Angelo Celli and research on the prevention of malaria in Italy a century ago

Eliana Ferroni, Tom Jefferson and Gabriel Gachelin
J R Soc Med 2012 105: 35
DOI: 10.1258/jrsm.2011.11k049

Angelo Celli and research on the prevention of malaria in Italy a century ago

Eliana Ferroni[1] • Tom Jefferson[1] • Gabriel Gachelin[2]

[1]Acute Respiratory Infections Group, Cochrane Collaboration, Rome, Italy

[2]Université Paris Diderot, Sorbonne Paris Cité, Laboratoire SPHERE, Paris, France

Correspondence to: Eliana Ferroni. Email: elianaferroni@yahoo.it

DECLARATIONS

Competing interests
None declared

Funding
None

Ethical approval
Not applicable

Guarantor
EF

Contributorship
All authors contributed equally

Acknowledgements
The authors thank Rosella Del Vecchio (Library of the Sanarelli Public Health Department, Sapienza University, Rome) and Michele Catarinella (University Library of Bologna) for providing us with very useful material; and Paul Garner and Steve Lindsay for helpful comments on earlier drafts of this article. Additional material for this article is available

From 'seasonal and intermittent fevers' through '*mal'aria*', to 'malaria'

The parasite responsible for severe malaria (*Plasmodium falciparum*) has recently been demonstrated to have been transmitted to humans from gorillas,[1] a finding that substantiates an earlier hypothesis that malaria spread from monkeys to early neolithic peasants at the dawn of land cultivation.[2] The first written records of seasonal and/or intermittent fevers – which are widely assumed to be malaria – are found in Sumerian, Babylonian, Assyrian, Chinese, Egyptian and Indian texts.[3]

In the fifth century BCE, these fevers became widespread in ancient Greece, prompting Hippocrates to investigate them and to attempt a detailed description. He tried to understand the relationship between the timing and frequency of intermittent fevers and the swelling of the spleen, as well as their relationship to where patients lived, identifying swampy areas as particularly inhospitable. These intermittent fevers affected the inhabitants of wetlands in and around ancient Rome, a situation most probably aggravated by population flows from North Africa around the time of the Punic wars.[2] Some classical civilizations – for example, the Etruscans – channeled water flows and drained marshes, although this may have been primarily for land reclamation.

In 1717, the Italian physician Giovanni Lancisi described factors associated with intermittent fevers and postulated that mosquitoes might have a role in transmitting them.[4] Lancisi gave the word malaria its present medical meaning. The word began to be adopted in Italian and English medical texts in the eighteenth century, the word itself reflecting the popular belief that malaria was caused by stagnant air ('*mal'aria*') rising from swampy areas.

Identifying the mode of transmission of malaria

Although numerous authors postulated a link between mosquitoes and malaria, no proof of this way of transmitting a disease was forthcoming until the end of the 19th century. In 1880, the French military physician Alphonse Laveran described the parasite (*Plasmodium*) that causes malaria, later (1907) receiving the Nobel Prize for Medicine for his discovery. The Italian pathologist Camillo Golgi (Nobel Prize 1906) studied the parasite's cycle in human blood, linking the onset of intermittent fever with the breakdown of red blood cells and the spread of parasites into the blood. After the development of a method for staining malaria parasites in blood smears, Ettore Marchiafava and Amico Bignami investigated the suspicion that different species of *Plasmodium* might be responsible for different clinical manifestations of the disease. This led in 1892 to the identification of *Plasmodium falciparum* as the species responsible for fatal cases of malaria.

Meanwhile, British researchers had shown that human filariasis and blackwater fever in cattle could be transmitted by mosquitoes and ticks.[5,6] These observations prompted Patrick Manson to consider Lancisi's earlier and Laveran's more recent suggestion that mosquitoes might have a role in the transmission of malaria. He encouraged Ronald Ross (Nobel Prize 1902), a medical officer in the British Colonial Medical Service, to perform experiments in India to investigate from The James Lind Library website (www. jameslindlibrary.org), where it was originally published

whether malaria in birds was transmitted through mosquitoes. These studies demonstrated the development of the malaria parasite in mosquitoes, thus identifying how the disease was transmitted.

