MALARIA
JOURNAL

# Malaria's contribution to World War One – the unexpected adversary

Bernard J Brabin[1,2]

## Abstract

Malaria in the First World War was an unexpected adversary. In 1914, the scientific community had access to new knowledge on transmission of malaria parasites and their control, but the military were unprepared, and underestimated the nature, magnitude and dispersion of this enemy. In summarizing available information for allied and axis military forces, this review contextualizes the challenge posed by malaria, because although data exist across historical, medical and military documents, descriptions are fragmented, often addressing context specific issues. Military malaria surveillance statistics have, therefore, been summarized for all theatres of the War, where available. These indicated that at least 1.5 million solders were infected, with case fatality ranging from 0.2 -5.0%. As more countries became engaged in the War, the problem grew in size, leading to major epidemics in Macedonia, Palestine, Mesopotamia and Italy. Trans-continental passages of parasites and human reservoirs of infection created ideal circumstances for parasite evolution. Details of these epidemics are reviewed, including major epidemics in England and Italy, which developed following home troop evacuations, and disruption of malaria control activities in Italy. Elsewhere, in sub-Saharan Africa many casualties resulted from high malaria exposure combined with minimal control efforts for soldiers considered semi-immune. Prevention activities eventually started but were initially poorly organized and dependent on local enthusiasm and initiative. Nets had to be designed for field use and were fundamental for personal protection. Multiple prevention approaches adopted in different settings and their relative utility are described. Clinical treatment primarily depended on quinine, although efficacy was poor as relapsing *Plasmodium vivax* and recrudescent *Plasmodium falciparum* infections were not distinguished and managed appropriately. Reasons for this are discussed and the clinical trial data summarized, as are controversies that arose from attempts at quinine prophylaxis (quininization). In essence, the First World War was a vast experiment in political, demographic, and medical practice which exposed large gaps in knowledge of tropical medicine and unfortunately, of malaria. Research efforts eventually commenced late in the War to address important clinical questions which established a platform for more effective strategies, but in 1918 this relentless foe had outwitted and weakened both allied and axis powers.

**Keywords:** World War One, Malaria, Quinine

## Background

An unexpected adversary in the First World War was malaria. It attacked all combatant armies, with adverse consequences for vast numbers of troops, and devastated large civilian populations as a result of the environmental, civil, and demographic effects of troop dispersions and activities. The term 'war malaria' describes this paradigm [1], and captures the fact th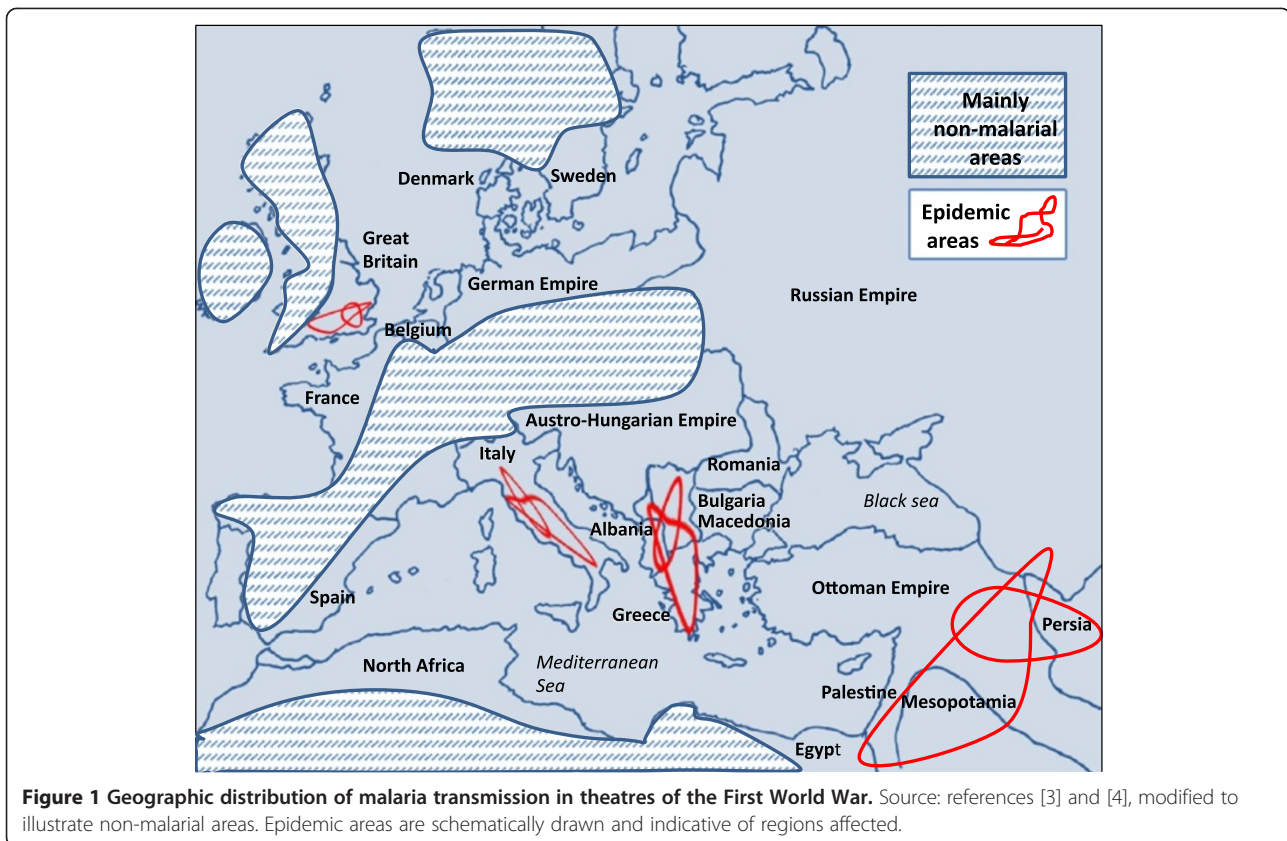at malaria control in peace-time differs from that in war. This difference was exaggerated at the beginning of the First World War because military personnel were unaware that malaria was so widespread through many parts of Western and Eastern Europe (Figure 1). Although historians have recognized that a high proportion of troops died from disease rather than combat [2], malaria has received little emphasis, such that the subject is frequently not indexed in historical books or referenced in First World War manuscripts.

By 1914, parts of Europe had made considerable progress in malaria control, particularly in Italy and Greece

Correspondence: b.j.brabin@liverpool.ac.uk
[1]Clinical Division, Liverpool School of Tropical Medicine, Pembroke Place, L35QA Liverpool, UK
[2]Global Child Health Group, Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands

**Figure 1 Geographic distribution of malaria transmission in theatres of the First World War.** Source: references [3] and [4], modified to illustrate non-malarial areas. Epidemic areas are schematically drawn and indicative of regions affected.

[5,6] which was a major achievement considering that, around 1900, the anopheline mosquito cycle was only just becoming accepted, and the important vectors, as well as the developmental cycle in the red cell, were only recently recognized. The damage the War inflicted on the political, social, and economic progress achieved in malaria control lasted until well into the twentieth century. There are questions as to why the First World War was so conducive to an explosion of malaria, leading to epidemics, conflicts on solutions, and clinical controversies on how to manage the basic disease in individual troops in different malaria endemic settings. These issues affected all armies as the malaria parasite had no alignment and could be transmitted unseen across theatres of war. The activities of soldiers aided its progress by increasing mosquito numbers through operational activities favouring transmission, especially as soldiers tended to burrow underground which is conducive to water – logging and favourable to mosquito breeding. By 1916, as more countries became involved, these effects multiplied creating ideal war conditions for the outbreak of several European malaria epidemics. The consequences compromised military planning, logistics, and the battle prospects of combatants, who became increasingly ineffective, as well as affecting huge swathes of civilian populations [6]. Re-deployment of non-immune

troops to replace sick troops in malaria-affected war zones enhanced the problem, as did the inability to effectively treat soldiers suffering from malaria. Deployment of large numbers of troops from tropical Africa and India introduced into the European theatre a large human reservoir of infections with new parasite strains carried by semi-immune soldiers. The lack of knowledge of the hepatic stage of development of the *P. vivax* malaria parasite, which was only described in 1948 [7], compounded the situation and was instrumental in recurrently ineffective treatments being prescribed, and evacuations of vast numbers of sick troops from combat zones.

Only late in the war was it appreciated that preventive measures were possible. In the interim medical doctors struggled against this clinical adversary. The war documentation on the topic is diverse and has not previously been assimilated. Much reporting on the size of the problem has been anecdotal, due to limitations in surveillance statistics. This review aims to summarize available information and contextualize the main aspects in order to establish the nature of this formidable adversary in times of war.

**Search strategy**

Physical searches for historical information used library resources at the Liverpool School of Tropical Medicine,

and the inter-library loan facilities of the University of Liverpool. Journal references in English, French, German and Italian were searched for the years 1914–1925. The Historical Library Collection of Tropical Medicine at the Liverpool School of Tropical Medicine and the Ronald Ross Archive at the Sydney Jones Library, University of Liverpool, were searched. For recent publications electronic databases were examined for historical context and scientific content. These included PubMed, Scopus, ISI Web of knowledge, the UK Parliamentary Records Resource, The Guardian newspaper and The Times newspaper Histories of the War. Reference lists from both general medical and historical journals were searched. Lack of appropriate indexing terms in early publications restricted the search for articles written before availability of electronic databases. The Official UK volumes published by His Majesty's Stationary Office on Medical Services, Hygiene, Pathology, Casualties and Medical Statistics of the War were an important resource and are page referenced, as information on malaria was widely indexed across all volumes [2,8-14] (Figure 2).

## Military malaria surveillance statistics 1914–1918

Initially it is necessary to estimate the military populations at risk, and associated malaria related mortality. Central to estimates of malaria exposure risk is information on troop numbers in the exposed military populations, which is data largely available in historical references and archives. Officially reported annual strengths of the British Expeditionary Forces in all theatres of the War were published in 1931 [2]. Figures are also available from historical sources that take account of troop movements and re-deployments. Few statistics are available for 'followers', or attached military personnel, who were not fighting troops. Table 1 provides information of military populations exposed for both the allied and axis powers. This includes regional areas of troop locations. Also provided are malaria surveillance case numbers, and malaria incidence estimates per 1,000 troops for the periods specified in the table. When publications included numbers of deaths related to malaria, this information was used to estimate case fatality, which is as a range when sources giving variable mortality estimates were available. Estimates of the approximate military populations exposed are provided taking account of their variable composition. Troop numbers are often provided on an annual basis, which would include many of the same troops tallied annually in sequential years. In terms of malaria risk per annum these numbers should be interpreted additively, ie 100,000 men present over four years in a military zone equate to a total of 400,000 persons years malaria risk for the time period of the war. Another problem is that, although reference sources are listed in the table, there are differences in published troop numbers between sources. For this reason ranges of troop numbers are provided. This table is the first compilation of global malaria troop statistics for the First World War. It is divided according to the regional locations of troops of both allied and axis powers located in Europe and the Middle East, or outside this area in sub-Saharan Africa. In the European theatre there is the Western front in France and Belgium bordering with Germany; the large Eastern Front which stretched across the Austro-Hungarian border with Russia and Romania; a more Southerly front in the Balkan region of Macedonia including borders with Greece, Bulgaria, Albania and Turkey; an Eastern Front of the Ottoman Empire borders in the Middle East including Syria, Palestine, as well as Egypt, and Mesopotamia (modern Iraq). In sub-Saharan Africa locations are listed in East, West and South-West Africa. Allied armies were: Great
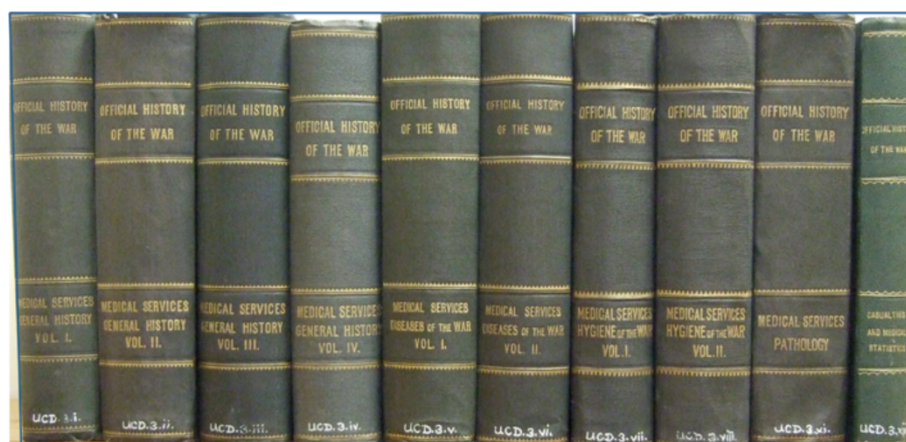


**Figure 2 Official UK Government War Volumes on Medical Services, Hygiene, Pathology, and Medical Statistics.** References: [2,8-14]. Volumes on Surgery of the War also published [15].

