were designated as a Regional Influenza Centre in 1951, upgraded to Collaborating Centre in 1992, until 2006 when the responsibility for the Centre was transferred to the Victorian Infectious Diseases Reference Laboratory. Today, there are 141 national centres in 101 countries and six WHO Collaborating Centres for Influenza in London, Atlanta, Melbourne, Beijing, Tokyo and Memphis, the latter concerned with the Ecology of Influenza in Animals. The efficacy of the network in surveillance was demonstrated during the 1957 and 1968 pandemics and the re-emergence of H1N1 in 1977[20].

The pandemics of 1957 (Asian) and 1968-69 (Hong Kong) were far milder than that of 1918–1919. The first was moderately severe globally and spread quickly, reaching Australia within 3 months of its origin in China[21], while the second was a 'smouldering' pandemic and had a delayed peak in many countries including Australia in 1970[22]. In addition to demonstrating the difficulty in producing vaccine in the necessary timeframe[23], these pandemics provided the viruses which allowed elucidation of the origins of pandemic viruses.

The Fort Dix episode

In 1976 a small influenza outbreak occurred among military recruits at Fort Dix, New Jersey, with severe respiratory disease in 13 soldiers and one death. The outbreak involved a combination of H3N2 virus and a virus related to early swine-like H1N1 strains derived from the 1918–1919 pandemic[24]. Concerned that it might signal a re-introduction of a 1918 pandemic-like virus, and in a divisive decision, the US Government planned to immunise the whole country; scientific and medical evidence did not support the decision. The program was stopped after an epidemiologic association between vaccination and increased incidence of Guillain-Barré Syndrome was

reported, something which has not been significant in subsequent surveillance[25]. The incident prompted the beginnings, in 1978, of formal pandemic preparedness planning by the USA and a handful of other countries, although WHO did not release its first pandemic planning document until 1999.

Avian influenza and recent pandemic concerns

The 1950s discovery that fowl plague was due to an influenza A virus, followed by the isolation of many additional avian influenza viruses, revealed the role of birds as a virus reservoir and the multiplicity of virus subtypes. H7 (responsible for fowl plague) and H5 can be highly pathogenic in domestic poultry, with exceptionally high mortality, and outbreaks of both subtypes have been recorded around the world, including Australia, since the 1950s[26]. Before 1997, recorded transmission of avian influenza to humans was rare, restricted to H7 viruses and almost always mild[27].

In 1997, 18 H5N1 cases in humans with 6 deaths signalled poultry infections in Hong Kong. Culling appeared to stamp out the virus; however it reappeared in Thailand and Vietnam in 2003, and has since spread widely in birds and caused over 660 human cases with more than 390 deaths across 16 countries[28]. Global concern over the pandemic potential of H5N1, so soon after SARS, reinvigorated pandemic planning nationally and internationally. An International Partnership on Avian and Pandemic Influenza was forged at a high-level Plenary Meeting of the United Nations (UN) General Assembly in 2005, and the UN Secretary-General, Kofi Annan, subsequently pledged that the UN would do all it could to ensure all countries, rich and poor, were protected and prepared for an avian influenza pandemic. A UN Systems Coordinator for Avian and Human Influenza (UNSIC) was appointed and International Ministerial Conferences on Avian and Pandemic Influenza (IMCAPI) were convened. These provided the impetus for a global response to emerging diseases and a One Health approach to manage zoonotic diseases[29]. In Australia, the National Action Plan for Human Influenza Pandemic and the Australian Health Management Plan for Pandemic Influenza have continued to be refined[30,31].

Strain sharing: a new challenge for international collaboration

The H5N1 zoonotic also prompted the Government of Indonesia in 2006 to raise an issue of international equity. Developing countries share potential pandemic influenza viruses, such as A(H5N1), with WHO to support the development of vaccines and other interventions but cannot afford to purchase those products for the protection of their own people. Indonesia stopped sending H5N1 viruses to international WHO laboratories in protest. Several other countries lent their support to the campaign.

In response, WHO convened a series of technical, intergovernmental and working group meetings between 2007 and 2011. Discussions were technically, legally and politically complex, spanning influenza virology, commercial vaccine development and production, intellectual property, and sovereign rights of nations over their biological materials[32]. Ultimately, the meetings produced a new framework, the *Pandemic Influenza Preparedness Framework for sharing of influenza viruses and access to vaccines and other benefits*, adopted by the World Health Assembly in 2011[33,34], a crucial feature of which is the sharing of vaccines, antiviral drugs and other benefits through donations and financial contributions to WHO by manufacturers.

Implementation of the Framework faces challenges, including the use of genetic approaches to vaccine development that bypass the need to share the viruses themselves. Regardless, the Framework has embedded the principle of equity in the activities of the WHO's Global Influenza Surveillance and Response System. The true test will come with the next pandemic.

First pandemic of the 21st century

In March 2009 a respiratory outbreak in Mexico was caused by a reassortant swine H1N1 virus more closely related to pre-1950s viruses than to recent strains. With initial indications of high mortality in Mexico and rapid spread through North America and beyond, the WHO issued escalating alerts until 11 June when a pandemic was declared. Many countries, including Australia, had already activated their pandemic plans and placed orders for many millions of doses of vaccine. In retrospect mortality was well below the early indications from Mexico and, while virus spread and major target groups were generally similar to previous pandemics, overall impact was moderate. Vaccine availability again lagged behind the peak of the outbreak, invigorating efforts to develop "universal" influenza vaccines that will protect against diverse subtypes, as well as novel delivery systems and faster production processes[35]. There were allegations that the WHO and national responses had been unduly influenced by commercial interests and it became clear that planning documents lacked the flexibility to tailor responses according to ongoing assessment of severity[36]. While these issues have been largely addressed, pandemic preparedness and public support may have been damaged[37].

The next pandemic

Today, H5N1 remains widespread in poultry and human infections continue. This large family of viruses has diversified genetically and antigenically, to the extent that a single vaccine would not protect against all circulating strains. In some H5N1 strains, only a

few further mutations may enable respiratory droplet transmission between mammals[38].

In 2013, a new threat emerged with human infections (>440) and deaths (>120) due to a novel H7N9 avian influenza in China[39]. Although this virus, unlike H5N1, causes a silent infection in poultry, human infections are strongly associated with exposure to live bird markets. These viruses have several features of adaptation to mammalian infection.

Although these and other novel influenza viruses pose a continuing pandemic risk, China's response to H7N9 exemplifies the benefits of the international networks and frameworks developed as a result of the 1918–1919 pandemic and later events outlined here. Early announcement of the outbreak, sharing of sequences and viruses, and openness about the epidemiology enabled rapid preparation of diagnostic reagents and candidate vaccine viruses by WHO laboratories and early interventions to limit spread. While sporadic influenza pandemics are an inevitable companion to human history, such international cooperation is the key to minimising their future impact on its course.

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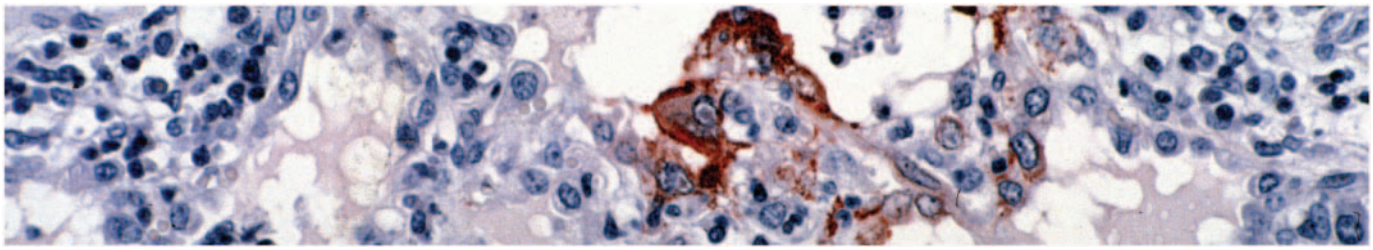
Biographies

Professor Anne Kelso, AO, BSc, PhD has been Director of the WHO Collaborating Centre for Reference and Research on Influenza (Victorian Infectious Diseases Reference Laboratory) since 2007. She serves on NHMRC Council and several other boards and advisory committees and holds an honorary professorial appointment in the Department of Microbiology and Immunology at the University of Melbourne where she is part of an NHMRC Program working on immunity to influenza viruses.

Professor John S Mackenzie, AO, BSc, PhD, FASM is a Research Associate and Professor of Tropical Infectious Diseases at Curtin University, Perth. He is also an Honorary Professor in the School of Chemistry and Molecular Biosciences at The University of Queensland, and Honorary Senior Principal Fellow at the Burnet Institute, Melbourne. He was chair of the World Health Organization (WHO) International Health Regulations Emergency Committee for H1N1 influenza in 2009, and currently serves as a member of the steering committee of the WHO Global Outbreak Alert and Response Network and the Technical Advisory Group of the WHO Asia-Pacific Strategy for Emerging Diseases. He is a former President of the Australian Society for Microbiology, Inc.

Dr Alan Hampson, BSc, MSc, MD(Hon), FASM, OAM is a virologist with 50 years experience working with influenza in research, vaccine development and as Deputy Director of the WHO Collaborating Centre for Reference and Research on Influenza. He contributed to Australian and WHO influenza pandemic preparedness planning and expert committees. Currently he is Chairman of the Influenza Specialist Group, Senior Editor of *Influenza and Other Respiratory Viruses* journal and adjunct Senior Research Associate, Federation University.



Impact of the 1918–1919 influenza pandemic on the New Zealand military and persisting lessons for pandemic control



Nick Wilson[A,C], *Jennifer Summers*[B,D] *and Michael G Baker*[A,E]

[A]Department of Public Health, University of Otago, Wellington, New Zealand

[B]Division of Health and Social Care Research, King's College London, UK

[C]Corresponding author. Email: nick.wilson@otago.ac.nz

[D]Email: jennifer.a.summers@kcl.ac.uk

[E]Email: michael.baker@otago.ac.nz

We aimed to briefly review literature on the impact of the 1918–1919 influenza pandemic on New Zealand's military forces in the First World War. Collectively, this work identified established risk factors, for example, relating to age, pre-existing chronic conditions, a relatively short time from enlistment to foreign service, and crowded conditions (e.g. in military camps and on a troop ship). But novel risk factors were also identified, e.g. larger chest size and relatively early year of military deployment. The historical experience also has some potential lessons for future pandemic control including: the need to minimise crowding in institutions and other settings; being prepared for future pandemic waves; and planning for 'protective sequestration' in some settings.

The New Zealand military forces did not escape the global spread of the 1918–1919 influenza pandemic, which also had a severe impact on the whole of New Zealand society[1]. We have estimated a total of 930 pandemic-attributable deaths among personnel who were in the New Zealand Expeditionary Force (NZEF)[2]. This number represented 5.1% of all NZEF deaths from the First World War (WW1), making pandemic influenza the main specific cause of disease deaths (ahead of such causes as malaria and dysentery[3,4]). The epidemic curve for pandemic deaths was more drawn out in the Northern Hemisphere compared with the Southern Hemisphere, where it was concentrated in the month of November 1918. Mortality rates also varied greatly by setting and were particularly high amongst troops in military camps[2,5]. Significantly higher mortality rates were found amongst NZEF personnel who were: aged 30–34 years, of Māori ethnicity (indigenous New Zealanders), from a rural background, and who left New Zealand for Europe in 1918.

More specifically, the mortality rate for Māori military personnel was 2.3 times higher (95% CI: 1.6–3.1) than for those of European ethnicity (rates of 2.5 vs 1.1 per 100 personnel[6]). This unequal burden for Māori was also present for civilians in two subsequent pandemics, including the 2009 one. New Zealand military personnel of Pacific peoples ethnicity (e.g. Niue and the Cook Islands), also had a raised mortality rate in 1918, but the absolute number of deaths was small and the difference was not statistically significant.

To help understand the risk factors for death from pandemic influenza in the NZEF we conducted a case-control study using individuals situated in the Northern Hemisphere during the

pandemic period ($n = 218$ cases, $n = 221$ controls)[7]. In the fully adjusted multivariable model, the following were found to be significantly associated with increased risk of death from pandemic influenza: 'age (25–29 years), pre-pandemic hospitalisations for a chronic condition (e.g. tuberculosis), relatively early year of military deployment, a relatively short time from enlistment to foreign service and having a larger chest size (e.g. adjusted odds ratio for 90–99 cm vs <90 cm was 2.45; 95% CI = 1.47–4.10)' (p. 329)[7]. Some of the findings in this study were consistent with previous research on risk factors (such as chronic conditions and age groups); however, others appear novel (e.g. larger chest size). In contrast, this study found no significant associations with military rank, occupational class at enlistment and rurality at enlistment.

One of the worst discrete outbreaks from the pandemic, in terms of high mortality rates for the NZEF personnel, occurred on a troop ship (*Tahiti*, July 1918). In this outbreak the mortality risk was increased amongst those aged 25–34 years[8]. Being accommodated in cabins rather than sleeping in hammocks in other areas was also associated with increased mortality risk (rate ratio 4.28, 95% CI: 2.69–6.81). Similarly, being in a particular military unit, the 'field artillery' (who were probably housed in cabins), was also associated with increased risk (adjusted odds ratio in logistic regression 3.04, 95% CI: 1.59–5.82). The poor ventilation of the cabins along with crowding may therefore have played roles in the mortality risk in this outbreak.

Relevance for today?

The 1918–1919 influenza pandemic is still probably the greatest natural disaster in recorded history in terms of loss of human life. It is therefore important to understand the risk factors, some of which may be modifiable, that determined vulnerability during this event. The detailed military records for the First World War period at an individual and group level, allow for the exploration of such risk factors (as with the various studies detailed above). But there is still much to learn and in particular, the strange age-distribution of mortality risk still needs to be better explained (although it may relate to exposure to a previous pandemic[9]).

Reflecting on the historical experience of how the military authorities responded to this pandemic may also be useful in guiding future pandemic planning and response. We briefly discuss some possibilities below.

The need to minimise crowding in institutions and other settings. The 1918–1919 pandemic involved relatively high death rates in the military training camps in New Zealand[2], and it seems likely that crowding in these camps was a likely contributing factor. The situation in the Featherston military camp (in the lower North Island of the country) was probably made worse by some of the men using tents for accommodation, many of which had been blown down during a severe storm[5]. Furthermore, the crowding on the troop ship *Tahiti* is likely to have contributed to the particularly high mortality rate in this outbreak.

In planning for future pandemics, military authorities could therefore consider plans to rapidly reduce personnel numbers in crowded or high population density settings such as in some military camps and on non-essential military vessels. Such an approach could also apply to boarding schools, university hostels and even low security risk prison inmates. Of course crowding is good to avoid in terms of preventing other infectious diseases in the modern era as well[10].

Being prepared for future pandemic waves. During the First World War, a mixed bacterial vaccine was delivered to some of the New Zealand troops. Somewhat surprisingly, given the state of vaccine technology at the time, it seems to have been effective in reducing mortality rates from the 1918–1919 pandemic according to a modern analysis[11]. Unfortunately the use of this vaccine was not continued and so an opportunity to reduce mortality from the subsequent February/March 1919 wave in Europe was not realised. The epidemic curve for this subsequent wave is detailed in figure 2 of Summers *et al*.[2].

Fortunately in the modern era it may be possible to institute a range of control measures after wave one of an influenza pandemic. These measures include vaccination for the pandemic strain (potentially prioritising vaccination towards high-risk groups identified from surveillance of seasonal influenza and previous pandemics), restocking supplies of antivirals (if appropriate), increasing coverage of pneumococcal vaccination for vulnerable groups and intensifying mass media campaigns that promote hygiene and other measures to reduce transmission. At least for New Zealand, there appears to be substantial scope for improving respiratory[12] and hand hygiene[13].

Planning for 'protective sequestration' in some settings. This particular control measure refers to preventing human movement at a border or area boundary so as to limit the spread of infection into such an area (it differs somewhat from *quarantine* – where the focus is on preventing spread from potential cases who may be incubating disease, and *isolation* where the focus is on preventing spread from identified cases). Such a control measure failed in 1918 in the case of the troop ship *Tahiti* as the measures to prevent disease spread from the shore or other ships were inadequate. Promptly closing military camps to try to protect them was not

attempted in New Zealand, even though this approach was successful for schools in New Zealand[1] and for a township[14]. Internationally, some military installations closed themselves off and successfully kept out the pandemic[15], including a naval base in San Francisco and American Samoa (the site of a US naval base). Iceland also successfully protected one part of the country from the pandemic with travel restrictions[16].

At a national level, New Zealand also failed to keep the pandemic out of the country – in contrast to Australia (at least in 1918), and some other parts of the Pacific[17].

In a modern age with high-speed air travel, controlling pandemic spread is likely to be substantially harder (indeed the 2009 pandemic reached New Zealand fairly quickly[18]). Furthermore, available border screening measures do not appear to be particularly effective for detecting influenza in arriving passengers[19,20]. Nevertheless, there could be further consideration of options for island countries such as New Zealand (and for smaller populated islands in New Zealand's territorial waters) around highly systematic use of border control measures and protective sequestration. Such planning may inform protection against other pandemics, for example, arising from possible genetically engineered bioweapons.

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Biographies

Nick Wilson trained as a public health physician and now works as an associate professor in public health at the University of Otago, Wellington, New Zealand. He has worked on a wide range of infectious disease topics, but particularly the epidemiology and control of pandemic influenza and enteric diseases such as campylobacteriosis.

Jennifer Summers was awarded her PhD in Public Health and Epidemiology in early 2013 from the University of Otago, New Zealand. She works as a Post-Doctoral Research Fellow in Medical Statistics at King's College, London, United Kingdom. Jennifer has research interests in historical epidemiology, military history, pandemic preparedness, disease modelling (including transmission dynamics), health workforces and policy, and statistical methodologies.

Michael Baker is a Professor of Public Health at the University of Otago, Wellington, New Zealand. He has a long-term research interest in infectious disease, particularly seasonal and pandemic influenza. His work in this area has been supported by research grants from the New Zealand Health Research Council and the United States Centers for Disease Control and Prevention.

The Gallipoli gallop: dealing with dysentery on the 'fringes of hell'



Steve Flint[A,C], *Glyn Harper*[A] *and Nick Wilson*[B]

[A]Massey University, Palmerston North, New Zealand

[B]University of Otago, Wellington, New Zealand

[C]Corresponding author. Email: S.H.Flint@massey.ac.nz

The Gallipoli campaign is a well recorded piece of New Zealand history, particularly remembered every year on ANZAC Day. Dealing with the seemingly hopeless task of facing an enemy in well entrenched positions on higher ground was made even more challenging by the appalling conditions the soldiers had to face in terms of addressing basic survival needs and dealing with infections. A particularly burdensome part of the latter was dysentery.

Dysentery is an enteric infection frequently caused by *Shigella* bacteria, typically associated with unhygienic water supplies or contaminated food in developing countries. It is also caused by *Entamoeba histolitica*, an amoeba, but this is more common in the tropics. The type of dysentery facing the New Zealand troops in Gallipoli was most probably bacillary dysentery (or shigellosis) caused by the *Shigella* bacterium, most likely spread by contaminated water and/or food (with flies also playing a key role in this contamination[1].

