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Italian controlled trials to assess prevention and treatment of malaria, 1900–1930s

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Introduction

As in other countries, medicine in Italy evolved from subjective and arbitrary interventions with mixtures of herbs and animal organs, to treatments based on observing the sequelae of therapy. Indeed, in 1615, Bernardo Zedrin declared: 'Medicine should follow physics and base its activities only on facts…'.[1]

Most of the important early Italian contributions to medicine were based on research on the treatment and prevention of malaria. In 1663, for example, Sebastian Bado published a book about one of the first remedies for malaria – *quina-quina* (Cortex peruvianus or cinchona bark). A few years later, Francesco M Nigrisoli was so convinced of the value of this treatment that he penned an article in Latin with the title 'Febris china-chinae expugnata' (removal of fever with quina-quina). The use of quina-quina had become so widespread by 1712 that Francesco Torti was able to establish which fevers were sensitive to quina-quina, in which doses and for how long.[1,2]

Italian controlled trials of quinine and house screens to prevent malaria around 1900

Quinine

The synthesis of quinine[2,3] – the active principle of quina-quina – led to its use for treatment. It was not until the end of the 1800s, however, that formally controlled trials were done in Italy by Angelo Celli (1857–1914), professor of hygiene at Rome University and a member of the Italian Senate for 20 years. Together with Ettore Marchiafava, Amico Bignami and Giuseppe Bastianelli, Celli was involved in studies of the pathogenesis, prevention and treatment of malaria in the early decades of the 20th century.

Celli's contributions were numerous and significant,[4] starting with the epidemiology of malaria. He estimated that two million of the 30 million Italians were infected, and that just under 20,000 of them died from the disease in any one year.[4] He reported:

> 'I made experiments with various substances, such as ointments, soaps and odours supposed to drive away mosquitoes, and I satisfied myself that they were of little use, even the best of them, as for instance, those with turpentine'.[5]

Accordingly, Celli turned his attention to investigating the efficacy of quinine. He collected data from a total of 913 people given 0.2 to 0.4 g of quinine per day, according to age, in 12 Italian towns, and from 626 untreated people in seven control towns (probably assigned by chance). The rates of fever differed dramatically – 5% among those given quinine compared with 40% among those in the control towns. He found that quinine was active both for new cases of malaria and for relapses in patients already infected, and that daily treatment was better than weekly treatment with the same dose.[5]