The specific species of mosquito responsible for malaria transmission to humans was discovered in Italy by Giambattista Grassi, a zoologist at La Sapienza University in Rome. Between 1898 and 1899, in collaboration with Amico Bignami and Giuseppe Bastianelli, Grassi showed that *Anopheles claviger* was the specific carrier of malaria in Italy, and described the development of the *Plasmodium* in the mosquito. Bignami and Bastianelli sent populations of infected mosquitoes to London (where there was no *Plasmodium falciparum*), and where Manson transmitted the infection to his son and to one of his colleagues. Manson's findings thus confirmed, on a firmer experimental basis, Grassi's earlier discovery that malaria was caused by infected *Anopheles*.[7]

These observations extended to malaria the insect vector theory of the transmission of diseases. Italy, which was already the main centre of malaria research, became the dominant place in Europe for studying the disease under field conditions, and a Society for the Study of Malaria was created there in 1898 to promote dissemination and application of the new discoveries. Over the following 15 years, more than 500 articles covering basic research and interventions to prevent and treat malaria were published in the Society's proceedings. As Bruce-Chwatt and Zulueta remarked nearly a century later:

> *To speak of malaria in Italy is to speak of the fundamentals in our knowledge of the disease. The Italian contribution in this field is immense. Not only is the now almost universally accepted name of the disease Italian, but the basis of the science of malariology is Italian as well. The malariologist from other lands when treading upon Italian ground can only do so with admiration and respect*.[8]

Italian research on the prevention of malaria

A map showing the distribution of the disease in Italy was first published in 1882, and a nationwide census in 1887 showed that malaria was present in almost a third of the Italian peninsula. It was estimated that two million Italians (out of a population of 30 million) suffered from the disease, and that it was killing over 20,000 of them every year. Malaria affected various provinces of Italy differently: in the north (except for the Venetian coast), a mild form of the disease prevailed; in the south (including the Tuscany and Latium coasts), the disease was more severe. About 10% of the population in the south lived in permanently endemic areas, and the case fatality rate in parts of Calabria, Basilicata, Sicily and Sardinia was sometimes as high as 20–30%. Furthermore, since malaria affected the cultivation of around two million hectares of land, the economy of the south suffered badly, the disease exacting a heavy burden from the agricultural workforce. These circumstances meant that the motivation for developing and applying policies to prevent malaria were particularly strong in Italy.

At the end of the 19th century, Giambattista Grassi showed that avoiding mosquito bites conferred protection from malaria. He sent 112 volunteers to the Capaccio Plains (a malarious area in south west Italy), and protected them from mosquito bites from dusk till dawn. Only five of the protected volunteers contracted the disease, compared to all 415 members of a comparison group (method of assembly not specified) who were unprotected.[9] The Italian hygienist Angelo Celli, director of the Department of Hygiene at La Sapienza University in Rome was concerned by the impact of economic and social factors on health.[10] He noted that the mild form of malaria in the north of Italy did not prevent industrial and agricultural development there, while the more severe cases in the south impeded both economic and social development. In collaboration with physicians, engineers, farmers, and teachers, Celli proposed a variety of public health interventions, including adequate drainage and water management interventions, full local employment, and public education. He argued for combined efforts, not only against the direct causes of malaria (the parasite and mosquitoes), but also against the concomitant causes of the disease – the environmental and living conditions of the affected populations. In a book published in 1899, he recommended that malaria prophylaxis should be based on blood disinfection, patient isolation, physical protection from mosquitoes of exposed parts of the body and of homes, and mosquito extermination. As Celli recognized the practical difficulties of disinfecting blood (the concept of disinfecting blood was probably derived from Behring's earlier suggestion of *in vivo* disinfection[11]) and exterminating mosquitoes, he decided to concentrate on testing ways of preventing mosquito bites.

Angelo Celli's controlled intervention study

Celli established a research centre in Casale della Cervelletta, a small town in Latium, 8 km from Rome on the railway line to Tivoli. After an initial trial during the summer of 1899, he conducted a study in the summer of 1900 to assess the effectiveness of a package of measures to prevent malaria by preventing mosquito bites. He began by recording the numbers of malaria cases in the local railway workers and their families living near five malarious railways lines. Then, in some of the homes, he screened the porches, doors and chimneys with wire mesh and covered the windows with thick muslin. The inside walls of these homes were whitewashed, as mosquitoes appear to be repelled by reflective surfaces and also could be better seen and subsequently killed. To prevent bites at night in houses in which mosquitoes were noticed, families were told to burn special powders (probably pyrethrum, an effective insecticide). Railway workers from these homes who were working on night shifts were equipped with veiled hats similar to those used by beekeepers, and given large leather gloves to prevent mosquitoes biting them. Quinine was administered to some of these workers. None of these interventions were used in the remaining, control families.[12–15]

Celli's report[16] does not provide a clear account of how families were chosen for assignment to the experimental and control groups, although it gives some insights into his thinking. He describes the importance of comparing like with like in terms of exposure and outcome:

> *Out of similar staff with similar living conditions those who were defended by us have remained immune from fever, while the remaining exposed staff were almost all sick. It is as if in a book we had a white page and a black page, the first would represent our protected dwellings and families, the second would represent our unprotected dwellings and families…*[16]

However, other elements of his text make clear that experimental and control groups sometimes differed. For example, there were new and old railway dwellings along the Castelgiubileo line.

