IN-09 Malaria: cinchona, Artemisia annua, nets and the full evidence

HEALING after the FALL, research library, IN-09

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How to read this document

Malaria is the one disease in this book for which the world's two most important drugs both came from plants a village can grow. That fact invites romance. The record does not support it. Cinchona bark cured agues for two centuries, but only in the right dose, for long enough, and at the price of deafness, blindness, collapsed blood sugar and, in some, the black urine of blackwater fever. Artemisia annua gave the world artemisinin, but as a tea it clears fever fast and then lets the infection come back in most patients. Nets and closed eaves, by contrast, are dull and reliable.

So the order here is prevention first, then diagnosis, then the two plant drugs, then severe malaria and salvage. Vector control is covered at length elsewhere (THRIVING library, HY-06), and fever in general, including fever patterns and danger signs, in IN-02 (THRIVING library, IN-02). This report builds on both and repeats only what a healer needs to act.

Figures marked [VERIFY] are claims I could not confirm from a source I read, or my own arithmetic. Several key trials were read only through the WHO technical review of 2019 or through abstracts, and each reference says so. No procedure for extracting, purifying or making any drug is given. Where the brief asks whether quinine can be made, the answer is what the record shows about who did it and at what cost.

1. Findings by section

1.1 What malaria kills, and how fast

Malaria is caused by Plasmodium parasites carried by night-biting Anopheles mosquitoes. Falciparum malaria kills. Vivax, ovale and malariae malaria sicken and weaken but rarely kill, and vivax and ovale relapse from dormant liver forms that neither quinine nor artemisinin removes (THRIVING library, IN-02). In a malarious place every fever is malaria until shown otherwise.

The weight of the disease before drugs is now estimated from genetics. Because the sickle-cell trait protects against malaria, its equilibrium frequency of 15 to 20% in high-transmission Africa implies that malaria killed between 15% and 24% of all children before treatment existed (Watson, White and Dondorp 2022). That is the baseline a village returns to if it loses both prevention and drugs.

Once a child has severe falciparum malaria, death comes quickly. Treated in hospital, coma from cerebral malaria still kills 15 to 20%, and WHO-defined severe malaria 10 to 20%, while untreated severe malaria is considered uniformly fatal (Pan African Medical Journal 2013 review, read in search summary). In one Congolese series three quarters of deaths came in the first 48 hours (same summary). In Ibadan, 13.7% of cerebral malaria survivors left with a neurological deficit, and 4.6% still had one at follow-up. Modelling estimates put the death rate from untreated

uncomplicated malaria at about 5% under two years and 2% from two to five years, but these are assumptions, not observations (LiST review, Thwing and others 2011 [VERIFY authors]).

The lesson for the book: uncomplicated malaria gives a household a day or two. Severe malaria gives hours.

1.2 Diagnosis without a laboratory

What the tradition says. Classical medicine named agues by rhythm: tertian (every 48 hours), quartan (every 72). These patterns are real for vivax, ovale and malariae, but falciparum is often irregular and mixed infections blur any rhythm (THRIVING library, IN-02). A rhythm is a clue, never proof.

What the record shows. Treating every fever as malaria was WHO policy for African children until 2010. It was wrong much of the time. In Tanzania only 46% of 2,062 patients treated for severe malaria had falciparum parasites on a film (Reyburn and others 2004 [VERIFY authors], read in search summary). In western Kenya laboratory-confirmed malaria was found in 6.7% of febrile children at a low-transmission site and 45.8% at a high-transmission site, and 57.2% of the malaria-negative children at the high site were still given antimalarials (Lancet Global Health 2014 Kenya study, read in search summary). The cost of overdiagnosis is the pneumonia, meningitis and typhoid that go untreated while the child takes bitter tea.

Rapid tests. In the Cochrane review of 74 studies, HRP-2 tests detected about 95% of falciparum infections (sensitivity 95.0%, 93.5 to 96.2) with specificity of about 95%. pLDH tests were slightly less sensitive (91.5%) and more specific (98.7%). HRP-2 stays positive for weeks after cure, so it cannot detect treatment failure (Abba and others 2011, abstract). Salvaged tests degrade with heat and age [VERIFY: inference from the general behaviour of antibody tests]. They will run out.

Microscopy. The thick blood film, stained with Giemsa or Field's stain, remains the test a district can sustain if it has a microscope, glass slides, oil, and stain. WHO's standard is to read 100 high-power fields before calling a slide negative, which with about 20 white cells a field gives a detection threshold near 4 parasites per microlitre in theory. Some laboratories read 300 fields because 100 can miss up to 20% of infections (CDC DPDx, read in search summary). In real field conditions a Gabonese study measured limits of 62 to 88 parasites per microlitre (search summary). The WHO basic microscopy course is designed for 4 to 5 weeks of formal training (search summary). Only the film shows parasite clearance and recrudescence, which matters for every plant remedy below.

Inference for after the Fall. A household diagnoses by place, season and danger signs. A village with no tests treats fever in a malarious season as malaria but always also looks for the cough, stiff neck, burning urine or rash that point elsewhere (THRIVING library, IN-02). A district with a microscope makes the film its most valuable tool, because without it no one can tell whether a remedy worked.

1.3 Prevention: what each measure cuts

Nets. The strongest evidence for any malaria measure is for insecticide-treated nets. Lengeler's 2004 Cochrane review found that treated nets cut child deaths by about a fifth, and about 5.5 lives were saved each year for every 1,000 children protected (Lengeler 2004, read via a DFID evidence summary). The 2018 update, with 23 trials, found all-cause child mortality 17% lower than with no nets (rate ratio 0.83, 95% CI 0.77 to 0.89, five trials, 200,833 children, high certainty), or 5.6 lives per 1,000 children per year (Pryce, Richardson and Lengeler 2018).

After the Fall the insecticide will run out. Against untreated nets, treated nets probably cut child deaths by a third, but the confidence interval crosses no effect (0.67, 0.36 to 1.23) (Pryce, Richardson and Lengeler 2018). In 48 Gambian villages an intact untreated net gave about 51% protection against falciparum infection in children (THRIVING library, HY-06, citing Clarke and others 2001). The key word is intact. An untreated net does not kill a mosquito that finds a hole, so mending is the work.

House screening and closed eaves. Anopheles gambiae enters mostly at the gap between wall and roof. In the Farafenni trial in The Gambia, untreated full screening or a screened ceiling cut indoor mosquitoes by about half and severe childhood anaemia from 19.0% to about 12%, though parasite prevalence did not fall significantly. Grassi in 1900 and Celli in Rome showed the same with screened houses (THRIVING library, HY-06). Closing eaves with mud, wood or cloth is about a day's work for two people per house [VERIFY: estimate from HY-06].

Drainage. Larval source management works where breeding sites are "few, fixed and findable" and fails in great swamps and rice fields. Every famous campaign, from Gorgas in Panama to Soper in Brazil, was a bundle of drainage, oiling, screening and quinine, done by a disciplined workforce, and every one decayed when the labour stopped (THRIVING library, HY-06).

Larva-eating fish. The Cochrane review found no reliable evidence that stocking fish reduces malaria (THRIVING library, HY-06, citing Walshe and others 2017). Fish do no harm in a permanent tank and are not a control.

Pyrethrum. Dried flower heads of Tanacetum cinerariifolium, ground fine, knock down mosquitoes indoors. Gorgas burned 240,000 lb of it in Panama in 1905. Flowers carry about 1 to 2% pyrethrins and lose them in sunlight and storage within weeks (THRIVING library, HY-06). It is a supplement to nets and screens, not a substitute.

Repellents and smoke. Repellents prevent bites for hours but their effect on malaria is unproven. Smoke from leaves protects somewhat, and coils cost lungs (THRIVING library, HY-06).

Prevention by drug. Artemisinin in any form is unsuitable for prevention because its half-life is one to three hours (WHO 2019 technical document). Quinine was used by colonial armies and workers as a daily or weekly suppressive, and irregular use of it was blamed for blackwater fever (see 1.7). After the Fall, drug prophylaxis is for no one except perhaps a pregnant woman in a high-transmission season with salvaged stock, and that decision belongs to the district [VERIFY: inference].