There are four different species of *Shigella*: *Shigella sonnei*; *Shigella flexneri*; *Shigella boydii*; and *Shigella dysenteriae.* The first is the most common and the last produces the most severe symptoms. Shigellosis is typically associated with watery stools (diarrhoea), which may include blood and mucus. This is associated with abdominal pain, tenesmus, fever and dehydration. Constipation and fatigue may also develop. The symptoms normally appear one to three days following infection and can persist for up to one week. According to the WHO, there are approximately 120 million cases of severe dysentery annually around the world, mainly in developing nations and generally affecting children.

Treatment is based on coping with the dehydration by drinking water; however, getting clean water would have been a challenge for the soldiers at Gallipoli. Getting enough water to combat dehydration is critical. In severe cases, where rehydration is not possible, dysentery can be fatal. At least 200 of the deaths among the New Zealand soldiers at Gallipoli were from infectious diseases such as dysentery and typhoid[2]. 'Lack of clean water and sanitation in the trenches meant that diarrhoea and dysentery were common place, for the better-fed officers as well as the troops'[3].

While there is evidence to show that the New Zealand soldiers at Gallipoli generally had sufficient food in terms of energy, the military rations were deficient in some micronutrients[4]. In particular the low intake of vitamin A may have contributed to the risk of becoming infected with dysentery and dying from it (given the role of vitamin A in immune function and protecting against infectious disease mortality[5]). Furthermore, there were difficulties in getting sufficient water for the troops, largely due to the need to bring in the water across difficult terrain. 'There was always a shortage of water and the possibility of no water at all. One pint of water a day was the usual issue'[6]. The official ration for New Zealand soldiers was somewhat larger at two quarts (2.3 litres) a day, but it still had to be used for all purposes: drinking, cooking and washing.

Most went to make tea. As one New Zealand soldier wrote: 'water is worth its weight in gold here'[4].

As the campaign progressed, the summer heat with the hordes of flies that came with it, when combined with the open latrines, inadequate diet and limited water supplies contributed to extremely high rates of dysentery on Gallipoli. By the end of May 1915, as the weather warmed and the flies appeared, the first isolated cases of dysentery occurred[7]. By July a particularly virulent form of dysenteric diarrhoea had spread through the whole allied army but was most serious at ANZAC Cove because of closely packed conditions there. The affliction was colloquially known as 'the Gallipoli trots' or 'the Gallipoli gallop'[7]. By August 1915, just prior to the great allied offensive, 80 percent of the troops at ANZAC and Cape Helles had it[8].

This high prevalence of dysentery continued well into October 1915 until the cooler weather arrived. That month alone, 5000 men were being evacuated from Gallipoli each week through illness, with the most prevalent cause being the 'Gallipoli Trots'[9].

The whole situation was exacerbated by the preparation of food by individual soldiers in the trenches. Clearly there were issues in dealing with basic hygiene[4]. The following quote, paints a clear picture of what the conditions for food preparation were like, 'The baneful system of individual cooking, then prevalent, would have ruined any ration however good; every man cooked for himself, every dug-out became a midden of fly contaminated food and food refuse'[10]. Flies were referred to in frequent reports, and they would have almost certainly helped in the spread of the disease.

The following excerpts from the diary of Major William McAra[11] help paint the picture of the scene at Gallipoli. McAra was a doctor from Gore, Otago, who arrived on Gallipoli with the Fifth Reinforcements in August 1915. By November he was feeling the effects of the restricted diet.

> *Been sick for three days – never ate a bit, felt savage & wanted to be left alone, just too much meat & tea & no potatoes or green vegetables.*
> 6 November 1915

Two days later McAra was incapacitated with dysentery. He wrote in his diary:

> *Was very ill – had abdominal pain all afternoon which became so acute that hadn't time to dodge for latrine with disastrous results. Sent for Sergeant & got him to carry me up on stretcher to 16th Casualty Clearing Station. There headache seemed worse & while they gave me bromides without avail while dysentery went on increasing. Had no sleep all night.*
> 8 November 1915

Next day, with a temperature of 38.9°C and constant bowel pain, McAra was evacuated from Gallipoli.

Fortunately in subsequent campaigns in the First World War the enteric disease burden for New Zealand soldiers was much less. Innovations such as typhoid vaccine probably helped[12], but there was also more scope for providing water and better sanitation systems on the Western Front. Even so, for many in the front line trenches during the rest of this War, there were persisting threats to hygiene in terms of mud and rats.

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Biographies

Steve Flint is Professor of Food Safety and Microbiology and director of the Food Division of the Institute of Food Nutrition and Human Health at Massey University. Steve leads a team of postgraduate research students studying a variety of food safety and quality issues with an emphasis on understanding biofilm development and control. Approximately half of these projects are associated with the dairy industry. Future research will focus on bacterial interactions in biofilms and mechanisms of biofilm dispersion. Steve has more than 100 scientific publications and more than 100 presentations at national and international scientific conferences. He lectures in food safety and microbiology and does consultancy work for food manufacturers. Steve is a Fellow of the New Zealand Institute of Food Science and Technology, president of the New Zealand Microbiological Society and a certified food scientist with the Institute of Food Technology.

Glyn Harper is Professor of War Studies at Massey University in Palmerston North. He is Massey's Team Leader for the Centenary History of New Zealand and the First World War project and is writing one of the first volumes. A former teacher, he joined the Australian Army in 1988 and after eight years transferred to the New Zealand Army, where he rose to the rank of lieutenant colonel. Glyn was the army's official historian for the deployment to East Timor and is the author of 13 books for adults. These include: *Kippenberger: An Inspired New Zealand Commander*; *In the Face of the Enemy: The complete history of the Victoria Cross and New Zealand*; *Dark Journey: Three Key Battles of the Western Front*; *Images of War: World War One: A Photographic Record of New Zealanders at War 1914–1918*; *Letters from Gallipoli: New Zealand Soldiers Write Home*; and his most recent, *The Battles of Monte Cassino. The campaign and its controversies.* Glyn also enjoys writing books for children. Some of his children's books include *The Donkey Man*, *My Grandfather's War* and *Le Quesnoy. The Town New Zealand Saved*. Glyn's eighth book for children, *Jim's Letters*, was released in March.

Nick Wilson trained as a public health physician and now works as an associate professor in public health at the University of Otago, Wellington, New Zealand. He has worked on a wide range of infectious disease topics, but particularly the epidemiology and control of pandemic influenza and enteric diseases such as campylobacteriosis.

Losses related to infectious diseases in the Turkish army during World War I

Sadık Emre Karakuş

Turkish Ministry of Defence,
Archive Command
Ankara, Turkey
Email: sadik.karakus@msb.gov.tr

Ahmet C Baş ustaoğlu

Eastern Mediterranean University
Faculty of Pharmacy
Department of Microbiology
Famagusta, Turkish Republic of
Northern Cyprus
Email: basustaoglu@gmail.com

The lengthy period that encompasses the Balkan War (8 October 1912 to 29 September 1913), followed by WWI (28 July 1914 to 30 October 1918) fought by the Ottoman Empire and the subsequent Turkish War of Independence initiated by the secret arrival of the great leader Mustafa Kemal (in the Republican era Atatürk) at the Black Sea town of Samsun on 19 May 1919 came to an end with the signing of the Mudanya Agreement on 11 October 1922 and formally terminated with the Lausanne Agreement on 24 July 1923. Turks bravely fought at different fronts over three different continents and by the end of a decade of war the losses amounted to 1,000,000 lives as well as 4,000,000 square meters of the Ottoman Land[1].

Reasons for the failure of Ottoman Forces with around 3,000,000 conscripts at many fronts, and the signing of the ceasefire agreement at Moudros (The Armistice of Moudros, 30 October 1918) as the defeated party are still subject of much investigation and analysis for many historians and researchers, today. There have so far been political, military and economic explanations. However, none of these investigations included infectious diseases as a possible explanation for the heavy losses suffered by the soldiers throughout these wars. Detailed records and statistical data related to infectious diseases and their impact on the final decades of Ottoman military history have been so far unavailable. Similar to the allies, the Turkish side also started compiling records related to the losses and casualties immediately after WWI; however, records based on different sources compiled since 1919 are still far from representing the real cause of deaths. This fact is clearly presented in a book by Hikmet Özdemir[2] who describes in detail the losses suffered by all parties.

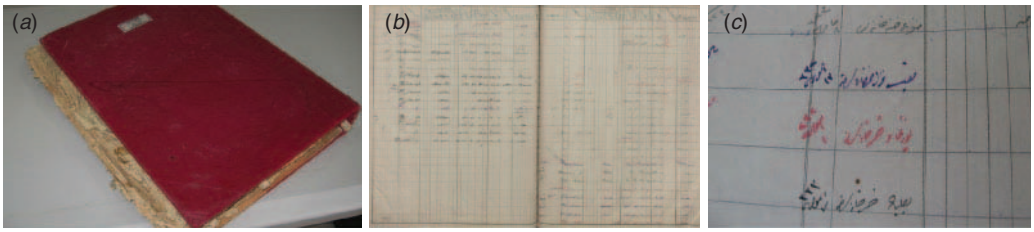

Figure 1. (a) *Record Book of Losses*, (b) Page details of the *Record Book of Losses*, (c) Martyrdom recorded in red, infectious disease-related deaths recorded in blue and other causes recorded in black ink (kept in Ottoman script: pre-Republican era official script).

Table 1. World War I major causes of death in the Ottoman Army.

Cause of death	Total loss		Gallipoli		Caucasus	
	Number	%	Number	%	Number	%
Infectious diseases	185,619	43.80	28,286	23.94	43,210	49.30
Other diseases	83,257	19.65	13,865	11.74	15,987	18.24
Other causes	154,903	36.55	75,985	64.32	28,454	32.46
Total	423,779	100	118,136	100	87,651	100

Table 2. Deaths related to infectious diseases.

Cause of death	Total loss		Gallipoli		Caucasus	
	Number	%	Number	%	Number	%
Lung infections	22,487	12.11	4,533	16.03	3,570	8.26
Other gastrointestinal infections	65,092	35.07	8,658	30.61	16,646	38.52
Urinary tract infections	11,935	6.43	1,385	4.90	2,680	6.20
Other infectious diseases	4,539	2.45	751	2.66	1,507	3.49
Smallpox	181	0.10	14	0.05	24	0.06
Diphtheria	92	0.05	1	0.00	3	0.01
Dysentery	30,696	16.54	8,557	30.25	4,642	10.74
Infection of the joints	224	0.12	31	0.11	63	0.15
Syphilis	65	0.04	9	0.03	9	0.02
Influenza	2,415	1.30	327	1.16	538	1.25
Cholera	1,750	0.94	31	0.11	339	0.78
Meningitis	951	0.51	272	0.96	58	0.13
Sepsis	836	0.45	303	1.07	141	0.33
Malaria	11,291	6.08	786	2.78	1,599	3.70
Fever	10,616	5.72	1,332	4.71	4,126	9.55
Tetanus	305	0.16	96	0.34	105	0.24
Typhoid	1,910	1.03	148	0.52	881	2.04
Typhus	17,016	9.17	608	2.15	5,874	13.59
TB	3,218	1.73	444	1.57	405	0.94
Total	185,619	100	28,286	100	43,210	100

The aims of present analysis can be grouped under two headings:

1. Aspects of military history

In this section, full details of 423,779 deaths during the WWI, dates and places of death will be communicated.

2. Aspects of medical history

In this section, the impact of infectious diseases on the army and civil population behind each front as well as the relationship between the war environment and emergence of infectious diseases will be discussed.

The investigation presented here has been carried out with the approval of the Turkish Ministry of Defence (MSB) as an evaluation of data generated by the MSB-Archives Division regarding war-related losses[3]. The causes of 423,779 deaths from written records were analysed (transcriptions from Ottoman into current Turkish language were carried out) and 587 different causes were entered into the system database. The aim of the *Loss Documentation Project* is to identify all combat deaths since the Crimean War (1853–1856). The major source of reference is an Ottoman collection of 67 hand-written registers of 400 pages in alphabetical order, with each page covering 25 records and different ink colours

Table 3. Deaths related to other diseases.

Cause of death	Total loss		Gallipoli		Caucasus	
	Number	%	Number	%	Number	%
Respiratory tract disease	230	0.28	123	0.89	101	0.63
Allergy	290	0.35	23	0.17	35	0.22
Intestinal disease	215	0.26	36	0.26	68	0.43
Eating disorders	22,137	26.59	2,252	16.24	6,282	39.29
Urinary tract disease	64	0.08	10	0.07	8	0.05
Surgery related	938	1.13	178	1.28	94	0.59
Other	765	0.92	45	0.32	81	0.51
Disease (relates to deaths recorded as a result of 'disease' and these 63.7% disease-related deaths have to be distributed into the right categories, e.g. infectious disease-related deaths)	53,070	63.74	10,285	74.18	8,002	50.05
Internal disease	1,162	1.40	51	0.37	547	3.42
Heart disease	1,939	2.33	412	2.97	316	1.98
Bleeding	276	0.33	35	0.25	42	0.26
Gangrene	1,131	1.36	226	1.63	231	1.44
Cancer	62	0.07	13	0.09	11	0.07
Complications	65	0.08	3	0.02	11	0.07
Neurological	305	0.37	66	0.48	42	0.26
Disease without diagnosis	110	0.13	0	0.00	0	0.00
Orthopaedic	197	0.24	39	0.28	51	0.32
Psychological	170	0.20	22	0.16	27	0.17
Burns	27	0.03	16	0.12	0	0.00
Intoxication	104	0.12	30	0.22	38	0.24
Total	83,257	100	13,865	100	15,987	100

marking different causes of death (Figure 1). While it is estimated that the number of deaths will be above 700,000 once the Project is complete (the margin of error related to different causes of death will remain around ±2), Gallipoli and Caucasus fronts were selected to form case studies for comparative reasons.

Findings

A comparison of 423,779 deaths sorted in terms of causes at two major war fronts, Gallipoli and Caucasus respectively, is summarised in Table 1 and the details of the disease-related deaths are given in Tables 2 and 3.

(1) Out of the 423,779 deaths 43.8% (185,619) were caused by infectious diseases, 19.6% (83,257) were due to other disease-related causes and the remaining 36.5% (154,903) had other war-related causes.

(2) Interestingly, Ottoman Empire was the only country in WWI, which had an exceeding number of disease-related deaths over those combat related.

(3) Deaths at combat were recorded as *Martyrdom* (for Moslem Ottoman soldiers) and *Killed in Action* (for non-Moslem Ottoman soldiers) with a ratio of 25.9% (109,815). The percentage of deaths reaches a substantial 34.5% when undocumented deaths marked as 'unidentified' due to drowning, freezing and so on are also taken into consideration.

(4) The first three major causes of death due to infectious diseases appear to be other gastro-intestinal infections (35%), dysentery (16.5%) and respiratory tract infections (12.1%).

(5) In Gallipoli, deaths related to infectious diseases were identified as 23.9% (28,886), whereas in the Caucasus, it stood at 49.3% (43,210). Intense war conditions experienced in Gallipoli battle-fields were the major cause of deaths ahead of infections.

(6) At Gallipoli, respiratory tract infections (16%) and dysentery (30.2%), whereas in the Caucasus region gastro-intestinal infections (38.5%) and typhus (13.5%) were the major causes of death.

(7) Other non-infectious diseases, which played a role in wartime deaths, were scurvy, malnutrition and anaemia constituting 30% of the deaths over other disease-related causes (Table 4).

Discussion

In WWI, one in every three soldiers in the Ottoman Army lost their lives due to malnutrition and disease. The whole picture related to

Table 4. Deaths related to causes other than infectious diseases.

Cause of death	Total loss		Gallipoli		Caucasus	
	Number	%	Number	%	Number	%
Martyrdom[A]	98,223	63.39	54,362	71.54	15,993	56.21
Corpse missing[B]	34,022	21.96	16,957	22.32	7,786	27.36
Killed in action[C]	11,592	7.48	3,422	4.50	672	2.36
Death of unknown reason[D]	6,541	4.22	670	0.88	2,670	9.38
War conditions[E]	2,651	1.71	210	0.28	1,136	3.99
Wound related[F]	1,270	0.82	295	0.39	76	0.27
Accident	532	0.34	66	0.09	105	0.37
Capital punishment	72	0.05	1	None	10	0.04
Murder	52	0.03	2	None	6	0.02
Total	154,955	100	75,985	100	28,454	100

[A]Ottoman record books refer to direct *Martyrdom* or *Martyrdom* as the result of the battle field wounds.
[B]Refers to losses without corpse recovery (no evidence of decamp or prisoner of war): mostly includes casualties at the Gallipoli and Caucasus fronts.
[C]Ottoman record books refer to non-Muslim soldiers who were killed in action.
[D]Refers to deaths under the category of 'without cause' (e.g. death in sleep (60), pronounced dead at the arrival to the hospital (4,202), death due to the arrival at the hospital with severe wounds (1,120), sudden death: e.g. heart attack (56), natural death (679)). It is not clear if any of those were related to disease caused ones.
[E]Refers to deaths such as: frozen to death (1,815), drowning (191), sun stroke (147) and due to hardship during translocation (480).
[F]Wound-related deaths (wounds other than the ones encountered at the battle field).

the Balkan War, WWI and Turkish War of Independence (19 May 1919 to 24 July 1923) indicates 22.5% losses due to infectious diseases and 4.62% from other disease-related causes. In the chain of command, one fourth of the officers lost their lives due to an infectious disease. In the Balkan Wars and WWI, the number of infectious-disease related deaths was higher but this rate decreased during the Turkish War of Independence.

In his memoirs[3] Prof. Dr Tevfik Sağlam (in the Ottoman era Tevfik Salim) describes the adverse conditions experienced during WWI:

> *That the armed forces succumb to infectious disease in such a short time shows how poor sanitary conditions have been. This situation is the result of malnutrition, lack of protection against severe weather and duty under extreme conditions. It is not possible for soldiers to survive prolonged malnutrition and low-calorie diet. Soldiers who lose weight every month can succumb even to flu and easily die within a few months. Skeletal statuses of the soldiers at arrival in hospitals are indicative of these facts and this condition of prolonged malnutrition will easily destroy the armed forces before they are hit by any disease. Improved conditions can only be achieved if regular and adequate food intake of the soldiers is ensured as well as preventative measures in public health. The major cause of these difficult conditions is the lack of senior officers and medical doctors who themselves have been struck by the disease.*

The Ottomans entered WWI without any preparatory steps and preventative measures, hence the resulting miserable conditions. Medical aspects of the war were not perceived important when the war started. Evacuation routes for the sick and wounded were not planned; however, Turkish medical teams solely with their extraordinary efforts and self-sacrifice attended to most casualties as described in the memoirs of Military General and Medical Doctor Prof. Tevfik Sağlam. They even produced vaccines against typhoid fever, typhus, cholera and smallpox under primitive conditions in Anatolian towns (Sivas, Kayseri and Erzurum) and administered these not only to soldiers but also to the general public. They implemented public health measures and prevented greater disasters from happening, and these practices successfully reduced the percentages of death and disease from 1916 onwards[4].