**Table 1 Military malaria surveillance statistics 1914 – 1918**

| Military forces | Location | Years | Military case (n) and incidence estimates | Military deaths (n) | Case fatality, % | Military population exposed (n) | Malaria species[a] | References |
|---|---|---|---|---|---|---|---|---|
| *Europe and Middle East* | | | | | | | | |
| British | Macedonia and Salonika plain | 1916 (Oct) -1918 | 162,517, 369 per 1000[c] | 787 | 0.2-0.48 | 404,207[b] – 549,111 British, French 150,000, Serbs 200,000 | Mostly Pv | [16], ([2] p2, p80), [1,17] |
| French | Macedonia | 1916–1917 | 66,271 | 667 | 2.10[d] | | | [18-21] |
| British | North Russia | 1918–1919 | 35, 8.7 per 1000, 32,688 | ? | | 22,258 | Pv, Pf | ([2] p2,p80) |
| German, Bulgarian | Balkans | 1915–1918 | 113 per 1000 | | – | 380,000 - 462,000 | Pv | [22,23] |
| | Macedonia | 1916-1917 | 21,672 | ? | 0.92 | – | Mostly Pv Pf, Pm Pv, Pf | [19,22] |
| British, French | Italy | 1917-1918 | 7373 (40% relapses) | ? | – | 145,764 - 210,943 | Pv, Pf | ([2] p2,p80), |
| Italian | | 1915-1918 | Many thousands | ? | 0.03-1.3 | | | [6,12] |
| Australian Desert Mounted Corps | Palestine | 1918 (May-Dec) | Of 19,652 illnesses, 6,347 slide positive | | | 40,000 | Mostly Pf | [24] |
| | Palestine | 1918 (Sept-Oct) | 1940 | 98 | 5.05[e] | | | [24] |
| British & Dominion | Egypt and Palestine | 1914–1918 | 40,144 | 854 [f] | 2.13 | 1,192,511 | Pv, Pf | ([2] p80), [24] |
| British | Palestine | 1918 (Apr-Sept) | 7,270 | | | 70,000 | | [25] |
| Turkish | Ottoman territory | 1914-1918 | 412,000 - 461,799 | 20,000 -23,351 | 4.8 | 350,000 | Pv, Pf | [26,27] |
| German | Ottoman territory | 1915-July 1918 | 4,763, 308 per 1000 | ? | – | 5540 | | [22], ([28] p231) |
| German | Dardanelles | Apr 1915-Jan 1916 | 200 per 1000[g] | ? | – | 1000 | | ([28] p231), [29] |
| Mixed allied force | Mesopotamia | 1914-1918 | 59,323 | 284 [h] | 0.76 | 889,702 – 969,388 | Mostly Pv | ([2] p2 p80) |
| | Kuwait, Nasiriya | 1915–1917 | 1,365, main admission | ? | – | 468,987 - 489,000 | | [10] |
| | Dardanelles | Apr 1915-Jan 1916 | 1,473 | 5 | 0.34 | | | [1], ([2] p80) |
| Western Front: Allied & United States | North-East France and Belgium | 1914-1918 | 9,022, outbreaks of <20 | 14 | 0.16 | 5,399,563 - 6,843,563 | Mostly Pv | ([30] p75,p115), ([2] p80), [31], ([32] p439-441) |
| Western Front: German | | 1914-1918 | 11,222, <1 per 1000 | ? | – | 5,200,000 | Pv, Pf | [22], ([32] p439), [33] |
| Eastern Front Allied: Russian, Romanian | Russia, Romania, Armenia, Georgia. Anatolia, Albania | 1915-1916 | Albanian armies suffered severely from malaria | ? | – | 525,000 [i] | Pv, Pf, Pm | ([30], p153), [21,34,35] |

**Table 1 Military malaria surveillance statistics 1914 – 1918** (Continued)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Eastern Front Axis: German | Galicia and Anatolia | 1914–1918 | 29,952<br><br>5.1 per 1000 | ? | ? [k] | 228,000 – 750,000[j] | | [22,28] p137, [35] |
| Turkish, Austro-Hungarian | Yugoslavia | 1917-1918 | 128 per 1000 | ? | – | 270,000 – 1,045,050 | | ([30] p47), ([36] p399) |
| Evacuations to England from Europe and Africa | UK | 1917-1918 | 34,000, 500 local cases in Southern England | 323 | 0.95 | ≥34,000 | Pv, Pf | ([17] p140), [37] |
| *Outside Europe and Middle East* | | | | | | | | |
| British expeditionary | East Africa, Kenya, Tanganyika | 1915-1918 | 145,850 troops and 68,914 indigenous, 51.000 hospitalized, 126 per 1000(troops), 20 per 1000 (others) | 831 troops with 2839 indigenous | 0.57<br><br>4.12 | 250,000 British (75,366) and indigenous with 150,000 Indian | Mostly Pf | [2] p2, p80, [39] |
| | South-West Africa | 1914–1915 | 518 | 2 | 0.39 | 33,000 | Mostly Pf | ([2] p2, p80) |
| | Cameroon | 1915–1916 | 2410 | 5 | 0.21 | 3000 | Pf | [14,40] |
| | Sierra Leone | 1914 | 401, 1839 per 1000 | ? 0 | ? 0.00 | 218 | Pf | [41] |
| German expeditionary | Togo, East and South-West Africa | 1914-1918 | Lower incidence as mostly indigenous forces used | ? | – | 18,000 [l], 3000 German troops, remainder indigenous | Mostly Pf | [35,42] |
| USA naval | Americas, Caribbean | 1917-1918 | 4,746 hospital cases, 68,373 man-sick days | 7 | 0.15 | – | Mixed | [43] |

Dashed indicate information not identified, and question mark unknown mortality case numbers.

[a]Pv: *Plasmodium vivax*; Pf: *Plasmodium falciparum*; Pm: *Plasmodium malariae*.

[b]Estimate includes British, French, Serbian, and Russian troops.

[c]13.7% in British troops; 27.4% in Indian troops.

[d]Of 100 autopsies of influenza pneumonia, 83 showed definite evidence of previous malaria [19].

[e]Estimated from graphic data from all cases in Sept-Oct and deaths reported in October [24].

[f]Deaths due to *P.falciparum* infections. Confirmed diagnoses in 32 of 67 autopsies; many complicated by dual infection with influenza bronchopneumonia [44].

[g]Estimate for German troops only.

[h]Deaths for years 1917–1918 only.

[i]Brusilov offensive 1915–1916.

[j]Russo-Turkish offensive winter 1915 – 1916.

[k]Of 2,873,000 men mobilized on the Turkish side in Ottoman territory, approximately 466,759 died of disease [28].

[l]Estimate for East African German forces.

Britain, France, Italy, Russia, Serbia, Romania and Albania. Central axis armies were: Germany, Austro-Hungary, the Ottoman Empire, and Bulgaria.

War-time statistics may be underestimated by health officials as some armies did not keep adequate records, and for several locations there is missing data, especially for mortality, and for civilians who were exposed to many of the same adverse conditions. One previous approximation of the number of allied troops with malaria was 500,000, although the basis for the calculation was unclear [30,37]. Incidence estimates per 1,000 men were available for some, but not all, locations. The sum total of case numbers for the War for the allied troops is 617,150 with 3,865 malaria deaths, which gives a case fatality estimate of 0.63%, or slightly more than one in every 200 infected soldiers dying from malaria. For the axis powers these estimates are 562,096, with 23,351 deaths, which gives a much higher malaria case fatality estimate of 4.15%, or more than four deaths for every hundred soldiers with malaria. This difference could reflect better management practices, and quinine regimens used by the allied forces in cases of severe malaria, or the influence of pre-War prevention measures developed by Ross on malaria control during the War. The table also lists the reported malaria case fatality estimates specific to different campaign areas. These vary between 0.15% - 5.05%. This variation partly arises due to troop composition, as regiments with larger contingents of tropical indigenous troops would be expected to have lower mortality risk due to their acquired immunity. Another factor is the proportional exposure risk in different areas for *P. falciparum* malaria compared to *P. vivax*. This data refers to the direct impact of malaria, but does not account for indirect effects on morbidity and mortality. For example soldiers anaemic with chronic malaria would succumb more readily following battle injuries or major surgery.

Table 1 indicates evidence for the intensity of malaria in several locations, particularly in Macedonia (present day Greece and environs), The Ottoman Empire (present day Turkey and environs), Mesopotamia (present day Iraq and Iran), Palestine, and East Africa. Malaria was a smaller problem on the Western Front, although the destruction of dykes in Flanders, causing local flooding, led to indigenous *P. vivax* cases. Prisoners of war returning to Flanders, who were infected in German concentration camps, is also reported [31]. In trenches where both European and African troops were present a small number of *P. falciparum* cases were reported amongst German troops [33]. In Gallipoli, malaria was never reported as a prominent cause of inefficiency, although the coastal area of the peninsula was considered highly malarious.

Malaria had a much greater impact on the Eastern Front involving the Russian, Romanian, and Albanian Troops, although quantitative information on malaria is not adequately defined for these countries. These armies were probably severely affected, with substantial malaria–related mortality [34]. Statistics shown in Table 1 for the German armies were reported by Zieman [22], although these did not provide mortality data, and he indicated they were underestimates. The accuracy of estimates of troop numbers resident in the Ottoman Front have been questioned [36], and Erickson considered that earlier estimates vastly underestimated the true number of Ottoman casualties from disease as well as combat [28]. By the end of the Brusilov offensive in late summer 1916, the Hapsburg army had officially lost 464,382 men and 10,756 officers, with 350,000 prisoners of war - a loss from which they never recovered. High malaria mortality estimates (23,000 approximately) have been reported for Turkish troops [26], but the number of cases and deaths for the army as a whole is difficult to quantify with no statistics for prisoners of war who would be likely to receive little in the way of protection from infection.

Underestimation in surveillance statistics is difficult to quantify due to failure to identify low grade or asymptomatic infections, which can cause debilitating chronic anaemia without occurrence of febrile episodes. The statistics also do not reflect the occurrence of relapsing vivax infections in soldiers taking low doses of prophylactic quinine, or falciparum infections in soldiers from the tropics with partial malaria immunity. Diagnostic misclassification would be expected unless a blood slide was taken, as clinical features of acute malaria have a broad differential diagnosis that includes diarrhoea and pneumonia. Febrile soldiers may also have suffered mixed malarial infections [45]. Autopsies conducted in Palestine by Manson-Bahr confirmed mixed infections with bronchopneumonia and malignant tertian malaria (*P. falciparum*), with influenza as dual infection. He considered that the mechanisms of early diagnosis and treatment broke down in rapidly advancing troops in malarious areas [44].

Use of regional malaria incidence data from Table 1 and the corresponding military population estimates allows the expected number of malaria cases in the military to be calculated for a given region (Table 2). Comparison of the expected and observed estimates shows some agreement except for the Ottoman territory and East Africa, where incidences are almost certainly underestimated, and do not take sufficient account of recrudescent or relapsing infections, which would greatly increase expectant numbers. This suggests that at least for these areas incidence rates underestimate the true rates. Malarial mortality due to Blackwater Fever was reported amongst expeditionary forces in East Africa [12], although there was no record of this occurring amongst

**Table 2 Estimated malaria cases based on size of military forces**

| Location | Period[a] (years) | Malaria incidence (per 1000 troops) | Estimated military population | Expected number of malaria cases[b] | Observed number of malaria surveillance cases |
|---|---|---|---|---|---|
| *British and Dominion forces* | | | | | |
| Macedonia | 3 | 369 | 404,207 | 149,076 | 162,517 |
| Western Front | 4 | <1 | 5,399,563 | <5,400 | 9,022 |
| | | | 6,843,563[c] | <6843 | |
| East Africa | 3 | 126 | 250,000 | 31,500 | 145,850 |
| North Russia | 2 | 8.7 | 22,258 | 194 | 35 |
| *German and Central Powers forces* | | | | | |
| Balkans | 4 | 113 | 380,000 | 42,940 | 32,688 |
| | | | 462,000 | 55,206 | – |
| Ottoman territory: | | | | | |
| - Turkish troops | 4 | 308 | 350,000 | 107,800 | 412,000 –461,799 |
| - German troops | 2 | 308 | 5540 | 1689 | 4,763 |
| Dardanelles – German troops | 1 | 200 | 1000 | 200 | – |
| Galicia and Anatolia Eastern Front | 2 | 5.1 | 228,000[d] | 1,163 | 29,952 |
| | | | 750,000[e] | 3,825 | – |
| | | | 1,045,050 | 5,330 | – |
| Yugoslavia | 2 | 128 | 270,000 | 34,560 | – |
| Western Front | 4 | <1 | 5,200,000 | <5,200 | 11,222 |

Dashes: information not identified.
[a]Approximate duration of exposure.
[b]Estimate based on single incident case per soldier, and does not include recurrent episodes or relapses for the same individuals.
[c]Expected malaria cases based on two estimates for Western Front troop sizes.
[d]Military numbers only for Russo-Turkish offensive winter 1915–1916 [35].
[e]Expected malaria cases using estimates for Hapsburg army size of 750,000[46] or 1,045,000 [32].

black African troops. Of German troops in East Africa who died other than from wounds, 64.2% died from Blackwater Fever between 1914 and 1917. In Macedonia, of 136 cases of Blackwater fever, 36 died (26.5%), and amongst the French, mortality was 30% [12]. It was reported less frequently in Togoland and Mesopotamia. In Macedonia, Wenyon considered that hardships, exposure and unpreparedness under war conditions explained the high case fatality from malaria in 1916 (1.01%), and that the lower mortality in 1917 and 1918 (0.37% and 0.31% respectively) would have been still further reduced if ordinary peace-time precautions had been available [19]. High mortality was due to life under war-time conditions and not any particular feature of the parasite, although it followed closely the incidence rate of falciparum malaria. Overall British mortality from malaria in Macedonia was 0.7 per 1,000 troops, while for the French, for the same period (January-June 1918), mortality was ten times higher (6.4%) [19].