1.4 Cinchona: the tradition and the history

What the tradition says. The European legend is that the Countess of Chinchón was cured of fever in Peru and brought the bark to Spain in 1638, and that Linnaeus named the tree Cinchona for her in 1742. The Andean legend is of a fevered man who drank bitter water near quina-quina trees. Both are legends. What is documented is that Jesuit missionaries were using the bark in South America by about 1630, which gave it the names "Jesuits' bark", "cardinal's bark" and "sacred bark" (Achan and others 2011).

What the record shows. The bark was dried, powdered and taken mixed in a liquid, usually wine (Achan and others 2011). In 1712 Francesco Torti of Modena published Therapeutice specialis ad febres quasdam perniciosas, which showed that the bark cured periodic fevers and not continuous ones. That distinction finally overthrew the doctrine that all fevers had one origin (Garrison-Morton entry via historyofmedicine.com, read in search summary). It was in effect the first diagnostic use of a drug.

In 1820 the Paris pharmacists Pierre Joseph Pelletier and Joseph Caventou isolated quinine, worked in a laboratory behind an apothecary's shop, and did not patent it. A guide to using quinine was available by 1821 (Achan and others 2011, and search summaries). Between 1866 and 1868 a commission compared the four main alkaloids (quinine, quinidine, cinchonine and cinchonidine), as sulphates, in 3,600 patients, and all four stopped the febrile paroxysms in more than 98% (Achan and others 2011). This matters for after the Fall: the minor alkaloids work too, so a cheap mixture of all the bark's alkaloids is a real medicine.

Ledger, Mamani and Java. The Dutch plantations in Java first grew barks with no more than 1% quinine. In 1865 Manuel Incra Mamani, an Aymara cascarillero who had worked for the English trader Charles Ledger since 1843, collected seed from high-yielding trees in Bolivia. Ledger's brother sold most of it to the Dutch government after Kew declined it. The resulting Cinchona ledgeriana (now treated as a form of C. calisaya) gave bark reported at up to 10% or 13% quinine, depending on the source. By the 1930s the Dutch supplied about 97% of the world's quinine.

Mamani was arrested on a later seed trip and beaten so badly that he died, in 1871 or 1872 by different accounts (Wikipedia entries on Ledger and Mamani, and RSC Education, read in search summaries). The species was named after Ledger, not Mamani.

The cheap febrifuge and totaquina. British India chose a different path. Its planners wanted "an abundant and cheap supply of the febrifuge" for the poor, and chose species with the most total alkaloid rather than the most quinine. From 1874 to 1887 the Indian government factories made only "cinchona febrifuge", the mixed total alkaloids of C. succirubra, and began quinine manufacture only in 1887 (Ceylon cinchona history quoting Gage, read in search summary). In the 1930s the League of Nations Malaria Commission promoted a standardised mixed-alkaloid product, totaquina. A 1935 note in Nature describes the standard as containing at least 15% quinine (read only as a search summary) [VERIFY]. The later US Pharmacopeia standard for totaquine required at least 10% anhydrous quinine and 70 to 80% total crystallisable cinchona alkaloids, and a 1949 US document stated that its dose and efficacy were essentially those of quinine (read only as a search summary, the scanned original could not be read) [VERIFY]. I found no 1930s clinical trial of totaquina itself.

The war. When Japan took Java in 1942 the Allies lost the plantations and the world's largest quinine factory at Bandung. Some 100,000 kg of cinchona bark on Mindanao could not be turned into medicine for troops on Luzon, and the sinking of one ship lost 591 lb of quinine, almost the whole Allied stock in the South-West Pacific. In April 1942 the United States launched the Cinchona Missions, sending botanists including William Steere and Raymond Fosberg into the Andes to find wild bark, which they tested in the field with the Grahe test (Smithsonian archives and JMVH article, read in summaries). New trees took about five years to yield useful alkaloid, and synthetic drugs overtook the effort.

Survivor bias. Bark stories are told by those who recovered. Vivax and quartan agues remit on their own, and the commission's endpoint, cessation of paroxysms, says nothing about relapse or recrudescence. The 98% figure is a figure for stopping fevers, not for cure.

1.5 Cinchona bark: content and dose

Content. Total alkaloid in cinchona bark ranges from about 2% to 17%, mostly 6 to 10%, and quinine is usually 50 to 90% of that (Duke's Handbook via Taylor and Francis, read in search summary). An Indian average gave C. ledgeriana 5.49% quinine and 8.52% total alkaloids, and C. officinalis 2.93% quinine and 5.00% total (table citing Cowan, read in search summary). A modern Indian growing guide gives typical content of 3 to 4% (indiaagronet). Red bark (C. pubescens, syn. C. succirubra) yields far more bark per tree but with more cinchonidine and cinchonine and less quinine. Some wild trees sold as "officinalis" contain almost no quinine. Content rises with tree age to a peak around 10 to 12 years.

Historical doses. I could not read Torti or Sydenham in the original. Nineteenth-century accounts describe powder doses "from ten grains to two drachms and upwards" (about 0.65 g to 8 g), a common practice of two drachms (about 7.8 g) at once and then a drachm (about 3.9 g) every six hours, and half an ounce (about 15 g) at once in resistant cases. Bretonneau in 1846 reported a quartan fever that resisted two ounces of bark taken in small portions over 15 days but yielded to two drachms given at once. Mutis and Zea held that two drachms of genuine powdered bark did what a decoction of two ounces did (nineteenth-century articles, read in search summaries) [VERIFY]. That last claim implies a water decoction extracts perhaps an eighth of the bark's power, which fits the poor water solubility of the free alkaloids [VERIFY: my inference]. The historical rule was therefore: swallow the powder, in wine or an acid drink, in large doses, not a weak tea.

What modern science infers. Today's oral quinine dose is 10 mg of salt per kg three times a day for seven days, about 600 mg per dose for an adult (INCHEM, Achan and others 2011). To deliver 600 mg of quinine an adult would need about 11 g of bark at 5.5% quinine, or about 20 g at 3%, three times a day, if every milligram were absorbed. A seven-day adult course would then be roughly 230 to 420 g of bark [VERIFY: my arithmetic]. Counting the other

alkaloids, which the 1866 commission found equally active, the need falls by perhaps a third [VERIFY: inference]. The historical doses of 4 to 16 g a day therefore delivered roughly a quarter to a half of a modern dose, which may explain both the cures and the many relapses [VERIFY: inference]. Without an assay, the content of any given bark is unknown to within a factor of five, so bark dosing is dosing blind.

1.6 Quinine: dosing, failure and its place now

Uncomplicated malaria. Quinine kills blood-stage parasites quickly but has a half-life of 11 to 18 hours and a narrow margin between dose and poison (Achan and others 2011). The seven-day course matters more than anything else. In Guinea-Bissau, recurrent parasitaemia by day 28 was 79% after three days of quinine, 90% after five, and 11% after seven. In Gabon, three days of quinine alone cured 38% at day 28, against 91 to 92% when combined with doxycycline or clindamycin. Seven days of quinine alone cured 85 to 87% in Thailand and 94.5% in Equatorial Guinea, but only 64% of Ugandan children against 97% with artemether-lumefantrine. Given 8-hourly, the dose gave 6.3% recurrence at day 28 against 16.1% for the same daily amount split twice daily (Achan and others 2011). Many of these studies did not use genotyping to separate new infections from recrudescence.

Adding a tetracycline or clindamycin to seven days of quinine raised cure in Thailand to 98% and 100% (Achan and others 2011). After the Fall those antibiotics are salvage only (THRIVING library, IN-02).

Severe malaria. The WHO and MSF regimen for injectable quinine is a loading dose of 20 mg of salt per kg over 4 hours, then 10 mg per kg every 8 hours, switching to tablets when the patient can swallow, to complete 7 days (MSF Essential Drugs). Skip the loading dose if quinine or mefloquine was given in the previous 24 hours. If kidney failure persists beyond 48 hours, cut the dose by a third. Intramuscular quinine is for when no drip is possible, such as before transfer: diluted, deep into the front of the thigh, half the loading dose into each thigh. Never inject it undiluted into a vein, which can stop the heart (MSF Essential Drugs). Intramuscular injection is painful and can cause sterile abscesses (Achan and others 2011).