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Biographies

Prof. Ahmet C. Baş ustaoğlu (MD) is a graduate of Gülhane Military Medical Academy (GATA), Ankara. Following his graduation in 1985 he served at the Turkish Naval Forces for 2 years as a medical practitioner. From 1987 until 1990 he returned to GATA for his specialisation in Medical Microbiology. Following his specialisation in the field he served in the Turkish Army for two years and subsequently returned to academia as Associate professor in 1995. From1995 to 1996 he was in the USA for his sabbatical at the Duke University and on his return to Turkey he was appointed as full professor at GATA and serving as the Discipline Director at the Department of Microbiology. He has recently retired from the Turkish Armed Forces (2013) and took up a new academic position at Eastern Mediterranean University, Faculty of Pharmacy, Department of Microbiology, Famagusta, Turkish Republic of Northern Cyprus. He has over 150 peer-reviewed publications. He has received awards on his translation work from English to Turkish for *Manual of Clinical Microbiology* (2009), *Medical Microbiology* (2011) and *Clinical Microbiology Procedures Handbook* (2014) from the Turkish Academy of Sciences.

Mr Sadık Emre Karakuş (BA, MA) is a graduate of Fırat University, Faculty of Science and Arts, Department of History. He completed his post-graduate work (MA) on the assessment and translation (from Ottoman to Turkish) of the Edirne Sharia Records No: 270 related to the years 1802 and 1803. He is currently a PhD candidate at the same University as well as working at the Turkish Ministry of Defence, Archive Command in Ankara, Turkey as an expert in History. He has publications related to History of Ottoman cities, Turkish Military History and Medical History. He has expertise in the Ottoman language and script which is invaluable for translation of records belonging to Ottoman the era (pre-Republican era of Turkey).

The fight against typhus in the Ottoman Army during World War I

Ahmet C Başustaoğlu

Eastern Mediterranean University
Faculty of Pharmacy
Department of Microbiology
Famagusta
Turkish Republic of Northern Cyprus
Email: basustaoglu@gmail.com

Sadık Emre Karakuş

Turkish Ministry of Defence
Archive Command
Ankara, Turkey
Email: sadik.karakus@msb.gov.tr

Five major outbreaks were encountered in the armed forces: (1) typhoid fever; (2) typhus (*Rickettsia* spp.); (3) *Borrelia reccurentis*-induced relapsing fever; (4) dysentery; and (5) cholera. Infectious diseases had a devastating effect on Turkish soldiers and in particular typhus was one of the most recognised and widespread diseases throughout Ottoman Empire.

As outlined in our previous article during WWI, Ottomans were fighting not only against the allies but also severe weather conditions and infectious diseases and as a result deaths from such causes exceeded the number of deaths at combat. During the war, 62% of the deaths were due to diseases, including 43% from infectious diseases, as well as a lack of expert medical teams and effective drugs. Health Minister of the 3rd Army Prof. Dr Tevfik Salim (in the Republican era Tevfik Sağlam, hereafter in the text Tevfik Salim (Sağlam) explained these tragic losses in terms of four main reasons: (1) seasonal extremes; (2) transport and travel difficulties; (3) lack of proper clothing; and (4) malnutrition. Even a much useful remedy such as Neosalvarsan, which was effective against the *Borrelia reccurentis*-induced relapsing fever, had become unavailable. It was difficult to dispatch vaccines since transport from İstanbul stopped at a certain point and in order to reach the combat field, motorcars (if possible) or horses and mules were needed (Figure 1). Medical personnel did not have any medication or vaccines but only had the practical knowledge gained from their seniors at the Gülhane Military Medical Academy as well as through their experiences during the Balkan War. They were fully aware of the urgency to

Figure 1. Medical Arm of the Arburnu Şimal Group on its way to provide medical supplies.

ensure public health first and also the need to increase awareness and information regarding the diseases among the institutional staff. However, the area to be covered was vast and the means of communication were limited. The fight against the five diseases by under-resourced Turkish medical personnel, in particular eradication efforts against the causative agent carrying vectors were recognised internationally and has a place in the world military history[1–13].

First ever success against *Rickettsia* and *Borrelia* infections was achieved after then Lieutenant Colonel Dr Tevfik Salim (Sağlam)'s appointment to the 3rd Army in March 1915 (Figure 2). Because of typhus senior commanders of the 3rd Army were dying in hospitals and the Ottoman Army Health Commander Süleyman Pasha was also at the hospital. Dr Tevfik Salim (Sağlam)'s most significant observation was the shared room experience of patients infected with different diseases. It was known that both *Rickettsia* and *Borrelia* infections were introduced by the vectors that had to be eradicated. However, there was material shortage and also inadequate hospital wards, bedding, bandages and disinfectants as well as vaccines.

Soldiers reached the war region on foot and came into close contact with peasants on the way. Both the soldiers and village folk were infested with lice, as the soldiers found no washing facilities on the way to the warfront or when they arrived at their posts. Both cities and villages were in chaotic conditions where soldiers and the members of public shared the same shelters. In the early years of war, conditions were conducive to vector disseminated diseases, and the Turkish doctors were fully aware that these circumstances led to lice-disseminated diseases but lacked the infrastructure to rectify the situation. Disinfection equipment was almost non-existent and at the beginning of the WWI, in the 3rd Army possessed only two fixed (located in Erzurum and Trabzon) and two mobile autoclaves. There was no real disinfection gear, and no sterilisation ovens and steam chambers. It was not clear whether mobile autoclaves could be transported in winter times and if they would be functional at their place of arrival. Typhus rapidly became an epidemic under these optimal conditions. The war had started with bloody battles that lasted for 3 weeks followed by a month of slowdown. In 1914 from October to December 138 out of 357 typhus patients died as well as 72 out of 167 relapsing fever patients. The real tragedy came after the defeat of Sarıkamış where the majority of soldiers perished due to freezing conditions. The retreat of survivors in misery towards the villages of Erzurum, Hasankale and Pasinler, created a huge influx that filled the hospitals beyond capacity and infected the doctors and medical personnel working in those hospitals. Commander İsmail Hakkı Pasha died of the disease and Medical inspector Süleyman Numan was also infected with the disease. Although reliable statistical input was unavailable then, data from January 1915 indicate 522 typhus patients with 251 deaths and 223 *Borrelia reccurentis* infected patients with 121 deaths. In Erzurum, 20–30 civilians were dying of the disease every day. In March, after a heavy impact, the disease lost its severity at the war front; however, it continued to impact those at the back, such as the gendarmerie, as well as civilians.

Figure 2. Turkish Medical Doctors during the WWI. First three at the front with light colour uniforms are Dr Tevfik Salim (in the Republican era Emeritus Prof. Dr Tevfik Sağlam), Dr Adnan (in the Republican era Dr Adnan Advar) and Dr Mustafa Hilmi (in the Republican era Dr Mustafa Hilmi Sagun) who developed vaccines against plague and typhoid fever.

Differentiating diagnosis of *Borrelia reccurentis* infections was carried out by means of blood analysis where characteristic spirals were detected; some patients were even infected with both. The drug neosalvarsan was effective against relapsing fever; however, fight against typhus could only be achieved through the eradication of the vector lice. A patient without lice infestation did not constitute a danger to others. The most neglected sources of infection were transport centres, prisons, headquarters, and points of distribution. These were found in populated towns and were open to lice infestations and subsequent infections. Under poor sanitary conditions infested soldiers were shedding their lice, which in turn infested other soldiers.

Turkish 3rd Army was in desperate need for disinfection equipment that could be used and repaired with ease (Figure 3). Dr Abdülkadir Lütfi (in the Republican era Emeritus Prof. Dr Abdülkadir Noyan) even used bread ovens in which disinfection was possible due to dry air circulation. These ovens were easy to construct at every front. Due to lack of thermometers to measure the temperature the degree of heat was identified using a white sheet of paper. Optimum heat for lice disinfection changed the paper to a yellowish colour without it being burnt. Fire was then removed, a wet sac placed on the oven base, sprayed with water and lice infested clothing would go in. After the closure of the oven lid the first

Figure 3. Autoclave used for disinfection during the World War I (Gülhane Military Medical Academy Museum, Ankara).

exposure would last for 10–15 min, second batch would stay for 20–25 min and the third would be kept in the oven for half an hour.

After the initial heat generation in the oven, three batches of clothing would be disinfected. The practice was recommended to troops under the title of 'Hot air circulation and disinfection oven'. The only risk was the complete burning of the items. Dr Tevfik Salim (Sağlam), to prevent this, recommended that 4 to 5 litres of water be placed in the oven to ensure mist, although it did not completely eliminate the risk of burning. Villagers also used ground ovens for disinfection purposes although the oven size was too limited to cater for large number of clothing items.

From the spring of 1915 onwards, oven disinfection method was widely used with successful outcomes. The real innovation was introduced in 1916 by Chief Medical Officer at the Sivas front, Dr Ahmet Fikri Bey (in the Republican era Dr Ahmet Tüzer), who designed a steam chamber and recommended its use in the army (Figure 4).

The steam chamber consisted of a boiling pot and a cased box. An ordinary kitchen receptacle was encased in a cook-top with a flat surface. The cased box was made of timber 2 metres high and one metre wide. A hole was made underneath the cased box smaller than

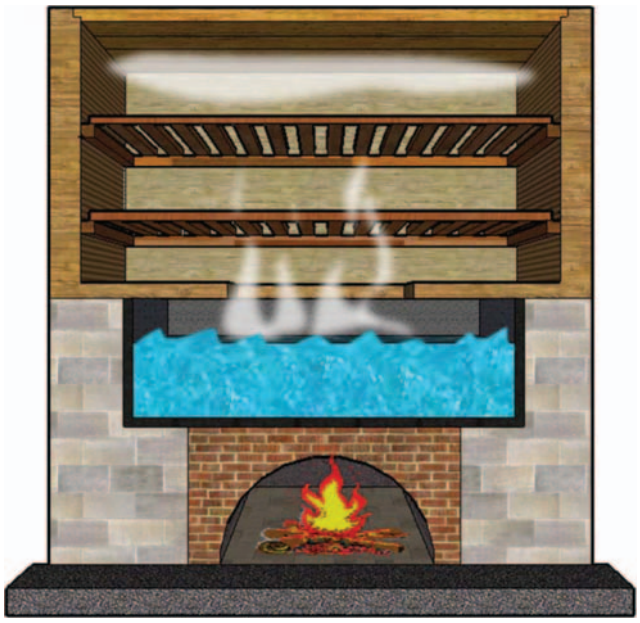

Figure 4. Dr Ahmet Fikri's steam chamber.

the pot and covered with felt in order not to allow the steam out of the lid. The box was then sealed on the cooker with mud and hooks.

In the chamber, steaming water made it possible to eliminate lice and ensure disinfection. It was a real breakthrough and easily applicable anywhere. Anyone with basic carpentry skills could build a steam chamber and repair if broke down, the cost of construction was low and there was no risk of burning the clothes placed inside. After preliminary testing and successful outcomes, the steam chamber became widespread and used in the army, health centres and homes to fight infectious diseases and only after the steam chamber lice were completely eradicated from the barracks. The role of the centres for disinfection based on the steam chamber use can be appreciated if figures from a period of 13 months in 1917–1918 are taken into account. A total of 2,225,262 clothing items and 2,283,095 individuals were disinfected in these centres.

Vaccination practice

Dr Tevfik Salim (Sağlam) and his colleagues were aware that the officers who gained immunity against typhus were those who had survived the disease in Yemen. During WWI, medical doctors came to the conclusion that the disease they had failed to diagnose previously when encountered in Yemen was also typhus. Vaccine was thus administered against typhus in the 3rd Army. Before his departure for the 3rd Army in 1915, Dr Reşat Rıza (in the Republican era Dr Reşat Kor) discussed the measures against typhus with Dr Tevfik Salim (Sağlam), and he proposed the administration of a vaccine as designed by himself. The weakened infective agent would be administered on the body to provoke a reaction from the immune system. The infective agent of typhus was still unknown but

they made the assumption that it was present in the blood, therefore blood samples from a typhus patient could be used to prepare the vaccine rather than a cultured sample. The typhus agent lost its strength if kept at 55°C for 15 minutes, so the blood sample could be inactivated at 58–60°C. Sterile blood samples of 10–20 mL taken from a typhus patient at the peak moment of the disease were placed in a glass bottle containing glass beads and shaken well for fibrin removal. Next, the bottle, completely immersed in water, was heated in a bain-marie at 55–58°C and rotated frequently. After it was taken out, the neck of the bottle would be flame-sterilised and the blood sample poured into a container to be administered subcutaneously (1–2 mL) using a syringe.

The typhus vaccination of this type had two major flaws. Firstly, the amount of blood was empirically limited to 1–2 mL without any specification of the infective agents contained. The results varied due to the disease's strength, its actual phase and many other factors yet unknown to those who administered the vaccine. Secondly, the blood samples could not be collected in large batches from typhus infected patients, and only 2–4 people could be vaccinated at a time once a sample was taken. Due to such limitations, the vaccine was administered only in the case of high-risk personnel in hospitals.

The first ever typhus vaccine worldwide was prepared on 28 March 1915 at Hasankale by Dr Tevfik Salim (Sağlam) himself and the first ever volunteers to be vaccinated were Dr İhsan Arif, Dr Tevfik İsmail, Dr Haydar Cemal, Dr Salahaddin, Dr Süreyya Ali, Major Zihni, Lieutenant İsmail Hakkı, Cemil Bey and Namık Bey, a total of nine army officers with five of these working as medical doctors at Hasankale hospital among typhus-infected and lice-infested patients. Dr Salahaddin fell ill the day he was vaccinated, Dr Haydar Cemal three days after the vaccination, Dr İhsan Arif five days after the vaccination and Dr Tevfik İsmail seven days after the vaccination. The remaining five officers were unaffected. Dr Salahaddin and Dr Haydar Cemal suffered a very heavy form of the disease for two weeks whereas Dr İhsan Arif and Dr Tevfik İsmail were light cases. The appearance of these cases led to scrutiny over the vaccine's success, but it was concluded that as the medical staff worked among typhus patients with lice, they had been infected previously, and received the vaccine at the moment of incubation. Those late cases of infection suffered a weaker form of the disease, which was welcomed as a successful outcome brought about by the vaccine. The same method was applied to a greater number of people by his colleagues later on (see below). The administrations in the 3rd Army and during the Turkish War of Independence also proved that the vaccine posed no risk.

In Erzurum, Dr Alaattin administered the vaccine on 263 persons between 23 April and 7 June 1915 with only three catching the disease. The demographic breakdown of these 263 vaccination cases is as follows: 234 Muslims, 26 Armenians, 3 Greeks with a total of 47 army officers, 9 medical doctors, 174 hospital workers, 6 civil servants, 27 soldiers on special duty. Bacteriologist Dr Abdülhalim Asım also vaccinated 130 individuals in Bayburt. Vaccination practice in Sivas was undertaken by Lieutenant İzak, a medical doctor and out of 156 hospital workers he vaccinated five caught typhus and one died. Out of a group of 35 hospital workers who also worked under similar conditions and received no vaccination, two caught the disease and one died. Dr Tevfik İsmail administered the vaccine on 110 soldiers in Erzurum, and Erzurum Red Crescent Hospital staff also administered the vaccine on 166 individuals between 28 April and 19 June 1915, who were tracked until 25 October. Only one person caught the disease and survived, and around Hasankale, some 44 persons were vaccinated by Dr Mihran. As the vaccine administration continued, many high rank army officers, army and medical personnel, and civil servants volunteered to be vaccinated and priority was given to health workers and those professionals in high demand at the time of war. Vaccine applications were not limited to the 3rd Army. Dr Abdülkadir (in the Republican era Dr Abdülkadir Noyan) extended the administrations to the 6th Army in Baghdad, and vaccinated the Army Chief Kazım Karabekir together with 76 officers, 20 doctors and 20 nurses. The Commander of the 6th Army General von der Goltz Pasha and his private doctor Oberndorfer who rejected the vaccination due to mistrust, later died of the disease, when all other vaccinated patients survived. Figures 5 and 6 below show a drop in infected cases by 42% in 1916, by 75% in 1917, by 94% in 1918 compared to the high number of infected cases and deaths in 1915. The improvement of hygiene and hospital services across that period played the biggest part in this drop.

As can be seen from the figures above, typhus reached its peak during the winter months of 1914–1915, slowed down in the summer of 1915 with an increase again in October. The reduced numbers of cases from January to March were due to military movements in those months. After a peak in April, it reached its

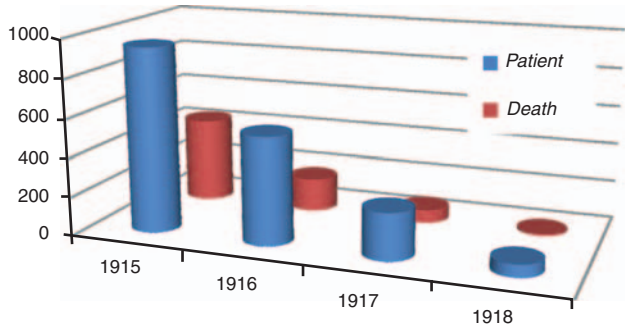

Figure 5. Overall patient to death ratio from 1915 to 1918.

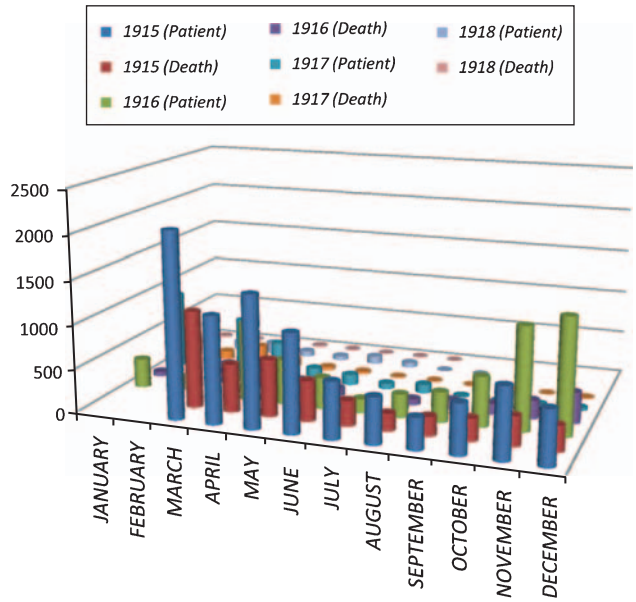

Figure 6. 3rd Army monthly death and infected patient ratio (1915–1918).

lowest in July and steadily increased month by month after that with a peak again in December and a slowdown followed. From the winter of 1917–1918 onwards, its peaks were not as high and typhus almost disappeared after August–September 1918.

The severity of typhus might have been related to the factors listed below:

(1) Seasonal impact (cold months were more conducive to disease)
(2) Infection rate went down during troop movements but gained severity again afterwards
(3) With effective disinfection processes its impact was reduced
(4) With effective treatments seasonal impact was eliminated (e.g. 1917–1918 winter).

In 1918 out of the 101 infected patients were members of the 123rd Regiment who carried it from İstanbul. As illustrated in the figures above, from March 1915 to September 1918, 19,619 members of the 3rd Army had typhus and 7,310 died of it. Typhus patients were 3.4% of all the patients (564,498) and 6.6% of the total deaths (105,761) occurred at the time.