## Malaria epidemics during the war

A number of basic conditions cause epidemics [47], sometimes separately, or together as in the First World War. These occurred in the regions of Macedonia, Palestine and Egypt, and in Western Europe following the return of troops to England, Italy and elsewhere. An increase in vectorial capacity due to high production of vector anopheline mosquitos was probably critical. This could have resulted from more breeding places (or deterioration in larval control), prolonged mosquito survival, or increased man-vector contact. In desert fringe regions rainfall and malaria transmission are often connected. The El Nino Southern Climatic Oscillations (ENSO) for the years of 1914–1915 and 1918–1919 may have produced favourable climatic conditions for epidemic transmission as the impact of ENSO in malaria epidemic prediction is well-established [38]. The ENSO for 1918–1919 was one of the strongest in the twentieth century [48]. The movement of infected persons, as troops migrated from India and sub-Saharan Africa, combined with the immigration of non-immune European soldiers further created ideal conditions for the explosive epidemics which occurred.

## The Macedonian epidemic

This event was one of the greatest medical surprises of the war with more than a quarter of the half a million allied troops immobilized with sickness and equivalent

numbers of Bulgarian and German troops (Table 1). Amongst British troops, peak prevalence patterns were observed seasonally from July to November in 1916 and 1917, and with double peaks between May and November in 1918 (Figure 3). Relapsing vivax cases infected in the previous year may have contributed to the early peak prevalence in 1918, and falciparum malaria may have induced some vivax relapses in the late second peak in 1918 [49]. The species pattern observed amongst French troops in 1916 showed peak vivax prevalence preceding peak falciparum prevalence by three months (Figure 4) [20]. This was similar to the species pattern seen in British troops in Palestine and Egypt in 1918 [49]. No deaths were reported between January and March 1916, and epidemic peaks in mortality followed corresponding peak prevalence patterns (Figure 3), with mortality peaks in 1916 corresponding to the monthly peak prevalence periods of vivax and falciparum malaria. Mean malaria mortality remained below 2%, with peak mortality of 5.1% in September 1917.

The malaria epidemic in Greece resulted in ten allied casualties for every one inflicted by the axis powers [35]. There was no escape from the mosquito under the endemic conditions in which these armies fought. The surprise of the high mortality and the magnitude of the immobilized forces induced Generals to respond to the malaria crisis, which required a greater expenditure on labour to clear mosquito breeding sites. This effort was insufficient as it was not known that mosquitoes could spread beyond about 500 metres from their breeding sites. The main vectors were *Anopheles maculipennis* and *Anopheles superpictus,* and the sporozoite rate varied between 0.5% and 5.5% [19,50]. The British, French and German armies were virtually immobilized for three years, with a French General telegramming that his army was in hospital with malaria [16,18]. This caused French military authorities to think seriously about the crisis, hugely improved efforts at quinine prophylaxis of troops [18], and rapid evacuation of infected troops. As a result they experienced less malaria than the British. The British introduced the Y management scheme of quinine treatment (15 gr/day x 14 days, then 60 gr/wk x 6 days in optional divided doses; every soldier to keep 60 gr for self-treatment if relapses), which included removal of heavily infected individuals, with 25,000 men evacuated in 1917 [19]. Other measures included every known method of combating the disease including swamp and stream clearance (Figure 5), oiling, treatment of breeding
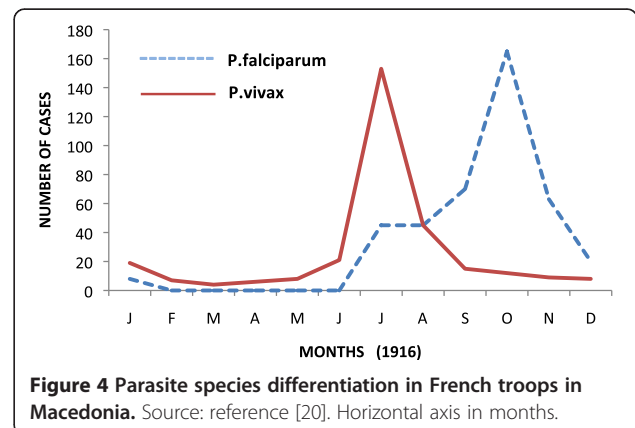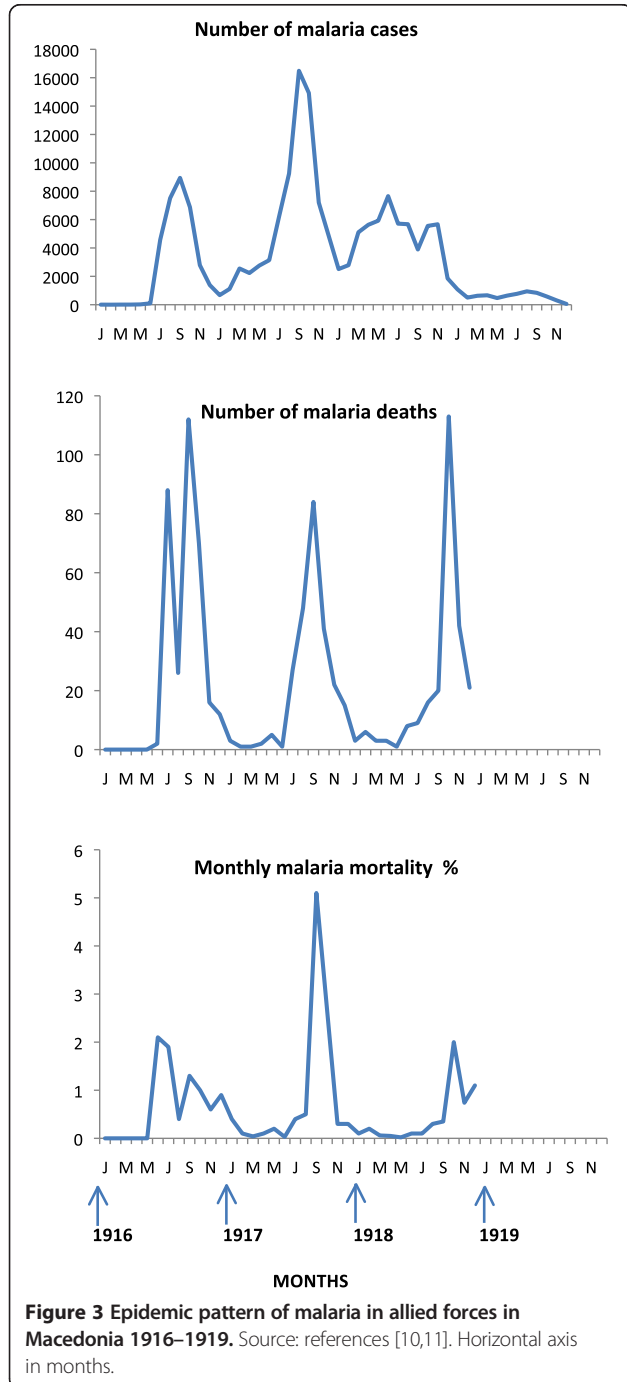


**Figure 3 Epidemic pattern of malaria in allied forces in Macedonia 1916–1919.** Source: references [10,11]. Horizontal axis in months.



**Figure 4 Parasite species differentiation in French troops in Macedonia.** Source: reference [20]. Horizontal axis in months.

**Figure 5 Draining the marshes to prevent malaria on the Eastern Front.** Source: reference [52], published under the Open Government Licence, v 2.0.
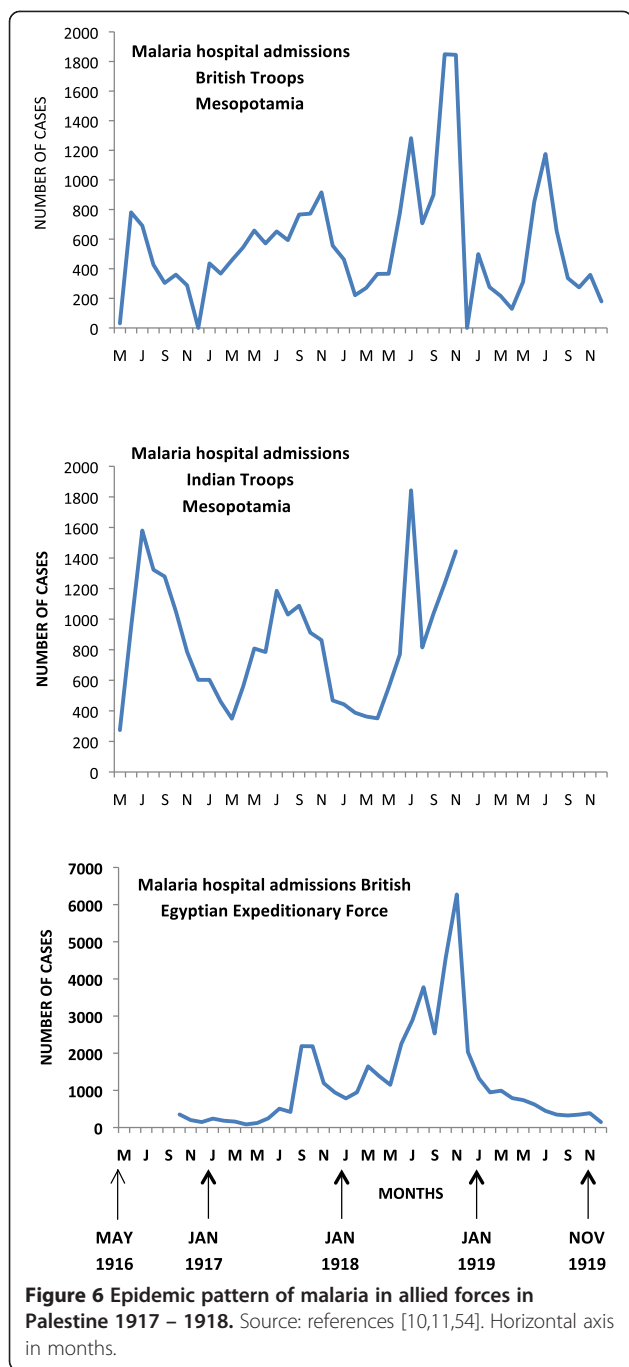
places, fumigation, spraying, mosquito proofing and quinine prophylaxis. Despite these efforts, it is doubtful whether any appreciable reduction in infectious episodes occurred [19]. Most of these measures were introduced effectively too late in the campaign, partly due to conflicting opinions on prioritization, but also delays in obtaining netting and sufficient quantities of quinine [10]. Quinine prophylaxis had been recommended by Ronald Ross, consultant Physician to the Mediterranean Expeditionary Force, but was not favourably reported on by medical officers. Ross visited the area between 26th November 1917 and 18th January 1918, yet surprisingly makes no mention of the epidemic in his memoirs [51]. The area became a large military hospital and the spectacular image of a well-equipped army paralysed by malaria is a sober reminder of its potential severity.

### The Palestine and Mesopotamia epidemic

The epidemic amongst British troops commenced immediately after they moved into this malaria endemic area in early 1916, and after the incubation period had passed (Figure 6). Malaria was also introduced into the Sinai region by troops from India, who eventually comprised about three quarters of troop numbers. It was difficult to locate camps away from highly endemic areas in southern Mesopotamia (modern Iraq.) Cases of marine malaria were reported with higher incidence in ships anchored closer to the shore [53]. Initially cases were mostly caused by *P. vivax* infection. Malaria became more widespread during the campaign with the largest epidemic occurring in 1918, with proportionally more *P. falciparum* infections. The operations of Indian and British forces in 1918 involved campaigns in some of the most malarious areas. Successive advancing

fronts across the whole region continuously placed troops in new transmission areas (Figure 7). The British military failure at the siege of Kut in 1916 (Figure 7), and the overall military failure of the Turkish army was related to soldiers being overwhelmed by malaria, although the disabling of soldiers by the disease was not to the same extent as in Macedonia. Accurate returns on malaria were mainly available to the end of September 1918, and the main British military attack then occurred on September 19th [25]. The 1918 epidemic did not commence until temperature averages had risen above 15.5°C in early June, which were climatic conditions favouring mosquito breeding. If the British advance in mid-September had been delayed the successful outcome might have been different. Incidence was falling by November, which was considered due to the extent of the anti-malarial measures undertaken earlier in the year [25]. In addition to British and Indian troops, Australian mounted forces also experienced epidemic malaria with a high case fatality of 5%, which related to dual infections with *P. falciparum* malaria and influenza (Figure 8) [24]. Australian statistics on their cavalry advance showed that the sick outnumbered the battle wounded by 37:1 [49].

A small number of malaria diagnostic stations providing malaria microscopy were established in April 1918, by British and Australian commands, and with specially trained medical officers and orderlies [9]. Rapid diagnosis may have reduced case fatality and helped to check the epidemic in Palestine. Over 111,000 blood smears were examined by the Australian New Zealand Army Corps laboratory, and of 40,000 slides examined by British diagnostic stations 28.9% were positive [49,55]. A number of other measures were introduced and by 1918 the extent of anopheline breeding meant there was no time to be lost.

**Figure 6 Epidemic pattern of malaria in allied forces in Palestine 1917 – 1918.** Source: references [10,11,54]. Horizontal axis in months.