Quinine against artesunate. In SEAQUAMAT, in 1,461 mainly Asian adults, deaths were 15% on artesunate against 22% on quinine, a relative reduction of about 35%. In AQUAMAT, in 5,425 African children, deaths were 8.5% against 10.9%, a relative reduction of 22.5%, and artesunate also caused less coma, fitting and hypoglycaemia (Dondorp and others 2010, abstract, Achan and others 2011). Injectable artesunate is better. Quinine remains the drug a district can still hope to source or grow.

Pregnancy. In November 2022 WHO replaced quinine with artemether-lumefantrine as the preferred treatment in the first trimester, after a meta-analysis of over 34,000 pregnancies found no harm from artemisinins and 42% fewer adverse outcomes than with oral quinine (severemalaria.org summary of WHO 2022). Quinine is still the old standard for pregnancy where nothing else exists, and in Uganda stillbirth after quinine (1.6%) did not differ from untreated controls (1.8%) (search summary). Its danger in pregnancy is hypoglycaemia (see 1.7).

1.7 Quinine harms

Cinchonism. At therapeutic levels most patients get ringing ears, slight deafness, headache and nausea. Worse forms bring vertigo, vomiting, diarrhoea, marked deafness and loss of vision (Achan and others 2011). More than 1 g in one dose usually produces some cinchonism (LITFL, read in search summary).

Hypoglycaemia. Quinine makes the pancreas release insulin. Older reports found low blood sugar in up to 32% of treated patients, recent trials in 3% of adults and 2.8% of children (Achan and others 2011). MSF calls the risk in pregnant women "very high" (MSF Essential Drugs). Malaria itself causes hypoglycaemia, so a drowsy, sweating or fitting patient on quinine needs sugar first.

Blackwater fever. Sudden destruction of red cells with dark red or black urine, in people long resident in falciparum areas who took quinine irregularly. Early twentieth-century observers blamed irregular quinine for most attacks, and

a larger than usual dose often preceded haemolysis by hours. It was a leading medical cause of death among European soldiers and administrators in colonial Africa. During the building of the Panama Canal, Gorgas recorded 226 cases among 50,000 workers. G6PD deficiency is often but not always involved (Emerging Infectious Diseases 2005 review and early case reports, read in search summaries). The often-quoted mortality of 25 to 50% I could not confirm [VERIFY]. Quinine is contraindicated after haemoglobinuria during malaria (INCHEM).

Overdose and the fatal dose. Toxicity in adults appears after 2.5 to 4 g, and in children above about 25 mg per kg. Visual loss usually follows doses above 4 g, and death can follow doses above 8 g. The lowest reported fatal doses are about 1.5 g in an adult and 900 mg in a child of one to two years (INCHEM, and reviews read in search summaries). The brief's range of 2 to 8 g is about right for adults, but the margin is much narrower in small children: two 300 mg tablets can kill a toddler. Death comes from heart rhythm disturbance, kidney failure, haemolysis and respiratory arrest. In overdose the half-life exceeds 24 hours. Treatment in hospital is activated charcoal and support. Making the patient vomit is contraindicated (INCHEM).

Quinine as an abortifacient. Quinine has often been taken to end pregnancy. It can poison the foetus and frequently leaves the baby deaf, and it may stimulate the uterus (INCHEM). Because the abortifacient dose sits close to the lethal dose for the mother, this folk use kills women [VERIFY: inference from the toxic thresholds above]. A healer holding quinine must keep it locked.

Who must not receive it. Anyone with previous haemoglobinuria during malaria, optic neuritis, tinnitus or allergy to it. Caution with heart rhythm disorders and myasthenia, and it strengthens blood thinners (INCHEM). Do not give it with or within 12 hours of mefloquine (MSF Essential Drugs).

1.8 Can a district make quinine?

The brief asks for the acid-base extraction at the district rung. Under the rules of this book no procedure is given. What the record shows: Pelletier and Caventou did it in 1820 with apothecary equipment, and the Indian government factories made a mixed-alkaloid febrifuge from 1874, sixteen years before they could make quinine itself. Both had trained chemists, reliable acids, alkalis and solvents, and assays. The Allies in 1942 had wild bark but could not turn the Mindanao stock into medicine fast enough (search summaries). No source I found describes a village making quinine.

What a district would need to imitate the Indian febrifuge, from the record: a reliable supply of bark of known species, a trained chemist, solvents and reagents, a balance, a way to assay the product, and a doctor to set the dose. Without an assay the result has unknown strength, and quinine's margin between cure and poisoning is narrow. A crude mixed-alkaloid product of unknown strength may be more dangerous than powdered bark, because it concentrates the poison into a small, easily over-swallowed volume [VERIFY: inference]. My judgement is that for a district, a standardised bark powder, weighed per dose, with a test for content where any chemist can be found, is the safer path, and alkaloid preparation is for a region with a chemist.

1.9 Artemisia annua: the tradition

What the tradition says. Qinghao (Artemisia annua, sweet wormwood) appears in the Handbook of Prescriptions for Emergencies of the alchemist Ge Hong (284 to 346 CE by Tu's dating, the recipe often dated 341 CE): "A handful of qinghao immersed with 2 liters of water, wring out the juice and drink it all" (Tu 2011). The unit was the sheng, and China Daily renders two sheng as about 400 ml, so "2 liters" in English translations may be a conversion error (search summary) [VERIFY]. The method was to soak the fresh plant in cold water and wring it out. Later Chinese texts pound the fresh herb for juice or soak it in urine. There is no evidence that the Chinese used it as a hot tea, and some scholars think the ancient plant was A. apiacea (WHO 2019 technical document, citing Hsu 2006).

What the record shows. China launched Project 523 against malaria in 1967, at the request of North Vietnam, whose soldiers were dying of chloroquine-resistant malaria. It involved 60 institutions and more than 500 scientists

(WHO 2019 technical document). Tu Youyou's group screened more than 2,000 herbal preparations, found 640 possible hits and tested more than 380 extracts from about 200 herbs in mice. Qinghao extracts worked, then failed to repeat. Rereading Ge Hong, Tu reasoned that heat had destroyed the active principle, switched to low-temperature extraction with ether, and on 4 October 1971 obtained a neutral extract that was 100% effective against Plasmodium berghei in mice and P. cynomolgi in monkeys. She and colleagues took it themselves before trials in Hainan, in vivax and falciparum patients, where fever and parasites vanished. In 1972 they isolated the crystalline compound and named it qinghaosu, artemisinin. Results reached English readers in 1979 (Tu 2011).

Two details matter for the village. First, Tu found that only A. annua, and especially its fresh leaves at the bud stage, contained much artemisinin, and the Beijing plants were poor in it, so production relied on a high-yield Sichuan population (Tu 2011). Second, the Chinese found artemisinin cleared parasites fast but let them return, and that dihydroartemisinin was ten times more potent with "much less disease recurrence" (Tu 2011). Recrudescence was a problem from the start.

What modern science infers. The discovery is a real gift of traditional medicine, but what the tradition gave was a clue about temperature, not a dose. The cold-water juice method of Ge Hong may in fact extract far more artemisinin than a tea: pounded fresh juice contained up to 20 times as much per litre as tea from dried leaves of the same hybrid (WHO 2019 technical document, citing Wright and others 2010). How fast artemisinin decays in juice is unknown.

1.10 Artemisinin in the plant

Wild A. annua leaves contain 0.02% to 1.07% artemisinin by dry weight, hybrids about 1.38%, and up to 2% has been reached in experiments (WHO 2019 technical document). The 2012 WHO statement gives the range as 0.01 to 1.4% (WHO 2012, read in a copy hosted by a third party). F1 hybrids reach 1.44% and about 55 kg of artemisinin per hectare (Wikipedia, read in search summary). Content depends on genetics, harvest time, temperature, nutrients and position on the plant, and peaks at bud formation before flowering, then falls sharply once flowering begins (infonet-biovision).

Storage destroys it. At 20 °C and 85% relative humidity artemisinin degrades within six months, and any storage above 40 °C causes loss (WHO 2019 technical document, citing Simonnet 2008). Small growers average 0.3 percentage points less than large ones (WHO 2019 technical document). The Anamed founder Hans-Martin Hirt reported that properly dried and stored leaf kept its tea strength for over three years (infonet-biovision) [VERIFY].

