IN-14 Sexually transmitted and urinary infections

HEALING after the FALL, research library, IN-14

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Findings by section

1. Scope, and the three voices kept apart

This report covers the infections of sex and of the urinary tract for a community that has no laboratory, no reliable drug supply and no one with a medical degree. Three kinds of claim are kept separate throughout. **What the tradition says** is what healers in a given culture believed a remedy did. **What the record shows** is what was measured, chiefly in the pre-antibiotic clinical series, the untreated cohorts, the placebo arms of modern trials and the humanitarian field guidelines. **What modern science infers** is the mechanism or the extrapolation, which is often weaker than either.

Two facts shape everything that follows. The first is that the great sexually transmitted diseases are slow. Syphilis kills over thirty years, gonorrhoea sterilises over ten, and neither announces itself in a way a frightened village will act on. The second is that the whole of the preventable harm, which is to say congenital syphilis, blindness in the newborn and tubal infertility, is prevented by a handful of injections and two drops of antiseptic in an infant's eyes. Of all the chapters in this book, this is the one where the smallest material input buys the largest reduction in lifelong disability.

The urinary chapter runs the other way. Most lower urinary infection in women resolves without any drug at all, and the healer's task is mostly to tell the bladder from the kidney, and to spend the salvaged antibiotic on the kidney.

2. Syphilis: the natural history, the treatments and the lesson

What untreated syphilis does. The best data in medicine on this question come from a study that would now be criminal. At Rikshospitalet in Oslo between 1891 and 1910, Cæsar Boeck withheld treatment from roughly 2,000 patients with early syphilis, on the view that mercury suppressed the body's own response. His successor Edvin Bruusgaard traced 473 of them from 1925 and reported in 1929 that 27.9 per cent showed spontaneous cure, with no signs and a non-reactive test, and that about 70 per cent had suffered no serious inconvenience from the disease (Oslo study, via Wikipedia summary of Bruusgaard 1929).

Trygve Gjestland's re-study, published as a supplement to Acta Dermato-Venereologica in 1955, covered 1,404 cases, about 80 per cent of those denied treatment, and followed up 953 of them including 331 men. By 1949 to 1950, 694 of the 953 had died, 267 of them within the first twenty years after infection, and only 259 were still alive. Syphilis was held responsible for 75 of those deaths, 39 of them in men, and 28 of the 75 were from neurosyphilis. There were 19 cases of general paresis, all fatal, four of active tabes dorsalis with one death, and 17 other major neurological forms with eight deaths. Complicated aortitis was diagnosed 61 times, including 15 aneurysms, 34 of them in men (Gjestland 1955, as summarised in the Oslo study entry).

A Danish review of tertiary syphilis cites the Oslo figures as neurosyphilis in 6.5 per cent, cardiovascular syphilis in 10.4 per cent and benign tertiary syphilis in 15.8 per cent, with 62 neurosyphilis and 92 cardiovascular cases in absolute terms. The denominator for those percentages could not be confirmed against Gjestland's own tables [VERIFY]. Taken together they sum to about a third, which matches the rule of thirds taught from the Oslo data and repeated in Norwegian public-health teaching: roughly a third of untreated people clear the infection, a third remain latently infected for life without harm, and a third develop tertiary disease, of which roughly half is gummatous, roughly a third cardiovascular and roughly a fifth neurological (NHI, Norwegian health information, secondary). The brief's "about a third with late complications" is therefore sound.

The practical summary for a lay reader is this. In the first year, syphilis is a painless ulcer that heals by itself, followed some weeks later by a rash that also fades. At ten years, most people are well and some are quietly carrying it. At thirty years, one in ten has a diseased aorta and one in fifteen has a diseased brain or spinal cord, and both of those will kill or cripple. The disease is a slow sentence passed early, served late.

Infectiousness. Canadian national guidance estimates the per-partner risk of transmission in primary, secondary and early latent syphilis at 51 to 64 per cent, and Australian contact-tracing guidance puts it above 20 per cent per unprotected act, rising to about 50 per cent over a long partnership. Late latent syphilis is not considered infectious to sexual partners. In pregnancy the stage governs the fetal risk: 70 to 100 per cent transmission with primary or secondary disease, about 40 per cent in early latent and about 10 per cent in late latent (Canadian guidelines, secondary summaries). The brief's claim that late harms are preventable with a few doses is fully supported.