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The malaria war

Aya C Taki and Peter M Smooker

Biotechnology and Biological Sciences Discipline
School of Applied Sciences
RMIT University
PO Box 71
Bundoora, Vic. 3083, Australia
Tel: +61 3 9925 7129
Fax: +61 3 9925 7110
Email: aya.taki@rmit.edu.au
Email: peter.smooker@rmit.edu.au

The 25th of April is a national day to honour the members of the Australian and New Zealand Army Corps (ANZAC), who gave their lives at Gallipoli during the First World War (WWI). The 25th of April has also been designated World Malaria Day by the World Health Organization (WHO), and is commemorated every year to bring awareness of deaths caused by malaria infection and global efforts to control infection. There is no coincidence that these two commemorative events are on the same day, as military campaigns suffered great burdens caused by malaria infection during WWI. Malaria infection is yet to be eradicated from human history; fundamental discoveries of malaria and its control were developed during WWI and the fight against malaria continues to this date. This article focuses on the discovery of malaria prior to WWI, the impact that malaria had on military in the war, and the development of control measures taken to minimize these effects and to subsequently eradicate the disease in many countries.

Malaria is one of the most prevalent parasitic diseases, and is caused by a eukaryotic protist of the genus *Plasmodium*, a member of the phylum Apicomplexa. The species of *Plasmodium* that are pathogenic for humans are: *P. falciparum,* responsible for approximately 80% of malaria cases, *P. vivax*, *P. ovale*, and *P. malariae*. These four were originally considered to be the only species to cause infection in humans, until in 2004 a zoonotic malaria species *P. knowlesi* identified in Malaysian Borneo was recognized as a fifth human malaria species[1]. The malaria parasite exhibits a complex life cycle, ultimately transmitted via a bite of a female *Anopheles* mosquito. Therefore, infection mainly occurs in the sub-Saharan African and South-East Asian regions, where the tropical climate provides a sustainable environment for the mosquito vector to flourish. In locations where the theatres of war and malaria transmission coincided there were significant impacts on military performance.

The mortality rate from malaria remains high and in 2012 was responsible for more than 200 million cases of infection worldwide and 627,000 deaths, predominantly in children under the age of 5[2]. Infection begins with the inoculation of sporozoites, which travels from the injection site into the bloodstream and infects liver hepatocytes to proliferate to tens of thousands of haploid forms. It then re-enters the bloodstream where the intracellular parasite undergoes asexual replication and a cycle of erythrocyte infection proceeds. This rapid intra-erythrocyte multiplication stage of parasites is mainly responsible for the severe morbidity and mortality of malaria, in addition to the incidence of 'cerebral malaria' caused by the blockage of blood vessels in the brain in *P. falciparum* infections[3].

WWI: malaria infection and the monumental discoveries in the 1880s to 1910s

In the 19th and early 20th Century, the Greek region was a major malaria endemic site and approximately 40% of British and French troops (120,000 soldiers out of 300,000) contracted malaria and became incapacitated in Macedonia during 1916 and 1917. There were 1.3 million hospital cases for the total of 1 million Allied forces in the theatre between 1916 and 1918[4]. In the Middle Eastern region where the Tigris and Euphrates run, with an environment for the *Anopheles* mosquito to prosper, the Gallipoli campaign including ANZACs suffered as 90,000 soldiers were evacuated due to malaria.

Malaria caused a significant burden on European members during the time leading to, and also during WWI. Therefore, it is no surprise that the cause of infection and the mechanism of transmission were discovered by military surgeons during this time. In 1880, Charles

Louis Alphonse Laveran, a French military physician posted in Algeria, discovered that the protozoa-bearing black pigment found in malaria patient's blood was the cause of disease[5]. Laveran also showed that malaria parasites can be found in a patient's brain, spleen and liver[6]: some of his drawings are shown in Figure 1. In 1897 Ronald Ross, of the British Indian Medical Service in India, elucidated that the transmission of malaria parasites was due to the *Anopheles* mosquito, by discovering the malaria protozoa in the stomach wall and salivary glands of the insect[7]. Both men were later awarded the Nobel Prize in Physiology or Medicine (in 1907 and 1902, respectively), for their invaluable contributions to the understanding of malaria infection.

Malaria control in WWI and post war periods

After the discovery by Ross, the prevention of malaria included control of mosquito breeding sites and use of mosquito bed nets[8], often supplemented with the use of quinine, a naturally occurring antimalarial compound from the bark of the Cinchona tree, native to South America. Quinine was the primary treatment for malaria throughout WWI; however, its strong adverse effects and the short action period of the drug made quinine a suboptimal treatment[9].

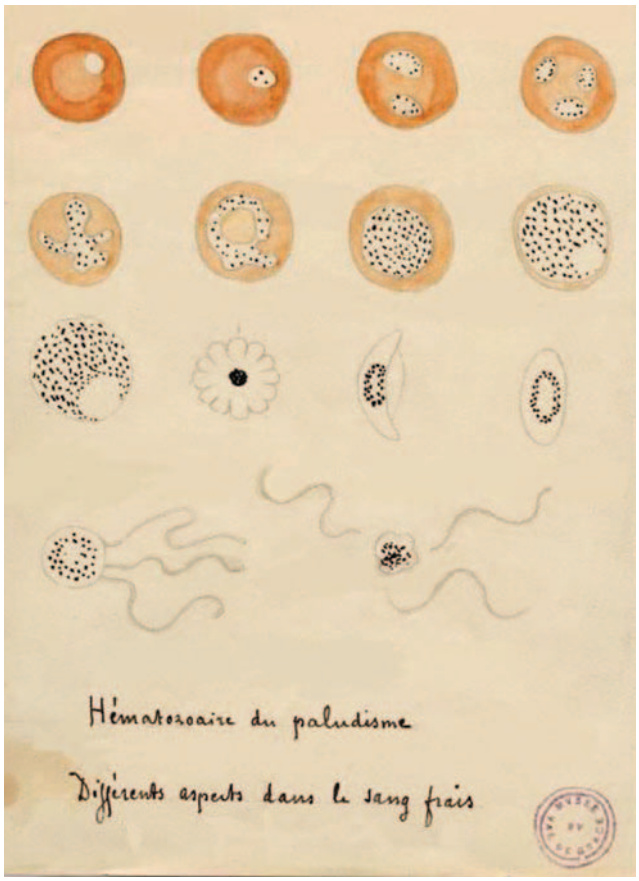

Figure 1. Laveran's 1880 illustration of various stages of malaria parasites as seen on fresh blood. Dark pigment granules are present in most stages. The bottom row shows exflagellating male gametocytes, which produces filiform elements. Courtesy of Center for Disease Control and Prevention.

The Cinchona tree was cultivated into the world's largest supply source in Java, monopolised by the Dutch. However, the plantation later fell into the hands of the Japanese who, as Britain's ally in WWI, occupied South Pacific islands. Therefore, the Germans lost their supply of quinine, forcing them to develop alternative antimalarial drugs.

One of the first synthetic antimalarial drugs was introduced by German scientist, Paul Ehrlich, in 1891. He was the first to report the antimalarial property of methylene blue, which is particularly effective in staining and killing intracellular malaria parasites, and was shown to cure two patients[10]. This later led the German dye company Bayer to become a pharmaceutical company for the production of a methylene blue-based synthetic drugs for malaria treatment. A more defined compound from another dye, 9-amino acridine, related to methylene blue, was described in 1932 by Bayer and was later named as the new and more effective antimalarial drug Atabrine[9]. Atabrine production was greatly expanded in the United States and Britain when Java was captured once again by the Japanese Imperial army and also when Germany seized the quinine stored in Amsterdam during WWII. In 1945, Bayer released another synthetic antimalarial drug named chloroquine, which contributed to saving countless lives from the infection for the next 20 years[11].

Towards the end of WWII, malaria control began in many European countries such as Spain, Italy and especially Greece, where a quarter of the total population was infected in the 1930s[12]. The eradication of malaria was achieved by the introduction of the insecticide DDT (1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane) by the Allies, which was initially used by the US Army to control lice vectors of typhus[13]. Several field studies conducted in these southern European countries demonstrated the powerful efficacy of DDT on *Anopheles* mosquitos, resulting in malaria almost being eradicated from some areas where it was previously endemic late 1940s[13,14]. Coating the surface of interior walls with residual DDT and spraying homes to control the *Anopheles* mosquito had a significant impact on the reduction of global malaria cases, and also helped eliminate the disease in the US by 1951[15,16]. The Global Malaria Eradication Programme was launched by the WHO in 1955 with the use of chloroquine and DDT against malaria (the eradication programme was however discontinued in 1972 due to the financial burden on the WHO)[17]. Although malaria was permanently eliminated from some regions, the emergence of drug resistant parasites and insecticide resistant mosquitoes became apparent[18,19].

Lessons from the past and challenges today

Sanitation and mosquito bite prevention are key to reducing malaria infection. Mosquito control has been shown to be one of the most

effective control measures, as was clearly evident from the malaria eradication campaign. Development and administration of antimalarial drugs also greatly reduced the morbidity and mortality of malaria infection since the early 20th Century. While these intensive measures marked significant and lasting benefits in malaria history, they have not resulted in the complete eradication of disease. The threat of multi-drug resistance in the malaria parasite, as well as pesticide resistance in mosquito vectors coupled with the failure to continue the global eradication campaign due to unsustainable financial resources, left less developed African and South-Eastern Asian countries vulnerable. Moreover, the shortage or complete failure of the antimalarials can possibly lead to a catastrophic situation in countries where disease transmission is possible.

The prevention of malaria infection, especially in developing countries, has become one of the most challenging goals in the field of modern science. The development of an effective vaccine is required to achieve complete eradication and prevention from disease. Numerous malaria vaccine studies have been attempted, including the development of a liposome-based vaccine RTS,R as a most promising vaccine candidate[20]. However, there is insufficient efficacy to provide an adequate level of protection in all populations[21]. Nevertheless, research into malaria control has advanced greatly since the discovery of the parasite under the microscope prior to the WWI era by Laveran and Ross, and the eradication of disease was achieved in some parts of the world. However, infants and children are still dying every minute, and until the day that no casualties due to the parasite occur, the war against the disease continues.

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Biographies

Aya Taki is a PhD candidate in Biotechnology who has recently submitted her thesis at RMIT University, Australia in June 2014. Her research interest is in vaccine development against infectious diseases using nanoparticles as an antigen delivery system. A particular interest is in the field of malarial protein engineering and vaccine design.

Peter Smooker is a Professor of Biotechnology and head of the Biotechnology laboratory at RMIT University. The laboratory's main activities are in vaccine design, including antigen identification and engineering, and vector development.

History and eradication of smallpox in Turkey

Osman Şadi Yenen

İstanbul University
İstanbul Medical Faculty
Department of Medical Microbiology
Çapa, İstanbul, Turkey
Email: yenen@istanbul.edu.tr

Turkey has played a prominent role for the Western World in the prevention of disease from two different angles. The first is the İstanbul connection from where the variolation originated. The Ankara connection, on the other hand, provided the source for the modified *Vaccinia Virus Ankara* (MVA) as both the third generation smallpox vaccine and the recombinant vector for modern day vaccine development. In this article, the history of disease and eradication efforts both in the Ottoman Empire and in the Republic era of Turkey will be discussed with an emphasis on the worldwide significance of İstanbul and Ankara connections in the history of smallpox.

During the 600 years of Ottoman history smallpox was ever-present alongside other epidemics such as plague and cholera. The proximity of the Anatolian plateau to South-western Asia and major trade routes where it is believed to have originated from was probably the reason for its presence in Asia Minor since ancient times. Written records before the 15th Century are scarce and details of the disease in the Empire remain under-documented. Even after the 15th Century, record-keeping was inadequate due to a lack of understanding of infectious disease control and its importance in public health. The Ottoman Empire was represented at the *First International Sanitary Conference* in Paris (1851), which ended without any successful resolution to disease control. At the 13th International Sanitary Conference (1926), smallpox and typhus were recognised as diseases to be controlled with quarantine measures[1]. Most documents related to the disease in the empire date back to 19th Century. While disease prevention and Jenner type vaccination started during the collapse of the empire, full eradication occurred only after the foundation of the Republic of Turkey.

Causative agent and short history

The causative agent of smallpox is the variola virus (*Orthopoxvirus*) within the family *Poxviridae*. Genomic studies indicate the presence of two or three different clades of the virus[2]. The date of origin of the virus is unknown. Although disease-indicating scars were detected on Egyptian mummies, the virus itself has never been identified[3]. So far the only molecular evidence for the existence of the virus was detected in 300-year-old Siberian mummies. Further analysis indicated the roots of the virus date back to 928 AD[4]; however, some historians take the origin back to 10,000 BC, speculating on its possible relationship with the cowpox virus[5]. On the other hand, Gubser and Smith[6], following their studies on the DNA analysis of the virus, revealed a relationship between the virus and the camelpox virus: possibly these two viruses originated from the same ancestor. Babkin and Babkina[7] suggested that the taterapox, camelpox and variola viruses originated from the same ancestor around the Horn of Africa and spread to East Africa through camel movements dating back 3500 years.

Manifesting itself with fever and flaky skin, the disease has four different clinical types: ordinary; (vaccine) modified; flat; and hemorrhagic smallpox[2]. Strains resulting in varying degrees of manifestation have been identified as (i) the variola major resulting in 10–30% in death and (ii) the variola minor that results in <1% in death. Historical records show diseases similar to smallpox were transmitted by ancient Egyptians to Hittites (1350 BC), from there to Iran (430 BC), to Sicily (395 AD) and to China (48–49 AD), from Mesopotamia to Rome (165 AD) and from China to Korea (583 AD) and finally from Korea to Japan in 585 AD[8]. However, difficulties encountered in those days in distinguishing between diseases showing similar symptoms render the records vague in relation to smallpox. The first clinically valid record for distinguishing between smallpox and measles was achieved by the Iranian physician El-Razi (910 AD)[9] (Box 1), who considered smallpox as a form of coagulation in children's blood.

Smallpox repeatedly arrived in Anatolia through the crusades (1096–1291) and spread through trade routes crossing the great Sahara and reaching East and West African ports[10]. In the early 16th Century, it became widespread in most European cities and with the first explorers it spread to Americas, Australia and Africa. With the Spanish conquistadors it was transmitted to the native population of Cuba and Hispaniola (today's Dominican Republic) resulting in the extermination of the Aztecs and Incas. These epidemics also resulted in the loss of work-force and subsequent introduction of African slaves in Americas[11]. The Spanish and Portuguese, respectively, introduced the disease to Chile in 1554 and to Brazil in 1555. It

Box 1. Excerpts from Rhazes' *Smallpox and Measles Treatise*[9]

Now the Small-Pox arises when the blood putrefies and ferments, so that the superfluous vapours are thrown out of it, and it is changed from the blood of infants, which is like must, into the blood of young men, which is like wine perfectly ripened: and the Small-Pox itself may be compared to the fermentation and the hissing noise which take place in must at that time. And this is the reason why children, especially males, rarely escape being seized with this disease, because it is impossible to prevent the blood's changing from this state into its second state, just as it is impossible to prevent must (whose nature it is to make a hissing noise and to ferment,) from changing into the state which happens to it after its making a hissing noise and its fermentation. (p. 29)

You should know that the Measles which are of a deep red and violet colour are of a bad and fatal kind; and that the Small-Pox in which the pustules are yellow, hard, close together, confluent, numerous, and of a deep red or violet colour, and that kind which spreads like herpes, and gives the surface of the body the appearance of vibices, are all bad and mortal. (p. 94)

was introduced to North America by the British in 1617 with serious consequences to American Indian populations. The disease was reported in South Africa in 1713, in Australia in 1872, New Zealand and Pacific Islands from 1872 onwards, thus becoming a problem worldwide[8,12,13].

Following the 1953 proposal of Dr Brock Chisholm, General Secretary, WHO and the 1958 call by USSR delegation member Victor Zhdanov, WHO initiated a global eradication campaign in 1967. With the last case reported in October 1977 it was declared eradicated (reviewed in Fenner *et al*.[8] and Henderson[14]) and the final report of the Global Commission, WHO for the Certification of Smallpox Eradication confirmed these results (1979). The final declaration was made by the World Health Assembly at the Geneva Meeting (1980) to the health ministers of all participant countries. Today limited amounts of variola strains are kept in two different WHO collaborative reference centres: (i) Centre for Diseases Control and Prevention (Atlanta, GA, USA); and (ii) The State Research Centre of Virology and Biotechnology (moved from Moscow to Novosibirsk, Russia after 1994)[8,15].

Smallpox prevention: variolation and vaccination

Variolation (or *inoculation*; during the 18th Century these two terms were used interchangeably) technique was based on the observation that the patients had gained immunity against a second infection. In ancient China, powdered variola crusts were used to infect healthy individuals via nasal inoculations or insufflations. In ancient India, intradermal inoculations of lesion material were practised. Although information prior to 1550 was reported to be speculative by Boylston[16], in the Ottoman Empire similar practices to those in India were used (see below). Vaccination, on the other hand, was derived from the observation that human beings gained immunity against smallpox after exposure to cowpox. Materials taken from cowpox lesion were inoculated intradermally to healthy people. Similar administrations were carried out in England on a popular level, which was later given a scientific basis by Edward Jenner in 1796 (reviewed in Boylston[16] and Bazin[17]).

Smallpox and variolation in Ottoman times

The evidence of disease existence near Anatolia dates back to the Elephant War (570 AD). The arrival of the disease in Constantinople dates back to 12th Century and important evidence can be found in the poem of Theodore Prodromos:

> *The body is heated violently through with extraordinary torches from the fever. . . little by little* [the pimples] *gradually on the seventh day become murderous pustules. Have you ever seen a violent shower of rain coming down on a lake, how the entire surface of the lake swells up on account of the closely packed bubbles?* (cited in Hopkins[18], p. 27)

Evidence of the application of inoculation technique in Ottoman Empire can be found in the letters of two Greek Physicians. These two letters written by Emanuel Timonis (born in Chios, Greece of Italian parents; family physician to the British Ambassador to the Porte, Sir Robert Sutton, and to his successor, Lord Edward Wortley Montagu); and Jacob Pylarini (a native of Cephalonia and a graduate of Padua in both law and medicine, previously, physician to Tsar Peter the Great in Russia, practised in İstanbul and served as Venetian Consul at Smyrna) were presented to the British Royal Society[19]. Both physicians witnessed the application of inoculation technique, and also administered it themselves during the smallpox outbreak in Constantinople in 1701. Also, Timonis later sent a communication to the Royal Society for the meeting in May 1714, describing in detail how to collect variola crust, when to sample, how to preserve and apply[20] (Box 2).

According to Pylarini, the inoculation technique was introduced to Constantinople by a Greek lady in 1660 that was welcomed by the Christian population, yet declined by the Moslem population of the city due to their belief[21]:

> *The Turks alone, so addicted are they to their predestinarian notions, and so riveted to ancient prejudices, neglect to reap any advantage from it.*

Box 2. Excerpts from Emanuel Timonis' Communication read by John Woodward[20]

The writer of this ingenious discourse observes, in the first place, that the Circassians, Georgians, and other Asiatics, have introduced this practice of procuring the smallpox by a sort of inoculation, for about the space of forty years, among the Turks and others at Constantinople.