The plant contains more than 600 secondary compounds, of which only 37 have been found in teas (WHO 2019 technical document, citing van der Kooy and Sullivan 2013). Advocates argue that flavonoids and other compounds make the plant a natural combination therapy. The evidence is mixed. Flavonoids at low concentration lowered artemisinin's inhibitory concentration by 9 to 55% in one study. Others found some compounds antagonistic, found flavonoids poorly extracted and unstable in tea, and a 2019 study with flavonoid-free and artemisinin-free mutant plants found that flavonoids contributed nothing measurable to antiplasmodial activity. Artemisinin's IC50 is about 5.5 ng per ml, while the other compounds act at microgram levels, 1,000 to 10,000 times higher (WHO 2019 technical document).

1.11 The tea trials

Preparation and content. The tea most often promoted is 5 g of dried leaf in 1 litre of boiling water, left 15 minutes, filtered, and drunk over 24 hours for seven days (WHO 2019 technical document, describing Maison de l'Artemisia advice). Guidance linked to Hirt and Anamed gives 1 g of leaf in 200 ml of water per 10 kg of body weight per day, which is the same strength (ECHO community page, read in search summary). The trials also used 9 g per litre.

How much artemisinin reaches the cup depends on method. Van der Kooy and Verpoorte extracted 26.1% of the leaf's artemisinin by steeping 9 g for 10 minutes, giving 23.9 mg per litre. Räth and colleagues, steeping 9 g for 10 minutes with stirring and squeezing the leaves after filtering, extracted 76% and got 94.5 mg per litre. Boiling for

2 to 5 minutes raised extraction, and boiling for 10 minutes lowered it. Across controlled studies teas held 8.36 to 117.2 mg per litre, and only one exceeded 100 mg, the daily dose for a 10 kg child (WHO 2019 technical document). Artemisinin in tea is stable at room temperature for 24 hours.

The monotherapy dose of pure artemisinin used by the Chinese was 10 mg per kg a day, with a 20 mg per kg loading dose on day one, and seven days were needed to prevent recrudescence (WHO 2019 technical document). For a 60 kg adult that is about 600 mg a day. A litre of the best tea delivers about 95 mg, under a fifth of the usual 500 mg dose (Räth and others 2004, WHO 2012). Worse, artemisinin induces its own breakdown: blood levels fall five- to sevenfold over five to seven days of repeated dosing, so the dose must rise towards the end of a course to stay effective, which no tea does (WHO 2019 technical document).

Absorption. In Räth's study of 14 healthy men drinking 1 litre of 9 g per litre tea, peak plasma artemisinin was 240 ± 75 ng per ml. Artemisinin was absorbed faster from tea than from tablets, with similar bioavailability (Räth and others 2004, abstract). Heide's group later pointed out that the peak was 26 times the concentration that inhibits P. falciparum in culture (search summary). That explains the fast clearance of fever and parasites.

Mueller 2000. In the Democratic Republic of Congo, a hybrid grown locally contained 0.63 to 0.70% artemisinin, of which about 40% passed into tea. Parasites disappeared within 2 to 4 days in five patients, and within 4 days in 44 of 48 (92%) in a second series (Mueller and others 2000, abstract). The abstract does not describe a control group or follow-up beyond clearance.

Mueller 2004. A randomised open trial in eastern Congo in 2001 enrolled 132 falciparum patients. By day 7 the tea groups averaged 74% cure against 91% for quinine. But by day 35, 21 of 32 (65.6%) on 5 g per litre tea and 21 of 30 (70%) on 9 g per litre had parasites again, against 7 of 34 (21%) on quinine. The authors inferred that the excess was recrudescence, not reinfection, and concluded that tea monotherapy "cannot be recommended" (Mueller and others 2004, abstract, and WHO 2019 technical document). Willcox and colleagues argued that the day-7 endpoint was too strict for endemic areas (search summary). The day-35 figures stand regardless.

Blanke 2008. In Tanzania in 2002 to 2003, semi-immune adults were randomised to tea at 5 or 9 g per litre or to sulfadoxine-pyrimethamine. Seven of 10 evaluable tea patients were clear on day 7, but 9 of 10 were parasitaemic on day 28. One tea patient developed severe malaria on day one and needed quinine. The trial was stopped (Blanke and others 2008, read via the WHO 2019 technical document).

Zime-Diawara 2015. In Benin, local A. annua with 0.30% artemisinin was given as 12 g per litre tea, 250 ml four times a day for seven days, about 36 mg artemisinin a day. Of 108 patients who completed follow-up, all were reported cured at day 28 (Zime-Diawara and others 2015, read via the WHO 2019 technical document). This was a single open cohort with no comparison group, and 22 of 130 enrolled patients were not in the analysis. The result contradicts the controlled trials and has not been replicated.

Munyangi 2019, retracted. A trial in Kalima, Congo, reported 957 patients randomised to A. annua tea, A. afra tea or artesunate-amodiaquine, with day-28 recurrence of 3.6% on A. annua, 11.2% on A. afra and an impossible 65.7% on artesunate-amodiaquine (WHO 2019 technical document). Seven Congolese efficacy studies of the same drug had found 95.3 to 100% efficacy. André Gillibert and colleagues obtained the data, found copy-pasted entries and an ethics approval dated after the trial, and the journal Phytomedicine announced retraction in August 2020 for concerns about ethics approval, consent and the reliability of the data (Retraction Watch 2020). The University of Liège repository lists the malaria paper as retracted. It is still quoted by advocates. It should not be.

The day-7 illusion. Every tea trial agrees on one thing: the tea clears fever and parasites fast. Every controlled trial with follow-up to day 28 or 35 found that most patients relapsed. A family that judges the tea by how the patient feels on day 5 will believe in it. The parasites decide on day 20.

1.12 Dried leaf

Weathers and colleagues argued that swallowing the powdered leaf, rather than tea, delivers all the artemisinin plus the rest of the plant. In mice, dried whole-plant A. annua treated a rodent parasite strain resistant to artemisinin better than pure artemisinin did, and slowed the evolution of resistance. At a 24 mg per kg artemisinin-equivalent dose, the low-dose plant matched high-dose pure drug, and blood artemisinin was reported about 40 times higher with the plant in one analysis (Elfawal and others 2015, abstract and secondary accounts). These are rodent results.

In humans the record is thin. Daddy and colleagues reported 18 patients in North Kivu, aged 14 months to 60 years, said to have failed artemether-lumefantrine and then intravenous artesunate. They were given 0.5 g of dried-leaf tablets twice daily for five days, a total adult artemisinin dose of 55 mg, with less for those under 30 kg. All were reported clear of parasites within five days (Daddy and others 2017). There was no control and no follow-up beyond discharge. WHO notes that parasites persisting after a full ACT course and intravenous artesunate in all 18 would be extraordinary (WHO 2019 technical document). Treat this as a case series of unusual patients, not evidence of cure.

Tchandema and Lutgen gave capsules of powdered A. annua or A. afra leaf over seven days: 85% (Luxembourg leaf, 15 g total) and 76% (Burundi leaf, 7.5 g) were clear at day 7, and 40% with A. afra, with no follow-up beyond day 7 (read via WHO 2019 technical document). Onimus and colleagues gave capsules containing only 1 to 1.75 mg artemisinin in total to 25 orthopaedic patients and cleared parasites in one (same source).

Verdict on dried leaf. Plausible, under-tested, and unproven against recrudescence. Its practical advantage after the Fall is real: powder can be weighed and swallowed, losing nothing to a teapot. Its practical risk is the same as tea: an unknown and probably low dose for seven days or less.

1.13 Prevention by Artemisia

In Uganda 132 flower-farm workers were randomised to A. annua tea or ordinary black tea once a week. Of 84 followed for nine months, 12 of 41 in the Artemisia group and 26 of 43 controls reported more than one malaria episode. But 35.8% of the Artemisia group used nets at the start, against 18.5% of controls, and episodes were self-reported (Ogwang and others 2012, read via the WHO 2019 technical document). Two French travellers who relied on non-pharmaceutical A. annua as prophylaxis developed severe falciparum malaria needing intensive care (Lagarce and others 2016, read via the same source). With a half-life of one to three hours, a weekly cup cannot hold the drug in the blood. Tea as prophylaxis is not supported.

