The art of medicine

Artesunate versus quinine: the controlled trials watershed

Earlier this century, two inter-related randomised controlled trials—the first in southeast Asia and a second in Africa—provided an incontrovertible breakthrough in the treatment of severe falciparum malaria. The trials, of artesunate versus quinine, proved beyond doubt for the first time that quinine, which had long been the mainstay of treatment for severe malaria, was no longer the most effective drug available, and thus catalysed a watershed in clinical practice and policy making. Like almost all decisive moments, this advance had a backstory that stretched several decades.

The trials would not have been possible without a wartime collaboration during the Vietnam War (1955–75): after a request from the Government of North Vietnam for assistance with the treatment of malaria, the Chinese Government had launched a secret operation codenamed 523 Project in May, 1967. This clandestine programme of applied discovery science led, in 1972, to the rediscovery of the active antimalarial elements from the qinghaosu plant, which we know today as artemisinin. The subsequent synthesis of the water soluble artesunate offered the promise of a new class of antimalarial drug. The path to translate this discovery from its origins in communist China to worldwide use would, however, take a generation. Tu Youyou, a respected Chinese pharmaceutical chemist and malariologist, shared the 2015 Nobel Prize in Physiology or Medicine for her discovery of artemisinin.

Severe malaria is fatal if untreated—in 2021 there were an estimated 619 000 malaria deaths globally. In highly endemic areas, mortality is especially high among young children if they do not receive prompt treatment. This troubling reality galvanised researchers in the late 20th century to develop new and better treatments for the infection. In the forefront of this movement was a group of investigators led by the distinguished malariologist, Nick White, Professor of Tropical Medicine at the University of Oxford. Since 1980, White has led the pathbreaking research partnership between Thailand's Mahidol University and the UK's University of Oxford and the Wellcome Trust at the Mahidol–Oxford Tropical Medicine Research Unit (MORU), in Bangkok, Thailand. At the time, quinine was the recommended treatment of severe malaria, and indeed had held that trusted pharmacological status since the 1630s, when cinchona bark was introduced to European medicine. White had first become aware of the artemisinin derivative artesunate at the beginning of the 1980s, when he read a paper in a Chinese medical journal that described artesunate's activity in English. "When I read the article", he recalled in an interview with me, "frankly it seemed too good to be true." However, during a visit to China in 1981, he met some of the Chinese scientists, including Liu Xu, an artesunate specialist who had developed and tested the new drug. Their persuasive scientific evidence converted his initial scepticism into "huge enthusiasm" for the new drug's potential. Moreover, the Chinese physician, Professor Li Guo Qiao offered to provide White with enough artesunate to enable him and his colleagues to assess the efficacy of the drug in a controlled trial in patients with severe malaria. Nevertheless, in subsequent years, western priorities would lie with a rival derivative of artemisinin: artemether. White and his close-knit group would go on to develop a well deserved reputation for seeking new treatments for severe malaria. During the 1990s, they did a comparative trial in adults in Viet Nam of quinine and artemether and found artemether a satisfactory alternative to quinine, but not the breakthrough they were looking for. It was around this time that Li Guo Qiao made available a supply of artesunate, a drug he thought superior in the treatment of severe malaria. Artesunate offered a trialable hypothesis that stirred the team's imagination and investigative instincts. Their aim was to initiate a randomised comparison trial to determine whether parenteral artesunate or parenteral quinine was the more effective treatment of severe malaria. This study became the South East Asian Quinine Artesunate Malaria Trial, better known by its acronym SEAQUAMAT.

A pioneer of randomised controlled trials in medicine, the statistician and epidemiologist Austin Bradford Hill had emphasised a need for "simplicity of design" and this principle guided the SEAQUAMAT group. The tropical health physician Nick Day, based at the University of Oxford and MORU and today Director of the Wellcome Trust Thailand Asia and Africa Programme, was involved in designing and coordinating the study. He understood that the combination of proper randomisation and having a simple case report form that avoided collecting unnecessary information about each patient would hasten recruitment and lead to bigger numbers and hence better science. "The innovation of SEAQUAMAT was to make it multi-centred as we needed large scale randomised evidence in order to measure a 30% reduction in mortality which meant we had to enrol about 2000 people", Day told me in an interview. Building on the simplicity of the case report forms was the invention of the SEAQUAMAT hardcover box, which had the same dimensions as a ream of A4 paper, and contained everything that a clinician needed for the trial, perfect for a multicountry study. SEAQUAMAT was an open-label trial and not a blinded trial because quinine and artesunate have different treatment regimens—quinine requires an intravenous infusion to run for about 4 h and the attending physician would know which drug was being used. Importantly, the two-stage randomisation process, which was coordinated from Bangkok, included the use of sealed opaque envelopes which ensured that assigning a patient to a treatment group was not at the discretion of the attending