> *Old* [dwellings] *do not lend themselves to have protective modifications made, and as a consequence were left as controls. This is all the more important as old and new are located almost in alternate positions.*[16]

Later in the text, Celli describes a cross over in exposure and outcome which had resulted from an administrative decision by the railway company at the height of the 1900 malaria 'season':

> *We also observed two control episodes. On the 23rd of August, for service reasons, the family in dwelling 17 was moved. The family (made up of father, mother and son), which had always been well, was moved to the nearby dwelling 16. About a month later the mother and child became ill with fevers. The incoming dwelling 17 family (parents and 6 offspring) had all been unwell with malaria. We immediately instituted a prolonged and plentiful quinine cure followed by a tonic cure with arsenic and iron. This family blossomed, convalescing and recovering during the height of the malaria season in a dwelling protected from the poisonous flies. Only one child who had resistant episodes is still quite weak. So that in this Castelgiubileo line, proof the new prophylaxis has been more decisive and clear than ever.*[16]

Celli provided detailed results in some elaborate Figures:

> *To provide an overview of the experiments carried out during 1899–1900 I have drawn tables 3–10 where unprotected railway workers dwellings, in other words controls, are in black ink, and protected dwellings are in red ink: the respective dwellers are displayed as larger disks for adults and smaller disks for children. The disk representing the head of the family is circled and the red outline shows*

those which didn't have fever and black outline those who did.[13]

The difference in malarial parasitic incidence was dramatic: 92 per cent of the families left unprotected contracted malaria compared to only 4% of those in the protected group (and several of this minority had ignored Celli's advice to cover themselves when outdoors) (Table 1).

For the first time since the railways had been constructed, the families of railway workers in endemic areas were able to spend the summer and autumn protected from malaria. As Celli concluded:

> *... For the present I wish to conclude that with the mechanical* [physical] *preventive treatment – protecting the houses and the exposed part of the body – a great stride has been made in the field of practice among railway hands, keepers, peasants even, in the malarial districts. The experience of recent years has been so successful that all those who acted as controls want protection during the forthcoming fever season. Now before long all houses in malarious districts will be protected against the entrance of these insects; and in this way during the day there will be no more trouble from flies and from other dirty or vexatious or injurious insects; at night there will no longer be the inconveniences and the evil results of the mosquito. And in all low, hot, moist places where myriads of insects of all kinds thrive, the mechanical* [physical] *protection against their invasion will become the best of all preventive rules against malaria and against other diseases.*[16]

Table 1
Effect of physical anti-mosquito measures for preventing malaria*

Railways lines	*Persons (n) (Intervention houses)*	*Cases (%)*	*Persons (n) (Control houses)*	*Cases(%)*
Prenestina – Salone	52 (8)	2 (3.8)	18 (3)	16 (88.9)
Castegiubileo	57 (7)	0	51 (8)	44 (86.3)
Pontegalera	35 (5)	3 (8.6)	53 (10)	49 (92.4)
Anzio	8 (2)	0	58 (10)	55 (94.8)
Terracina	29 (4)	2 (6.9)	37 (8)	36 (97.3)
Total	**181 (26)**	**7 (3.9)**	**217 (39)**	**200 (92.2)**

*Table based on data in Celli[13]

The difference between treated and untreated families in Celli's study was impressive, but Patrick Manson[7] was concerned that physical protection was not the only way in which the protected families had differed from control families. His concerns about possible biases had led him previously to repeat Grassi's experiment of malaria transmission using the malaria infected *anopheles* brought to London.[7] Although he had been impressed by the results of Celli's 1899 study, he was concerned that, in addition to physical measures of protection, some workers had been prescribed quinine.