Guaiacum and mercury. Guaiac wood, from *Guaiacum officinale* and *G. sanctum*, heartwood and resin, arrived in Europe in the early 1500s on the theological argument that God had placed the cure where the disease had arisen. It was given as a hot decoction followed by a sweating regimen. Ulrich von Hutten was its most famous advocate, having lost his teeth to mercury. Paracelsus dismissed it as useless and expensive, and the record contains no evidence that it cured anything. Grade D at best, and functionally X for syphilis.

Mercury was the standard treatment for roughly four centuries, as ointment, fumigation and oral dose, and its logic was that salivation was itself curative. Physicians aimed at salivation and some judged three pints of saliva a day a good result. The harms are documented as extensive tooth loss, ulceration of the mouth and gums, neurological damage and death from mercury poisoning, with a nineteenth-century warning that salivation in the young "may prove fatal" (historical reviews collected under The Remedial Value of Mercury and On the Impropriety of Mercurial Salivation). The proverb the brief asks about is "One night with Venus, a lifetime with Mercury", whose exact origin and date are not settled. Whether mercury ever helped is unresolved. The Oslo cohort was created precisely because Boeck believed it did not. For the book, mercury is the central example of a treatment whose visible effect was mistaken for its benefit.

Salvarsan. Compound 606, arsphenamine, was synthesised in Paul Ehrlich's laboratory by Alfred Bertheim in 1907, its antisyphilitic activity found by Sahachiro Hata in 1909, and it was marketed by Hoechst as Salvarsan from 1910. It worked, and it displaced mercury quickly. It also had to be dissolved immediately before use in several hundred millilitres of distilled sterile water with minimal exposure to air, which is the sort of handling a district infirmary could just about manage and a hamlet could not. By 1913 at least 126 deaths were attributed to it, about one fatality per 2,000 injections, with a later composite figure of about one per 7,000 injections for 1916 to 1924 (secondary histories, Science History Institute and others). "Arsphenamine jaundice" was described in 1920 alongside exfoliative dermatitis, gangrene and thrombosis. Some of the harm was blamed on improper handling.

Fever therapy. On 14 June 1917 Julius Wagner-Jauregg inoculated nine patients who had general paresis with malarial blood. Six recovered well enough to return to work, though four of the six later relapsed. By 1926 enough replications existed for a pooled review, which reported full remission in 27.5 per cent, partial remission in 26.5 per cent and death or no change in 46 per cent. Mortality from the procedure itself is given as 2 to 13 per cent in one review and about 15 per cent in a popular account. He received the Nobel Prize in 1927. A 1992 JAMA review by Austin

and colleagues concluded that it remained unclear whether malariotherapy ever helped. The honest reading is that a treatment with a one in ten chance of killing you produced durable remission in about a quarter of people whose alternative was certain dementia and death, and that this was a reasonable trade in 1920 and is not one now.

Penicillin and the single dose. Penicillin became the treatment for syphilis from 1943 (standard accounts attribute the first series to John Mahoney and colleagues at Staten Island, which this agent did not read directly [VERIFY]). Modern practice is a single intramuscular dose of benzathine penicillin G, 2.4 million units, for primary, secondary and early latent disease. The NIH-sponsored phase 4 randomised trial NCT03637660 enrolled 249 adults with early syphilis, 64 per cent of them living with HIV and 97 per cent men, and compared one dose with three weekly doses. Serological response at six months, defined as a fourfold fall in RPR titre or seroreversion, was 76 per cent with one dose and 70 per cent with three, meeting the non-inferiority criterion, and there were no clinical relapses or treatment failures in either arm (NIH news release and secondary coverage of the NEJM report). About a quarter of each arm did not meet the serological definition at six months, which reflects slow titre decline rather than proven failure.