Courtesy of Arjen Dondorp

The AQUAMAT study group at the investigators' meeting in Nairobi, Kenya, in 2009

physician. The primary endpoint of the trial was death from severe malaria. The trial was funded by the Wellcome Trust, coordinated by the Wellcome Trust–Mahidol University–Oxford Tropical Medicine Research Programme, and carried out between June, 2003, and May, 2005, in Bangladesh, India, Indonesia, and Myanmar.

The Bangkok team knew that artesunate would be easier to administer than quinine, and their hope was that it would be safer and more effective against the fatal disease. All the patients' data and outcomes were passed to an independent Data and Safety Monitoring Committee (DSMC) whose remit included advising the team to stop the trial if there was clear evidence that the results would change clinical practice. The Chair of that committee was the tropical health physician Tim E A Peto, Professor of Medicine at the Nuffield Department of Medicine, University of Oxford, and by the spring of 2005 he recognised that there was a large reduction in mortality that was consistent across all participating countries. "There was a clear-cut benefit of artesunate versus quinine", he recalled when I interviewed him, "with an absolute reduction in mortality of 34·7%." Such conclusive findings, of a substantial survival benefit in favour of artesunate, provided the necessary evidence required to stop the study. However, conscious that it would be a momentous decision to stop the trial early, he thought it only sensible to seek the advice of the then Professor of Medical Statistics and Epidemiology at the University of Oxford, Sir Richard Peto. "Richard gave me his time and when I showed him the evidence and asked if it was convincing, he replied, 'This is one of the most convincing trials I've ever seen. You can stop the study.'" Thus, after enrolling 1461 adults and children White received a phone call from the DSMC advising him to stop the trial. "It was a great moment. I knew artesunate was good, but I didn't think it was that good", he said. In August, 2005, the SEAQUAMAT group published their lodestar findings in *The Lancet* and a year later WHO changed its guidelines to recommend artesunate—at that time the drug was not approved by the US Food and Drug Administration—for severe malaria in adults.

The researchers had proved to themselves that artesunate, with its easier administration and superior pharmacokinetics profile, worked better than quinine. Nonetheless, they were conscious that their good evidence, obtained in mainly adult patients in southeast Asia, might not be enough to change policy in Africa, where quinine was unchallenged and where about 90% of the world's severe malaria infections and deaths occurred. The majority of this malaria burden was in sub-Saharan Africa, with most deaths among children younger than 5 years. Rational sceptics working in Africa had an understandably strong attachment to a tried and tested medication. Looking back almost two decades later, White described the genuine equipoise that existed at the time: "Good malariologists, people who knew how to treat severe malaria in Africa, didn't think artesunate would work in Africa. They said, 'SEAQUAMAT is a good result, we believe it. We believe you've got the right answer. But the disease in African children might be a bit different.'" Thus, the reality for the SEAQUAMAT researchers was that potential differences in the natural history and drug susceptibility of severe malaria between children in Africa and patients in southeast Asia left genuine "uncertainty about the optimum treatment for this important patient group", as they wrote in *The Lancet*. To move the needle of perception in the minds of unconvinced malariologists and influential actors in malaria control programmes in Africa, the investigators needed to provide additional and incontestable evidence if they were to succeed in changing clinical practice.

A scientific resolution came when Lorenz Von Seidlein, the SEAQUAMAT group's soon-to-be recruited colleague and now Professor of Global Health at MORU, suggested replicating the trial in Africa. Such an undertaking was unprecedented and would necessitate a huge logistical effort. Yet for many reasons it made sense: White had been involved in the first ever drug study for severe malaria among children in Africa during the 1980s; it helped that Thailand was a malaria endemic country; and running the trial from Bangkok would avoid any North–South power imbalance. The new trial would be an East–West collaboration rather than a project directed from the UK or USA (MORU's TRAC II and DeTACT studies in malaria control have built on this earlier foundation). Under the expert supervision of Principal Investigator (PI) Arjen Dondorp, Professor of Tropical Medicine at the University of Oxford and Deputy Director of MORU, the open-label randomised trial of artesunate versus quinine in the treatment of severe malaria in African children (AQUAMAT) was launched in 2005. The first site established was in Beria, Mozambique, and the trial was then expanded to enrol 5425 children in 11 sites in nine sub-Saharan countries (Mozambique, The Gambia, Ghana, Kenya,