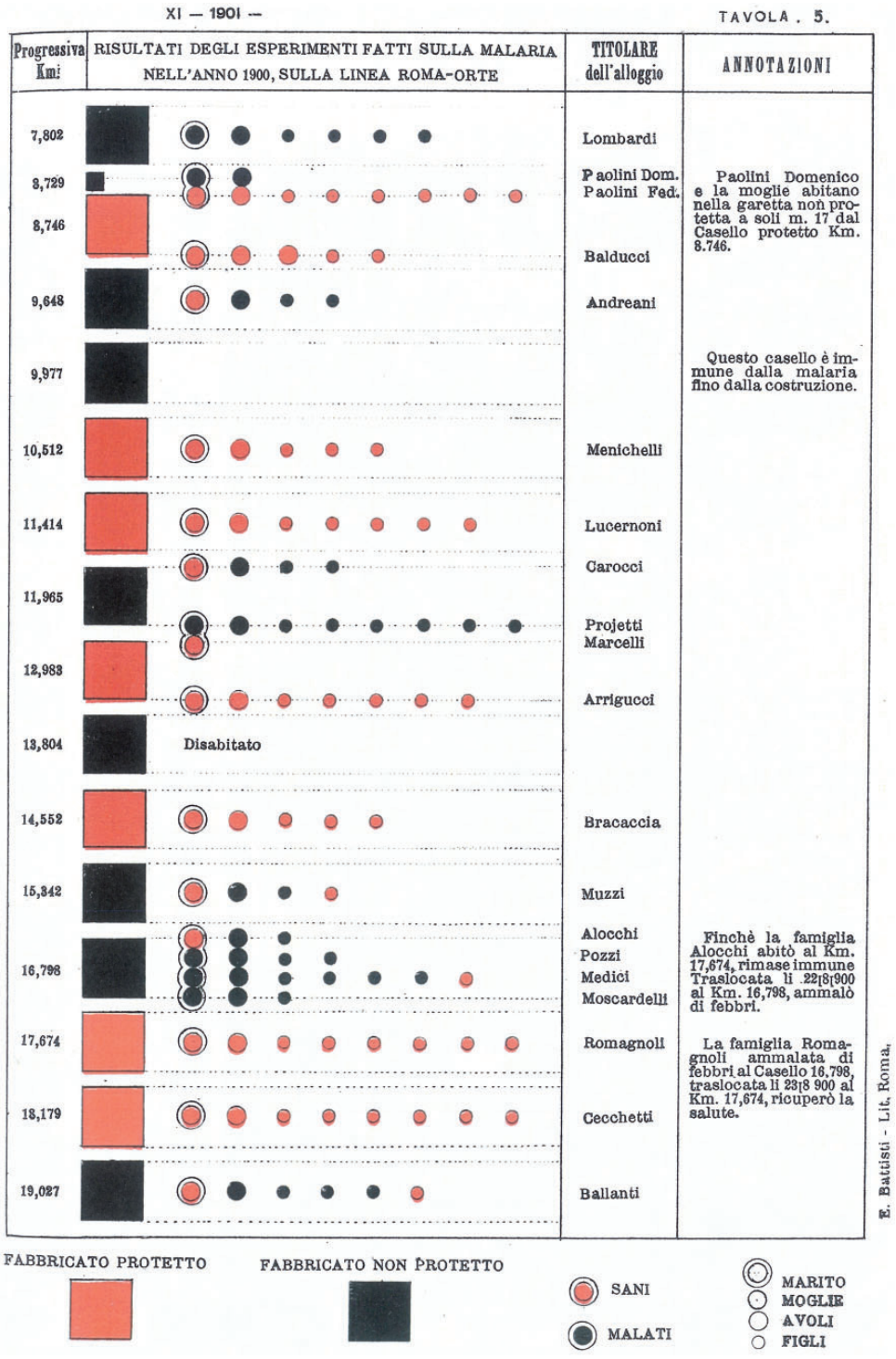
Celli designed another controlled trial[2,6] to assess whether salts of iron and arsenic reinforced the action of quinine. One hundred and forty workers were divided (method not stated) into three groups of 57, 54 and 35 people, and treated with quinine either given daily or in a higher dose weekly, with or without iron and arsenic. The comparisons provided no evidence that that iron and arsenic enhanced the effects of quinine. Making use of his position in politics, Celli succeeded in convincing the Italian Government in 1903 to give quinine free of charge to all working people.

The success of Celli's studies was acknowledged by a senior surgeon in the US Public Health Service, MR Carter,[7] who recommended that preventive use of quinine be extended to 'other highly malarious farming countries, such as Greece, Algeria and other countries… as its good results had been seen'.

House screens

Another of Celli's important contributions was a new type of prophylaxis – house-screening:[4,5,8,9]

Figure 1. Barrier prophylaxis of railway houses, by kilometres protected (red) or not protected (black), healthy (red) or sick (black), and names of families and numbers of family members (husband/wife/grandparents/sons).



We covered windows with frames of tulles, this allowing air and light, but no mosquitoes to pass. At the top of the staircase a door with a similar frame was placed, the better to protect the bedrooms. This door was made to close automatically so as not to demand too much of human apathy.