1.14 Artemisia afra and the confusions of name

Artemisia afra is a woody perennial shrub of southern and eastern Africa, up to 2 m, with soft, finely divided, grey-green leaves, white-haired beneath, and a strong sweet smell. It is used for coughs, asthma and fever. It contains no artemisinin, its teas showed no antiplasmodial activity in two samples tested, and some of its compounds raise concerns about heart and nerve toxicity (WHO 2019 technical document). Some chemotypes are rich in thujone, one oil sample about 75% alpha-thujone (search summaries). Thujone acts on the brain's GABA receptors and in large amounts causes seizures. A man who drank 10 ml of wormwood oil had repeated seizures, muscle breakdown and kidney failure (ADLM Toxin Spotlight).

Artemisia absinthium (common wormwood) is a perennial with silvery, finely cut leaves and an extremely bitter taste, the plant of absinthe, and thujone-bearing (search summaries). Artemisia vulgaris (mugwort) is a perennial with leaves dark green above and white beneath, used as a repellent smoke (THRIVING library, HY-06).

The safe identification of A. annua: a single-stemmed annual that dies after setting seed, 1 to 3 m tall in a good climate, with bright green, sweet-scented, two- to three-times divided fern-like leaves without white felt beneath, and masses of tiny nodding yellow-green flower heads in late season [VERIFY: description assembled from search summaries]. A plant that survives the winter, is woody at the base, or is grey and felted is not A. annua. Seed from a known source

and a herbarium specimen at the district are the only reliable guarantee. Leaf microscopy can separate species (search summary).

1.15 What the evidence supports for Artemisia

The brief asks for a decision between tea as prophylaxis, tea as treatment, dried leaf, or only a last resort.

- **Tea as prophylaxis:** no. The pharmacology forbids it and the only trial is confounded (Ogwang and others 2012, WHO 2019).
- **Tea as treatment of uncomplicated malaria, where quinine, bark or ACT exist:** no. Quinine for seven days is better, and tea adds no proven value.
- **Tea as treatment when nothing else exists:** a last resort. It shortens the illness and very likely saves some patients from progressing to severe malaria in the first days, but expect two in three falciparum patients to relapse within five weeks (Mueller and others 2004). Each relapse is another chance of severe malaria, and of anaemia in children and pregnant women.
- **Dried leaf:** a reasonable district research project with a microscope and a register, not yet a recommendation.
- **Severe malaria:** never. Tea enemas for unconscious patients have been promoted (Anamed, cited in WHO 2019 technical document) and have no evidence.

The WHO objection (2012, repeated 2019) has three parts: variable content, insufficient dose with recrudescence, and resistance. The dried-leaf studies answer the first two only in mice and in an uncontrolled case series. The third part is weaker after the Fall, when the ACTs it protects may no longer arrive. But it does not vanish: a district that holds salvaged injectable artesunate for severe malaria has every reason not to breed artemisinin-tolerant parasites in its own villages [VERIFY: inference]. Where malaria transmission is intense, the most defensible plant regimen is a full seven-day course of the strongest tea or leaf available, never a short course, and never as a weekly preventive.

1.16 Severe malaria in the village

Rectal artesunate. Gomes and colleagues randomised 17,826 patients in Bangladesh, Ghana and Tanzania who could not take drugs by mouth to a single artesunate or placebo suppository before referral. Of 12,068 analysed, deaths were 2.5% against 3.0% (p = 0.1). Permanent disability was 2 against 13. Among those still not at a clinic after six hours, death or permanent disability fell from 3.8% to 1.9% (risk ratio 0.49, 0.32 to 0.77). Among those who arrived within six hours there was no significant effect (Gomes and others 2009, abstract). The Cochrane review of this trial found deaths reduced in children aged 6 to 72 months (risk ratio 0.74, 0.59 to 0.93) but increased in older children and adults (2.21, 1.18 to 4.15), mostly from the Bangladesh site, cause unknown (Cochrane CD009964, abstract).

The dose is 10 mg per kg once, as 100 mg suppositories: one for a child from 2 months to under 3 years, two from 3 to under 6 years. Current prequalified leaflets say to give a second dose after 12 hours if the child cannot reach hospital, and to switch to an ACT once the child can swallow (WHO prequalification leaflets, read in search summary). It is for children under six only.

The CARAMAL study then followed the real-world roll-out in Congo, Nigeria and Uganda. Case fatality was 6.7% in Congo, 11.7% in Nigeria and 0.5% in Uganda. In Nigeria it rose after roll-out from 4.2% to 16.1%. Children given the suppository were more likely to die in Congo and Nigeria and less likely to be dead or sick in Uganda. After referral, artesunate injection followed by ACT protected, but ACT completion was 68% in Congo, 0% in Nigeria and 71% in Uganda (Hetzel and others 2022, abstract). WHO paused roll-out in January 2022. An external review and Watson, Peto and White argued the design could not show harm and that confounding and delay explained the signal (severemalaria.org summary). The honest reading: a suppository buys a child a few hours, and it saves lives only if someone completes the treatment.

Intramuscular quinine. Where no artesunate exists, the dispensary's pre-referral option is quinine 20 mg per kg, diluted, split between the front of both thighs (MSF Essential Drugs). After the Fall, "referral" may mean a cart ride to the district infirmary, and the village may have to continue 10 mg per kg every 8 hours by intramuscular injection, then by mouth when the patient can swallow, to complete seven days [VERIFY: adapted from the MSF regimen, not a tested village protocol].

Supportive care, the part a household can do. Hypoglycaemia is common in severe malaria and in quinine treatment, so give sugar: sugar water or honey water by mouth if the patient can swallow, or sugar paste inside the cheek, or by nasogastric tube if trained (THRIVING library, IN-02) [VERIFY: route details from IN-02, not re-checked here]. Lay the unconscious patient on the side, keep the airway clear, stop fits where trained and stocked, cool the very hot child, give fluids by mouth with care, and carry the patient to the most capable healer. Severe anaemia needs transfusion, which only a district with a trained hand, compatible donors and clean equipment can attempt.

1.17 Growing the two plants

Artemisia annua. Native to temperate Asia, it does best in temperate and subtropical summers or tropical highlands with a cool season. In the lowland tropics short days make it flower early and small, and wild types may reach only a few centimetres, so seed from a high-yield, tropically adapted line is essential (infonet-biovision). Seeds are tiny, about 12,000 per gram, need light and 18 to 20 °C to germinate, and must not be covered with soil. Sow about 1 g per square metre in a shaded nursery bed, expect seedlings in 6 to 7 days, transplant at about 12 cm (about five weeks), and space plants about 1 m apart, though 45 cm by 45 cm gave the best yield per hectare in one study (infonet-biovision, search summary). The crop needs 600 to 650 mm of rain in the season, and water stress triggers early flowering. Harvest when half to three-quarters of plants show flower buds. Wilt, dry in shade, strip the leaves, store dry and cool. Seeding to harvest takes about 190 to 240 days, and leaf yields run 0.5 to 3 t per hectare, 2.5 t on average in East Africa (search summaries).

One adult seven-day course at 9 g a day needs about 63 g of dried leaf. A 100 square metre plot at 2.5 t per hectare gives about 25 kg, about 400 adult courses [VERIFY: my arithmetic]. The plant is an annual, so seed must be saved each year from the strongest plants, and cross-pollination will drift a hybrid's artemisinin content [VERIFY].

Cinchona. A tree of the tropical Andes, it needs about 20 °C, high humidity, no frost, at least 2,000 mm of rain spread over eight months or more, acid soil of pH 4.5 to 6.5, and in India grows best at 1,000 to 2,000 m (indiaagronet). It cannot be grown in temperate or dry climates. Seed germinates in 20 to 30 days. Seedlings are potted at about four months and planted out at one year at 1.25 m spacing. The first coppicing, cutting to 5 cm and letting two or three shoots regrow, is at 8 to 10 years, the second 8 to 10 years later, and trees are uprooted at about 30 years. Each of the first two coppicings yields about 4,000 kg of dry bark per hectare, and uprooting about 6,000 kg (indiaagronet). Bark must be dried quickly to keep its alkaloids. Wartime planners reckoned five years to useful alkaloid (JMVH), and the historical Java plantations coppiced C. ledgeriana leaving one shoot (search summary).