Large sums of money were spent on oiling and drainage, with £10,000 for drainage clearance alone [9]. Deep shell holes rapidly fill with water, and British clearance work was hampered by Turkish shelling of working parties. Some tributary origins were within Turkish lines and the British felt that the Turks failed to appreciate that the destruction of mosquito breeding places by the allies would also be beneficial to their own army as mosquitoes traversed front lines [25]. As a consequence, malaria amongst allied troops increased in frequency with further advances

into Turkish positions (Figure 7). The micro-epidemiology of malaria in this varied terrain was challenging, and the operations were difficult and costly to sustain. The full effects of these anti-malarial measures are difficult to assess, and they were introduced late in the campaign. The drafting of replacement troops to Palestine from Macedonia introduced an additional human reservoir for mosquito infection, which reduced benefits achieved from the evacuation of infected troops.

**The epidemics in England and Italy**
In England between 1900 and 1914 only two cases of malaria had been observed in soldiers who had never been out of the country [56,57]. Following 1914, cases gradually increased reaching epidemic proportions in 1918 (Figure 9). In 1917, Ross had concluded that true indigenous malaria foci had never disappeared from the island of Sheppey on the north Kent coast, where healthy carriers of *P. vivax* were identified [58]. The Ministry of Health did not station soldiers returning from malarious regions in parts of Kent or Sussex because of concerns about local transmission. The First World War brought the problem of malaria back to England, leading to the last epidemic of malaria in the country and substantially increased local transmission (Figure 9). The problem arose from troops returning from Egypt, Turkey, Macedonia, Italy, West and East Africa. Table 3 shows malaria statistics on reinforcements to the British expeditionary Force arriving in France from Macedonia and Palestine in June 1918 and illustrates the magnitude of the problem [59]. These soldiers brought back infections of *P. vivax* and *P. falciparum* malaria to areas which had been free of disease for many years, and many had to be evacuated from France to England for treatment. Soldiers returning from a wide diaspora were admitted with malaria to the London Hospital during 1918 and 1919 (Table 4). Before the end of the war, 34,000 military cases returned to five camps set up in England for their treatment, and 500 locally transmitted infections were identified [60]. In 1919, the Ministry of Health made malaria notification compulsory [30] in order to identify infection foci.

In a military camp on the Isle of Sheppey soldiers in training who had never left England contracted malaria, and in one regiment 30 cases occurred. These were locally contracted as *An. maculipennis* mosquitoes could be found without difficulty in occupied huts [60]. In the ports of Liverpool, London and Bristol, during 1917, more than 500 cases of malignant tertian malaria were introduced mostly from West Africa. The newly completed building of the Liverpool School of Tropical Medicine was nominated for use for hospital treatment of infected soldiers and undertook clinical trials of quinine treatment [62,63]. The main source of infection for
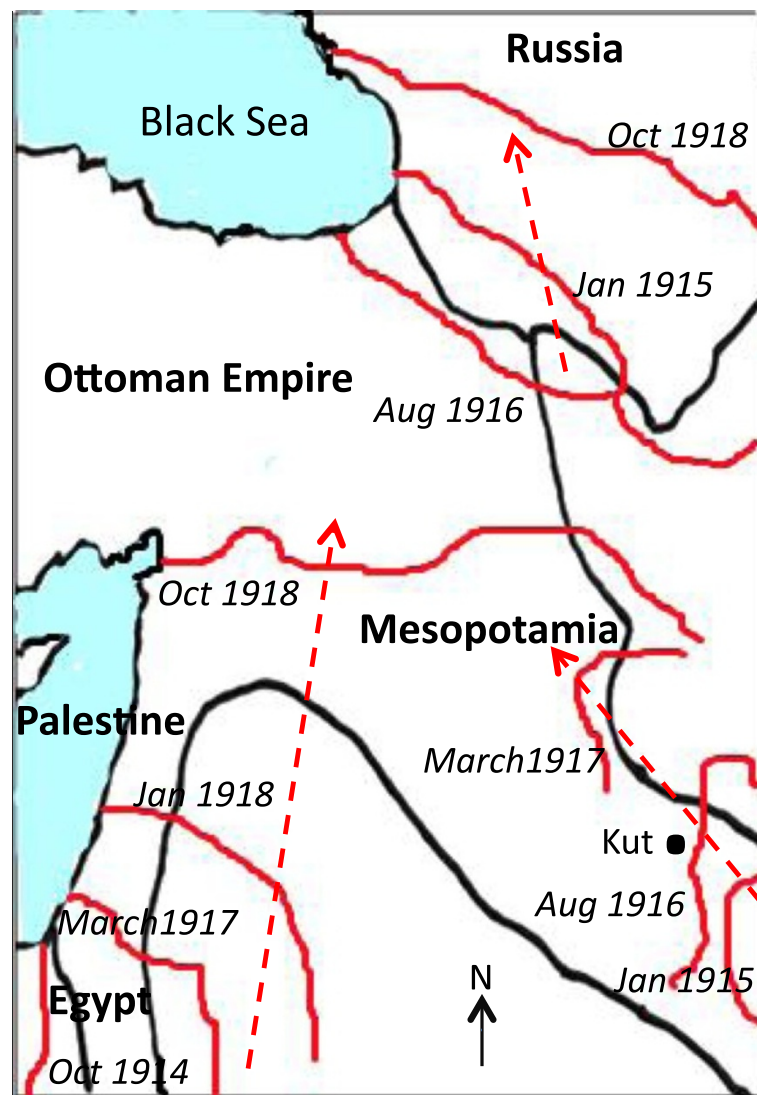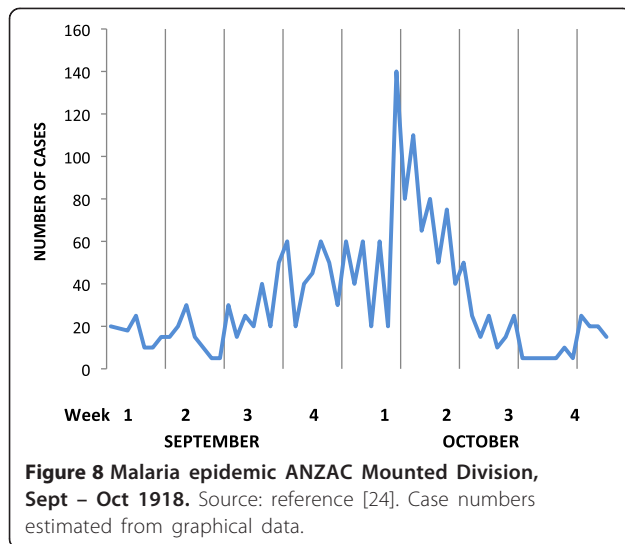
**Figure 7 Dynamics of troop movements in the Middle East, 1914–1918.** Source: adapted from reference [32].

most naval and military cases, and nearly all civilian cases, which occurred after 1916, was relapsing vivax malaria among returned soldiers [64,65]. Prompt identification of infection foci, and quarantining infected soldiers and sailors in a small number of dedicated hospitals, enabled effective epidemic control and limitation of indigenous transmission [65].

There was a rise in reported cases in several other European countries due to malaria introduced by returning troops [30]. In Vienna, 3717 cases were reported in 1919, and epidemics occurred in Albania and Corsica, although in Germany it was not as serious a problem after the War. There were post-war epidemics in Ukraine and Russia, and an outbreak occurred as far North as Arkhangelsk ('Archangel') in the arctic [2,30]. In Russia 360,670 cases were reported in 1919, rising to

5,865,828 annual cases in 1924, when incidence reached 446 per 10,000 population with at least 600,000 case fatalities [30]. In Italy, there was a ferocious epidemic, which devastated the nation in 1917–1918, in which tens of thousands of civilians and soldiers perished (Figure 9) [6]. The Italian Front was as violent as the Western Front, and Snowden reports that the horrors of battle were so great that some soldiers purposefully avoided taking quinine in order to become malaria-infected and be evacuated – a response described as '*malaria defeatism*' [6]. The large number of evacuated troops and prisoners of war, collapse of the pre-war Italian malaria campaign, requisitioning of Italian hospitals by Austrian forces, shortages of quinine, and war-time disruption left the Italian population at high risk of malaria infection. In 1917–1918, the epidemic was at its peak and lead to

**Figure 8 Malaria epidemic ANZAC Mounted Division, Sept – Oct 1918.** Source: reference [24]. Case numbers estimated from graphical data.

Italy experiencing the worst malaria epidemic of the twentieth century [6]. Almost 50,000 soldiers were repatriated from highly endemic areas and created an epidemic route through to Southern Italy, which experienced an excess of falciparum infections compared to Northern provinces.

**Malaria in sub-Saharan Africa**
African expeditionary forces were at high risk for *P. falciparum* infection. British and German armies were constituted with a majority of indigenous or Indian troops who should have been less susceptible due to their acquired immunity [2]. Table 1 gives estimates of the proportions of these contingents, and shows that in East Africa, whilst malaria incidence was lower in indigenous and Indian troops, their total malaria mortality was higher as they were a much larger fighting force. Imperial troops and supporting bearers serving in East Africa had a death rate that exceeded any other theatre of war [66], and measured up to those in the great European bloodbaths [67]. The medical provisions for the African and Indian troops were poor, and they were exempted from the general order for quinine prophylaxis. The Germans, who were a relatively small force, had a higher ratio of porters to soldiers (7:1) than the allies (4:1), and also high standards of disease prevention. They nevertheless reported some deaths from Blackwater Fever from staff receiving one grain quinine daily as self-treatment [68]. Ocean Road Hospital in Dar es Salaam was requisitioned from the Germans by the British at the outbreak of the War and was used for treating British soldiers. Although some attempts at malaria control were introduced in 1914, including sanitary inspections and importation of anti-larval fish [40], General Smuts, who commanded the British forces, may have

been negligent with regard to malaria control offering too little, too late [66,69]. The numerous preventive approaches so carefully developed in Macedonia and Salonika were not attempted, as most reliance was placed on quinine prophylaxis. Quinine supplied to the Army and Navy was below indicated strength due to war profiteering, whereas specimens captured from the Germans (and of German manufacture) produced quinine toxicity or cinchonism with much smaller doses. In July 1918, a small outbreak in marines visiting East Africa was attributed to sub-standard prophylaxis due to this problem [70]. Germany subsequently used the research station at Amani in Tanganyika (now Tanzania) to produce its own quinine supply. Sub-standard quinine was an important reason for the resurgence of malaria in other regions during and after the War [5,71].
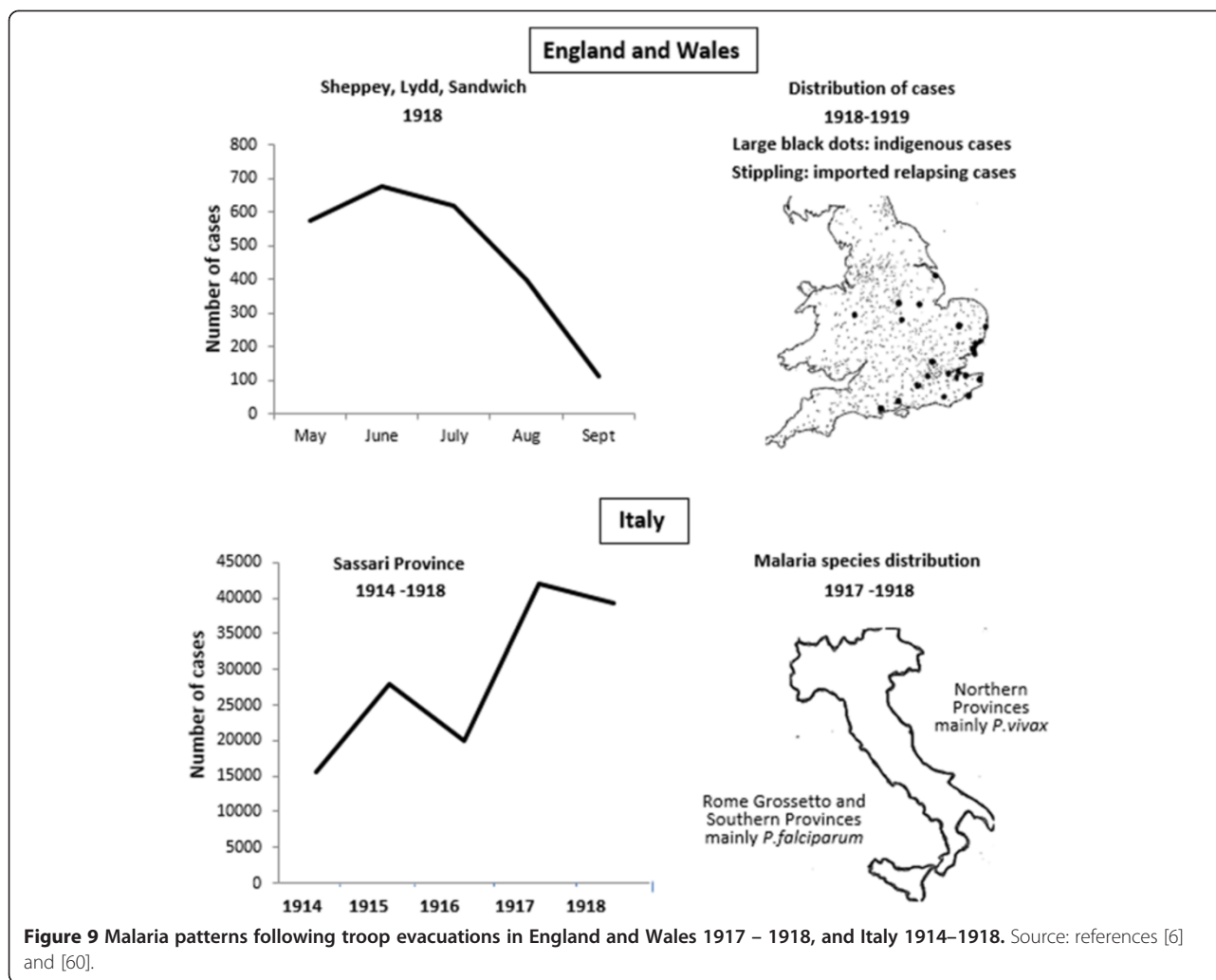
In Cameroon and Sierra Leone in West Africa, smaller numbers troops were deployed compared to East Africa, and few military deaths from malaria were reported [40,41,72]. Malaria incidence was high, despite troops using mosquito nets and quinine prophylaxis, and many troops had repeated admissions with marked anaemia and debility [41]. Expert microscopy and treatment was available. Amongst reinforcements arriving from India to Muscat, on the southern Arabian coast opposite East Africa, 25% had splenomegaly [73]. The extent of infection in these soldiers was not appreciated and many returned to India on account of fever after residence for only a short period in battle zones.