That although at first the more prudent were very cautious in the use of this practice; yet the happy success it has found to have in thousands of subjects for these eight years past, has put it out of all suspicion and doubt; since the operation, having been performed on persons of all ages, sexes, and different temperaments and even in the worst constitution of the air, yet none have been found to die of the smallpox; when at the same time it was very mortal when it seized the patient the common way, of which half the affected dyed. This he attests upon his own observation.

Next he observes, they that have this inoculation practised upon them are subject to very slight symptoms, some being scarce sensible they are ill or sick; and what is valued by the fair, it never leaves any scars or pits in the face.

The method of the operation is thus. Choice being made a proper contagion, the matter of the pustules is to be communicated to the person proposed to take the infection; whence it has metaphorically, the name of incision or inoculation. For this purpose they make choice of some boy, or young lady, of a found healthy temperament, that is seized with the common smallpox (of the distinct, not flux fort) on the twelfth or thirteenth day from the beginning of his sickness; they with a needle prick the tubercles (chiefly those on the shins and hams) and press out the matter coming from them into some convenient vessel of glass, or the like, to receive it; it is convenient to wash and clean the vessel first with warm water: a convenient quantity of this matter being thus collected, is to be stopped close, and kept warm in the bosom of the person that carries it, and, as soon as may be, brought to the place of the expecting future patient.

The patient therefore being in a warm chamber, the operator is to make several little wounds with a needle, in one, two or more places of the skin, till some drops of blood follow, and immediately drop out some drops of the matter in the glass, and mix it well with the blood issuing out; one drop of the matter is sufficient for each place pricked. These punctures are made indifferently in any of the fleshy parts, but succeed best in the muscles of the arm or radius. . .

Box 3. Excerpts from Patrick Russel's communication[22]

. . .About nine or ten years ago, while on a visit at a Turkish Harem, a lady happened to Express much anxiety for an only child, who had not yet had the Smallpox; the distemper at that time being frequent in the city. None of the ladies in the company had ever heard of inoculation; so that, having once mentioned it, I found myself obliged to enter into a detail of the operation, and of the peculiar advantages of it. Among the female servants in the chamber was an old Bedouin, who having heard me with great attention, assured the ladies, that my account was upon the whole a just one, only that I did not seem so well to understand the way of performing the operation, which she asserted should be done not with lancet, but with a needle; she herself had received the disease in that matter, when a child; had in her time inoculated many; adding moreover, that the practice was well known to the Arabs, and that they termed it buying the Smallpox.

For these several years past, very few slaves have been brought from Georgia. From what I could collect among those already here, who remember anything of their own country, inoculation was well known there: I have seen several old Georgian women, who had been inoculated, when children, in their father's houses.

In Armenia, the Turcoman tribes, as well as the Armenian Christians, have practised inoculation since the memory of man; but, like the Arabs, are able to give no account of its first introduction among them.

It has already been mentioned, that the Turks at Bagdad and Mousul make no scruple to inoculate their children. I have seen also some Turkish strangers here, who had been inoculated at Erzeroon. Hence it is probable that the Turks, in other parts of the Ottoman empire, do not merely, as fatalists, reject inoculation; but that other considerations, which have influence in countries where fatalists are ridiculed or anathematized, concur likewise in Turkey, to oppose the reception of a practice to beneficial to mankind.

Despite these early communications, European interest in the inoculation technique in Ottoman Empire was achieved after the efforts of Lady Montagu, Dr Charles Maitland and Sir Hans Sloane in Britain (see below). On the other hand, the technique was used to apply partly in the Empire by the Moslem population[22] (Box 3). The Ottoman Court also endured the disease including the sultans themselves as did their children and wives. Sultans Ahmet I (1604), Ahmet III (1708) and Abdülmecid (before 1839) all had the disease[23]. Daughters of Murad III (1599) and Abdülhamid I (1782) and the sons of Mustafa III (1771) and Mahmut (1825) both died of the disease although the sons of Abdülhamid I and Mahmut both survived the infection (including the crown prince Mehmet

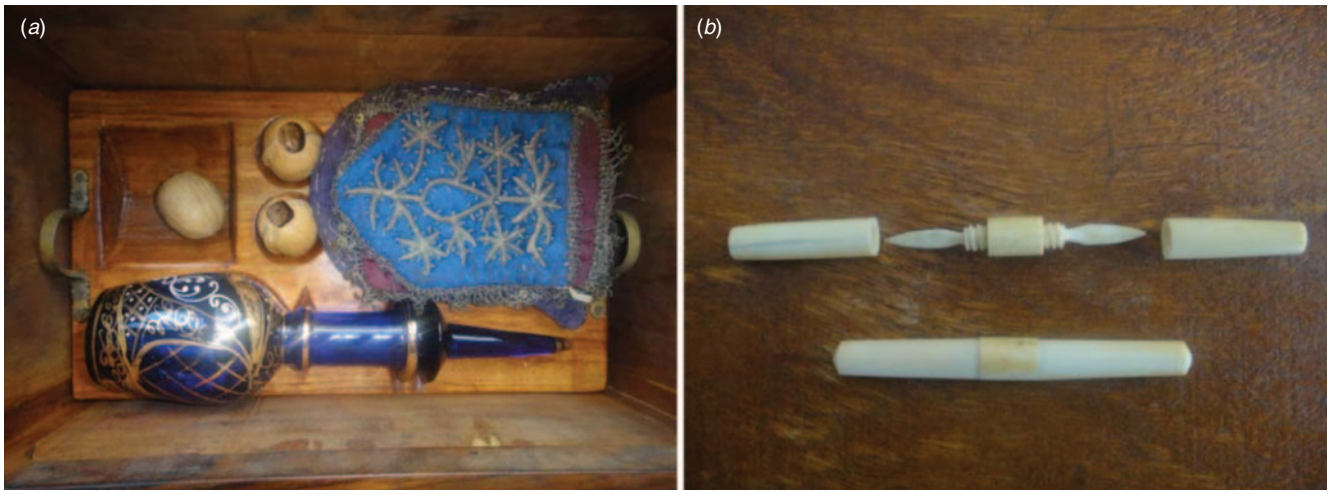

Figure 1. (a) Vaccinator's bag of collection for vaccine material, rosewater bottle and walnut shells used to hydrate dried vaccine material, (b) ivory vaccination needle, or *vaccine pen* (19th Century) (Courtesy of Prof. Dr İlter Uzel).

Nusret)[18,23,24]. Such information indicates the lack of any inoculation practice in the Ottoman Court although it was practised in other parts of the Empire.

Smallpox was experienced in İstanbul as an epidemic in 1701, 1706, 1825 (extension of the European pandemic between 1824–1829), 1845, 1871 and 1877–1878 as well as small outbreaks of 1881, 1887, 1890, 1891, 1894, 1908, 1809 and 1923. Istanbul had always been the most crowded city of the Empire and most epidemics hit this city first, although outbreaks occurred haphazardly in provincial towns from time to time (e.g. 1847–1887)[25]. The first records of inoculation practice in the Ottoman Court derives from the palace physician İsmail Pasha's lithographic book *Menafiül'etfal* (Benefits for Children)[23,25]. In this book, an Anatolian man arrives in İstanbul in 1679 and applies the inoculation technique to children.

The inoculation technique spread with the Seljuks (1055) from the Caucasus region to Asia Minor and subsequently passed on to Ottomans[23]. The technique was mostly applied by house women who dried samples of variola crusts inside walnut shells, which were applied to healthy individuals inter-dermally after re-suspension using rose water in May (Figure 1). Inoculation needles and implements have also been through series of changes, used also for vaccination, and the current design bifurcated needle was introduced in 1965 (reviewed in Baxby[26]).

The İstanbul Connection

British interest in the inoculation technique dates back to the appointment of Lord Edward Wortley Montagu as the Extraordinary Ambassador to Constantinople in 1716. His wife Lady Montagu was already a victim and carried scars on her face (1715): she had also lost his brother to the disease (1713). A keen observer and a writer, Lady Montagu first mentioned the inoculation technique to her friend Sarah Chiswell (who later died of the disease in 1726), in her letter posted from Adrianople on the way to Constantinople (1717)[18,27] (Box 4). Following her observations in Constantinople, she got her 5-year-old son inoculated with the support of the Embassy doctor Maitland (1718)[28]. On her return to England, she also got her 3-year-old daughter inoculated during the 1721 epidemic in England. This application was the first example of the inoculation technique in Britain, generating interest widely among aristocrats. To test the safety of the inoculation technique before it was given to the daughter of Prince of Wales, Princess Caroline, six prisoners from Newgate were inoculated with the virus and the success of the application led to the release of these prisoners[28–30].

> *Upon these trials, and several others in private families, the late queen, then princess of Wales. . . sent for me to ask my opinion of the inoculation of the princesses. I told her Royal highness, that by what appeared in the several assays, it seemed to be a method to secure people from the great dangers attending that distemper in the natural way.* (Sloane and Birch[31])

Princess Caroline, following her successful inoculation, also had her 11- (Amelia) and 9- (Caroline) year-old daughters inoculated.

Smallpox and vaccination in Ottoman and Republic era of Turkey

Due to lack of interest in the inoculation technique at the Ottoman Court applications were conducted regionally. Jenner's definition of vaccination (*An Inquiry into the Causes and Effects of the Variolae Vacciniae, or Cow-pox*, 1798[32]) was generated in the western medical environment of inoculation[17,33]. His book titled *Inquiry* was printed in England in multiple copies from 1798 and new copies were also produced in Geneva, Hannover and Wien. Reprints of the

Box 4. Excerpts from Lady Montagu's letters[27]

To Sarah Chiswell, *Adrianople, 1 April 1717*

A propos of distempers I am going to tell you a thing that I am sure will make you wish yourself here. The smallpox, so fatal and so general amongst us, is here entirely harmless by the invention to engrafting, which is the term they give it. There is a set of old women who make it their business to perform the operation. Every autumn in the month of September when the great heat is abated, people send one another to know if any of their family has a mind to have the smallpox. They make parties for this purpose and when they are met (commonly fifteen or sixteen together) the old woman comes with a nutshell full of the matter of the best sort of smallpox, and asks what veins you please to have opened. She immediately rips open that you offer to her with a large needle (which gives you no more pain than a common scratch) and puts into the vein as much venom as can lie upon the head of her needle, and after binds up the little wound with a hollow bit of shell, and in this manner opens for or five veins. The Grecians have commonly the superstition of opening one in the middle of the forehead, in each arm and on the breast to mark the sign of the cross, but this has a very ill effect, all this wounds leaving little scars, and is not done by those that are not superstitious, who choose to have them in the legs or that part of the arm that is concealed. The children or young patients play together all the rest of the day, and are in perfect health until the eighth. Then the fever begins to seize them and they keep their beds two days, very seldom three. They have very rarely above twenty or thirty in their faces, which never mark, and in eight days' time they are as well as before their illness. Where they are wounded there remains running sores during the distemper which I don't doubt is a great relief to it. Every year thousands undergo this operation, and the French Ambassador says pleasantly that they take the smallpox here by way of diversion, as they take the waters in other countries. There is no example of any one that has died in it, and you may believe I am well satisfied of the safety of the experiment, since I intend to try it on my dear little son. I am patriot enough to take pains to bring this useful invention into fashion in England and I should not fail to write to some of our doctors very particularly about it if I knew anyone of them that I thought had virtue enough to destroy such a considerable branch of their revenue for the good of mankind. But that distemper is too beneficial to them not to expose to all their resentment the hardy weight that should undertake to put an end to it. Perhaps, if I live to return, I may, however, have courage to war with them. Upon this occasion admire the heroism in the heart of your friend, etc.

To Wortley, *Constantinople, 23 March 1718*

. . .The boy was engrafted last Tuesday, and is at this time singing and playing and very impatient for his supper.

. . .I cannot engraft the girl; her nurse has not had the smallpox.

To Wortley, *Constantinople, 1 April 1718*

Your son is as well as can be expected, and I hope past all manner of danger.

original article were in free circulation as well translations in various languages allowing the method to be introduced in many countries[17]. The Ottomans first read *Inquiry* in 1801, as Giuseppe Marchal's Italian text was translated into Turkish by Mustafa Behçet Efendi with the title *Risale-i Telkih-i Bakari*[25,34]. Subsequently, in 1811, Şanizade Ataullâh Efendi conducted a series of tests on his farm animals at Ayasağa and made a number of recommendations to Sultan Mahmut II such as a new vaccination centre and mass vaccinations while dedicating a chapter of his book to this practice[23]. Vaccination might have been known to the Ottomans since 1810, however, Sultan Abdülmecid (born 1823, died 1861) had caught smallpox in infancy and this was probably the reason why caution was exercised in his administration. According to Walsh[35], the first instance of vaccination was at the time of Sultan Mahmut II, who allowed it to be administered to his children (by a French physician) after the death of his the eldest son in 1825, hence its acceptance by the rest of his subjects. Initially, imported vaccines were used throughout the empire however small amounts from Europe were insufficient to meet the demand and vaccination teams preserved quality lesion material after successful vaccinations of upper class children[25]. In fact, the first vaccination took place at the British Embassy in İstanbul, as a Swiss man, Jean de Carro, had secured a small amount of Italian vaccination material, which was taken to İstanbul by some friends of the British Ambassador (Thomas Bruce; Lord Elgin) and administered to the children at the Embassy in December 1800[28]. Vaccination material supplied by de Carro reached as far as Bombay via Greece and Bagdad[17].

The first imperial decree regarding smallpox vaccine was issued on 20 May 1840[23]. Religious concerns expressed in Europe earlier[36,37] were also voiced in İstanbul at this time and only after a fatwa by the Şeyhülislam declaring vaccination permissible according to the Islamic law, large-scale vaccination campaigns started at no cost to the public[23]. Regardless, vaccine production did not start until 1872, and imported vaccine material was administered only on critical population segments such as military cadets or in cases of emergency, by vaccination teams from İstanbul[25]. Vaccination professionals were trained at the School for Vaccinators within the vaccine production centre from 17 May 1898, which graduated 319 professional vaccinators until 1903[23]. By 1910 village school teachers and

midwives were also admitted to this school and its name was later changed to Minor Health Officers School as minor surgery operations also became part of the school's curriculum. Despite interruptions to the program, the school stayed in existence until 1950s and trained countless vaccinators[23].

The Ottoman Empire made it an obligatory vaccine for children of school age and the *Regulation on Smallpox Vaccination* of 8 July 1885 denied school registration to those unable to produce any proof of vaccination. The second *Regulation on Smallpox Vaccination of* 21 July 1894 also dictated that newborns be vaccinated within six months of birth[23]. Updates to the regulation were incorporated in 1904 and 1915 increasing the number of vaccinations for an individual to 3 by age 19. The common practice of human to human vaccination (variolation) also became strictly prohibited[23]. Despite regulatory effort, the administration of smallpox vaccine hardly reached all corners of the empire, and a report titled *Reconstruction in Turkey* by the American Committee of Armenian and Syrian Relief in 1918 confirms the lack of systematic campaigns: 'Vaccination is practised in larger towns and cities and in the army. Only in the army is it systematically carried out.'[35] (cited in Özdemir[38], p. 224). After the foundation of the Republic, the Public Health Bill came into force (24 April 1930) and made smallpox vaccination obligatory for all citizens[23].

The Ottoman production of smallpox vaccine started with the reopening of The Imperial Vaccine Production Centre (*Telkihane*) in 1892 in 1892 and domestic production was distributed all over the country bringing an end to imported vaccines[25]. An inspectorate was established in 1890–1891 and Colonel Hüseyin Rahmi Bey became the first vaccine inspector (Figure 2). Later in 1894, the vaccine production centre was allocated a proper building during senior Inspector Remzi Bey's time (1895–97). After his death in 1896, the production centre directors were Dr Hasan Zühtü Nazif Bey (1896–1897) and Dr Rifat Hüsamettin Pasha (1897–1913) respectively[24].

After the Young Turk Revolution of 1908, it became the 'Ottoman Vaccination Centre'[23]. In the years following, the centre directors were Dr Kemal Muhtar Bey (1913–1920), Dr Rifat Hüsamettin Pasha again (1920–1922), Dr Kemal Muhtar Bey again (February 1922 to September 1922), Dr Şerafettin Mustafa (in the Republican era Dr Şerafettin Mustafa Kam) (1923–1934). Between 1892 and 1913 a total of 7,260,784 tubes; and between 1914 and 1919 a total number of 27,688,449 tubes of vaccine were produced at this centre. During the War of Independence, The Red Crescent transported vaccines from this production centre to Anatolia; 566,000 in 1920, 1,770,000 in 1921 and 1,283,000 tubes in 1922 respectively. Between 1892 and 1923 inoculation viruses for

Figure 2. Cover page of the Servet-i Fünun magazine published on 17 November 1892. Hüseyin Remzi Bey (in the middle) and Telkihane staff are seen together with the calf used at the centre for vaccine production (courtesy of Volkan Gülçek).

vaccines were imported from Paris[39] even though information regarding the doses contained is unavailable. Vaccine standardisation until the 1960s was unknown; and in this period, 10-dose-tubes or 250 (5 mL) and 500 (10 mL) dose bottles were in circulation[39].

The Vaccine Production Centre moved to Ankara in 1934 and the production continued under supervisions of Dr Şerafettin Mustafa Kam (1934–1936), Dr Niyazi Erzin (1936–1942), Dr Nusret Fişek (1942–1947), Prof. Dr Zühdi Berke (1947–1962), Dr Elhan Özlüarda (1962–1977) and virologist Çiğdem Artuk until the production ended in 1981 (Mustafa Hacıömeroğlu, personal communication, 2004)[24]. Vaccine production occurred also elsewhere in the empire such as Mecca, Basra, Sana'a, Bagdad and Damascus, and in Sivas, a production centre for rabies and smallpox vaccine was also established[24]. However, these centres were short-lived and the main centre for production remained İstanbul. After the foundation of the Republic in 1923, records regarding smallpox improved considerably: the official number of infected cases and resulting deaths are provided in Table 1.

Table 1. The number of infected cases and resulting deaths during Republican Era.

Years	Infected	Deaths
1925	483	69
1926	429	117
1927	99	6
1928	47	8
1929	1746	870
1930	830	160
1931–1939	2524	727
1940	958	130
1942	1871	174
1943	12395	1380
1944	6093	678
1951	152	3
1957[A]	128	7

[A]The last smallpox outbreak.

As a result, between 1925–1957 a total of 27,755 infected cases and 4039 deaths were reported[38,40,41]. No smallpox infection was seen in Turkey after 1957 and the vaccine production came to an end in 1981 (Çiğdem Artuk, personal communication, 2004).

The Ankara Connection

As mentioned above, following the eradication of smallpox, only two collaborative reference centres recognised by WHO are officially entitled to hold live variola strains, however it is not known whether unauthorised laboratories have any holdings. Since the 1980s, smallpox vaccination has come to a stop but the majority of the world population is not immune to smallpox, nor to cross-infection with animal orthopoxviruses and concerted efforts to specifically develop vaccines against smallpox and all poxviruses have intensified[42]. Limitations of space do not allow further details here but the *Modified Vaccinia Virus Ankara* (MVA), which led to the development of (Imvamune®), a third generation vaccine will be explained. The origin of MVA dates back to the CVA dermovaccinia strain[43], which was the cross strain of those obtained from donkeys and calves. Dr Şerafettin Mustafa (Kam) claimed to have produced these specific strains (maintained between donkeys and calves) first at İstanbul Vaccine Production Centre in 1932[44]. For the maintenance of the vaccine strain donkeys and calves were used and during the eradication campaigns seed cultures were obtained from WHO (Elhan Özlüarda, personal communication, 2005). Fenner *et al.*[8] indicates the use of the Paris strain for vaccine production in Turkey between 1968 to 1971. German researchers took the CVA dermovaccinia strain to Germany and started its passage in 1958 using chicken embryo fibroblast cultures[43,45]. After 300 passages changes in the plaque morphology of the strain were observed and at its 516th passage it was named MVA to differentiate it from other attenuated vaccine strains. The strain MVA was created as result of 574 dilution passage of the attenuated strain[43,45].