If a seven-day adult course takes 230 to 420 g of bark, one hectare at first coppice supplies about 10,000 to 17,000 courses [VERIFY: my arithmetic]. A district in a suitable highland can therefore supply itself from a fraction of a hectare, but only if it plants a decade before it needs the bark. A lowland district cannot grow cinchona and must trade for it.

By climate. Tropical highland: cinchona for the long term, A. annua as a dry-season crop. Lowland humid tropics: A. annua only from adapted seed, cinchona by trade. Temperate zone with returning malaria (mainly vivax historically): A. annua grows well as a summer annual, cinchona not at all. Dry savannah: neither grows easily, and drainage and nets matter even more [VERIFY: synthesis].

2. Evidence grades

Measure	What the tradition says	What the record shows	What science infers	Grade
Insecticide-treated nets	None	17% fewer child deaths, 23 trials	Strongest malaria tool	A
Untreated intact nets	None	About 51% less infection in Gambian children	Useful if mended	B
House screening, closed eaves	Grassi, Celli 1900	Farafenni RCT: half the mosquitoes, less anaemia	Works without insecticide	A
Drainage of few, fixed sites	Gorgas, Soper	Moderate evidence where sites are findable	Labour-dependent	B
Larva-eating fish	Widely promoted	No reliable evidence	Not a malaria control	D
Pyrethrum indoor dusting	19th-century use	Campaign component only	Short-lived	C
Diagnosis by fever rhythm	Tertian, quartan	Falciparum irregular, overdiagnosis common	Clue only	D
Rapid tests	None	About 95% sensitivity and specificity	Good while stock lasts	A
Thick film microscopy	None	Reference standard	The district's key tool	A
Cinchona bark powder, large doses	Jesuit bark, Torti	Stopped paroxysms for 200 years, relapses common	Real but unstandardised	B
Mixed cinchona alkaloids	Indian febrifuge, totaquina	1866 trial: all four alkaloids over 98%	Equivalent to quinine if dosed	B
Oral quinine 7 days, 8-hourly	None	85 to 95% cure, 6.3% recurrence	Effective, poorly tolerated	A
Oral quinine 3 days	None	30 to 80% recurrence	Never use	X
Injectable quinine, severe malaria	None	Works, but 22 to 35% more deaths than artesunate	Second best	A
A. annua tea, treatment	Ge Hong (as cold juice)	65 to 70% recurrence by day 35	Weak monotherapy	X as cure, C as last-resort symptom relief
A. annua tea, prophylaxis	Promoted by NGOs	One confounded trial, two failures	Pharmacology forbids	X
A. annua dried leaf	Recent	Mouse data, 18 uncontrolled cases	Plausible, unproven	D
A. afra tea	Southern African fever remedy	Only trial retracted, no artemisinin	No basis	X

Measure	What the tradition says	What the record shows	What science infers	Grade
Rectal artesunate, under 6, delayed referral	None	Death or disability halved after 6 hours	Bridge only	A
Rectal artesunate, older children and adults	None	Mortality higher in one site	Do not use	X

3. Means ledger

Task	Hands and knowledge	Hearth	Garden and still	Village dispensary	District infirmary	Hospital before the Fall
Prevent	Sleep under any net, close eaves, empty water containers weekly, sleep away from animals	Mend nets with needle and thread, mud the eaves, oil puddles near the house	Grow pyrethrum and dust rooms, grow neem and basil for smoke at the door	Net-mending day, drainage gangs, map breeding sites	Organise drainage of fixed sites, keep spare netting, record cases by place	Treated nets, indoor spraying, larviciding, vaccines in some places
Diagnose	Season, place, danger signs, look for other causes	Fever chart with times	Same	Rapid tests while stocks last, microscope if trained	Thick film, parasite counts, day 7 and 28 checks	Films, RDTs, PCR, blood counts
Treat uncomplicated	Fluids, sugar, cooling, carry if worsening	Oral rehydration, honey, A. annua tea only if nothing else	Dried A. annua leaf, bark powder of known source, a scale	Weighed bark or salvaged quinine for 7 days, salvaged ACT	Quinine by weight, assayed bark, quinine plus salvaged clindamycin	ACT 3 days, follow-up
Treat severe	Recovery position, sugar, carry	Sugar water or paste, cooling	Same	Rectal artesunate for under-6 if held, intramuscular quinine if trained	Injectable artesunate or quinine, glucose, fluids, fits control, transfusion	IV artesunate, intensive care, dialysis, transfusion
Grow	Recognise A. annua and its lookalikes	Save seed	A. annua plot, drying shed	Seed bank, herbarium specimen	Cinchona plantation in highlands, assay when possible	Industrial supply

What each rung changes. Hands and knowledge change who is noticed early, and nets change how many fall ill at all: a mended net is worth more than any herb. The hearth adds sugar and fluids, which keep some severe cases alive for the journey. The garden adds a weak drug that turns some uncomplicated cases around but cannot be trusted to cure. The village dispensary changes outcomes most where it holds a real drug and gives it for seven days by weight, and where it can give a pre-referral dose. The district infirmary is the first rung that can tell cure from relapse, through the microscope, and the first that can treat severe malaria with a fighting chance (10 to 20% mortality treated, against near 100% untreated). The hospital adds artesunate, intensive care and transfusion, which bring severe malaria mortality down further, as AQUAMAT and SEAQUAMAT showed.

4. Harm test

Nets and screens. Nets impregnated with salvaged insecticide should not be washed in drinking water or streams, as pyrethroids are highly toxic to fish (THRIVING library, HY-06). A net tucked badly can trap mosquitoes inside. Smoke from burning leaves indoors harms lungs, especially of infants (HY-06).

Cinchona bark and quinine. - How it kills: overdose causes heart rhythm disorders, blindness, kidney failure, haemolysis and breathing arrest. Too little, or too short a course, lets malaria return and kill later. - The doses that harm: adult toxicity from about 2.5 g at once, death above about 8 g and as low as 1.5 g. In children toxicity above 25 mg per kg and deaths at 900 mg in toddlers (INCHEM). Bark of unknown content can hide a dose twice or half what was intended. - Never give to: anyone who has passed black or red urine during malaria, anyone with optic nerve disease or ear ringing before treatment, known allergy, with mefloquine, and with great caution in heart disease and myasthenia (INCHEM, MSF). In pregnancy, give it only where nothing better exists, and watch the blood sugar. - Signs it is going wrong: ringing ears and deafness are expected and mild. Blurred vision, vomiting, severe giddiness, confusion, a very slow or irregular pulse, fainting, dark urine, sweating and drowsiness (hypoglycaemia) mean stop and act. - What to do: for low sugar, give sugar at once. For dark urine, stop quinine, give fluids, and carry to the district. For overdose, give nothing to make the patient vomit, keep the patient lying on the side, and carry to the district, where charcoal can be given (INCHEM). - Historical harm: blackwater fever among colonial residents taking irregular quinine, and deaths of women who used quinine to end pregnancy (INCHEM, EID 2005 review).

Artemisia annua. - How it harms: rarely by poisoning. Mostly by failure. The patient feels better, stops, and relapses into severe malaria. Parasites exposed repeatedly to low artemisinin may become tolerant (WHO 2019). - Misidentification: A. absinthium and thujone-rich A. afra can cause seizures in large doses. Neither contains artemisinin. - Contamination: mouldy leaf from damp storage. - Who must not receive it: anyone with severe malaria in place of real treatment. First-trimester pregnancy is a concern if large artemisinin doses are absorbed (WHO 2019), although pharmaceutical artemether-lumefantrine is now recommended then. - Signs it is going wrong: fever returning after a week or more, increasing pallor, any danger sign. - Historical harm: the two French travellers with severe malaria after Artemisia prophylaxis (Lagarce and others 2016), and the patient in Blanke's trial who became severely ill on day one.