WHO's 2021 symptomatic STI guidelines give early syphilis as benzathine penicillin 2.4 million units intramuscularly in a single dose, with doxycycline 100 mg twice daily for 14 days or erythromycin 500 mg four times daily for 14 days as substitutes. Late latent and tertiary syphilis take benzathine 2.4 million units weekly for three weeks, or procaine penicillin 1.2 million units daily for 20 days, or doxycycline 100 mg twice daily for 30 days. In pregnancy the recommendation is benzathine penicillin, with erythromycin only as a substitute and with the explicit warning that erythromycin does not cross the placenta completely, so the newborn must be treated after delivery (WHO 2021, Table 7).

Pregnancy and the newborn. Gomez and colleagues pooled six case-control studies covering 1,715 pregnant women with untreated syphilis and 22,515 without, and found crude adverse birth outcomes in 66.5 per cent of the untreated syphilitic women, range 53.4 to 81.8 per cent, against 14.3 per cent of the others. The component proportions are read by later authors as early fetal loss or stillbirth 21 per cent, neonatal death 9 per cent, prematurity or low birth weight 6 per cent and infection in a liveborn infant 15 per cent, totalling about 52 per cent, though the original abstract's wording is ambiguous on whether these are proportions or differences [VERIFY]. A later meta-analysis including Chinese literature gave 26.4 per cent for stillbirth or fetal loss.

Blencowe and colleagues estimated the effect of detecting and treating active syphilis in pregnancy with at least 2.4 million units of benzathine penicillin: a 97 per cent reduction in clinical congenital syphilis, 95 per cent CI 93 to 98, from three studies, an 82 per cent reduction in stillbirth, CI 67 to 90, from eight studies, a 64 per cent reduction in preterm delivery and an 80 per cent reduction in neonatal death. They graded the evidence low quality but made a strong recommendation on the size of the effect and the clear mechanism. This single finding is the most important number in the report. One injection, given once in pregnancy, prevents nineteen of every twenty cases of congenital syphilis.

Tuskegee. From 1932 to 1972 the United States Public Health Service followed 399 impoverished African American men in Macon County, Alabama who had latent syphilis, against 201 uninfected controls. The men were told they were being treated for "bad blood" and were given free examinations, meals and burial insurance. No consent was taken. Penicillin was withheld after it became standard in 1947. The study ended on 16 November 1972 after Jean Heller's Associated Press story in the Washington Star on 25 July. By then 28 men had died directly of syphilis and about 100 more of related complications, 40 wives had been infected and 19 children had been born with congenital syphilis. An interim PHS report by Heller and Bruyere in 1946 recorded 101 deaths among 410 untreated men by 1945 against 28 of 201 controls.

Tuskegee belongs in this book not as history but as a working rule. A healer who withholds a treatment they possess, in order to learn something, or who conceals a diagnosis from the person who has it, has crossed the line that this case defines. The Oslo data were gathered under a genuine, if mistaken, belief that treatment harmed. Tuskegee continued for twenty-five years after that belief became impossible.

3. Gonorrhoea, pelvic infection and the newborn's eyes

Natural history. The incubation period is 1 to 6 days. Transmission from an infected man to a partner is estimated at 50 to 73 per cent and appears largely independent of the number of exposures, while transmission from a woman to the male urethra is 20 to 35 per cent with a single exposure, and about a third of exposures do not transmit at all (figures collected in the gonorrhoea health map, Whelan and colleagues, correction notice). Untreated infection eventually clears on its own, after weeks or months of unpleasant symptoms in men, during which transmission and complications are both likely. Most women with lower genital tract infection have no symptoms they would call symptoms, which is why the disease does its damage unopposed. The proportion of untreated infections that goes on to complications is stated in the review literature as unknown.