Complete genomic sequence analysis of the strain has been carried out revealing circa 15% gene loss compared to the original genome[46,47]. MVA fails to replicate in human cells, which sets it apart from vaccinia virus. Thus, it poses no risk of spreading in or among the carriers, and gains importance in vaccine research as well as a vector delivery system[48,49]. In the 1970s, MVA was used in clinical trials and regardless of minor local or general reactions, the resulting standard vaccinia virus reduced the diameter of skin lesions proving to be safe for human use[50]. However, it should be stressed that this vaccine has not been tested against a major outbreak of smallpox so far. According to some writers[51–53] MVA vaccine was tested on over 100,000 individuals in Germany and in Turkey without any complications, yet information about its use in Turkey is awaiting confirmation (Elhan Özlüarda, personal communication, 2005)[54,55]. In Bayern, Germany, Gerner *et al.*[56] also mention the administration of this vaccine to around 140,000 children in the mid-1970s but there is no confirmation that this vaccine, produced by the Bavarian Vaccine Institute, reached Turkey.

Conclusions

In her review of the Ottoman Physicians and Medical Sciences, Historian of Medicine, Sarı mentions the lack of data on the capabilities of the Ottomans in generating theory and their interest in the generation of new knowledge via research[57]. Most medical reports produced in the Ottoman era were based on medical practice rather than the philosophical background or clinical observations, which was also the case in dealing with smallpox throughout the empire. Ottoman medical circles had no interest, even at the level of intellectual curiosity, in inoculation that was applied widely among the Sultan's subjects. Necessity led them to resort to vaccination as a novel technique in the 19th Century. Finally, due to the global quest for a better understanding of the nature of what causes the disease, they distanced themselves from Islamic traditions (Divine Wisdom) and Galenic understanding of diseases and for the first time in 1885 the vaccine was only applied to children[23] whereas it was compulsory in many other countries long before it was applied in the Ottoman Empire (Bavaria, 1807; Denmark, 1810;

Norway, 1811; Russia 1812)[18]. Although it is still unclear how German scientists obtained the strain that resulted in the development of the MVA, the Republican era of Turkey used contemporary scientific principles for disease prevention and eradication.

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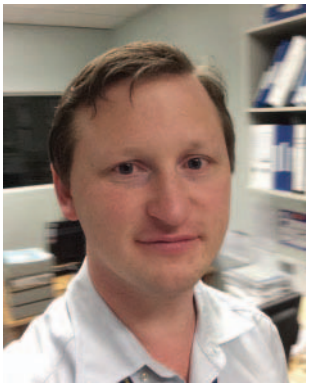
Biography

Prof. Osman Şadi Yenen (MD) is a graduate of İstanbul University, Medical Faculty (1974). Until 1997 he served as medical personnel in the Turkish Naval Forces, at Gülhane Military Medical Academy (GMMA), Ankara and at GMMA Teaching Hospital in İstanbul respectively as an expert of Infectious diseases and clinical microbiology. He was appointed as a full professor at the İstanbul University, Medical Faculty in 1997 and currently serves as a teaching academic at the Department of Microbiology, Virology and Immunology of the same faculty. He has over 100 peer-reviewed publications both in Turkish and English. He served as the secretary and the president of the Turkish Society for Clinical Microbiology and Infectious Diseases (KLIMIK) and was the co-convener of the 11th European Congress on Clinical Microbiology and Infectious Diseases held in İstanbul (ECMID 1–4 April 2001) as well as being part of the organisation of many international conferences took place in Turkey including the IUMS in 2008.

The global eradication of smallpox and the work of Frank Fenner



CR Robert George and William Rawlinson

Virology Division, SEALS Microbiology
Prince of Wales Hospital
Randwick, NSW 2031, Australia
Email: w.rawlinson@unsw.edu.au

The 1950s and 1960s represented a golden era in scientific discovery when many believed science would solve the world's greatest problems. It was the era when colour television was introduced and the role of DNA described, space programmes, the introduction of vaccines for polio, measles and mumps, and the structures of proteins began to be described. Many discoveries were controversial, but there was a strong belief science was taking the world forward and reducing medical problems rapidly. The Intensified Smallpox Eradication Program (ISEP) won united support from both the Union of Soviet Socialist Republics (USSR) and the United States of America (USA). The initiative was passed by only a small margin (two votes) and came on the back of several failed disease eradication programmes[1].

As documented in Professor Yenen's accompanying paper, smallpox was a scourge with a long history of different interventions that had been only been partially successful. Contrary to this long history of partially successful interventions using different methods in different countries, the ISEP was unequivocally successful globally. The programme resulted in eradication of smallpox in every country where case-notification was undertaken, marking the first infectious disease of humans to be eradicated via human intervention. It demonstrated that coordinated vaccination programmes could succeed on a global scale despite political, economic and scientific barriers. Instrumental to documenting the ISEP's success was Professor Frank Fenner, an Australian scientist and clinician who was elected Chairman of the committee certifying the programme's success, the Global Commission for the Certification of Smallpox Eradication (GCCSE). His work had put Australia at the forefront of poxvirus research, and he was closely associated with international poxvirus research. Multiple obituaries document his life, achievements, and his death in November 2010[2–10].

A DNA virus called variola (Orthopoxvirus, Poxviridae) causes smallpox. Case fatality rates varied depending on the infection type, reaching up to 30% in the historically most common form variola major[11]. Smallpox has influenced the course of history and decimated populations. For example, historians have debated whether up to one-third of the Aztec population was decimated by smallpox in 1520 after Hernando Cortes accidently introduced the virus thus facilitating the European conquest of South America[12]. Elsewhere, native Virginian inhabitants were depopulated to one-third of their former number in 1689, and numerous North American tribes were affected[13]. Similarly, Australian Aborigines suffered widespread variola following European colonisation of Australia[14]. In remedy, various methods were attempted to control the disease with varying success. There were numerous methods tried, and this included establishing dedicated hospitals (in 1374 a Japanese Emperor established a smallpox hospital after repeated epidemics)[15], and many different vaccination methods, as documented elsewhere in this volume of *Microbiology Australia*. Variolation, a method of exposing skin to material from smallpox pustules and thus inducing immunity had been employed by several cultures, and was eventually introduced to Great Britain (see Professor Yenen's accompanying paper). Utilising this technique, in 1793, Haygarth proposed an eradication programme for Great Britain[16]. In 1796 Edward Jenner famously demonstrated immunity in an individual inoculated with a related poxvirus from a cow's udder[17]. It may have seemed that resolution was within grasp. However, another 184 years would pass before Fenner announced to the World Health Assembly that smallpox had been eradicated. In the intervening

period, incremental steps were made, and slowly the burden of disease was reduced. Cowpox was gradually replaced with vaccinia as the vaccine. Freeze dried vaccine was introduced, and national vaccination programmes begun by many nations. By 1950, although in decline, the disease remained endemic in areas of Central and South America, Africa, and Asia[1]. In 1958, Professor Victor Zhdanov, the chief of Soviet delegation to the World Health Assembly proposed a global eradication programme that resulted in resolution WHA11.54 planning eradication within 10 years[1]. While some success was achieved (for example, China), eradication was not achieved within the ambitious timeframe, in part due to resource constraints. In response, in 1967 the World Health Organization (WHO) launched the IESP with the renewed objective of global eradication, with the Smallpox Eradication unit headed by Donald Henderson from 1966 to 1977.

Financial support was provided through a special budget of US$2.4 million per annum to the IESP, a figure overshadowed by the estimated US$315 million spent during the life of the programme[18]. Meanwhile smallpox remained endemic in 31 countries, with 10–15 million cases of annually[19]. Decisions were made to reduce the risk of early failure[1]. Reference centres were established for vaccine, and a quality programme established to ensure all vaccines used (including those produced in endemic countries) met strict standards regarding potency, stability and purity. The approach involved systematic vaccination, with rigorous surveillance and containment, whereby cases were reported weekly and special containment teams targeted outbreaks[20]. Rewards were paid to those who identified new cases[21]. This approach uniquely engaged and empowered local staff, whilst also minimising depletion of vaccine.

Between 1975 and 1977, smallpox had been contained to Bangladesh, Ethiopia, Kenya, and Somalia. The last case from Ethiopia was on 9 August 1976, from Kenya on 5 February 1977, and from Somalia on 26 October 1977 (the last wild case)[22,23]. At this time, the GCCSE was established to certify the eradication of smallpox, with Frank Fenner elected Chair. Eradication was defined as no cases from a country for 2 years[21]. Between inception of the GCCSE and 8 May 1980 when the final report was presented to the World Health Assembly, ongoing field studies, many of which Frank Fenner directly participated in, were performed to ensure no further cases occurred[24]. It was only after this work had been completed that the GCCSE was able to report: '1. Smallpox eradication has been achieved throughout the world. 2. There is no evidence that smallpox will return as an endemic disease'. The GCCSE made 19 recommendations to the World Health Assembly (Table 1), which have informed modern conduct in relation to smallpox.

Frank Fenner's role in certifying smallpox eradication (as described in interviews in 1992–1993 with Dr Max Blythe) was to meet over three successive years, organising 21 international commissions that visited all countries where smallpox had been endemic since 1967. The goal was to obtain signatures from every country verifying that no cases of smallpox had occurred, thereby certifying disease elimination. In retrospect, it is interesting to see the degree of cooperation between the USA and USSR, with meetings of the monkeypox committee in Moscow in 1969 in the midst of the cold war. It is also interesting that, similar to recent early, mistaken diagnoses for other viruses, Russian investigators mistakenly believed that white-pock variants of monkeypox were identical to vaccinia virus. They were not, and were subsequently shown to be laboratory contaminants, again as has occurred with some recent emerging viruses.

Although it is not the intention here to revisit all of the considerable achievements of Frank Fenner, it is important to note that his training, interests and skills made him an ideal candidate for the position as Chair. He was predominantly a scientist of viruses including poxviruses of humans and animals, but was trained originally in medicine, with a research degree early in his career (1942). During World War II, he served as an officer in the Australian Army Medical Corps in Australia, Palestine, Egypt, PNG and Borneo. This included clinical work, as well as specific studies of malaria, and as pathologist in a general hospital. He had interests and training in tropical medicine, and during smallpox certification, he visited many of the tropical countries to review eradication first hand. Further, he undertook research in different institutes – the Walter and Eliza Hall Institute in Melbourne (studying mousepox), the Rockefeller in New York (studying tuberculosis), and the John Curtin School of Medical Research in Canberra (studying myxoma, then as Director gaining management experience). He was also the President of the International Committee on Taxonomy of Viruses (1970–1975), and his attention to detail combined with writing skills contributed to this work, and the subsequent publication 7 years following eradication of the definitive text on smallpox history and eradication – *Smallpox and its eradication*. This unique combination of basic science, research, medical, managerial, and specific knowledge of poxviruses made him an ideal Chair for the GCCSE, that culminated in his announcement to the World Health Assembly that smallpox was eradicated.

It is possibly less well known, but equally relevant, that Professor Fenner was a key member (and subsequently Chair) of the committee examining whether animal viruses, specifically monkeypox virus, might constitute an animal reservoir of smallpox. Fenner's experience with animal poxviruses was key in this role, and in many

Table 1. Recommendations of the Global Commission for the Certification of Smallpox Eradication (GCCSE).

No.	Recommendation
1	Smallpox vaccination should be discontinued in every country except for investigators at special risk.
2	International Certificates of vaccination against smallpox should no longer be required of any travellers.
3	Sufficient freeze-dried smallpox vaccine to vaccinate 200 million people should be maintained by the WHO in refrigerated depots in two countries, together with stocks of bifurcated needles.
4	The stored vaccine should be periodically tested for potency.
5	Seed lots of vaccinia virus suitable for the preparation of smallpox vaccine should be maintained in designated WHO collaborating centres.
6	National health authorities that have vaccine stocks should be asked to inform WHO of the amount of vaccine maintained.
7	In order to maintain public confidence in the fact of global eradication, it is important that rumours of suspected smallpox, which can be expected to occur in many countries, should be thoroughly investigated. Information should be provided to WHO, if requested, so that it can be made available to the world community.
8	WHO should maintain an effective system to coordinate and participate in the investigation of suspected smallpox cases throughout the world. The international small-pox rumour register should be maintained.
9	No more than four WHO collaborating centres should be approved as suitable to hold and handle stocks of variola virus. A collaborating centre would be approved only if it had adequate containment facilities. Each such centre should report relevant information on its safety measures annually to WHO and be inspected periodically by WHO.
10	Other laboratories should be asked to destroy any stocks of variola virus that they hold, or transfer them to an approved WHO collaborating centre.
11	In collaboration with country health services, WHO should organize and assist a special surveillance programme on human monkeypox, its epidemiology, and its ecology in areas where it is known to have occurred. The programme should continue until 1985, when a further assessment of the situation should be made.
12	WHO should continue to encourage and coordinate research on orthopoxviruses.
13	WHO should maintain the system of WHO collaborating centres for carrying out diagnostic work and research on orthopoxviruses.
14	Research workers who do not work in a WHO collaborating centre and who wish to carry out experiments with variola or whitepox virus that are approved by the appropriate WHO committee should be offered the use of the special facilities in a WHO collaborating centre.
15	Research on poxviruses other than variola or whitepox viruses should not be performed under circumstances where there is any possibility of cross-contamination with these two agents.
16	WHO should ensure that appropriate publications are produced describing smallpox and its eradication and the principles and methods that are applicable to other programmes.
17	All relevant scientific, operational and administrative data should be catalogued and retained for archival purposes in WHO headquarters and perhaps also in several centres interested in the history of medicine.
18	An interregional team consisting of not less than two epidemiologists with past experience in the smallpox eradication campaign, plus supporting staff, should be maintained at WHO headquarters until at least the end of 1985. At least one additional field officer should be assigned to cover areas where human monkeypox is under investigation.
19	WHO should set up a committee on orthopoxvirus infections.

ways presaged the more recent one-health initiatives for human and animal health programmes His other key was final certification, and authorship of the WHO document *Smallpox and its eradication* in 1988, along with Donald Henderson, Isao Arita (Chief of the Smallpox Eradication unit 1977–1984), Zdenek Ježek (Chief of the Smallpox Eradication unit from 1985) and Ivan Ladnyi (Assistant Director-General of the WHO 1976–1983)[1]. Together, Fenner, Henderson and Arita were nominated for the Nobel Prize in Physiology or Medicine in 1985, 1986 and 1987, and shared the Japan prize in 1988.

Although the eradication of smallpox overseen by Frank Fenner and the GCSSE was widely praised, other issues remain controversial. While the virus is widely regarded as a potential biological weapon, it has been suggested that destruction of remaining stocks could set back scientific discovery and prevent the design of new antiviral agents in the event of a future outbreak[25]. In 1990 the WHO requested smallpox strain mapping, with subsequent stock destruction scheduled for 31 December 1993. Destruction has been repeatedly deferred and debate continues[26]. Meanwhile, the virus continues to play into international events. In 2002–2003 during a period of claims that the Iraq regime had amassed weapons of mass destruction, the White House released 28 news releases mentioning smallpox[27]. Vaccinia derived illness has occurred, particularly in relationship to vaccination[28,29]. Most recently, in 2014, vials reportedly from the 1950s and labelled 'variola' were discovered in a storage room in a US Food and Drug Administration laboratory in Maryland[30,31], continuing the importance of variola in our lives.

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Biographies

Dr Robert George is the Microbiology Registrar at SEALS Randwick. He completed a PhD at the University of Queensland where he worked on spatial modelling of entomological outbreak systems. He has also completed a BA majoring in history.

Professor William Rawlinson is head of the Division of Virology, in the Department of Microbiology SEALS. He has conjoint positions in the Department of Infectious Diseases, Prince of Wales Hospital, and as Professor in the School of Medical Science and the School of Biotechnology and Biomolecular Sciences at The University of New South Wales. He supervises PhD, Masters and science Honours students in studies of viral pathogenesis, with his research funded by NHMRC, ARC, and others. He is Director of the TGA licensed laboratory testing all increased risk donors in NSW for blood borne viruses. This laboratory has established new algorithms for testing, and continues to publish findings in evaluation of donors for infection.

History of tuberculosis and tuberculosis control program in Turkey

Cengiz Çavuşoğlu

Ege University Faculty of Medicine
Department of Medical Microbiology
Mycobacteriology Laboratory
Bornova, İzmir, Turkey
Email: cengizc2003@yahoo.com

Tuberculosis (TB) is debatably the most infectious disease with highest rate of causalities throughout human history. The Ottoman Empire also had the profound effect of the disease; however, following the establishment of the Republic of Turkey in 1923 effective TB control programs were implemented at times jointly with the WHO. From 1949 onwards, significant reduction in disease incidence and death rates in Turkey was recorded due to the significant efforts of the state and civil established *Tuberculosis Associations*. These successful Turkish control programs as well as the history of TB and the current global challenges related to the re-emergence of this deadly disease will be communicated in this article.

Tuberculosis was named *Phthisis* by Ancient Greek physicians[1,2]. Although its meaning is unclear, it might have originated from 'spitting' (saliva) or 'exhaustion' (consumed) in Greek[1,2]. For centuries, Anatolians have called it 'verem' (TB), 'ince ağrı' (subtle pain), 'ince hastalık' (thinning disease), or 'kuru hastalık' (dry illness). It is important to note this name has a unique definition in various languages: 'fading, weakened, exhausted'[2]. Currently, each of the human-infecting strains of *Mycobacterium tuberculosis* complex (MTBC) derives from a different common ancestor forming six major lineages. Lineages 5 and 6, which include *M. africanum strains*, are encountered in Western Africa. However, other lineages display significant variation in their distribution. The strains of lineage 1 within the EAI [East African-Indian] spoligotype cluster are accepted as the 'ancient' *M. tuberculosis* strains. They are frequently encountered in India and on the shores of Indian Ocean. Ancestral strains of *M. tuberculosis* spread via migration from India evolving into 'modern' lineages 2 (Beijing), 3 CAS (Central Asian Indian) and 4 (X, Haarlem, LAM [Latin-American Mediterranean]). In Turkey, the latest evolved lineage 4 has been most dominant. Current evidence might suggest migratory movements over the past 35,000–89,000 years from Africa spread four main lineages into Eurasia, while the remaining two phylogenetically 'ancient' lineages stayed in Africa. These lineages were later spread to the Sub-Indian continent and from there into Europe, sub-Saharan Africa and America, following a wave of reverse *Homo sapiens* migrations and conquests. Analysis of known mutation rates of the *M. tuberculosis* reveals that the differences among strains started to appear 250–1000 years ago[3–9].