House screens were installed in residences along the railway tracks since railway personnel were frequently infected with malaria. Their houses were either old or new and only the new houses lent themselves to protective screening. Celli describes the advantage of this situation. 'This turned out to be a fortunate circumstance because the old and the new cottages, as nearly as possible, alternate one with another'. The alternating layout provided a controlled comparison, albeit confounded by the age of the dwelling. Figure 1 gives an example of difference between the protected and the unprotected houses,[9] which is clear without any sophisticated statistical analysis. A century later, Celli's results led Lindsay et al.[10] to write 'From these early studies the practice of house-screening against mosquitoes began to spread to different parts of the world. By 1910, it was used to protect Europeans living in the tropics and those building the Panama Canal'. Celli's work formed part of a general move to use physical protection.[11]

The use of quinine and house-screening enabled Celli to conclude that

> the average number of deaths per year in the 10 years preceding 1902 in all of Italy was 14,048 while for the years following, from 1903 to 1911 included, the average annual number of deaths was 5,435, and in the previous 5 years, only 3,858 per year.[7]

At around the same time as Celli's work in Italy, alternation was being used in controlled trials in several countries by investigators of various nationalities, including other Italians.[12] For example, Lustig and Galeotti[13] and Polverini[14] used alternation to generate comparison groups to assess the effects of interventions to prevent plague.

Italian trials of synthetic derivatives of quinine in the 1930s

Among early attempts to conduct modern clinical trials in Italy, it is appropriate to mention Giuseppe Bastianelli (1862–1959), a physician and zoologist mentioned above as a colleague of Angelo Celli, and director of the Institute of Malariology at the Sapienza University of Rome. Between 1934 and 1936, Bastianelli carried out two studies using synthetic drugs to treat malaria, as reported in a paper published in 1937.[15]

A prophylactic trial

The first was a preventive trial and aimed to establish the efficacy of atebrin, a synthetic antimalarial drug (Bastianelli et al.,[15] pp. 823–853). It was carried out in a small village, Posada, on the east coast of Sardinia, where endemic malaria was very prevalent. Since the infection peaked in July and August – as established by careful epidemiological studies covering the previous seven years – treatment started in May 1935 and continued till the end of the year. The authors involved the whole village of 781 inhabitants.

> The population was divided into three groups, care being taken to make them as homogeneous as possible. Group 1 was given atebrin every day and group 2 twice a week on non-consecutive days [except for children under the age of four, who were given the drug every other day], while group 3 was given no treatment, but kept under observation as controls. (Bastianelli et al.[15], p. 827)

The doses of atebrin administered to those in group 1 were 25 mg up to eight years of age and 50 mg if over eight years. Group 2 received a higher dose of atebrin twice weekly – 50 mg up to two years old, 100 mg up to four, 150 mg up to eight, and 200 mg over eight years of age. Group 3 received no treatment but was kept under observation. Any cases of malaria in the three groups were treated with atebrin at therapeutic doses (100–300 mg, depending on age, every day for seven days).

Compliance was probably good because two visiting nurses made the patients 'take [the drug] in their presence'. Baseline temperature measurements, blood tests and spleen index were recorded, followed by fortnightly blood tests up to the end of December, then monthly tests up to the end of April 1936. All the blood tests were done at the Institute of Malariology in Rome by investigators using standardised methods who remained unaware of the group to which samples referred.

The paper reports that there were 57 drop-outs (i.e. less than 10% of the population studied) and attention was paid to side-effects: '[nor] were any noteworthy intolerance phenomena observed, except for a slight irritation of the nasal mucosa'. As expected, there was yellow discoloration of the skin and urine due to the acridine component of atebrin, particularity in children under 12 years of age, but the colour disappeared when treatment ended. Follow-up was extended for a further six months.

The endpoints included the number of malaria cases and the number of carriers of malarial parasites. Besides the concurrent controls in Posada, the authors decided to have additional (historical) controls by taking account of cases of malaria in previous years, as well as cases observed in the same period in another village, Torpé, 5 km from Posada.