What it costs in the long run. The best quantification is Lars Weström's Lund cohort. Between 1960 and 1984, 2,501 women underwent diagnostic laparoscopy for suspected acute pelvic inflammatory disease, of whom 1,844 had abnormal findings and 657 were normal and served as controls. Confirmed tubal factor infertility was found in 141 of the patients, 10.8 per cent, and in none of the controls. A further 165, 12.2 per cent, had abnormal tubal function or morphology, against four controls, 0.9 per cent. Ectopic pregnancy complicated 9.1 per cent of first pregnancies after the index laparoscopy against 1.4 per cent of controls. Of those who tried to conceive, 16.0 per cent of patients and 2.7 per cent of controls failed. Risk rose with the number and severity of episodes (Weström et al 1992). The brief's figures of 8 and 19.5 per cent could not be found in the abstract and should not be used [VERIFY].

A separate cohort finding matters for a village with no tests: subclinical pelvic inflammatory disease reduces later fertility even when the gonorrhoea and chlamydia are treated. Some of the infertility is caused before anyone could have known there was anything to treat.

The resistance history. This is the clearest cautionary tale in antimicrobial medicine, and it bears directly on what a salvaged chest is worth. Sulfonamides were used from the 1930s, and by 1944 about 75 per cent of soldiers in the Italian theatre failed them. Penicillin replaced them in the 1940s, reduced susceptibility appeared in the 1960s, and by the 1970s isolates with minimum inhibitory concentrations up to 128 mg/L ended the penicillin era. Tetracycline served from the 1950s, and high-level plasmid-mediated resistance to both penicillin and tetracycline was described by the 1980s. Ciprofloxacin reached the market in the late 1980s, and in China resistance rose from 12.7 per cent in 1995 to 93.8 per cent in 2003. CDC stopped recommending fluoroquinolones for gonorrhoea in 2007 and removed cefixime as a recommended option in 2012. In December 2020 CDC moved to a single 500 mg intramuscular dose of ceftriaxone alone, dropping azithromycin because reduced susceptibility had risen more than sevenfold in five years, from 0.6 per cent in 2013 to 4.6 per cent in 2018, with 1 g for people weighing 150 kg or more, and doxycycline 100 mg twice daily for seven days given separately if chlamydia has not been excluded.

For the village this means three things. Salvaged penicillin, amoxicillin, tetracycline and ciprofloxacin should be assumed not to cure gonorrhoea. Salvaged ceftriaxone should be assumed to cure it and should be hoarded for that and for the few other syndromes in IN-05 that need it. And the resistance that made all those drugs useless was created by use, not by time, so a population cut off from new supply does not automatically inherit the resistance of the world it left behind. Over a generation of isolation some susceptibility may return, and nobody can say how much [VERIFY, this is inference].

Ophthalmia neonatorum, and the two drops that prevent blindness. Without prophylaxis, 30 to 50 per cent of infants born to a mother with gonorrhoea acquire conjunctival infection, which can progress within days to corneal ulceration, perforation of the globe and permanent blindness. Gonococcal disease appears from birth to about day 5, chlamydial from about day 5 to day 14.

Karl Credé reported in 1881 from the Leipzig maternity clinic that the rate of ophthalmia had been about 9.8 per cent in 1878, fell to 7.6 per cent in a period when only infants of known diseased mothers were treated, and fell to 0.5 per cent, one case in two hundred, between 1 June and 8 December 1880 after universal instillation of silver nitrate, and that in that single case the instillation had been accidentally omitted. He used a 2 per cent solution, which was later

reduced to 1 per cent because it irritated the eyes. Ernst Fuchs's 1884 prize essay gives 10.8 per cent before and 0.1 to 0.2 per cent after. Schaller and Klauss estimate that at the end of the nineteenth century prevalence in maternity hospitals exceeded 10 per cent, with corneal damage in 20 per cent and blindness in about 3 per cent of those affected, and that up to half the children in schools for the blind were there because of it. In the United States, blindness from ophthalmia among pupils in schools for the blind fell from 28.2 per cent in 1906 to 1907 to 0.1 per cent in 1958 to 1959.