Tanzania, Nigeria, Uganda, Rwanda, and the Democratic Republic of the Congo). "It was the right size of trial", Dondorp told me, "to provide a definite answer." Not only was the study the largest hospital-based clinical trial of severe malaria in medical history, it also helped foster a great sense of camaraderie among the researchers who shared insights with each other. Olugbenga Mokuolu, who is now Professor of Paediatrics at the University of Ilorin Teaching Hospital, Ilorin, Nigeria, was in 2005 the PI for his country's AQUAMAT study site. He underscores the enduring collectivist ethos that the trial nurtured. "The meetings were fantastic, they offered the opportunity of getting to know one another. We got to know each other very well, and some of the relationships and linkages that were established are still thriving", Mokuolu told me. Not everything went smoothly, however—trials can be prone to tribulations—and unsuccessful attempts were made to prevent and even curtail the study, while the Wellcome Trust, who funded the research, became in the memorable phrase of Day "increasingly exasperated" at the proliferating costs of the trial.

Reassuringly, AQUAMAT's findings were a vindication of the Wellcome Trust's commitment to supporting discovery research into one of the most devastating parasitical diseases of humans, and of the investigators' adhesion to the ideal of discovering better treatments for severe malaria. The trial revealed that artesunate substantially reduced the overall mortality of African children with severe malaria. Taken together, both SEAQUAMAT and AQUAMAT showed that artesunate was better than quinine in terms of the immediate saving of lives, and improvement in survival. The size of the trials, the consistency of the results, and the scale of the reduction in mortality in African children definitively settled the question of artesunate versus quinine.

Having shown that artesunate should replace quinine as the treatment of choice for severe falciparum malaria worldwide, the researchers then turned their attention to the presentation of the results. With this in the forefront of his thoughts, White secured from the Royal Society the use of an Elizabethan country house, Critchley Hall, near London, UK, as a retreat for the AQUAMAT team to collate data, and compile a real-time statistical analysis for the formal presentation of the trial's findings at the American Society of Tropical Medicine and Hygiene (ASTMH) meeting in Atlanta, GA, USA, in November, 2010. One of the people presenting the findings that day was Mokuolu, who recalled that, "We had the biggest audience at the ASTMH that year, and when we presented the results on the 22·5% reduction in mortality, they gave us a standing ovation and there was wide jubilation in the hall. The ASTMH is like the FIFA World Cup of the malaria world."

The collaborative study had showed that parenteral artesunate was safe, that it was easier to administer, and that it reduced mortality substantially compared with quinine. In the final sentence of their research article, published in *The Lancet* in November, 2010, the researchers described their findings clearly and delineated the clinical way forward: "If 4 million African children with severe malaria every year were to receive prompt treatment with parenteral artesunate instead of quinine, and the benefits were similar to those recorded in this trial, then approximately 100 000 lives might be saved per year." The leading malariologist, Brian Greenwood, the Chair of AQUAMAT's Steering Committee, is unequivocal in his view of the study's importance. "If you think of single trials that have changed policy, there are not many, but AQUAMAT would be one", he said in an interview with me. The two closely related trials SEAQUAMAT and AQUAMAT eventually transformed global malaria policy by producing the good evidence necessary to remove any persistent therapeutic uncertainty, and convincingly showed that artesunate should replace quinine as the treatment of choice for severe falciparum malaria. In this century global malaria deaths have reduced by about 42% and artemisinin and its derivatives have had a central role in this striking success. The story of these two experiments in therapeutic research is a powerful reminder of the capacity of large and well run randomised controlled trials to provide unbiased answers and to fundamentally improve clinical care. However, there are still many challenges to be addressed in global malaria control, especially in settings such as sub-Saharan Africa where progress has recently stalled in reducing malaria deaths and infections and under-5 malaria mortality remains troublingly high. New malaria tools, increased resources and investment, strengthened health systems, fresh thinking, and stronger political commitment are among the steps needed to move forward momentum in global malaria control.

Courtesy of Lorenz Von Seidlein

Paediatric ward, Teule Hospital, Muheza, Tanzania, 2005, one of 11 centres where children with severe malaria were recruited into the AQUAMAT trial

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