Tuberculosis was initially documented over 5000 years ago in Ancient Egypt; characteristic Pott deformations of TB were detected in mummies, and even represented in Ancient Egyptian art. Recently, DNA of *M. tuberculosis* was amplified from mummy tissues providing confirmatory evidence. There are documents dating back 3300 years in India, and 2300 years in China and archaeological evidence from the Andes also confirm the existence of pre-Columbian tuberculosis. In preserved mummies of Peru, bone tuberculosis was detected, as well as the pathogen DNA in mummy tissues[1,10–14]. It was fully defined by Hippocrates (b. 460 B.C.), while its infectious nature was first identified by Clarissimus Galenus of Pergamon (131 A.D.). Human-to-human transmission, on the other hand, was mentioned by İbn-i Sina (Avicenna, Bukhara 980–1038 A.D.) in his book *El-kanun fi't tıbb (Canon medicinae)*[1,15,16].

In medieval times, Europeans lived in small farming communities of 200–300 people and tuberculosis was not widespread. The Middle Ages saw the lymphadenitis form of tuberculosis named *Scrofula* as most dominant. Villagers, who suffered from Scrofula, believed they could regain their health with the king's touch so it came to be known as 'the King's Evil'. Scrofula was not the most severe form and recovering patients attributed their fortune to the king's divine power[1,2]. In 1720, Benjamin Marten described the lesions caused as 'wonderfully minute living creatures' in *A New Theory of Consumptions: More Especially a Phthisis or Consumption of the Lungs*, and proposed the *contagium vivum fluidum* theory, which provided an explanation based on the *Germ Theory*. Marteen was the first to describe its cause as 'animicula'. Following a series of autopsies, Laennec (1819) concluded that lesions, which appear in various forms in a number of locations in the body, were the result of a single

disease[1,2]. Schönlein defined TB as a proper disease and used the term *Tuberculosis* for the first time (1839). Despite all these observations, the common belief in 19th-Century Northern Europe remained that it was hereditary, whereas in Southern Europe it was believed to be contagious[1,2]. Although seen in mediaeval Europe, TB became widespread only after large-scale urbanisation in the second half of 17th Century. John Bunyan, in his book *The Life and Death of Mr. Badman* of 1680, defined TB as 'The Captain among these Men of Death'. In London, in 1600s, 1000–1250/100,000 persons had TB. At the time of Industrial Revolution in 1780, TB reached its peak and 1120/100,000 died as a result of it. Although casualties had a steady decrease by 19th Century, between the years 1831 and 1835 some 567/100,000 lost their lives in London due to TB. One fourth of the European population had TB, which was spread through migration of infected people into North and South America, Africa and the Pacific Islands[1]. Also in the Ottoman Court, TB was common and Sultan Mahmut II (1785–1839) as well as his mother and son died of it. Ottoman records appear as late as the reign of Sultan Abdülhamid II in 1901; however, it was evident that TB was a major problem throughout Ottoman Empire in the 18th and 19th Centuries[2,15,17]. In 19th-Century England, the pale face of TB patients was perceived as beautiful in literary circles, so it was associated with the birth of a new era called Romanticism[1]. Alexander Dumas (fils) wrote *The Lady of the Camellias* in 1848 and the consumptive heroine 'Marguerite Gautier' deeply influenced Turkish literature initiating a sentimentalist approach to TB.

TB's infectious nature was experimentally proved by J.A. Villemin, who published his findings in *Etudes sur la Tuberculosis*. Robert Koch, 14 years later, described the causative agent in his speech titled *Die Aetiologie der Tuberkulose* (Berlin Physiology Society, 24 March 1882). He not only defined the infectious agent but also laid the foundations for the Koch-Henle postulate linking the infectious agent to the formation of the disease, still in use today. Koch also (10th International Conference of Medicine in Berlin, 1890) claimed the discovery of an inhibitory agent, which stopped the growth of tubercle bacillus both in tube and in animal models. Koch's discovery (although the tuberculin has not the curative effect he had initially hoped for[1]) and similar developments in Europe were closely followed during the reign of Sultan Abdülhamid II, but the administration of tuberculin at the German Hospital in İstanbul turned ineffective. Upon this outcome, an Ottoman delegation was sent to Berlin and in a report published by this delegation in the 'Gazette Médicale d'Orient' (1891), it was stressed that the use of Koch's compound throughout the empire was subject to permission from the Sultan[2,15]. Koch's tuberculin, first tested (for detection of latent TB infections) in 1907 by von Pirquet, was actually a pioneering step towards the intra-cutaneous administration of PPD (purified protein derivative) also used today. This first attempt was followed by Mantoux's intra-cutaneous injection in 1908. In the 1930s, Seibert developed the standardised PPD used today and five units of PPD-S was subsequently used globally for detection of latent TB infections[1,3]. In the Ottoman Empire, the first tuberculin production and application commenced at Bakteriyolojihane-i Şahane between 1910–1913[2,15].

Following the discovery of the tubercle bacillus, public health authorities made significant attempts to prevent its spread in North America and Europe. The focus of early measures was to prevent spitting[1], which was also the case in Ottoman Empire and upon orders of Sultan Abdülhamid II, a comprehensive report was produced by Cemiyet-i Tıbbiye-i Şahane. In hospitals and prisons, TB sufferers were isolated and allocated a spitting bowl each. Spitting was strictly forbidden in military barracks and schools, and special TB wards were established in hospitals as a preventative measure[2]. Until the discovery of antibiotics, the establishment of sanatoria was the only effective strategy for treatment, and the first one opened in 1859 in Görbersdorf. Their curative effect has been unclear as the results obtained in New York sanatoria were similar to those spontaneous cases without sanatoria experience[1,3]. The first children's sanatorium Hamidiye Etfal Hastane-i Âlisi was opened in 1905 in Ottoman Empire. Efforts to establish these residences continued in the Republican era[2,15], and the most prominent sanatorium opened in 1925 on Heybeliada (Princes' Islands, İstanbul) located among pine trees for clean air (Figure 1).

It closed down in 2005 but left its mark during its years of service not only due to the treatment but also due to the training provided to equip the patients[15]. In Turkey, both at Ottoman times, and after the establishment of the Turkish Republic, the fight against TB was conducted via cooperation of the state and civil established *Tuberculosis Associations*. Dr. Besim Ömer Pasha was a pioneering figure, who had a ticket to travel on the Titanic in 1912 but missed it only to become the founder and the first president of the association (*Veremle Mücadele Osmanlı Cemiyeti*) established on 8 June 1918. With its offices around the country, the association survived thanks to donations from the public, private businesses, town councils and the sale of memorabilia[2,12,18,19]. In the USA, from 1947, mobile X-ray teams screened large numbers of Americans to keep the disease under control; however, as incidence rates went down, the 1960s saw mobile assistance replaced by special TB clinics[1]. In Turkey, pilot screens were conducted in the 1960s by similar mobile teams, and from 1966–1976 the entire population, even remote villages were screened for TB presence. In 1997, it was declared that TB had been in decline but mobile teams continued to screen high-risk areas such as prisons and correction facilities[2,20,21]. In the pre-

Figure 1. Heybeliada Sanatorium (source: courtesy of the Municipality of Princes' Islands).

antibiotic era, pulmonary collapse treatment was used to close the cavities caused by the disease. Surgically induced pulmonary collapse treatment started in the late 19th Century and became widely administered in the early 20th Century. The first successful pneumothorax treatment was conducted by Ramadge in London in 1834, and resulted in the recovery of the patient[1,3]. This was also adopted in Turkey and the results were published in 1922[2]. The first vaccine was developed by Albert Calmette and Camille Guérin at Pasteur Institute, Lille using the strain *Mycobacterium bovis* subcultured 230 times to achieve a low virulence vaccine strain. In 1919, the *Bacilli Calmette-Guérin* (BCG) vaccine strain was developed and orally administered to a 3-day-old baby for the first time (1921)[1,22]. Wallgren developed intra-dermal application of the vaccine in 1927, and BCG vaccine was approved for human use by UN in 1928. BCG was first applied orally in 1926 in Turkey. The vaccine was also produced at Refik Saydam Hıfzıssıhha Merkezi (RSHM) (Figure 2) until 1998 and was first administered intradermally by Dr Tevfik Salim Sağlam in 1948[2,15].

The fight against TB gained further momentum in Turkey starting from 1949 and by the 1950s international agreements with WHO and UNICEF made BCG an integral part of the control programs[2]. There were 10 major vaccine campaigns in Turkey between 1952–1985 jointly conducted with WHO and UNICEF[1,2] and seven of these were conducted by Dr Hamdi Açan. During his time, public screening campaigns were run by travelling teams and 90% of the population was successfully vaccinated in cities, towns and villages[2,15]. From 1997 onwards, the vaccine commenced to be administered to two-month-old babies as well as to primary school children bringing an end to large-scale public-screening campaigns subsequently[20]. While the success rate of BCG vaccine has always been an issue for debate, extensive studies have found it to be between 0–80%[1,22]. Currently, WHO recommends vaccine administration only to newborns and it is routinely administered to 2-month-old babies in Turkey. The first effective antibiotic streptomycin was discovered in 1944 and led to significant improvements in the condition of a female patient within a few months of its application[3]. This was followed by the orally administered mycobactericidal drug isoniazid in 1952 rendering the disease treatable. Subsequent effective antibiotics such as pyrazinamide (1954), ethambutol (1962), and rifampicin (1966) brought standard therapy time down to 6 months[3,15] which resulted in the closure of sanatoria. With wide-scale applications of effective treatment, prevention and control of TB entered a new phase, and was extended to cover voluntary requests from infected patients for new treatments[3]. Streptomycin administration started in Turkey at Çamlıca Sanatorium (1947). At Heybeliada Sanatorium isoniazid treatment occurred first in 1955 and was followed by combined rifampicin, isoniazid, pyrazinamide and ethambutol therapy following the WHO's recommendations in 1969[23,24].

From the mid-19th Century onwards, TB waves weakened in Europe and North America, and in Britain, between the years 1860 and 1900 the death rate was reduced 42% (348/100,000 to 202/100,000). Increased food production (better nutrition) and infection-spread prevention measures might have played a significant role in this

Figure 2. Refik Saydam Hıfzıssıhha Merkezi (current name: Public Health Institution of Turkey) was established with the support of Rockefeller Foundation in the capital city Ankara and building was designed by Austrian Arcitechs Theodor Jost and Robert Oerley. Construction of the Institute was completed between the years 1927 and 1932 (Source: courtesy of Mustafa Hacıömeroğlu).

reduction. There were also claims related to development of TB-resistant human populations as part of natural selection, contributing to reduced rates to some extent[1]. By 1901, the first record-keeping year in Ottoman Empire, the death rate from TB was 264/100,000 in İstanbul, which was 30% higher than that in England. During WWI, an increase was observed (351/100,000 in 1918 and 268/100,000 in 1922); however, in the Republican era, this number was reduced to 187/100,000 (1939). Despite the misery and difficult conditions of the Balkans, WWI and Turkish Independence War the death rate in İstanbul was reduced 29% within 38 years of initial record keeping. By 1949, out of a population of 20 million, the number of consumptive people stood around 300,000 and the death rate was 218/100.000. An increase between the years 1939–1949 may be attributed to a reduction in food supply and production (although Turkey did not participate in WWII), increased urbanisation and record-keeping efficiency. Similar increases were also observed in Europe during and after war years. Deaths from TB per 100,000 people were 204 (1950), 55 (1960), 8.8 (1980), and 1.8 (2000)[2,25,26] and incidence rates per 100,000 172 (1965), 52.2 (1980), 40 (2002), 28 (2010) and 19.4 (2012). From 1949 onwards, significant reduction in deaths rates and incidence rates in Turkey was recorded. Between the years 1949 and 1965, reported incidence rates went down by 88%, and between 1949–1960 death statistics showed a 75% decrease. Natural selection of individuals insusceptible the disease, fewer infections due to BCG vaccination, improved nutrition due to food-aid and also introduction of chemotherapy from 1940s have all contributed to this reduction. In 2010, the TB patient number reported was 15,183 in Turkey out of the total population of 73,722,988. The reported mortality rate from the TB in Turkey was 0.72 in every 100,000 in 2011[26,27].

Styblo and co-workers reported a decrease in TB incidences in Europe (1978) and in parts of Africa; however, the emergence of AIDS in 1980s altered the incidence again for 20 years. Strict control measures were subsequently introduced to monitor patients, especially, *Directly Observed Treatment Short Course* (DOTS) created new hopes for eradication in Africa, with a significant decrease from 2005. Turkey also implemented these strategies and jointly with WHO, DOTS started in 2002 in pilot regions to be later applied nationwide (2006)[2]. Despite these strategies, we are still far from the WHO 2050 target of one case in a million. Currently, the infection rate with multidrug resistant TB (MDR-TB) in sub-Saharan Africa and former Soviet Union (FSU) countries is extremely concerning[28,29]. In Turkey, surveys conducted in 2012 indicate that only 2% of the patients are MDR-TB[26,27]; however, detection of MDR-Beijing strain spreading via FSU countries is recorded frequently. As human travel increases, full international cooperation is

required for eradication. The history of tuberculosis suggests that the current wave will pass, even in the face of AIDS, although many will lie dead in its wake. Our challenge is to lower its crest and hasten its passing[1].

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Biography

Prof. Cengiz Çavuşoğlu (MD) is a graduate of Akdeniz University, Faculty of Medicine (1989). He practiced medicine in the Anatolian city of Kastamonu from 1989 to 1991 before joining the Ege University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology. He obtained specialisation in Clinical Microbiology and Infectious Diseases in 1996 and worked as a specialist until 2004 in the Department of Medical Microbiology. He became Associate Professor in 2004 and full Professor in 2011. He has been working in the Mycobacteriology Laboratory of the same department since 1998 and became the head of the laboratory in 2006. His research interests are in the field of mycobacteriology and molecular microbiology. He has 28 publications, international conference and workshop participations, 23 Genbank nucleotide deposits and Web of Science citations over 300 times. Presently he is a member of the Turkish Society for Microbiology and the Bacterial Genetics and the Mycobacterium Special Interest Groups.

Holistic approach to infection control and healing: the Florence Nightingale story

Bülent Gürler

İstanbul University, İstanbul Medical Faculty
Department of Clinical Microbiology
Çapa, İstanbul, Turkey
Email: gurlerb@netone.com.tr

Florence Nightingale (1820–1910), with a life devoted to the care of the sick and wounded, is the founder of modern nursing. She was named after the city 'Florence' in Italy where she was born. She belonged to a rich and aristocratic family in England and with the encouragement of her father she received education in mathematics, religion, history and philosophy of education, as well as the languages, Latin, German, French and Italian. Rejecting authority and religious dogmas, she became a pioneer of human rights movement, advocating holistic thinking for mankind. At a young age, she began to visit hospitals, saddened by the inadequacies in the physical structures of hospitals, poor sanitation and patient care. These visits had a profound effect shaping her future endeavours as the founder of the nursing profession. In 1851 she gained nursing training in Germany and on her return to England she started to work as a nurse in a private hospital in London.

The Crimean War and İstanbul

The turning point of her life came in 1854 when Britain entered the Crimean War (1854–1856) along with Ottoman Empire and France fighting against the Russian Empire. Constant combat during the war generated significant number of casualties who subsequently died due to a lack of doctors, nurses, healthcare workers and medical supplies. A family friend and a British Government official, Sidney Herbert, encouraged her to organise a group of nurses and other healthcare workers and travel to Crimea to give aid to the desperate, wounded soldiers.

The Selimiye Military Barracks in Üsküdar (Scutari), İstanbul were allocated to the British Army as it was on the way from Britain to Crimea. After the troops left for the front, the barracks were converted into a temporary military hospital. She arrived at Scutari in İstanbul (then the Ottoman capital) in November 1854 with a team of 38 volunteer nurses and they settled in the temporary 'Selimiye Barracks Hospital' (Figure 1) where up to 5000 injured were treated at peak times.

Under difficult and poor sanitary conditions, Florence Nightingale and her volunteer nurses provided excellent care for the injured, reducing the number of deaths. They worked tirelessly to improve the overall condition of the hospital as well as bed-side care including clean bandages, bedding and other supplies for the sick and wounded. She inspected the injured and sick every night with a lamp and she was then named as 'the lady with a lamp' (Figure 2). Florence Nightingale instituted a strict nursing timetable to insure that the soldiers were cared for and attended to on a regular basis to improve recovery which formed the basis of modern nursing practices employed since then. At the 'Scutari Barracks' she established fame as the pioneer of the nursing profession.

The Selimiye Barracks Hospital and beyond: theoretical foundations of nursing

After the war ended in 1856, she returned to England and published two books: ***Notes on Matters Affecting the Health, Efficiency and Hospital Administration of the British Army*** (1857) and ***Notes on Nursing/Hospitals*** (1859), which described her experience and innovative ideas on caring for the sick. Most of these experiences were gained at the 'Selimiye Barracks Hospital'. In 1860, she established the first modern nursing school **Nightingale Training School for Nurses** at St Thomas Hospital in London. She continued to publish and placed emphasis on the importance of hygiene and care in infection control as well as on nursing as a sacred profession for women, in particular. With her books, public appearances and the spread of **Nightingale Nursing School** graduates, Florence Nightingale's healthcare reforms and innovative practices spread throughout the world. She even provided advice to American nurses and healthcare workers during the American Civil War of 1861–1865.

She turned filthy military camps into clean and sanitised medical wards and transformed the military health care systems to such an extent that she was recognised by Queen Victoria who met with her to obtain views and advice for improving of military hospitals throughout the British Empire.