Isenberg, Apt and Wood randomised 3,117 infants at Kikuyu, Kenya between March 1991 and August 1993 to a drop of 1 per cent silver nitrate, a 1 cm strip of 0.5 per cent erythromycin ointment, or a drop of 2.5 per cent povidone-iodine. Povidone-iodine was significantly better than both comparators overall and especially against chlamydial ophthalmia, while gonococcal and *Staphylococcus aureus* rates were similar across arms. A later editorial in the British Journal of Ophthalmology summarises the reductions as 44 per cent with povidone-iodine, 34 per cent with erythromycin and 24 per cent with silver nitrate, and cautions that more than 18 per cent of infants were brought back for ocular inflammation while only 8 to 10 per cent were culture positive, so some of the counted cases were chemical conjunctivitis.

The practical conclusion for the book is firm. Dilute povidone-iodine is the best eye prophylaxis in the record, it is less toxic and cheaper than silver nitrate, and it is also the antiseptic most likely to be salvaged in quantity. Established gonococcal ophthalmia needs a systemic drug, a single intramuscular dose of ceftriaxone, given in the emergency literature as 50 mg/kg to a maximum of 125 mg, with a second source giving 25 to 50 mg/kg to a maximum of 150 mg, together with frequent saline irrigation of the eyes to wash away the discharge, and treatment of the mother and her partner. The two sources disagree on the ceiling and the WHO document itself could not be retrieved [VERIFY].

4. The other genital infections

Chlamydia. It is the commonest curable bacterial sexually transmitted infection and the quietest. Roughly half of untreated infections clear within a year (Geisler 2010 review). Modelling that allows for fast and slow clearing groups gives a mean duration of about 1.36 years in women, with about 23 per cent in a fast-clearing class, and about 2.84 years in men (Price et al, and Lewis et al 2017). A Dutch cohort of 30 untreated women measured 44.7 per cent clearance per person-year, and a United States cohort found 48 per cent of untreated urogenital infections cleared within 12 weeks. The treatment that matters is doxycycline 100 mg twice daily for seven days, extended to 14 days for pelvic inflammatory disease and 21 days for rectal lymphogranuloma venereum, or azithromycin 1 g as a single dose.

Trichomoniasis. More than half of infected women have an abnormal discharge and about half of those report vulval itching. The strawberry cervix is uncommon but highly indicative. Kissinger and colleagues randomised 623 women at three United States clinics to a single 2 g dose of metronidazole or 500 mg twice daily for seven days, and found infection at test of cure in 58 of 311, 18.6 per cent, after the single dose against 34 of 312, 10.9 per cent, after the week, p=0.001, relative risk 0.55. An earlier meta-analysis by Howe and Kissinger found 46 per cent fewer failures with the multi-dose regimen. For a village with limited metronidazole, the single 2 g dose remains defensible as the cheaper option, with the seven-day course for failures and for the partner.

Herpes. Primary infection follows 5 to 14 days after contact, with lesions lasting 15 to 20 days and systemic symptoms in the first 3 to 4 days. Recurrences average four to five days. About 90 per cent of people have at least one recurrence in the first year, 38 per cent have six or more and 20 per cent have more than ten, with a median of about four a year, and men have about 20 per cent more recurrences than women. Aciclovir shortens episodes but nothing cures it. The village danger is neonatal herpes: the risk to an infant delivered vaginally during a primary maternal infection is estimated at 25 to 60 per cent, against about 2 per cent with reactivation. Untreated neonatal disease carries roughly 50 per cent mortality in the central nervous system form and 85 per cent in the disseminated form, against nothing for skin, eye and mouth disease (figures attributed to Corey and Wald 2009 in a teaching slide set, not read directly [VERIFY]). A district infirmary that still has aciclovir should keep it for the newborn and for the first attack, not for the recurrences.

Chancroid. *Haemophilus ducreyi* causes painful, ragged, non-indurated ulcers with inguinal buboes that can suppurate and drain. About 5 per cent relapse. Its cytolethal distending toxin probably explains the slow healing. Clinically it cannot be reliably told from syphilis, which is why MSF instructs that both be treated together. MSF gives azithromycin 1 g orally as a single dose, or ceftriaxone 250 mg intramuscularly as a single dose, or erythromycin 500 mg four times daily for seven days, and instructs that fluctuant nodes be aspirated through healthy skin and never incised and drained. Genital ulcer disease of any cause raises HIV acquisition sharply, with odds ratios from 3 to 18.2 in endemic settings.