There were 161 cases of malaria (70.3%) in the control group but only 55 (23.4%) in the daily atebrin and 34 (13.9%) in the twice-weekly treatment groups. The twice-weekly treatment was more effective than the daily schedule and prophylaxis was also clearly active when other parameters (secondary endpoints, such as spleen index and fever) were considered. To confirm that the treatment was active, several subgroup analyses were done, such as by type of malaria (malignant tertian or benign) and the ages of patients. During the six-month follow-up, the group receiving treatment twice-weekly had 60% fewer cases of malaria, although the reduction was less dramatic among children. The follow-up was useful because it suggested that prophylaxis should be prolonged, particularly if outdoor temperatures were still high after October.

A treatment trial

The second trial reported by Bastianelli et al.[15] (pp. 854–891) assessed treatment of malaria among the 1100 inhabitants of the village of Torpé. It compared treatment with plasmoquine (from 5 to 20 mg depending on age, for five days) and a combination of atebrin (100 – 200 mg depending on age, for seven days) then plasmoquine for five days, given three days after atebrin (today this would be called an 'add-on' study). Recruitment required patients to have positive blood findings.

> Febrile patients were assigned alternately to the atebrin and atebrin+ plasmoquine groups in their order of arrival, irrespective of the degree of gravity of the case. (Bastianelli et al.,[15] p. 858).

As in the prevention study, nurses ensured compliance with medication. Temperatures were taken twice a day, and blood samples were taken daily during the atebrin period, then on days 8, 11 and 15. The onset of side effects attributed to plasmoquine required a protocol amendment, with a reduction of the plasmoquine schedule to only three days.

The results are not easy to interpret because much of the report is devoted to the effect of atebrin on various parameters and the comparison of atebrin with and without plasmoquine is relatively limited. Atebrin reduced fever, although its effect was stronger for the benign than for the malignant tertian form of malaria. The action on body temperature paralleled the disappearance of parasites from the blood. The two treatments were compared only by the extent of enlargement of the spleen. Among the 614 participants, atebrin reduced the volume of the spleen by 12.2%, while the combination of atebrin and plasmoquine reduced it by 14.8%. Additional comparisons were made on the prevention of relapses, but without distinguishing relapses from reinfections, distinguishing instead between the epidemic and the inter-epidemic period. Briefly, no differences were detected between the two regimens, even when various subgroups (age, type of malaria, epidemic period, etc.) were analysed. The authors' conclusions are consistent with the data presented: addition of plasmoquine to atebrin did not achieve improvements sufficient to justify use of the combination.

Methodological features of the Bastianelli trials

These Italian trials on antimalarial agents in the 1930s are important because the authors adopted important methodological features, possibly under the influence of the League of Nations. Before both trials, there were epidemiological studies of the entire population of the two selected villages, Posada and Torpé. Information on the prevalence of the disease and its symptoms was very useful, not only for planning the trials but also to ensure that historical controls were not used as substitutes for concurrent controls, but in addition to the latter.

Both studies had concurrent controls, usually with similar numbers in the treated groups. Selection in the prevention trial was based on similar demographic characteristics. In the therapeutic trial, patients were assigned alternately to the two comparison groups by the order of their presentation. This important methodological feature had been used increasingly frequently since the beginning of the 20th century[12] and was a prelude to the adoption of concealed random allocation in the 1940s.[16] There was no calculation of sample size as the whole population of the two villages was recruited for the prophylaxis study and all cases of malaria for the treatment study in Torpé.

No informed consent was required: as stated in the report, patients could refuse prophylaxis or treatment if they wished. Compliance was much better than in many trials, however, because two nurses made sure that they observed participants taking the drugs. The nurses also recorded body temperatures, to ensure uniformity of the results. Another important feature of the trials was the central analysis of blood samples at the Institute of Malariology in Rome.

The description of side effects was limited but accurate. The results clearly indicated the value of prevention with atebrin and require no formal statistical analysis. In the therapeutic trial, no benefits were

evident from adding plasmoquine to atebrine. Lastly, the researchers were interested not only in the short-term findings of their studies but also in relatively extended follow-up to assess whether the action of the preventive or therapeutic interventions persisted over time.