This led Manson to conduct a smaller controlled experiment in Italy in 1900, concurrently with Celli's main study. He sent five people from the UK to live in wooden huts that he had had constructed in England, shipped to Italy, and then erected in Fiumaroli, in the countryside around Rome. The only protection against malaria afforded to the volunteers was mosquito netting – wire mesh screens on the doors and windows of the huts, and muslin nets around the beds. Quinine was not administered.[7] None of the five volunteers contracted malaria, unlike their neighbours, who did. This could reasonably be taken as a further demonstration that these simple practices could help prevent malaria effectively. By withholding quinine, Manson's experiment provided the additional control needed to exclude possible bias due to the drugs used in addition to protective clothing by the night workers in Celli's study.

Manson's paper in the *British Medical Journal* presents results confirming Grassi's findings but does not mention Celli's research. It is dated 29 September 1900; Celli's conclusions are dated 19 October 1900. These two important reports were thus made public – in different languages – at the same moment. A translation of Celli's report was published in *The Lancet* on 1 December 1900.[17]

The use of physical protection against mosquitoes

The use of physical protection against mosquitoes and other flies has a history that antedates Grassi, Manson and Celli by a long time. Muslin and bednets had been used for centuries as physical protection of individuals and houses, and wire gauze has been proposed as a protection against flies in general and mosquitoes in particular for at least two centuries. In general, these measures were not promoted for protection against any specific diseases, although a brief note in the *Encyclopaedia Americana* in 1835 reports that a doctor in Connecticut had proposed using wire gauze to isolate houses and protect their inhabitants against malaria. After the manufacture of wire gauze had been industrialized and costs had fallen, particularly after the 1830s, its use became increasingly widespread. By the end of the 19th century, it was being used widely in the south of France to protect people and food from flies, and US patent records confirm its popular use to protect inhabited areas and people against mosquitoes.

The insect vector theory of disease transmission which was developed at the end of the 19th century, provided a medical rationale for an already widely accepted use of physical protection, initially against yellow fever, specifically. In the 1880s, in Cuba, Carlos Finlay recommended using physical measures as a barrier to the mosquitoes that he assumed were transmitting yellow fever.[18] There is no evidence that his recommendations were adopted during the 1880s, but in 1899–1900 physical protection was introduced at the Hospital Las Animas in Habana (as discussed by Juan Guiteras at the 1st International Sanitary Conference of American Republics, in Washington DC, on 2–5 December 1902). At more or less the same time, in Brazil, the Sao Sebastian Hospital in Rio de Janeiro, which specialized in the treatment of yellow fever, introduced similar equipment. Wire gauze caging (named Marchoux' chambers after 1903) soon spread from Latin America to the French Antilles and Senegal to protect people at risk of yellow fever, and was extended to Algeria in 1902, to protect railway workers against malaria.

A few months before Celli's principal report had been published, the use of wire gauze for physical protection against malaria was added to the British Pharmacopoeia, and an English summary of Celli's work was produced in February 1901 'By command of CH Harley Moseley, Acting Colonial Secretary', for distribution throughout the British Empire.[14] The Italian experience led to widespread screening of homes against mosquitoes in malarious areas, not only in Italy, but around the world.[15]

In spite of this enthusiastic promotion, physical measures to prevent malaria received less attention than Celli's pioneering evaluations suggest they deserved. The reasons are complex. Physical barriers are certainly more difficult to install and maintain than alternative approaches, like insecticide spraying, for example. There may also be socially and culturally unacceptable. Celli noted that attempts to implement these public health interventions sometimes met with 'apathy, ignorance, and prejudice', and that some people commented that they 'were not wild animals and did not want to sleep in cages'.[19] Furthermore, some Italian peasants distrusted medical doctors and the quinine used to treat malaria: they considered traditional folk medicine superior.

Within a few years of Celli's reports, however, physicians responsible for health policies (and possibly patients and the public as well) began to think in terms of drugs and vaccines for preventing malaria. As early as the 1920s and 1930s, attention had started to switch to mass medication with commercially attractive synthetic antimalarial drugs, not only in Italy,[20,21] but in many other countries as well.[22]

The physical protection measures against mosquito bites to prevent malaria which Grassi, Manson and Celli pioneered over a century ago remain as important today as they were then.[23,24] As recently as 2009, a randomized trial showed that house screening reduces anaemia in children, an important finding because anaemia is the main cause of malaria deaths in children under two years old.[25] Indeed, Celli's combined strategy against malaria can be considered an early manifestation of the Integrated Vector Management adopted by the World Health Organization (WHO) today for the control of vector borne diseases.[26,27]