Lymphogranuloma venereum and warts. MSF treats LGV with erythromycin 1 g twice daily or 500 mg four times daily for 14 days, and WHO extends doxycycline to 21 days for rectal disease. Genital warts cannot be cured by any drug a village will have and are not an emergency. They are left alone in this book except where they obstruct the birth canal, and the record on home destructive methods is not good enough to recommend any.

5. Managing genital syndromes without a test

The WHO 2021 guidelines exist precisely because most of the world treats these infections without a laboratory, and they are candid about what that costs. The honest numbers are these.

For a **genital ulcer**, clinical judgement by experienced clinicians is wrong in over half of cases. For detecting syphilis, where syphilis typically causes 5 to 10 per cent of anogenital ulcers, clinical diagnosis has sensitivity 64 per cent and specificity 84 per cent, so for every 100 people with ulcers about 2 to 4 cases of syphilis are missed and 14 to 15 people are treated who do not have it. If all 100 are treated for syphilis, 90 to 95 get a needless injection and nobody is missed. For herpes, which causes 30 to 70 per cent of ulcers, clinical diagnosis has sensitivity 40 per cent and specificity 88 per cent, missing 18 to 42 cases per 100.

For **lower abdominal pain** in women, the syndromic approach for detecting gonorrhoea or chlamydia has sensitivity 30 per cent and specificity 73 per cent. In a study of 623 women with suspected pelvic inflammatory disease, fever had sensitivity 47 per cent and specificity 64 per cent, vaginal discharge 7 per cent and 24 per cent, and tenderness of the pelvic organs on bimanual examination 99 per cent and 0 per cent. That last pairing is the single most useful line in the guideline for a lay healer. Cervical motion tenderness catches almost everyone with pelvic infection and excludes nobody, so it is a gate, not a diagnosis.

For **anorectal discharge**, syndromic management has sensitivity 32 per cent and specificity 82 per cent, missing 14 to 34 of every 100 and falsely treating 9 to 15.

WHO's own conclusion for anorectal discharge, and the logic generalises, is that where molecular testing is impossible, treating everyone who has the syndrome misses nobody, at the cost of a great deal of unnecessary treatment. This is the central trade of the whole chapter. A village with 300 people and a finite chest of ceftriaxone cannot treat everyone with an ulcer for syphilis for ever. It can for a year, during an outbreak, and that is probably the right choice.

The regimens, from WHO 2021 and MSF. For urethral discharge, WHO's 2021 table gives ceftriaxone 250 mg intramuscularly as a single dose plus azithromycin 1 g orally as a single dose, with cefixime 400 mg orally as the substitute for ceftriaxone, plus doxycycline 100 mg twice daily for seven days for chlamydia if azithromycin was not given. MSF's current page gives ceftriaxone 500 mg intramuscularly as a single dose, which matches the 2020 CDC change, with cefixime 400 mg orally if ceftriaxone is unavailable, plus azithromycin 1 g or doxycycline for seven days, and instructs that the partner receive the same treatment whether or not they have symptoms. Where discharge persists after seven days of an effective combination, MSF says to consider trichomoniasis and give tinidazole or metronidazole 2 g as a single dose, and to consider reinfection.

For pelvic inflammatory disease, WHO gives gonorrhoea cover plus doxycycline 100 mg twice daily for 14 days plus metronidazole 400 or 500 mg twice daily for 14 days. MSF gives the same oral pair for 14 days, substitutes erythromycin 1 g twice daily or 500 mg four times daily for 14 days in pregnancy and lactation, states explicitly that

single-dose azithromycin is not effective against chlamydia in this setting, and for hospital treatment uses ceftriaxone 1 g once daily with metronidazole, continuing 24 to 48 hours past the fall of fever and pain before stepping down to oral drugs to complete 14 days. It also instructs removal of any intrauterine device and treatment of the partner.