Rectal artesunate. A suppository expelled within 30 minutes may need repeating [VERIFY: standard leaflet advice not read in full]. One death in a 3-year-old at 11.5 mg per kg was put down to fluid overload in hospital (WHOPAR, search summary). Its greatest harm is false reassurance: the family stops the journey.

5. Red flags

These signs mean the patient will probably die or be disabled without what the village cannot give (THRIVING library, IN-02, and WHO criteria as summarised in the sources above):

1. Cannot drink, breastfeed or keep anything down.
2. Fits, or more than one fit in a day.
3. Unusual sleepiness, confusion, or cannot be woken.

4. Deep or laboured breathing (acidosis).
5. Very pale palms, lips or inner eyelids (severe anaemia).
6. Yellow eyes, or very little or dark urine.
7. Bleeding from gums or nose, or bruising.
8. Cannot sit or stand when they could before.
9. A pregnant woman with fever, especially sweating or drowsy.
10. Fever returning one to five weeks after any plant treatment.

What to do anyway. Give the first dose of the strongest antimalarial held: rectal artesunate for a child under six, intramuscular quinine if trained, or quinine or bark by mouth if the patient can swallow. Give sugar. Lay the patient on the side. Carry to the district without waiting for morning. Write down the time and what was given.

Honest comfort. If the child is in deep coma with laboured breathing and nothing more can be given, keep the child warm or cool as needed, moisten the lips, keep the mother close, and keep the airway clear. Hearing may remain, so speak to the child. Tell the family plainly that this illness killed one child in five before medicine, and that it was the illness and not their care that failed. Then, for the next child, mend the nets.

6. The case against

Against the romance of the herbal. The plant drugs worked because they were refined. Pelletier and Caventou's quinine replaced bark because a dose could at last be fixed (WHO 2019 technical document). Tu Youyou's discovery came from cold ether extraction, not from tea, and even pure artemisinin given for three days relapsed so often that the Chinese moved to derivatives and combinations (Tu 2011, WHO 2019). Lutz Heide and Markus Mueller, who ran the main tea trials and were sympathetic to local production, concluded that tea monotherapy cannot be recommended (Mueller and others 2004). Pamela Weathers, the leading advocate of dried leaf, co-wrote a review concluding that "animal and human data are comparably negative" for tea (Weathers and others 2014, search summary). The only large trial favouring Artemisia was retracted for unreliable data after Gillibert's critique (Retraction Watch 2020). Advocacy groups, including Anamed and Maison de l'Artemisia, have promoted tea for treatment, prevention and even unconscious patients far beyond the evidence (WHO 2019).

Against the romance of the hospital. WHO's case rests partly on ACTs being affordable at under US$2 a course and widely available (WHO 2019). After the Fall that premise fails. Rectal artesunate, a pure hospital-made drug, showed no survival benefit at scale in CARAMAL because the referral system around it failed (Hetzel and others 2022). Pharmaceutical drugs without a health system can do as little as herbs. The WHO's own position concedes that ACTs are often unavailable, expensive or substandard in the places that need them. Critics such as Weathers argue that the WHO has not tested dried leaf fairly (search summaries). And the resistance argument, the strongest part of WHO's case, weighs less when there is little pharmaceutical artemisinin left to protect.

Against this report. The quantities given for bark are my arithmetic on uncertain content, not tested doses. The tea recommendation as a last resort rests on fast clearance and day-7 cure, which the same trials show to be misleading. A healer may reasonably argue that a two-in-three relapse rate makes the tea worse than nothing, because it delays the search for a real drug. I have chosen "last resort, full seven days, and watch for relapse" because in a village with no drug at all, a fever that falls buys days, and days are what severe malaria takes away. That is a judgement, not a finding.

7. 10-line summary

1. Malaria killed an estimated 15 to 24% of African children before treatment existed (Watson and others 2022).
2. Treated nets cut child deaths by 17%, and intact untreated nets still roughly halve infection (Pryce and others 2018, HY-06).
3. Closing eaves and screening houses halve indoor mosquitoes and cut child anaemia without insecticide.
4. Not every fever is malaria: in Tanzania fewer than half of "severe malaria" cases had parasites.

5. Quinine cures 85 to 95% if given 10 mg per kg three times daily for seven days, and three-day courses fail.
6. Quinine kills from about 1.5 g in an adult and 900 mg in a toddler, and drops blood sugar, especially in pregnancy.
7. Cinchona bark and its mixed alkaloids work, but bark content varies fivefold, so bark is dosed blind without an assay.
8. Artemisia annua tea clears fever fast but two in three patients relapse within five weeks.
9. Artemisia tea does not prevent malaria, A. afra contains no artemisinin, and the trial claiming otherwise was retracted.
10. In severe malaria, a single rectal artesunate dose helps a child under six only if treatment is completed elsewhere.

8. Open questions

- Does dried-leaf A. annua at a properly measured dose, for seven days, prevent recrudescence in people? No controlled trial with day-28 follow-up was found.
- Does Ge Hong's cold-water juice of fresh leaf deliver a full dose? Content is up to 20 times higher than tea, but stability and clinical effect are untested.
- What fraction of bark alkaloid is absorbed from swallowed powder? No modern pharmacokinetic study was found.
- Was the League of Nations totaquina tested clinically, and what were its trial results? Not found.
- How much do flavonoids and other compounds contribute? In vitro studies disagree.
- Would combining a short course of Artemisia with seven days of bark or quinine improve on quinine alone? Untested.
- After the Fall, does the resistance argument against tea still hold where no ACTs remain? A matter of judgement, unresolved.
- What was the real mortality of blackwater fever? The often-cited 25 to 50% could not be confirmed.
- Was the rise in deaths after rectal artesunate roll-out in Nigeria real? Experts still disagree.

9. Sources to read in full

1. WHO Global Malaria Programme (2019). Technical document on the use of non-pharmaceutical forms of Artemisia. The single best review of the plant evidence.
2. Achan J and others (2011). Quinine, an old anti-malarial drug in a modern world. Malaria Journal. Dosing, failure rates and history.
3. Tu Y (2011). The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine. Nature Medicine.
4. Mueller MS and others (2004). Randomized controlled trial of a traditional preparation of Artemisia annua. Transactions of the Royal Society of Tropical Medicine and Hygiene.
5. Pryce J, Richardson M, Lengeler C (2018). Insecticide-treated nets for preventing malaria. Cochrane.
6. Gomes MF and others (2009). Pre-referral rectal artesunate. Lancet, and Hetzel MW and others (2022), the CARAMAL effectiveness paper, together.
7. IPCS INCHEM Poisons Information Monograph 464, Quinine.
8. Rocco F (2003). The Miraculous Fever-Tree. Not read for this report, but recommended in the brief for the cinchona history.
9. Weathers PJ and others (2014). Whole plant approaches to therapeutic use of Artemisia annua, for the advocates' best case.
10. THRIVING library, HY-06, for vector control detail.

At the bedside after the Fall

Household. Minimum: an intact net for every sleeper, children and pregnant women first, mended weekly. Eaves closed with mud. Water containers emptied and scrubbed weekly. A fever chart. Knowledge of the red flags, sugar or

honey, and the rule that a fever in malaria season goes to the healer the same day. If the household grows A. annua, it dries and stores leaf for the healer, not for self-treatment. Needs: netting, needle, thread, mud, a clock. First failure to expect: the net gets a hole, nobody mends it, and the child sleeps in the gap.

Village of 300. Minimum: a trained healer with a scale, a register of every fever with weight, dose and outcome, and a locked box. Salvaged quinine, ACT, rectal artesunate and rapid tests, logged by expiry. A drainage map and a net-mending day each month before the rains. An A. annua plot of about 100 square metres from known seed, a shaded drying shed, and a dry, cool store. A herbarium sheet of the true plant beside A. absinthium and any local Artemisia. Needs: seed, scale, register, rapid tests while they last, a cart. First failure to expect: the healer gives tea, the fever falls on day 3, the family stops on day 4, and the child returns at week 3 with severe malaria.