**The Pacific region**
In Pacific malaria endemic regions, the New Zealanders took German Samoa in August 1914, and the Australians German New Guinea in September [32]. The Japanese occupied the Marshall, Caroline, and Marianas islands the following month. Fighting in these regions, which possibly had the highest malaria vectorial capacity of any war zone, would have resulted in serious malaria-related illness, as their malaria control strategies were similar, or less developed to those used elsewhere. It was known that anophelene mosquitoes carried malaria but the identity of the local vectors had not been established [74].

**Malaria control approaches**
The greatest experience of preventive measures was derived from activities in Macedonia, and these were applicable to all theatres of the War and could be classified as: drug prophylaxis and treatment, mosquito deterrents, personal protection, or mosquito destruction [11]. New approaches were developed during the War which advanced practical and operational strategies. These are summarized and compared with pre-1914 approaches in Table 5. The lack of pre-war scientific evidence on all of these control strategies was a major restriction. There

**Figure 9 Malaria patterns following troop evacuations in England and Wales 1917 – 1918, and Italy 1914–1918.** Source: references [6] and [60].

was minimal data available on acquired immunity to malaria, as well as controversy in Germany before the War between Erhlich and Bordet on the nature of the immune response to infections [75]. During the War, operational evaluations of some prevention measures were developed, and the most feasible was testing quinine treatment and prophylaxis, as it was more readily controlled, follow-up was realistic, and outcome determinants were easily measured. In view of the extent of the variety of these wartime trials, data on quininization is covered in a separate section. Personal prophylaxis with quinine was chaotic with weak understanding of medicines in management, problems in drug delivery due to night operations, enemy bombs and attacks, and servicemen may also have hidden the drug to exchange for cigarettes [76]. The British questioned the use of quinine for prevention and placed more emphasis on preventing contact with mosquitoes. A survey of 129 officers on the utility of quinine by the War Office reported

only four felt it was of definite value, ten of some value, and the remainder of no value [11].

Personal anti-mosquito ointments were messy and head nets and gloves were very restrictive especially in active combat (Figure 10). It was actually as important to protect infected men from uninfected mosquitoes as it was the reverse. Environmentally, the need for frequent spraying of pyrethrum for mosquito control deterred its use by German forces although the British army used it occasionally (Lefroy's fluid) in the First World War [30]. In many areas, the very high density of mosquitoes made it impossible to control the vector. Extensive drainage was impossible in mountain terrain, or when campaigns were highly mobile. Identification of vectors gave a sounder basis for control and studies were undertaken on entomological parameters [50]. Notions of integrated control and the mapping of community reservoirs of infection were emerging and were completed in response to the epidemic in England [60], but remained

**Table 3 Malaria statistics on reinforcements to British expeditionary Force arriving in France in June 1918 [59]**

| Regiment[a] | % infected with malaria | Cases[b] (n) | Daily sick parade malaria statistics |
|---|---|---|---|
| 5th Connaught Rangers | 80 | 82 | If regiment ordered to service in forward area at least 50% unable to comply |
| 5th Royal Irish | 75 | 80 | 30/650 parasite positive[c] |
| 2nd Royal Dublin Fusiliers | 100 (last 2 years) | 175 | 25% parasite positive |
| 13th Black Watch Scottish | 80 | 573 | 30/day reported sick with malaria |
| 14th Kings Liverpool | 75 | 146 | 60-70/day with malaria |
| 5th Inniskillin Fusiliers | 75 | 175 | 600/824 have had malaria; 30% parasite positive |
| 1st Kings own Yorkshire Light Infantry | 70 | 42 | Only 30% of regiment never had malaria |
| 13th Manchester | 80 | 52 | Average 4/day relapsing |
| 9th Gloucester | 80 | – | 60-70/day with relapsing malaria |
| 2nd Royal Munster | 80 | 80 | Men with acute malaria may not report sick |
| 6th Inniskillin Fusiliers | 75 | 21 | 110 hospitalized since June 1918 |
| 6th Leinster | 75 | 87 | 480 with malaria since June 1st 1918 |
| 5th Royal Irish Fusiliers | 75 | 58 | 27 reported malaria within 3 days of parade |
| 7th Wiltshire | 50 | 165 | Less infected than other Battalions |
| 4th Kings royal rifle corps | 70 | 10 | Only 30% not had malaria |
| 2nd Northumberland Fusiliers | 80 | 209 | 146 hospitalized en route to France with malaria. Average daily sick parade = 60 |
| 10th Camerons (Lovat's scouts) | 80 | – | 57/210 suffering relapses on day of inspection |
| 3rd Royal Fusiliers | 70 | 20 | 32 hospitalized en route to France |
| 10th Black Watch | 80 | 140 | 17/42 had malaria in morning sick parade |
| 6th Royal Dublin Fusiliers | 80 | 110 | 40 with malaria en route to France |
| 12th Lancashire Fusiliers | 80 | 56 | 33 arrived with malaria |
| Total | Mean 76.7 | 2281[d] | – |

[a]Average Regimental strength = 800 men per regiment.
[b]Cases with diagnosis confirmed by microscopy.
[c]Blood smear positive on microscopy.
[d]Mean 15.0% parasite positive ( 2281/15,200, with average regimental strength of 800 men).

**Table 4 Malaria cases admitted London General Hospital February 1917 – January 1919 [61]**

| Location of origin | Admissions | *P.vivax* | *P.falciparum* | Mixed Pv and Pf |
|---|---|---|---|---|
| | (n) | (n) | (n) | (n) |
| Salonika | 1686 | 746 | 82 | 20 |
| East Africa | 1049 | 496 | 43 | 26 |
| India | 126 | 35 | 2 | – |
| Egypt | 86 | 29 | 3 | – |
| Palestine | 63 | 11 | 3 | – |
| Mesopotamia | 46 | 19 | – | – |
| West Africa | 35 | 4 | 2 | – |
| France | 48 | 15 | – | – |
| South Africa | 25 | 4 | 1 | – |
| Italy | 25 | 7 | 5 | – |
| Singapore | 16 | 4 | 1 | – |
| North America | 11 | 3 | – | – |
| Total | 3216 | 1373 | 142 | 46 |

notional in other areas. A large compendium of measures was required to tailor to the environment, although this was only really appreciated towards the end of the War. Negligence and scepticism with application of preventive measures were common and contradictory instructions were given by officers [18,77].

Late in the war, at least in Macedonia and Palestine, a considerable effort was placed on net design with the promotion of modified bivouac tents for rapid deployment (Figure 11). A small net for use by individual men was considered preferable but these were unavailable and two man tents were used in Macedonia. Reserve net supplies for damaged nets were not included in logistics requests and frequently there were operational shortages. Mosquito-proof canvas huts could have been adapted on a larger scale.

In view of these restrictions, and despite concerns over quinine efficacy, military orders prioritized quinine prophylaxis with the aim to interrupt transmission and eliminate the parasite reservoir. It was recognized that quinine treatment could lessen the severity of an

**Table 5 Approaches to malaria control prior to and during World War One**

| Pre – 1914 | 1914 - 1918 | |
| --- | --- | --- |
| *Prevention European theatre & British Dominions* [77-79] | *British* [9-11,13,17,25,30,44,66,73,80-83] | *French* [18,30,84] |
| - Systematic inspection and notification of cases | - Scientific evidence on control strategy required | - Preliminary study of epidemiological conditions [84] |
| - Protection against mosquito bites (portable nets) | - Specially trained medical officers and orderlies required [44] | - Appropriate housing |
| - Portable mosquito proof rooms | - Availability of malaria diagnostic units with microscopes [9,44] | - Eliminating parasite reservoir |
| - Protection of hands and feet (boots) | - Sanitary sections in field Divisions to supply material for anti-mosquito work [82] | - Small anti-larval measures and measures against adult larva |
| - Medicinal skin protection (effect transient) | - Mosquito brigades (in Palestine) | - Quinine treatment and prevention |
| - Mosquito reduction (fumigation, traps, fish as larvicides, oiling, drainage, screening breeding water, filling pools, piping to prevent leakage) | - Frequent inspections of anti-mosquito work [82] | - Collective mechanical defences |
| - Detection, isolation and specific treatment of all infected soldiers [79] | - Entomological studies of anopheles species [17] | - Bed nets and mosquito protection [84] |
| - Prevention by treatment | - Recognition problem of mistaken diagnoses [44] | - Reduction of negligence and scepticism of preventive measures by authorities [18] |
| - Personal domestic hygiene | - Siting of camps and evacuation of areas [11] | - Reduction of contradictory instructions on quinine use to avoid chaotic use of quinine |
| - Quinine prophylaxis | - Instructions on use of mosquito nets and net design. [45]Bivouac netted tents [17], (Figure 11) | - Urine inspection for quinine detection (Tarant's reagent) to control prophylactic administration of quinine [18] |
| - Consider public prophylaxis with quinine (if troops contracting infection outside barracks) | - Mosquito-proof canvas huts [17] | - Malaria specialists as advisers [84] |
| | | *- Australian* [24,55] |
| - Repeated measurements (malaria surveys) | - Mosquito swats [17] | - Malaria diagnostic units with field laboratories [55] |
| - Keeping troops in non-malarial hill areas [79] | - Occasional use of pyrethrum sprays (Lefroy's fluid) for mosquito control [30] | - Aggressive control of mosquito breeding along front lines [55] |
| - Imposition of fines for non-cooperation Legislation on engineering work | - Quinine prophylaxis recommended by Ross and Medical Advisory Committee, but unfavourable response from medical officers [10,80] | *- German* [85] |
| | | - High standards of disease prevention |
| *Prevention in German possessions* [86,87] | - Drainage operations, although impossible in mountainous terrain, or where campaign was highly mobile (eg, Palestine) [25] | - Emphasis on quininization [85] |
| - Local conditions decided most important activity | - Indian troops exempted from use of mosquito nets on grounds they were unpopular, and they had acquired malarial immunity [66] | |
| - Quininization (simplest and cheapest) | - Pamphlets explaining dangers [17] | |
| - Supervised quinine therapy and quinine prophylaxis trusted to exterminate malaria even in very badly infected areas, | - Recruitment blood examination for selection of smear negative candidates (West Indies) [13] | |
| - Environmental mechanical protection | - Instruction of medical officers on spleen examination technique of Indian troops [73] | |
| - Personal anti-mosquito measures | | |
| - Reliance on acquired immunity [87] | | |