WHO's own list of reasons to hospitalise is the village's list of reasons to send someone to the district: the diagnosis is uncertain, a surgical emergency such as appendicitis or ectopic pregnancy cannot be ruled out, a pelvic abscess is suspected, the illness is severe, the woman is pregnant, she cannot follow or tolerate the oral regimen, or she has failed it.

6. Urinary infection: the self-cure rate and what the drugs add

How much cures itself. This is the number the brief asks to have settled, and the best answer comes from the placebo arm of a general-practice trial rather than from the meta-analysis. Christiaens and colleagues randomised 78 non-pregnant women aged 15 to 54 with symptoms of lower urinary infection and a positive leukocyte esterase test to nitrofurantoin 100 mg four times daily for three days or placebo. Among those with bacteriologically proven infection, cure at day 3 was 21 of 26 on nitrofurantoin against 5 of 25 on placebo, number needed to treat 1.6, and at day 7 it was 17 of 23 against 9 of 22, p=0.05, number needed to treat 3. Among all women with clinically suspected infection, symptomatic improvement or cure at day 3 was 27 of 35 against 19 of 35, number needed to treat 4.4, and at day 7 it was 30 of 34 against 17 of 33, number needed to treat 2.7.

Read from the placebo side, which is what matters after the Fall, that is **about 54 per cent of women symptomatically better by day 3 on nothing, about 52 per cent by day 7, and about 41 per cent bacteriologically cured by day 7 on nothing**. Falagas and colleagues pooled five randomised trials and found clinical success significantly more likely with antibiotics, odds ratio 4.81, 95 per cent CI 2.51 to 9.21, from four trials and 1,062 patients, with cure odds ratio 4.67 and more adverse events in the antibiotic arms. The per-arm percentages from that meta-analysis could not be retrieved [VERIFY]. Secondary summaries of the wider literature put spontaneous resolution at 50 to 70 per cent. The brief's "a quarter to a half" is on the conservative side of the record. A quarter to a half is defensible for bacteriological cure, and about half is right for symptoms.

The practical rule: a woman with burning and frequency, no fever and no flank pain, in a village with a finite chest, should be offered fluids, warmth and time first, with the antibiotic held for failure at 48 to 72 hours, for pregnancy, and for anyone with fever or back pain. That rule spends roughly half as much drug for a delay of two or three days in the half who would have needed it anyway.

The drugs. MSF's cystitis page gives, for young non-pregnant women, fosfomycin-trometamol 3 g orally as a single dose or nitrofurantoin 100 mg three times daily for five days, with nitrofurantoin preferred when nitrites are negative and leukocytes positive, which suggests *Staphylococcus saprophyticus*, against which fosfomycin is not active. For treatment failure or recurrence more often than three or four times a year, ciprofloxacin 500 mg twice daily for three days. For pregnant or lactating women, fosfomycin 3 g single dose, or nitrofurantoin 100 mg three times daily for seven days but never in the last month of pregnancy, or cefixime 200 mg twice daily for five days. For girls aged two and over, cefixime 8 mg/kg once daily for three days or co-amoxiclav 12.5 mg/kg twice daily for three days. MSF notes that symptoms can last two to three days even on adequate treatment, and that in women a dipstick negative for both nitrites and leukocytes excludes infection.

A Dutch primary-care cohort of about 40,000 episodes found that at estimated glomerular filtration rate 60 mL/min or above, clinical failure was 14.6 per cent with five days of nitrofurantoin, 20.7 per cent with single-dose fosfomycin and 20.8 per cent with three days of trimethoprim, and that below 60 the order reversed, with 16.0 per cent for fosfomycin against 23.3 per cent for nitrofurantoin. In a village with no way to measure kidney function, the proxies are age, frailty and known kidney disease.