In conclusion

During the first half of the 20th century, the design of controlled trials evolved to include the basic features we recognise today. Italian researchers contributed to this methodological evolution in trials in their assessment of the effects of interventions to prevent and treat malaria. Angelo Celli did trials at the beginning of the century to assess the effects of prophylactic administration of quinine, and physical methods for protecting people from mosquitos, and Guiseppi Bastianelli and his colleagues in the 1930s did studies to assess the relative value of new synthetic antimaterial drugs for prevention and treatment.

Declarations

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References

1. De Renzi S. China China. Storia Della Medicina in Italia. *Tomo Quarto*. Napoli: Tipografia del Filiatre Sebezio, 1846, pp.394–410.
2. Gachelin G, Garner P, Ferroni E, Tröhler U and Chalmers I. Evaluating Cinchona bark and quinine for treating and preventing malaria. *JLL Bulletin: Commentaries on the History of Treatment Evaluation*. See https://www.jameslindlibrary.org/articles/evaluating-cinchona-bark-and-quinine-for-treating-and-preventing-malaria/ (last checked 26 June 2019).
3. Pelletier J and Caventou JB. *Analyse Chimique des Quinquinas*. Paris: C Colas, 1821.
4. Ferroni E, Jefferson T and Gachelin G. Angelo Celli and research on the prevention of malaria in Italy a century ago. *JLL Bulletin: Commentaries on the History of Treatment Evaluation*. See https://www.jameslindlibrary.org/articles/angelo-celli-and-research-on-the-prevention-of-malaria-in-italy-a-century-ago/ (last checked 26 June 2019).
5. Celli A. The new prophylaxis against malaria: an account of experiments in Latium. *Lancet* 1900; 156: 1603–1606.
6. Celli A. La malaria in Italia durante il 1902. Parte II: Profilassi della malaria. Malaria in Italy in 1902. Part II: Prophylaxis of Malaria]. *Annali di Igiene Sperimentale* 1903; 13: 322–343.
7. Carter HR. Quinine prophylaxis for malaria. *Public Health Rep* 1914; 29: 741–749.
8. Celli A. La nuova profilassi della malaria nel Lazio. *Supplemento al Policlinico* 1900; 6: 1601–1606.
9. Celli A. Sulla nuova profilassi della malaria. *Annali dell'Istituto di Igiene Sperimentale* 1901; 11: 97–141.
10. Lindsay SW, Emerson PM and Charlwood JD. Reducing malaria by mosquito-proofing houses. *Trends in Parasitology* 2002; 18: 510–514.
11. Finlay C. Yellow fever, its transmission by means of a Culex mosquito. *Am J Med Sci* 1886; 84: 395–409.
12. Chalmers I, Dukan E, Podolsky SH and Davey Smith G. The advent of fair treatment allocation schedules in clinical trials during the 19th and early 20th centuries. *JLL Bulletin: Commentaries on the History of Treatment Evaluation*. See https://www.jameslindlibrary.org/articles/the-advent-of-fair-treatment-allocation-schedules-in-clinical-trials-during-the-19th-and-early-20th-centuries/ (last checked 26 June 2019).
13. Lustig A and Galeotti G. The prophylactic and curative treatment of plague. *BMJ* 1901; 1: 206–208.
14. Polverini G. Serumtherapie gegen beulenpest. *Muenchener Medizinische Wochenschrift* 1903; 50: 649–651.
15. Bastianelli G, Mosna E and Canalis A. Prevention and treatment of malaria by synthetic drugs. *Bull Health Organ League Nations* 1937; 6: 822–891.
16. Chalmers I. Why the 1948 MRC trial of streptomycin used treatment allocation based on random numbers. *JLL Bulletin: Commentaries on the History of Treatment Evaluation*. See https://www.jameslindlibrary.org/articles/why-the-1948-mrc-trial-of-streptomycin-used-treatment-allocation-based-on-random-numbers/ (last checked 26 June 2019).