infection and shorten the period of early infectivity even though relapses invariably occurred. In the UK, during 1916, the total issue of quinine exceeded 25 tons, or nearly 66 million 5-gr doses [14], and because of supply issues the Government requisitioned all quinine stocks. The average monthly supply in 1917 and 1918 was 5.5 tons. The influence of Ross on this strategy was substantial [78,89]. Some doctors, however, thought that in regions of Macedonia, Albania, and the Tauris Mountains there were different forms of malaria that could not be treated by quinine [76]. This undermined confidence in its use although there could be no dilemma in drug
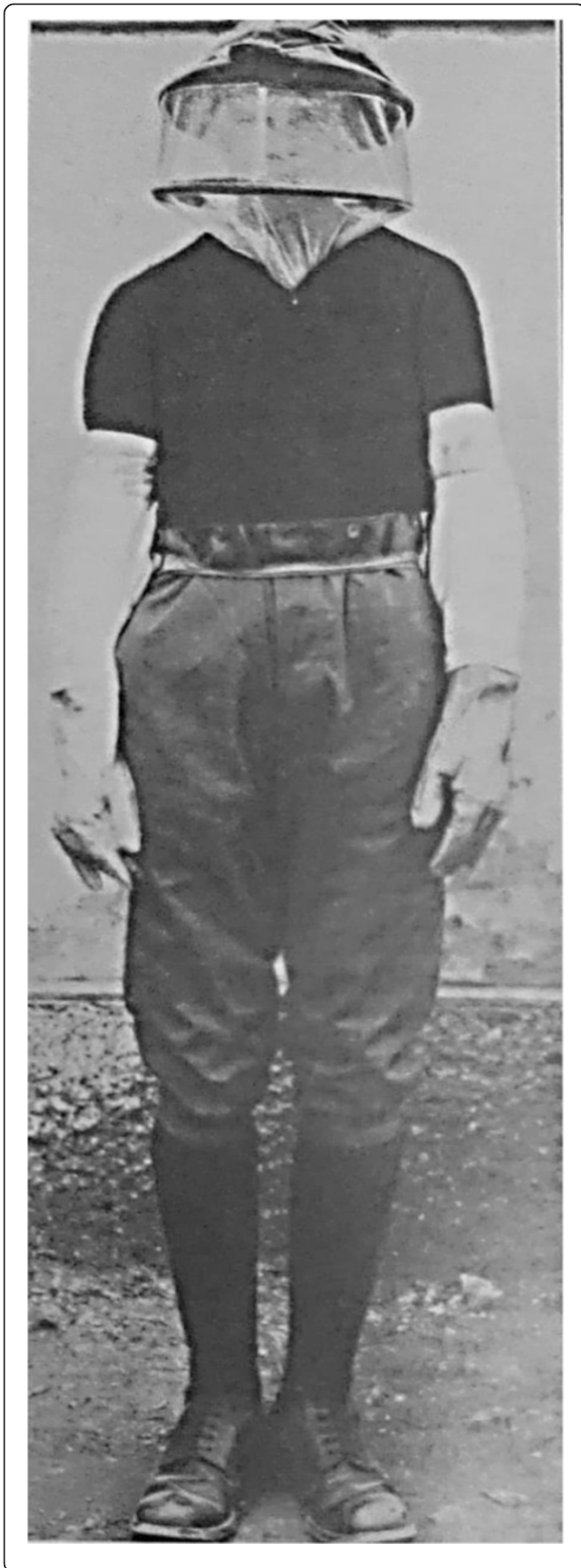
**Figure 10 Protective clothing for mosquito protection.** A general view of the special protective clothing in use. A head net is worn over a shrapnel helmet, and the special pattern shorts are turned down under the upper turn of the puttees. The gauntlet gloves are seen on the hands and forearms. (published under the Open Government Licence, v 2.0), [11].
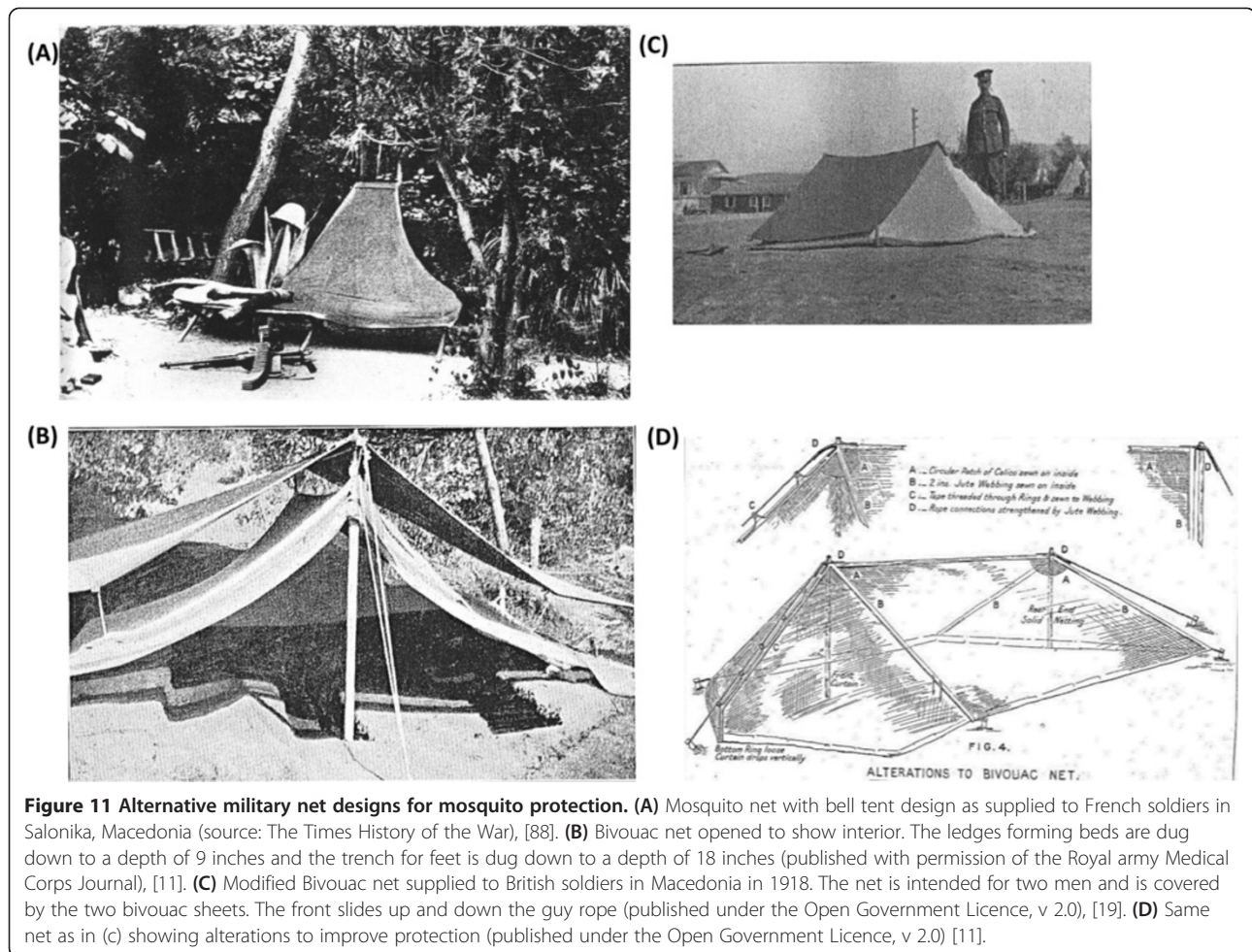
choice as no alternative was available. In German and Austrian publications unrestricted prophylaxis was promoted and its use was a military order [76].

Because of restrictions on supplies there was increased interest in Germany in manufacturing a synthetic alternative anti-malarial, although the chemical industry was more committed to developing poison gases [46]. It was only at the end of the War, when Germany was cut-off from the world supply of quinine, that Pamaquin development was stimulated and achieved by 1925 [71]. Questions of resistance to quinine became topical in view of the frequency of recurrences which lead to conflict in Germany on the distinction between acquired drug resistance, and drug selection of pre-existing resistant strains [76,90].

**Quininization**

Quinine prophylaxis was defined by Ross as 'treatment of persons who have not yet shown signs of illness but may possibly become infected' [78], and by Treadgold as 'regular administration of quinine with a view to prevent the development or recrudescence of clinical malaria' [80]. The first definition suggests it prevents new infections occurring, whereas the second emphasizes the prevention of recurrent infection due to failed primary clearance. This difference encapsulates the confusion and controversy that surrounded quinine treatment and prophylaxis at the time of the First World War. This was fuelled by widely varying practices and published recommendations in dosage and regimens which were mostly empirical, and subsequently were directed by military authorities following quinine trials in the UK, France, Macedonia, and Palestine (Table 6). Often trials did not assess the percentage not infected before prophylaxis commenced. Results on efficacy were variously reported as good or poor by different national authorities. Quinine was widely used by the German troops but data was censored on its evaluation, [68,85,91].

Although quinine prophylaxis was often ordered it was not enforced and officers were neglectful [18]. Ross considered that therapeutic efficacy in a war setting related to the level of supervision of intake preferring long-term daily prescription which was difficult to implement. He differed from several other European malariologists in recommending continuous dosage [78]. Quinine parades with supervised observation interrupted activities and falls in attendance were difficult to correct if 100,000

**Figure 11 Alternative military net designs for mosquito protection. (A)** Mosquito net with bell tent design as supplied to French soldiers in Salonika, Macedonia (source: The Times History of the War), [88]. **(B)** Bivouac net opened to show interior. The ledges forming beds are dug down to a depth of 9 inches and the trench for feet is dug down to a depth of 18 inches (published with permission of the Royal army Medical Corps Journal), [11]. **(C)** Modified Bivouac net supplied to British soldiers in Macedonia in 1918. The net is intended for two men and is covered by the two bivouac sheets. The front slides up and down the guy rope (published under the Open Government Licence, v 2.0), [19]. **(D)** Same net as in (c) showing alterations to improve protection (published under the Open Government Licence, v 2.0) [11].

troops were involved [1]. A great amount of preparation was required to make this strategy effective. During the First World War, *P. vivax* malaria showed a pattern of relapse within two months of initial treatment with a tendency to relapse about 8–10 months later, but it was unknown whether recurrences were recrudescent blood stage infection or derived from a latent tissue stage [101]. Ross later changed his opinion and conceded that some relapses occurred in spite of the most vigorous daily supervision, but disagreed with the French whose approach was to suspend quinine between relapses [89]. Memoranda from the British Ministry of War endeavoured to provide some clarity [10]. Initially orders were given from 1st June 1916 for daily doses of 6 gr quinine to troops in malarial areas following an attack of malaria, but as summer progressed, all troops, whether malarial or not, were given quinine as there was some evidence it mitigated the severity of an attack. The fundamental problem related to the knowledge gap concerning the exo-erythrocytic hepatic stage of development of *P. vivax*. Without this knowledge it was impossible for clinicians to distinguish between the need for a drug to provide a radical cure of *P. vivax* infection which cleared hepatic hypnozoites, from suppressive cure, which would control overt clinical attacks of both *P. vivax* and *P. falciparum* malaria [102]. As a result the war-time data on a large number of clinical trials from centres in the UK aiming to evaluate quinine, and routes of its administration, were difficult to interpret [63,94]. This dilemma was captured at a meeting of the Royal Society of Tropical Medicine and Hygiene held in London in late 1917 when, following the presentation of trial results by Ross comparing treatment regimens, two directly opposing opinions were expressed [103]. Sir William Osler emphasized that 'the man who could not treat malaria successfully with quinine should give up the practice of medicine', then adding 'in divided doses'. In contrast, Warrington-Yorke commented that 'no-one is able to state how quinine should be taken, in which manner, and in what doses'. He considered the results presented by Ross meaningless as all treated cases were not diagnosed following microscopic confirmation of malaria at the time of relapse. In conclusion, without definite evidence on efficacy the data was 'worse than useless, because it misleads other people and

**Table 6 British and German military quinine prophylactic and treatment regimens for malaria 1914–1918**

| Author or source [reference] | Area and subjects | Year | Prophylactic dose regimen[a,b] | Treatment dose regimen |
|---|---|---|---|---|
| British | | | | |
| Hehir [79] | India | 1914 | All troops quinine treated not < 4 months | – |
| Wenyon [17] | Macedonia | 1916 | 5,10,20,30gr/day tried | 30gr/day x 24 days + arsenic + iron |
| | | 1918 | | |
| Editorial BMJ [81] | No restriction | 1916 | Large doses needed | – |
| Laveran [92] | Macedonia | 1917 | 40gr/day (split dose) x 7.5 months | – |
| Treadgold [80] | Macedonia | 1917 | 5-15gr x 2 consecutive days at 1 wk intervals | – |
| Manson [93] | No restriction | 1917 | 5gr/day, or 10gr/x2wk, or 15gr x 10th day | 5gr x 3 days, or 15gr x1 dose x 1 wk; Iron + arsenic for 8wks; then 5gr/day x 3 months x every Spring x 2 years |
| Stephens [63] | Liverpool evacuated troops | 1917 | Interrupted courses preferable to continuous. Various doses and scheduling. Arsenic not beneficial, strychnine more beneficial | – |
| Ross [94] | UK special treatment centres | 1917 | 5-60gr/day investigated x 3 wks in various schedules and administration routes. Concluded 60gr/wk reduces relapses to 10% per month | Short and long sterilizing treatments. No difference with administration route |
| Regulations UK Govt [95] | UK troops | 1917 | **Y scheme**: Every soldier to keep 60gr for self-treatment if relapses. Report relapse day or night for blood film and fever check | **Y scheme**: 15gr/day x 14 days then 60gr/wk x 6 days in optional divided doses |
| Paisseau [96] | Balkans | 1917 | 1-2gr/day x 3 days x 1–2 months Iron + arsenic x 1–2 months | IV adrenaline if rigors 2gr preferred if *P. falciparum* |
| | | 1918 | | |
| Anderson [97] | Macedonia | 1917 | 20-45gr both intensive and interrupted x 1–2 months | IV strychnine and adrenaline |
| | | 1918 | | |
| Alport [98] | Salonika | 1917 | 1-10gr/day continuous; or 35gr/day x 71 days | Cerebral malaria: 60-100gr in 12 hours x 3 days IM,IV, rectal |
| War Govt Medical Services Publication [13] | Conflict zones | 1914 1918 | 10gr x 21 days. Arsenic to reduce anaemia with iron and strychnine (IV if severe). Opium (Warburg's tincture). Venepuncture to reduce toxaemia (≥1 pint), and replace with normal saline[c] | Consider blood transfusion twice fortnightly. Splenectomy in severe anaemia |
| German[d] | | | | |
| Bruns [91] | Macedonia | 1917 1918 | 0.3 -0.6 g/day + arsenic. Recommended 1.5 – 2.0 g/day x 2 weekly x 6–8 wks. Repeat annually for 3 years | – |
| Kestner [85] | Macedonia | 1916 | 0.3 -0.9 g/day | – |
| | Romania | 1918 | | |
| Stendel [99] | Eastern front | 1916 | 0.3 g alternating days x 6 wks | – |
| Abstracts [100] | No restriction | 1918 | Summaries on quinine studies. Various doses[e] | – |

[a]gr refers to grains of quinine. One grain = 64.8 mg quinine; IM: intra-muscular; IV: Intravenous.
[b]The modern treatment regimen is 20 mg/kg loading dose, and then 10 mg/kg x 3 daily x 7 days. This total loading dose in grains for a 75 kg man, equates to 23.1 grains. The maintenance dose equates to 11.6 grains x 3 daily.
[c]Needs further investigation.
[d]German studies use dose suffix of g (not gr).
[e]Details may have been censored.

so prevents progress' [103]. Data on the therapeutic value of iron, arsenic and strychnine which were sometimes used as adjunct treatments (Table 6) were not systematically assessed. A few small clinical trials that investigated treatment with and without arsenic came to varied conclusions [63,104]. Revised recommendations

called the Y scheme outlined in Table 6 were eventually implemented by the British.