Florence Nightingale completely revamped and modernised the entire healthcare delivery and sanitation systems building on her experiences at the 'Selimiye Barracks Hospital'[1]. Most remarkably, her background strength in mathematics led her to pioneer new

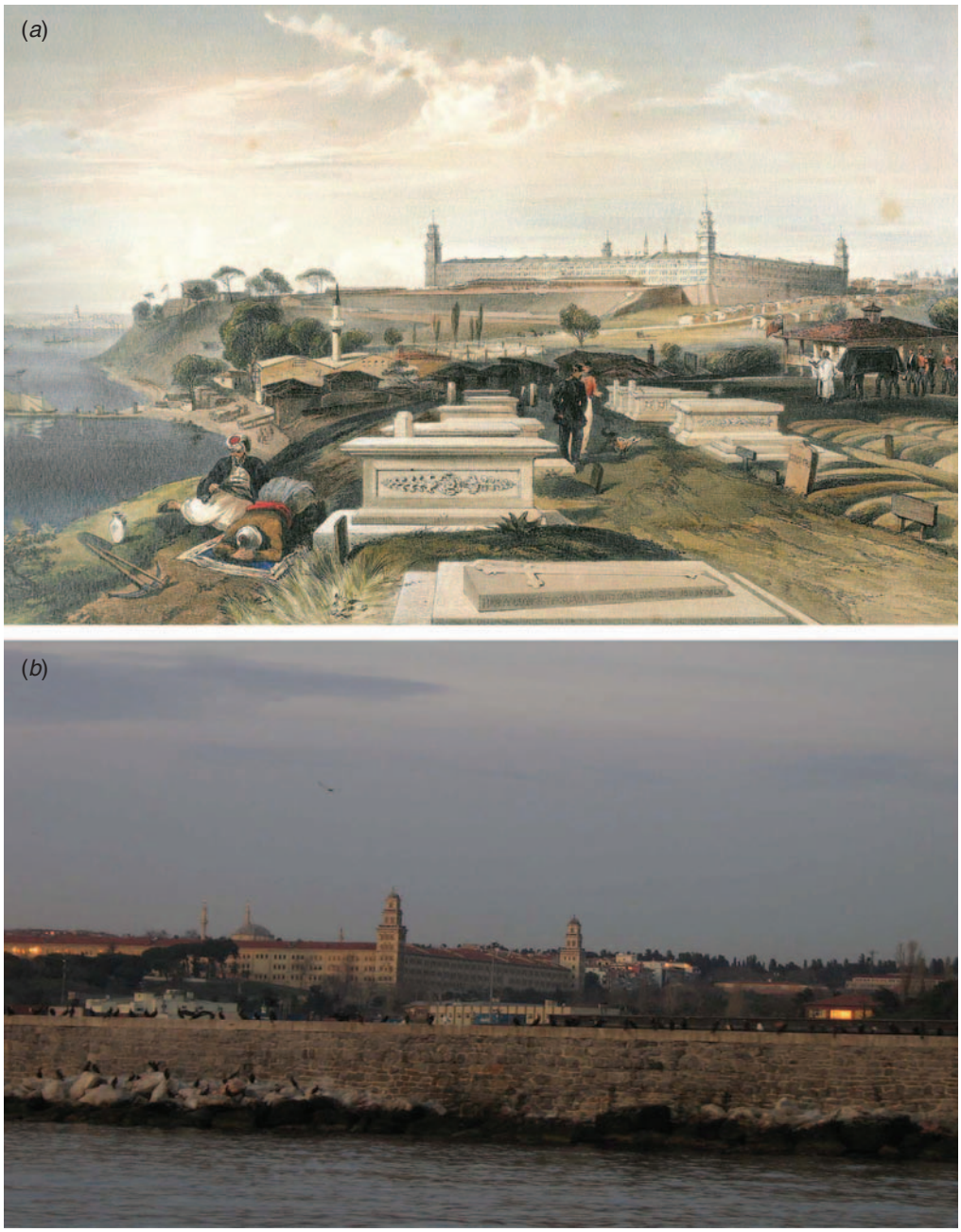

Figure 1. (*a*) Selimiye Barracks and Haydarpaşa British Cemetery during the Crimean War (original painting by William Simpson (1855), copy of the painting scanned from the 2007 Calendar produced for the 150th Anniversary of the Crimean War by the Museum of Sadberk Hanım, Vehbi Koç Foundation) and (*b*) Selimiye Barracks today (Üsküdar, İstanbul, Turkey).

techniques related to statistical data collection, analysis and display/delivery[2]. This was used to help improve poor medical care and unsanitary conditions of the established healthcare systems. She also implemented much innovative record keeping and impact analysis systems based on pioneering statistical techniques. She developed the **Polar-Area Diagram**[3] to identify, plot and display the needless deaths of soldiers caused by the lack of ongoing, dedicated care, lack of sufficient food and unsanitary conditions. She also proved that statistics provided a superior means of understanding of the overall status of healthcare delivery and such data collection and analysis led to improved medical and surgical delivery. Her innovative **Model Hospital Statistical Form** helped hospitals to better collect and generate consistent healthcare maintenance data for use in improving healthcare delivery. She also introduced **Florence Nightingale's Environmental Theory** that suggests that direct sunlight, fresh air, and cleanliness improves health. All these efforts had profound effect on the improvement of the practices and saving lives and even today studies are conducted using these approaches[4]. Other recent examples include inclusion of Nightingale's primary tenets, such as **building trust, self-assessment, and group leadership** during study designs[5].

She was the first to establish a theoretical foundation for nursing and stressed that the discipline is different from medicine and the goal of

Figure 2. The lady with a lamp (Florence Nightingale Museum in İstanbul).

nursing is 'to place the patient in the best possible condition for nature to act' and the environmental adaptation remains the basis of holistic nursing care[6–8].

Awards and recognitions

In 1858 she became a **Fellow of the Royal Statistical Society** and was made an honorary member of the **American Statistical Association** in 1874. She received the **Royal Red Cross** from Queen Victoria in 1907 and later that year at the age of 87 she became the first woman to receive **Order of Merit** from King Edward VII.

She also received awards of recognition from the Ottoman Sultan Abdülmecit and gained respect and recognition in Turkey. In 1961, İstanbul University established a school dedicated to nursing profession naming it after her '**The İstanbul University Florence Nightingale School of Nursing** (IUFNSON)'. The School aims to provide education 'that can improve healthcare to its highest level and develop national standards in this field following the philosophy established by her, which is based on the belief and the principle that a holistic approach to the individual, the family and the community requires close collaboration with the other members of the health team'. The general objectives of the School are developed within six basic concepts taking foundational principles from her approaches to nursing: scientific knowledge, clinical practice, education, management, leadership, research and development of nursing.

Florence Nightingale Museum in İstanbul

The Turkish Army Barracks (Üsküdar (Scutari), İstanbul), which served as a British military base and hospital from 1854 to 1856 during the Crimean War, is where the Florence Nightingale Museum is located today. The room she occupied, her original desk where she wrote her letters while overlooking the beautiful landscape and blue marine waters of İstanbul can still be seen. They provide an insight into the woman who bettered the conditions and reduced the mortality rates of the Crimean War soldiers.

Since 1954 (1964 in Turkey), her birthday of 12 May is celebrated as the **International Nurses Day** (IND). Florence Nightingale's way of thinking, beliefs and principles of nursing-related services are still valid today and they shaped the modern day nursing practices globally and in Turkey.

Acknowledgement

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Biography

Prof. Dr Bülent Gürler graduated from İstanbul Technical University, Faculty of Chemical Engineering in 1972. He conducted post-graduate research in Göttingen and Detmold, Germany (1981–82). After his return to Turkey he was awarded a doctorate in medicine (1989) and became a full professor in 1996 at one of Turkey's leading university hospitals; İstanbul University, Medical Faculty, Department of Microbiology and Immunology in İstanbul. His research activities have been directed to infection control, prevention of nosocomial infections, disinfection and sterilisation. He has been the founding member and the Honorary President of the Turkish Society for Disinfection, Antiseptics and Sterilization (DAS) as well as the President of the Turkish Society for Antibiotics and Chemotherapy (ANKEM). He represents Turkey at the European Culture Collections Organization (ECCO) Meetings. He is also the President of the Turkish Culture Collections (KUKENS) which is a member collection of the World Federation of Culture Collections (WFCC). KUKENS will host the 14th International Conference on Culture Collections in Antalya, Turkey in 2016.

Penicillin: World War II infections and Howard Florey

Ian Gust

Department of Microbiology and Immunology
University of Melbourne
Parkville, Vic. 3010, Australia
Tel: +61 3 8344 3963
Fax: +61 3 8344 6552
Email: idg@unimelb.edu.au

Howard Florey is celebrated for his major contributions to the large-scale production of the fungal product, penicillin, during World War II (WWII), leading to life-saving outcomes for many more than those with war wounds.

Howard Florey was born in South Australia in 1898. After studying medicine at the University of Adelaide he was awarded a Rhodes Scholarship to work in Oxford under Sir Charles Sherrington. After subsequently undertaking a PhD at Cambridge and a brief period as Professor of Physiology at The University of Sheffield, he was appointed to a chair in the Sir William Dunn School of Pathology at Oxford, where he remained until his retirement.

In the 1930s bacterial infections were an unimportant cause of illness and death in civilian populations were untreatable. In civilian life, diseases such as meningitis and pneumonia were frequently fatal, minor wounds could result in cellulitis or life threatening septicaemia and sexually transmitted diseases such as syphilis and gonorrhoea were serious conditions. On the battlefield it is estimated that up to one-third of lives lost were due to secondary infections.

Florey became interested in the use of natural substances to combat infections and in 1938, with biochemist Ernst Chain, began a systematic study of the antibacterial properties of substances produced by bacteria and fungi. They selected penicillin, a substance produced by the fungus *Penicillium notatum*, which had been described by Alexander Fleming almost a decade earlier, for further study. Chain and his colleague Norman Heatley were able to devise extraction and purification techniques which enabled them to obtain sufficient penicillin to test its efficacy in laboratory animals.

On 25 May 1940, a batch of laboratory mice were injected with a lethal dose of streptococci and half then treated with penicillin. The results were dramatic – the control mice rapidly succumbed, while all of the treated mice survived. These results attracted great interest from the scientific and military communities because, if replicated in humans, the drug had the potential to influence the outcome of WWII.

It took Florey and 16 colleagues several months to produce sufficient material to treat a handful of patients. The team worked under difficult circumstances with a lack of funding and equipment; at first penicillin was made using old dairy equipment. Hospital bedpans were later used to grow the mould and the liquid containing penicillin drained from beneath the growing mould and filtered through parachute silk.

The first patient they treated was a policeman, in whom an infected scratch had developed into a life threatening infection. He was given penicillin, and within a day began to recover. Unfortunately Florey's team only had sufficient drug for 5 days of treatment and when their efforts to recycle penicillin from the patient's urine failed, he relapsed and died. Because of this experience, the team then concentrated their effects on sick children, who did not require such large quantitates of the drug, demonstrating its value in a child with septicaemia and another with meningitis.

By mid-1941 the drug's potential was widely recognised and it was clear that the team needed the help of industry to produce it at large scale. Companies in Britain were unable to help out because of the war, so later that year Florey and Heatley took a dangerous flight to the United States in a blacked-out plane. Penicillin production was declared a war project and given high priority. Florey convinced four major pharmaceutical companies (Pfizer, Abbott, Merck and Lederle) and many smaller players to become involved.

During these meetings Florey encountered a scientist from the Department of Agriculture who was searching for a new use for a thick liquid that was a by product from the milling of corn. When this liquid was used, as a substrate the yield of penicillin was increased 10-fold. A further boost was given when Mary Hunt (known as Mouldy Mary) found a species of penicillin growing on a moulding cantaloupe (*P. chrysogenum*) was almost 200 times as successful again in producing penicillin as *P. notatum*. Further modifications resulted in strains almost 1000 times as productive as Fleming's original cultures.

By late 1943 mass production of the drug had commenced in 25,000 gallon aerated metal tanks, a process that Pfizer devised and made available to its rivals and later that year Florey was able to test the drug in soldiers in North Africa, with dramatic results especially in the treatment of gonorrhoea. Production continued to rise so that some 2 million doses were available for the D-day landings in June 1944. The results were dramatic, the survival rate for wounded soldiers rising from 4 per 100 (WWI) to around 50 per 100 and the death rate from pneumonia, falling from 18% to less than 1%. By the end of the war, many laboratories were manufacturing the drug, including Australia's Commonwealth Serum Laboratories.

In 1943, the public health worker, Bill Keogh, convinced the war cabinet that Australia needed to be self-sufficient in penicillin and identified a young vet, Val Bazely, who was serving in an armoured regiment in New Guinea, as the man for the job. Bazely was ordered back to Melbourne and almost immediately sent to the US. He spent three months visiting major manufacturers and returned in December with a great deal of new knowledge, most of it in his head.

Bazely set himself the heroic target of producing penicillin within six weeks and worked day and night to achieve it. He produced specifications and working drawings, designed purification processes, identified suppliers and fabricators, commandeered equipment and scrounged for scarce raw material. To obtain efficient staff, he persuaded soldiers who were awaiting discharge to assist him. By February, 1944, 10 weeks after his return, a sizable quantity of material had been produced and, by April, CSL became the first company in the world able to provide penicillin to both soldiers and civilians.

Despite living in Britain for all his working life, Florey took a great interest in Australia, hosting many young post-docs in his laboratories and visiting regularly.

A paper that he wrote played a seminal role in the decision to establish the Australian National University and during 1947–1958 he was closely associated with development of the John Curtin School of Medical Research, effectively acting as its non-resident head and declining several offers of the Directorship.

Florey was an excellent experimentalist, a gifted writer and a strong and effective administrator who had the knack of getting things done. His last major role, that of President of the Royal Society was outstandingly successful, resulting in major reforms.

Florey was an excellent sportsman, who excelled at tennis. He loved to travel, was an enthusiastic photographer and found pleasure in gardening.

Once the importance of penicillin was recognised, Florey received many honours. He became a member of the Royal Society in 1941, was knighted in 1944, received the Nobel Prize in 1945, the French Legion d'honneur in 1946 and the US Medal of Merit in 1948. In 1965 he was created Baron Florey of Adelaide and later appointed to the Order of Merit.

As one of Australia's greatest scientists, Florey has been rightly celebrated. His likeness adorns Australia's $50 note, and his name lives on – both a suburb in Canberra and a major research institute in Melbourne are named after him.

Biography

Professor Ian Gust A.O., is a medical virologist with advanced training in pathology and infectious diseases. In 1986 he established the Burnet Institute (1986) and became its founding director. In 1990 he became the R&D Director at CSL Ltd. More recently he has assisted public and private sector organisations, either as a board member or scientific advisor.

5th Australasian Vaccine and Immunotherapeutics Development Meeting, 7–9 May 2014

The AVID meeting is held every 2 years bringing together immunologists, virologists, microbiologists and vaccinologists both nationally and internationally. The AVID committee acknowledge the support of the ASM as a major partner to this meeting, together with generous support from CSL, QIMR, Burnet Institute, Australasian Society for Immunology, EMBO, Immunology Group of Victoria (IgV) and trade partners Miltenyl Biotec, Millennium Science and PALL Life Sciences. The IgV coordinated their Master Class with the AVID conference allowing them to uniquely expose students to a stellar line-up of researchers spanning multiple lines of microbial pathogen investigation. These included Prof. Federica Sallusto, Dr James Murphy, Prof. Elizabeth Hartland, A/Prof. Phillip Darcy, A/Prof. Kristen Radford, Prof. Rick Pearson, Dr Irina Caminschi and Dr Marco Herold.

The AVID conference saw a packed programme composed of 14 sessions with a clear focus on understanding how the body deals with viral, bacterial and parasitic infections and how best to generate effective vaccines for these that might be cheap and effective for developing countries.

Plenary and Keynote speakers for the conference included Prof. Antonio Lanzavecchia, Prof. James McCluskey, Prof. Adrian Hill, Prof. Julie McElrath, Prof. Federica Sallusto and Dr Brian Rudd. Session 2: Novel Vaccine Vectors and Delivery where Mark Kendall led the discussions on how nanopatches allow delivery of vaccines in a needle-free manner. The barrier provided by the skin and the importance of the microbes in the skin was a central theme of the session. Dr Manisha Pandey discussed the mechanisms involved effective action of a synthetic peptide vaccine in protection of the skin against Streptococcus pyogenes. Other speakers including Eugene Maraskovsky, Gavin Painter and Daniel Getts highlighted the importance of different adjuvants as carriers of antigens to fight viral and bacterial diseases. Fasseli Coulibaly introduced the concept of the microcube for the generation of HIV antigen. A full programme of all speakers in the sessions is attached.

There were 170 registrants at the 2014 conference, which was a 17% increase in attendees from the 2012 meeting held in Brisbane. The majority of the registrants predictably came from Victoria (66%) with 17% attending from Queensland and pleasingly over 7% of international delegates attended. A small representation attended from the other Australian states.

The committee is also pleased to report that student involvement at the conference was significant with over 20% of attendees being students. The committee is continually trying to foster the development of upcoming students with awarding of poster presentation prizes and oral positions in the programme.

In closing, the sponsors were wholeheartedly acknowledged for their contributions and this support was instrumental in allowing the stellar line-up of speakers and coordination of the Master Class to focus on student involvement across disciplines. Participants were encouraged to attend upcoming conferences related to the sponsors.

The 6th Australasian Vaccine and Immunotherapeutics Development Meeting will be held in Queensland in 2016.

Gabrielle Belz
Chair, AVID2014
Email: belz@wehi.edu.au

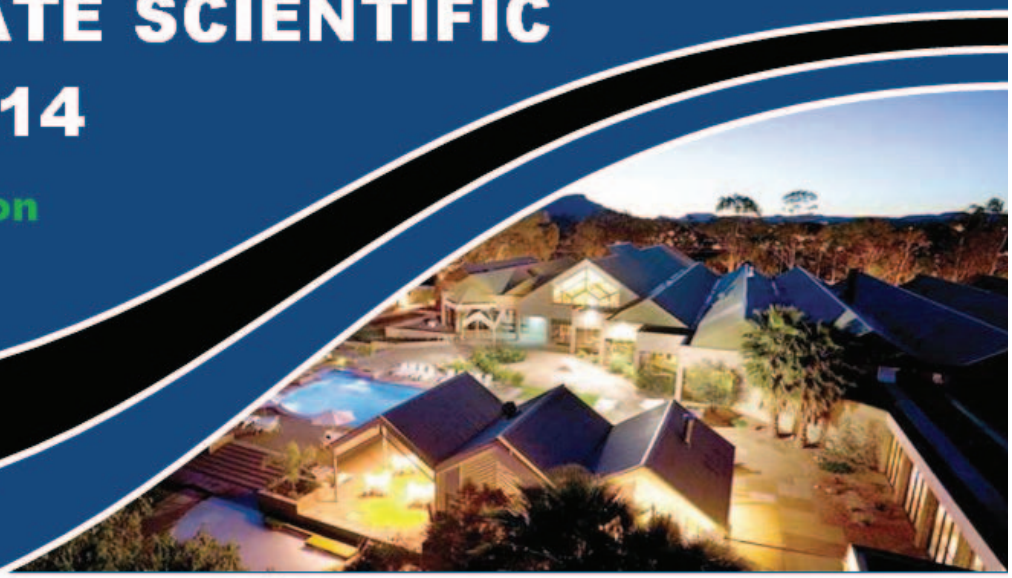
ASM2014

A report on the ASM2014 conference and ASM awards will appear in the next issue of *Microbiology Australia*.

31ST OCTOBER - 1ST NOVEMBER

ASM TRI-STATE SCIENTIFIC MEETING 2014

@ Doubletree by Hilton Alice Springs, NT



The WA Branch Committee is happy to host and organise this year's Tri-State meeting.

What you can expect:

A varied and engaging scientific program from some of the nation's leaders in their field
Fantastic location, good food and social/ networking opportunities

CONFIRMED SPEAKERS – FINAL PROGRAM TBC

- **Denque Vector Control – Prof. Scott Ritchie**
- **Ebola and MERS virus – Dr David Smith**
- **Stronglyloides – Dr Thersa Kearns**
- **Pertussis – Dr Paul Effler**
- **Arbovirus surveillance in North-West Western Australia – Prof. Lynda Selvey**
- **Diagnostic applications of whole genome sequencing – Prof. Phil Giffard**
- **Denque fever – Assoc. Prof. Allison Imrie**
- ***Clostridium difficile* – Prof. Tom Riley**
- **Human pappiloma virus – Dr David Smith**
- **Molecular-based enteric testing – Dr Shalinie Perreira**

REGISTRATIONS STILL OPEN @ www.trybooking.com/EZQG

Places are limited. Member rate - AUD 280.00, non-member rate AUD 300.00
Recommended accommodation: *Alice in the Territory* @ www.alicent.com.au

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bringing Microbiologists together

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