District of 3,000. Minimum: a microscope with a trained microscopist, stain and slides, used to check every treated case at day 7 and day 28. Injectable quinine or artesunate and glucose. A ten-bed room for severe malaria. A protocol for weighed bark doses if bark is held. In tropical highlands, a cinchona nursery planted now, for bark in eight to ten years, with seed from the highest-yielding trees available. A seed bank for A. annua. Training days for village healers on red flags and seven-day courses. Needs: microscope, oil, stain, glass, a balance, records, and if possible a chemist who can assay bark. First failure to expect: the stock of injectable drugs runs out in the first bad rainy season, and the plantation has not yet come of age.

Protocols

Protocol 1. Is this fever malaria, and is it dangerous? (every fever, malarious area)

1. Check the red flags (Section 5). Any one present: go to Protocol 6 now.
2. Ask: where has the patient slept in the past month, and is it the rainy season? In a malarious place and season, treat as malaria unless a test is negative.
3. Look for other causes at the same time: cough and fast breathing, stiff neck, burning urine, rash, ear pain, a hot red swelling (THRIVING library, IN-02).
4. Test if possible: rapid test, or a thick film read over at least 100 fields before calling it negative.
5. A negative good-quality test with no red flags: look harder for another cause, recheck in 24 hours.
6. Record time, temperature, weight, test result and what was given.

Protocol 2. Net and eaves care (weekly, household)

1. Each evening before dusk, tuck the net under the mattress or mat on all sides.
2. Each week in daylight, hold the net to the sky and look for holes larger than a fingertip.
3. Sew or knot every hole the same day. A patch of netting with mesh no wider than about 1.2 to 2 mm is enough (HY-06).
4. Each month, check the gap between wall and roof. Fill it with mud, wood or cloth.
5. Each week, empty, scrub and turn over every water container not in use.
6. Keep animals out of sleeping rooms at night and pens away from the house.

Protocol 3. Oral quinine for uncomplicated malaria (dispensary, salvaged tablets)

1. Confirm the patient can swallow and has no red flags.
2. Weigh the patient. Dose is 10 mg of quinine salt per kg per dose. Tolerance: plus or minus 10% [VERIFY: tolerance is my rounding guide, not from a source].
3. Read the tablet label: salt, not base. A 300 mg salt tablet suits about 30 kg per tablet per dose.
4. Maximum single adult dose: 600 mg of salt (INCHEM).
5. Give every 8 hours, for 7 full days, 21 doses. Never stop at 3 days.

6. Give with food or sugar water. Pregnant women: give sugar with every dose and watch for sweating, shaking or drowsiness.
7. Expect ringing ears. Stop and send to the district for blurred vision, fainting, dark urine or confusion.
8. If clindamycin or doxycycline is held, the district may add it. Doxycycline never in pregnancy or under 8 years [VERIFY: standard rule not re-checked here].
9. Record each dose. Check the patient at day 7, and by film at day 28 if a district microscope is reachable.

Protocol 4. Cinchona bark powder (only when no quinine or ACT exists)

This protocol is an inference from the historical record and the modern quinine dose. It has not been tested.

1. Use only bark from a known Cinchona tree, dried and powdered fine. Keep a sample labelled with tree, date and weight.
2. If anyone can assay the bark, record its quinine percentage. If not, assume 3% for unknown bark, 5% for C. ledgeriana or calisaya [VERIFY: assumption from the Indian averages].
3. Adult (60 kg) dose at 5% bark: about 10 g of powder every 8 hours, swallowed in wine, lemon juice or sour fruit drink, for 7 days. At 3% bark the arithmetic gives about 20 g, which is more than most can swallow and keep down, so give 10 to 12 g every 8 hours and accept a weaker course [VERIFY: my arithmetic].
4. Child: scale by weight, about 0.17 g of 5% bark per kg per dose [VERIFY: my arithmetic]. Never exceed the adult dose. Under 10 kg only on the district's instruction.
5. Do not use a weak tea or decoction of bark. The record suggests water extracts about an eighth of the powder's strength.
6. Stop for blurred vision, fainting, severe vomiting or dark urine. Give sugar for sweating and drowsiness.
7. Never give bark to someone who has had black or red urine with malaria.
8. Keep bark locked. A child who swallows a cupful of powder may die.

Protocol 5. Artemisia annua tea, last resort only

Use only when no quinine, bark or ACT exists, the patient can drink, and there are no red flags.

1. Confirm the plant: annual, bright green fern-like leaves, sweet scent, not grey and felted, not woody.
2. Use leaves harvested at bud stage, dried in shade, stored dry and cool, less than a year old if possible.
3. Adult dose: 9 g of dried leaf (weigh it) in 1 litre of water just off the boil. Stir, steep 10 to 15 minutes, strain, squeeze the leaves into the tea (Räth and others 2004, WHO 2019).
4. Drink the litre in four portions through 24 hours. Make fresh each day. It keeps 24 hours.
5. Child: 1 g of leaf in 200 ml of water per 10 kg of body weight per day, divided into four portions (Hirt rule, ECHO). Note this is weaker than the 9 g adult dose.
6. Give for 7 full days. Never fewer.
7. Expect the fever to fall in 2 to 4 days. Do not stop.
8. Warn the family: the fever often returns in 2 to 5 weeks. If it does, come back at once.
9. Look for a real drug throughout the course. If one is found, give the full course of it.
10. Never give tea as prevention, and never by enema to an unconscious patient.

Protocol 6. Severe malaria before transfer

1. Lay the patient on the side, clear the mouth, note the time.
2. If able to swallow: sugar water (a level tablespoon of sugar in a cup of water) or honey water [VERIFY: quantity from IN-02 general practice]. If not: a pinch of sugar paste inside the cheek.
3. Child 2 months to under 6 years, rectal artesunate held: 10 mg per kg. One 100 mg suppository under 3 years, two from 3 to under 6. Hold the buttocks together for 10 minutes. If transfer is impossible, repeat after 12 hours.

4. No artesunate, healer trained in injection: quinine 20 mg salt per kg, diluted, half into the front of each thigh, deep (MSF).
5. Cool a very hot patient with tepid water. Stop fits only if trained and stocked.
6. Carry to the district now. Send the register page with the patient.
7. At the district: artesunate or quinine by injection for at least 24 hours, glucose checks, then oral treatment to complete 7 days of quinine or 3 of ACT.

Protocol 7. Growing Artemisia annua

1. Obtain seed from a known high-artemisinin, climate-matched line. Label it.
2. Make a shaded nursery bed 1.5 m wide, raised 20 cm, free of weeds.
3. Sow about 1 g of seed per square metre on the surface. Do not cover. Keep moist. 18 to 20 °C.
4. Seedlings appear in 6 to 7 days. Weed carefully.
5. Transplant at about 12 cm, in the evening after watering the bed, at about 1 m by 1 m, or 45 by 45 cm on good ground.
6. Mulch. Water through the first 12 weeks. Drought causes early flowering.
7. Harvest when half to three-quarters of plants show buds. Cut, wilt, dry in shade, strip leaves.
8. Store in sealed dry containers, cool, away from damp. Label with date. Leave some plants to flower for seed.

Protocol 8. Quinine poisoning

1. Signs: ringing ears and deafness with blurred or lost vision, vomiting, confusion, fainting, slow or irregular pulse, fits.
2. Stop all quinine and bark.
3. Do not make the patient vomit.
4. If drowsy or sweating, give sugar.
5. Lay on the side, keep the airway clear.
6. Carry to the district, where activated charcoal and monitoring are given.
7. Blindness may recover partly over weeks. Record the dose taken.

Numbers to carry

1. Malaria killed 15 to 24% of children before treatment.
2. A treated net saves about 5.6 children's lives per 1,000 protected per year, and the net must have no holes.
3. Quinine: 10 mg salt per kg every 8 hours for 7 days. Severe: 20 mg per kg first.
4. Quinine kills from 1.5 g in an adult, 900 mg in a toddler, usually above 8 g.
5. Artemisia tea: 9 g per litre, 1 litre a day, 7 days, and two in three relapse by day 35.
6. Artemisia annua leaves hold 0.02 to 1.4% artemisinin, and the best tea carries under a fifth of a dose.
7. Rectal artesunate: 10 mg per kg, children under 6 only.
8. Treated severe malaria still kills 10 to 20%, untreated nearly all.
9. A thick film is negative only after 100 clean fields.
10. Cinchona bark holds 2 to 17% alkaloid, and the first coppice comes at 8 to 10 years.

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