There were concerns related to possible effects of quinine in reducing immunity to severe malaria, or advantages if released malarial antigen stimulated immunity [105]. Theories on malaria toxins lead some practice

to use venipuncture to remove the toxic substance, which had echoes of enlightenment blood-letting [13] (Table 6). It is unclear from the government publication mentioning this how frequently it was practised, or at what stage during the War. No really satisfactory result was obtained. No one treatment provided a certain cure and the most effective treatments, and those with multiple intra-muscular quinine injections, were almost more severe than the disease. The use of the maximum tolerated dose instead of the minimum effective dose was preferred in favour of reducing the risk of selecting resistant parasites. Some considered quinine was a useful prophylactic against Blackwater Fever, and it was also used for the treatment of pneumonia [106]. Conversely Treadgold concluded that the severity of malaria in Macedonia was increased in some cases by prior quininization. He quoted Celli who claimed quinine prophylaxis produced some effect, but compared to results of mosquito protection, the results were negligible [80].

### Lest we forget

The First World War was a vast uncontrolled experiment in politics, military innovation and medical practice. Malaria parasites were unaligned and unexpected adversaries which battered both the victors and the vanquished. Their control would require breaching political barriers as well as improved scientific knowledge and understanding. Medical progress would require much greater insight into experimental method and the complex nature of the adversary, the individual, and the environmental circumstances of war [107]. At the beginning of the War the extent of the malaria problem was effectively unknown to military planners and as a consequence there were insignificant efforts at containment. Malaria rapidly spread to civilian populations as well as to the military, creating a complex emergency. In temperate zones, where *P. vivax* was the dominant parasite, ideal conditions were developing for parasite and mosquito, possibly enhanced by the climatic conditions of the strong 1914–1915 and 1918–1919 El Nino events. The trans-migration of troops and parasites across Europe favoured the spread of new parasite strains, which flourished in non-immune host populations of soldiers. Textbook ideal conditions were created for multiple epidemics, which would involve vast numbers of soldiers, from South–East England to the shores of Arabia, from the Arctic to the Mediterranean. Moreover, the statistical estimates of the numbers of malaria cases derived in this analysis are likely to be sizable underestimates, not least because malaria surveillance data went un-reported from several war fronts, as did civilian related malarial deaths. Censorship of German data limited information available for axis forces on case numbers, mortality, as well as on their military and medical response.

The military and medical response of allied forces was at first limited, perhaps because of perceived greater demands for directed military action the response gathered pace in 1916 when it was understood that whole armies could be immobilized by the malaria parasite, defeating military objectives. Medical facilities were required on a very large scale to treat acutely affected and chronically disabled soldiers with recurrent symptoms. In the search for scientific evidence this became an experimental field of medicine with research on drug trials, haematology and immunology, including attempts to culture the malaria parasite [108-110]. The priority for an effective treatment was paramount but, in the absence of knowledge of the exo-erythrocytic developmental stage of *P. vivax*, these attempts would lack resolution. Not until the late 1920s was it apparent that *P. vivax* recurrences
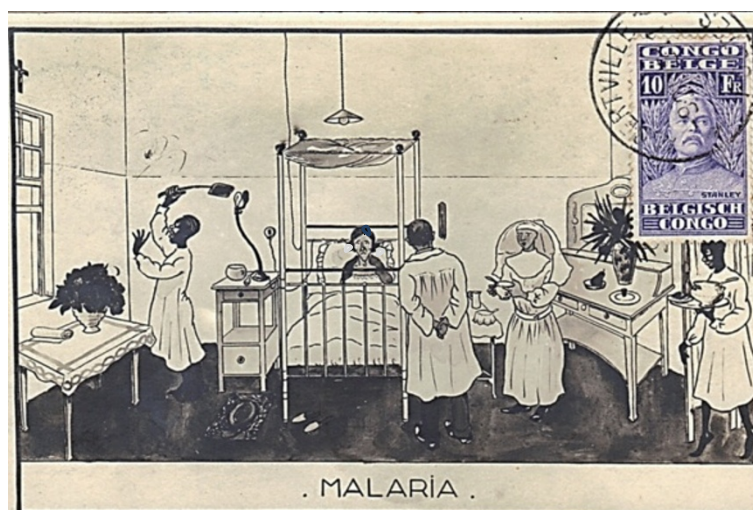


**Figure 12 Post-war postcard illustrating combination management of a malaria patient.**

followed a different temporal pattern to *P. falciparum* [101]. Prior to then the treatment response to the two parasitic species was frequently viewed as synonomous. The endeavour to defeat this enemy became controversial despite the efforts of Ross to co-ordinate treatment trials and it was not resolved until years after the War. It is a good example of the failure of the clinical trial approach to resolve treatment practices when the scientific mechanisms underlying the disease are unknown. The need for patient care of soldiers was paramount and in response, both in Liverpool and Sierra Leone, the Liverpool School of Tropical Medicine closed its research laboratories and converted them to hospital facilities that could accommodate clinical trials [62]. Grassi in Italy came out of retirement in 1917 to aid the Italian effort to cope with the malaria crisis by running a dispensary and research station [6]. The influence of Ross on prevention guided sanitation efforts and implementation of rapid malaria surveys, which included entomological investigations, which acted as a platform for control activities and aided the allied military effort. The lower reported number of allied compared to Turkish malaria deaths in Macedonia probably reflects better allied malaria control strategy. These efforts served to educate soldiers and officers on the malaria problem, which was no longer hidden.

Underlying national and international conflicts influenced progress. These varied from opinions on treatment such as 'there are almost as many treatments of malaria as there are people who have written on the subject' [103], to disagreements on ideas for bed net design [17], or more fundamentally, to differences in racial theories of immunity to malaria [76]. The culture of command was an umbrella over-riding alternative choices, and recommendations were difficult to reach by Committees whose agendas were broad, and at times imperialistic [64,111]. Much credit rests on individual medical officers whose clinical acumen and decision-making was paramount in patient care in rapidly changing local circumstances. Patients could be bewildered by the variety of treatment options as illustrated in this post-war cartoon postcard from sub-Saharan Africa (Figure 12). Allied activities become better integrated later in the War as demonstrated by the rapid control of the English outbreak. The nationalization of malaria control commenced rapidly after the War in those European countries most affected, Greece [5], Italy [6], and Palestine [112], but with little progress in Africa. The disease remains a threat in war zones today [113], and on the Centenary of the First World War, soldiers continue to experience high infection rates in malarious areas in Africa [114-116].

James in his Presidential address to the Royal Society of Tropical Medicine in London concluded that 'everyone who had actually taken part in efforts to deal with malaria in different parts of the world during the War came home with the uncomfortable feeling that we knew much less about the disease than we thought we did, and that it might be quite a good plan to sink our pride and to begin again, in all humility, and with greater respect and reverence, to try to fathom out some of its mysteries' [117]. A view that is as relevant today.

**Author's contributions**
I read, wrote and approved the manuscript.

**References**
1. Christophers SR: **Malaria and War.** *Trans R Soc Trop Med Hyg* 1939, **33**:277–304.
2. Mitchell TJ, Smith GM: *History of the Great War based on Official Documents. Medical Services. Casualties and Medical Statistics of the Great War.* London: His Majesty's Stationary Office; 1931.
3. Simmons JS, Whayne TF, Anderson GW, Horack HM: *Global Epidemiology. A Geography of Disease and Sanitation.* London: William Heineman Ltd; 1944.
4. Haworth J: **The global distribution of malaria and the present control effort.** In *Malaria, Principles and Practice of Malariology, volume2.* Edited by Wernsdorfer WH, McGregor I. London: Churchill Livingstone; 1988:1379–1420.
5. Tsiamis C, Piperaki ET, Tsakris A: **The history of the Greek Anti-Malaria League and the influence of the Italian School of Malariology.** *Infez Med* 2013, **21**:60–75.
6. Snowden FM: **The First World War and epidemic disease.** In *The Conquest of Malaria, Italy, 1900–1962.* Edited by Snowden FM. New Haven: Yale University Press; 2006.
7. Shortt HE, Garnham PCC: **The pre-erythrocytic development of** *Plasmodium cynomolgi* **and** *Plasmodium vivax.* *Trans R Soc Trop Med Hyg* 1948, **41**:785–789.
8. Macpherson WG, Leishman WB, Cummins SL: **History of the Great War based on Official Documents.** In *Medical Services, Pathology.* London: His Majesty's Stationary Office; 1923.
9. Macpherson WG: **History of the Great War based on Official documents.** In *Medical Services General History. Volume III.* London: His Majesty's Stationary Office; 1924:389.
10. Macpherson WG, Mitchell JJ: **History of the Great War based on Official Documents.** In *Volume IV, Medical Services General History, p107.* London: His Majesty's Stationary Office; 1924:264–265.
11. Macpherson WG, Horrocks WH, Beveridge WWO: **Prevention of malaria. History of the Great War based on Official Documents.** In *Medical Services. Hygiene of the War, Volume II.* London: His Majesty's Stationary Office; 1923:214–238.
12. Macpherson WG, Herringham WP, Elliot TR, Balfour A: *History of the War based on Official Documents. Medical Services. Diseases of the War, Volume 1.* London: His Majesty's Stationary Office; 1923.
13. Macperson WG, Horrocks WH, Beveridge WWO: *A History of the War based on Official Documents, Medical Services, Hygiene of the War, Volume II, p275.* London: His Majesty's Stationary Office; 1923.
14. Macpherson WG: *History of the Great War based on Official Documents. Medical Services General History. Volume I.* London: His Majesty's Stationary Office; 1924:179–306.
15. Macpherson WG, Bowlby AA, Wallace C, English C: **History of the Great War based on Official Documents.** In *Medical Services. Surgery of the War.* London: His Majesty's Stationary Office; 1922.

16. McGregor I: **Of men, mosquitoes and malaria.** In *17th Henry Cohen History of Medicine Lecture. Transactions and Report of the Liverpool Medical Institution 1989–1990; 15TH November 1989*. 30–41.

17. Wenyon CM, Anderson AG, Mclay K, Hele TS, Waterston J: **Malaria in Macedonia 1915–1919.** *J Royal Army Medical Corps* 1921, **37**:264–277.

18. Sergent E: **The Orient Army saved from malaria.** In *Verdun, the Battle for Freedom, Fortieth Anniversary. American Order of the Association Nationale des Croix de Guerre of France*. New York: French Printing and Publishing Co; 1959:138–142.

19. Wenyon CM, Anderson AG, Mclay K, Hele TS, Waterston J: **Malaria in Macedonia 1915–1919.** *J Royal Army Medical Corps* 1921, **37**:83–108.

20. Armand-Delille P, Paisseau G, Lemaire H: **Note sur les constatons d'hématozoaires au laboratoire de bactériologie de l'armée d'Orient pendant l'année 1916.** *Bull Soc Path Exot* 1918, **10**:284–287.

21. Jukes G: *Essential Histories: The First World War, the Eastern Front 1914–1918*. Oxford: Osprey Publishing; 2002:39.

22. Zieman M: **Über Kriegsmalaria und Kriegsmalariafolgen.** *Archiv für Schiffs und Tropen-Hygiene* 1937, **41**:73–90.

23. Bundesministerium fÜr Heerwesen und Kriegs archiv: *Österreich-Ungarns letzter Krieg 1914–1918, Volume. 1*. Wien 1930.

24. Shanks GD: **Simultaneous epidemics of influenza and malaria in the Australian army in Palestine in 1918.** *Med J Australia* 2009, **191**:654–657.

25. Sewell EP, Macgregor ASM: **An anti-malaria campaign in Palestine. An account of the preventive measures undertaken in the 21st Corps area in 1918.** *J Royal Army Medical Corps* 1920, **34**:204–218.

26. Koylu Z, Doğan N: **The struggle against malaria in the Ottoman Empire during World War I and the legal regulations made to this end.** *Tükiye Parazitoloji Dergisi* 2010, **34**:209–215.

27. Erickson E: *Ottoman Army Effectiveness in World War I*. London: Routledge; 2007:154.

28. Erickson EJ: *Ordered to Die. A history of the Ottoman Army in the First World War*. Westport, Connecticut: Greenwood Press; 2001.

29. Roer M: **Die Bedeutung der Malaria in Weltkrieg.** In *Thesis, 1937, Faculty of Medicine, Hamburg. Quoted in Bruce-Chwatt LJ, De Zulueta J. The Rise and Fall of Malaria in Europe. A Historico-epidemiological Study*. Oxford: Oxford University Press; 1980.

30. Bruce-Chwatt LJ, De Zulueta J: *The rise and fall of malaria in Europe*. A historico-epidemiological study: Oxford University Press; 1980.

31. Firket M: **Sur le traitement des paludéens en Belgique.** *Arches Méd Belg* 1919, **73**:660–679.

32. Stevenson D: *1914–1918 The History of the First World War*. London: Penguin Books; 2005.

33. Von Stabsarzt FD: **Malaria Infektion an der Westfront.** *Deutsche Medizinische Wochenschrift* 1917, **12**:316–317.