References

1 Liu W, Li Y, Learn GH, *et al*. Origin of the human malaria parasite Plasmodium falciparum in gorillas. *Nature* 2010;**467**:420–5

2 Packard RM. *The making of a tropical disease. A short story of malaria*. Baltimore, MD: Johns Hopkins University Press, 2007

3 Givigliano GP. Land and malaria in the Brutii. *International Journal of Anthropology* 1998;**3–4**:181–94

4 Lancisi G. *Noxiis Paludum Effluviis (On the Noxious Effluvia of Marshes)*. Rome 1717

5 Manson P. On the development of Filaria sanguis hominis and on the mosquito considered as a nurse. *J Linn Soc (Zool)* 1878;**14**:304–11
6 Smith T, Kilborne FL. Investigations into the nature, causation and prevention of Texas or southern cattle fever. *United States Department of Agriculture Bull Bureau Anim Indust* 1893;**1**:1–301
7 Manson P. Experimental proof of the mosquito malaria theory. *BMJ* 1900;**2**:949–51
8 Bruce-Chwatt LJ, de Zulueta J. *The rise and fall of malaria in Europe, a historico-epidemiological study*. Oxford: Oxford University Press, 1980
9 Grassi B. *Studi di uno zoologo sulla Malaria*. Rome 1900
10 Pazzini A. The work of Angelo Celli, hygienist, scientist and sociologist. *Scientia Medica Italica* (English ed.) 1958;**7**:233–41
11 Simon J. Emil Behring's medical culture: from disinfection to serotherapy. *Medical History* 2007;**51**:201–18
12 Celli A. Epidemiologia della malaria secondo le recenti vedute biologiche. *Annali dell'Istituto di Igiene Sperimentale* 1901a;**11**:44–95
13 Celli A. Sulla nuova profilassi della malaria. *Annali dell'Istituto di Igiene Sperimentale* 1901b;**11**:97–141
14 Celli A. The new preventative treatment of malaria in Latium. In *Collection of Papers on Malaria. Angelo Celli, 1899–1912*, pp. 1–12. London School of Hygiene and Tropical Medicine, 1901c
15 Lindsay SW, Emerson PM, Charlwood JD. Reducing malaria by mosquito-proofing houses. *Trends in Parasitology* 2002;**18**:510–4
16 Celli A. La nuova profilassi della malaria nel Lazio [The new prophylaxis against malaria in Lazio]. *Supplemento al Policlinico* 1900a;**6**:1601–1606
17 Celli A. The new prophylaxis against malaria in Lazio. *Lancet* 1900b;**156**:1603–1606
18 Finlay C. Yellow fever, its transmission by means of a Culex mosquito. *Am J Medical Sciences* 1886;**84**:395–409
19 Heid M L. Uomini che non scompaiono, Firenze. ['Heid' was the pseudonym that was used by Celli's wife Anna] 1944
20 Bastianelli G, Mosna E, Canalis A. Prevention and treatment of malaria by synthetic drugs. *Bulletin of the Health Organisation of the League of Nations* 1937;**6**: 822–91
21 Garattini S. (in preparation). Italian contributions to a multinational programme of controlled trials of synthetic anti-malarial drugs in the mid-1930s. *The James Lind Library*
22 Gachelin G. (in preparation). Pre-World War 2 research coordinated by the League of Nations to evaluate measures to control malaria. *The James Lind Library*
23 Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database of Systematic Reviews, 2004, Issue 2. Art No.: CD000363. DOI: 10.1002/14651858.CD000363.pub2. Confirmed up-to-date 2009
24 Kirby MJ, Milligan PJ, Conway DJ, Lindsay SW. Study protocol for a three-armed randomized controlled trial to assess whether house screening can reduce exposure to malaria vectors and reduce malaria transmission in the Gambia. *Trials* 2008;**9**:33. doi:10.1186/1745-6215-9-33. ISRCTN51184253
25 Kirby MJ, Ameh D, Bottomley C, *et al*. Effect of two different house screening interventions on exposure to malaria vectors and on anaemia in children in The Gambia: a randomised controlled trial. *Lancet* 2009;**374**:998–1009. doi:10.1016/S0140-6736(09)60871-0
26 WHO. Integrated Vector Management. Strategic Framework for the Eastern Mediterranean Region, 2004–2010
27 Celli A. Remarks on the epidemiology and prophylaxis of malaria in the light of recent Researches. *BMJ* 1900;**1**:301–6