34. Pielsticker F: **Die Malaria in Rumänien und ihre Bekämpfung biszum jahre 1916.** *Arch für Schiffs und Tropen-Hygiene* 1917, **21**:317–329.

35. Keegan J: *The First World War p304 and 308*. New York: Random House Inc; 1998.

36. Evered KT, Evered EO: **Governing population, public health, and malaria in the early Turkish republic.** *J Historical Geography* 2011, **37**:470–482.

37. Bruce-Chwatt LJ: **Malaria and its prevention in military campaigns.** *Zeitschrift Tropenmed Parasit* 1971, **22**:370–390.

38. Kavats RS, Bouma MJ, Hajat S, Worrell E, Haines A: **El Nino and health.** *Lancet* 2003, **362**:1481–1489.

39. Holmes R: *The Oxford Companion to Military History*. Oxford University Press; 2001.

40. United Kingdom Government: *Annual Colonial report for Cameroon 1914–1915*. No 881.

41. Pollock CE: **Notes on the incidence of malaria among European troops in the Sierra Leone Command with special reference to the effect of mobilisation.** *J Roy Army Medical Corps* 1915, **25**:122–124.

42. Crowson TA: *When Elephants Clash. A Critical Analysis of Major General Paul Emil von Lettow-Vorbeck in the East African Theatre of the Great War*. Kansas: Master of Military Art and Science; 2003.

43. Beadle C, Hoffman SL: **History of malaria in the United States naval forces at war: World War I through the Vietnam conflict.** *Clinical Infectious Diseases* 1993, **16**:320–329.

44. Manson-Bahr P: **Experiences of malaria in the Egyptian Expeditionary Force.** *Lancet* 1920, **1**:79–85.

45. Wilson DR: **Trench fever: a relapsing fever occurring among the British troops in France and Salonica.** *J Royal Army Med Corps* 2014, **160**(Suppl 1):4–6.

46. Coffey P: *Cathedrals of Science. The Personalities and Rivalries that Made Modern Chemistry*. Oxford: Oxford University Press; 2008.

47. Molineaux L: **Epidemiology relevant to distribution and control.** In *Malaria, Principles and Practice of Malariology, Volume2*. Edited by Wernsdorfer WH, McGregor I. London: Churchill Livingstone; 1988:913–998.

48. Giese BS, Slowey NC, Ray S, Compo GP, Sardeshmukh PD, Carton JA, Whitaker JS: **1918–1919 El Nino.** *Bull Am Meteorological Soc* 2010, **91**:177–183.

49. Shanks GD, White NJ: **The activation of vivax malaria hypnozoites by infectious disease.** *Lancet Infect Dis* 2013, **13**:900–906.

50. Waterston J: **Malaria in Macedonia 1915–1919, Entomological observations on mosquitos in Macedonia.** *J Royal Army Medical Corps* 1922, **38**:334–349.

51. Ross R: *Memoirs with a full account of the great malaria problem and its solution*. London: Murray; 1923.

52. The Times: *History of the War. Volume 20*. London: The Times Printing House; 1920:11.

53. Richardson QH: **The Shatt-el-Arab River with special reference to malaria.** *J Royal Naval Medical Service* 1917, **3**:33–37.

54. Christophers SR, Shortt HE: **Incidence of malaria among troops in Mesopotamia 1916–1919.** *Indian J Med Res* 1921, **8**:553–592.

55. Shanks GD: **Formation of medical units in response to epidemics in the Australian Imperial Force in Palestine 1918.** *J Military and Veterans Health* 2014, **22**:14–19.

56. Copeland RG, Smith F: **Malarial fever contracted in Portsmouth.** *J Royal Army Medical Corps* 1906, **7**:186.

57. Easton PG: **A case of malarial fever contracted in Aldershott.** *J Royal Army Medical Corps* 1909, **11**:585.

58. Shute PG: **Indigenous malaria in England since the First World War.** *Lancet* 1963, **2**:576–578.

59. Dalrymple J: **Report on the treatment of malaria infected troops in France.** In *Observations on Malaria by Medical Officers of the Army and Others*. Edited by Ross R. London: His Majesty's Stationary Office; 1919:132–148.

60. James SP: *Malaria at Home and Abroad*. London: John Bale; 1920.

61. Row RN: **Observations on the pathology and treatment of malaria cases admitted to No 4 London General Hospital.** In *Observations on Malaria by Medical Officers of the Army and Others*. Edited by Ross R. London: His Majesty's Stationary Office; 1919:259–298.

62. Power H: *Tropical Medicine in the Twentieth Century. A History of the Liverpool School of Tropical Medicine 1898–1990*. London: Kegan Paul International; 1999:34–36.

63. Stephens JWW: **Studies on the treatment of malaria XXXII. Summary of studies 1–31.** *Ann Trop Med Parasit* 1923, **17**:303–313.

64. Bassett-Smith PW: **Naval cases of malaria contracted in England in 1918.** *J Royal Naval Medical Service* 1919, **5**:201–202.

65. Macdonald A: **Report on indigenous malaria and malaria work performed in connection with the troops in England during tear 1918.** In *Observations on malaria by medical officers of the army and others pages 178–258*. Edited by Ross R. London: His Majesty's Stationary Office; 1919.

66. Harrison M: **Medicine and the culture of command: the case of malaria control in the British army during the two World Wars.** *Medical History* 1996, **40**:437–452.

67. Strachan HFA: *The First World War. Volume 1: To Arms*. Oxford: 2001:498–505.

68. Taute M: **Ärztliches aus dem Kriege in Ostafrika 1914–1918.** *Archiv für Schiffs und Tropen-Hygiene* 1919, **23**:523–524.

69. Samson A: *World War 1 in Africa: the Forgotten Conflict among the European Powers*, International Library of the Twentieth Century. London: IB Taurus Publishers; 2012. number 881.

70. Edgar WH: **On an outbreak of malaria.** *J Royal Naval Medical Service* 1919, **5**:322–323.

71. Greenwood D: **Conflicts of interest: the genesis of synthetic antimalarial agents in peace and war.** *J Antimicrobial Chemotherapy* 1995, **36**:857–872.

72. Green AD: **Notes on the incidence of malaria among European troops in the Sierra Leone Command with special reference to the effect of mobilisation by Pollock CE.** *J Royal Army Medical Corps* 2014, **160**(Suppl 1):4–6.

73. Gill CA: **The prevention of malaria in war with special reference to the Indian Army.** *J Roy Army Medical Corps* 1917, **29**:439–456.

74. Spencer M: **The history of malaria in the South-West Pacific region with particular reference to Papua New Guinea and the Solomon Islands.** *Papua New Guinea Medical Journal* 1992, **35**:33–66.

75. Crist E, Tauber AI: Debating humoral immunity and epistemology: the rivalry of the immunochemists Jules Bordet and Paul Erlich. *J Hist Biol* 1997, **30**:321–356.

76. Da Silva AFC, Benchimol JL: Malaria and quinine resistance: a medical scientific issue between Brazil and Germany (1907–1919). *Med Hist* 2014, **58**:1–26.

77. Sergent E: Prevention of malaria in Algiers. In *The Prevention of Malaria with contributions by LO Howard and others*. Edited by Ross R. London: John Murray; 1910:475.

78. Ross R: *The Prevention of Malaria with contributions by LO Howard and others*. London: John Murray; 1910.

79. Hehir IMS: Prevention of malaria in the troops of our Indian Empire. *J Trop Med Hyg* 1914, **17**:227–300.

80. Treadgold CH: The prophylactic use of quinine in malaria: with special reference to experiences in Macedonia. *BMJ* 1918, **1**:525–529.

81. Editorial. *BMJ* 1918, **1**:346.

82. Austin E: Anti-mosquito measures in Palestine during the campaign of 1917–1918. *Trans R Soc Trop Med Hyg* 1919–1920, **13**:47–62.

83. Morris LM: Practical anti-malaria work in the Aegean 1917–1918. *J Royal Naval Medical Service* 1919, **5**:261–269.

84. Sergent E, Sergent E: La prophylaxie antipaludique d'une armée en campagne. Armée d'Orient 1917. *Bull Soc Path Exot* 1918, **2**:641–648.

85. Kestner O: Zur Frage der Chininprophylaxe. *Archiv für Schiffs und Tropen-Hygiene* 1919, **23**:104–110.

86. Schilling C: Prevention of malaria in German possessions. In *The Prevention of Malaria with contributions by LO Howard and others*. Edited by Ross R. London: John Murray; 1910:451–474.

87. Travis AS: Models for biological research: the theory and practice of Paul Erhlich. *Hist Philos Life Sci* 2008, **30**:79–87.

88. The Times: *History of the War, Volume 17*. London: The Times Printing House; 1918:223.

89. Ross R: Preface to English translation of: *Malaria in Macedonia*. In *Clinical and Haematological Features and Principles of Treatment*. Edited by Armand-Delille P, Abram P, Paisseau G, Lemaire H. London: University London Press; 1918.

90. Schilling V: Zur Frage der Chininresistance. *Arch für Schiffs-und Tropen-Hygiene* 1923, **27**:115–118.

91. Bruns O: Ueber die Mazedonische Malaria und ihre behanduling. *Muenchener Medizinische Wochenschrift* 1919, **66**:684–687.

92. Laveran A: La prophylaxie du paludisme dans l'Armée d'Orient. *Bull Soc Path Exot* 1917, **10**:886–890.

93. Manson P: *Tropical Diseases. A Manual of the Diseases of Warm Climates*. London: Cassell and Co; 1917.

94. Ross R: An interim report on the treatment of malaria. *Trans R Soc Trop Med Hyg* 1917–1918, **11**:181–204.

95. Ross R: Observations on malaria by medical officers of the army and others. In *Provisional Instructions for the Treatment of Cases of Malaria in the United Kingdom*. London: His Majesty's Stationary Office; 1919:319.

96. Paisseau G: Malaria during the war. *Lancet* 1919, **i**:749–751.

97. Anderson AG: Clinical observations on the treatment of malaria in Macedonia. *J Royal Army Medical Corps* 1922, **38**:25–40.

98. Alport AC: The treatment of malaria. *J Royal Army Medical Corps* 1919, **32**:352–360.

99. Stendel D: Verlauf endemischer Malaria nach entfanungder Parasitenträger. *Archiv für Schiffs-und Tropen-Hygiene* 1917, **21**:3–29.

100. Anonymous: Besprechungen und literaturangaben. *Archiv für Schiffs-und Tropen-Hygiene* 1918, **22**:175–180.

101. White NJ: Determinant of relapse periodicity in *Plasmodium vivax* malaria. *Malar J* 2011, **10**:297.

102. Goodman LS, Gilman A: *The Pharmacological Basis of Therapeutics*. 5th edition. London: Baillière Tindall; 1975.

103. Discussion statements on Ross R, An interim report on the treatment of malaria. *Trans R Soc Trop Med Hyg* 1917–1918, **11**:200–204.

104. Editorial: Beneficial use of arsenic and quinine in treatment of malaria. *J Trop Med Hyg* 1917, **20**:39.

105. Yorke W, Macfie JWS: Observations on malaria made during treatment of general paralysis of the insane. *Trans R Soc Trop Med Hyg* 1924, **18**:13–44.

106. Chopra RN: *A Handbook of Tropical Therapeutics*. Calcutta: Art Press; 1930:579.

107. Reiter P: Global warming and malaria: knowing the horse before hitching the cart. *Malar J* 2008, **7**(Suppl 1):S3.

108. McLay K: Malaria in Macedonia 1915–1919. Haematological investigations in malaria in Macedonia. *J Royal Army Medical Corps* 1922, **38**:93–105.

109. MacDonald A: A note on the physical estimate of malaria disability. *J Royal Army Medical Corps* 1922, **38**:131–137.

110. Hele TS: Malaria in Macedonia 1915–1919. Chemical investigations on the excretion of quinine by soldiers in Macedonia. *J Royal Army Medical Corps* 1922, **38**:256–266.

111. MacLeod R, Lewis M: *Disease, Medicine and Empire: Perspectives on Western Medicine and the Experience of European Expansion*. London: Routledge; 1988:21–37.

112. Department of Health: *A Review of the Control of Malaria in Palestine (1918–1941)*. Jerusalem: Government Printing Press; 1941.

113. Alegana VA, Wright JA, Nahzat SM, Butt W, Sediqi AW, Habib N, Snow RW, Atkinson PM, Noor AM: Modelling the incidence of *Plasmodium vivax* and *Plasmodium falciparum* malaria in Afghanistan 2006–2009. *PLoS ONE* 2014, **9**:e102304.

114. Whitman TJ, Coyne PE, Magill AJ, Blazes DL, Green MD, Milhous WK, Burgess TH, Freilich D, Tasker SA, Azar RG, Endy TP, Clagett CD, Deye GA, Shanks GD, Martin GJ: An outbreak of Plasmodium falciparum malaria in U.S. Marines deployed to Liberia. *Am J Trop Med Hyg* 2010, **83**:258–265.

115. Elmes NJ: Malaria notifications in the Australian Defence Force from 1998 to 2007. *Int Health* 2010, **2**:130–135.

116. Tuck JJ, Green AD, Roberts KI: A malaria outbreak following a British military deployment to Sierra Leone. *J Infect* 2005, **50**:171–172.

117. James SP: Advances in knowledge of malaria since the War. *Trans R Soc Trop Med Hyg* 1937, **31**:263–280.