Pyelonephritis is the one that kills. MSF defines it as cystitis symptoms plus fever above 38 degrees with unilateral flank or abdominal tenderness, and warns that it is potentially severe in pregnant women, neonates and infants, and

that in a neonate fever may be the only sign while a normal temperature does not exclude it. Reported mortality in the modern record is 10 to 20 per cent when bacteraemic, 5.9 per cent of hospital deaths in a French national cohort, and 6.8 per cent against 0.1 per cent in a Korean cohort split by early clinical failure. A pre-antibiotic case fatality for pyelonephritis specifically could not be found [VERIFY]. Outpatient treatment in MSF's hands is a single dose of ceftriaxone 1 g intramuscularly or gentamicin 5 mg/kg intramuscularly followed by ciprofloxacin 500 mg twice daily for seven days, with co-amoxiclav or cefixime for 10 to 14 days as alternatives. Inpatient treatment is ampicillin 2 g intravenously six-hourly for at least three days plus gentamicin 5 mg/kg once daily for three days, or ceftriaxone 1 g once daily, stepping down to oral to complete 10 to 14 days. Children from one month take ceftriaxone 50 mg/kg once daily for at least three days then oral co-amoxiclav to complete ten days. MSF says to avoid non-steroidal anti-inflammatories and to keep an adult drinking about 1.5 L a day.

Pregnancy. Smaill and Vazquez's Cochrane review of antibiotics for asymptomatic bacteriuria in pregnancy found pyelonephritis in 199 per 1,000 untreated against 48 per 1,000 treated, from 2,017 women in 12 studies, low certainty, which is a number needed to treat of about 7. Low birthweight fell from 136 to 87 per 1,000, relative risk 0.64, CI 0.45 to 0.93, six studies and 1,437 babies, number needed to treat about 20, and preterm birth relative risk 0.34, CI 0.13 to 0.88, three studies, number needed to treat about 9. Only one of the fifteen trials was at low risk of bias across all domains. A separate review reports numbers needed to treat of 6 and 23 for the same two outcomes. The conclusion stands even on weak evidence: in a village, a pregnant woman with any bacteriuria is treated, and a pregnant woman with fever and flank pain is an emergency.

Catheters. The daily risk of acquiring bacteriuria with an indwelling urethral catheter is given as 2 to 7 per cent per day in one UK reference and 3 to 10 per cent per catheter day in a hospitalist review, with pooled cumulative incidence of 26 per cent for short-term use of 2 to 10 days, and bacteriuria in almost everyone after a month. Duration is the dominant risk factor. Intermittent catheterisation, suprapubic catheters and condom drainage are each preferable to an indwelling urethral catheter. For a village this translates into a single discipline: a catheter goes in only for retention or for a dying patient's comfort, it comes out the moment the reason has gone, and intermittent catheterisation with a clean boiled tube beats leaving one in.

7. The plants, the drinks and the other non-drug measures

Cranberry. Williams and colleagues' 2023 Cochrane update covered 50 trials and 8,857 participants, and it changed the verdict. Cranberry products reduced symptomatic, culture-verified urinary infection overall, relative risk 0.70, CI 0.58 to 0.84, moderate certainty. In women with recurrent infection the relative risk was 0.74, CI 0.55 to 0.99, moderate certainty, which is the 26 per cent reduction quoted in the press. In children it was 0.46, CI 0.32 to 0.68 in the text and 0.53, CI 0.36 to 0.78 in the summary table. In people susceptible after a bladder intervention it was 0.47, CI 0.37 to 0.61, low certainty. It did nothing for elderly institutionalised adults, 0.93, CI 0.67 to 1.30, nothing in pregnancy, 1.06, CI 0.75 to 1.50, and nothing in neuromuscular bladder dysfunction, 0.97, CI 0.78 to 1.19. Against antibiotics it may make little or no difference, 1.03, CI 0.80 to 1.33. Gastrointestinal side effects probably do not differ meaningfully from placebo, 1.33, CI 1.00 to 1.77. No proanthocyanidin dose has been established and the reviewers note that cranberry products are not formally regulated.

So the cranberry verdict the brief asks for is: real but narrow. It prevents recurrence in women and children who keep getting infections. It does nothing in the old, in pregnancy and in a neglected bladder, which are exactly the groups a village worries about most. The plant is *Vaccinium macrocarpon*, the fruit, and in Europe *V. oxycoccos*. The 2012 Jepson review that found no benefit and the 2023 update that found one differ mainly in the number of trials and the restriction to culture-verified outcomes, and a reader should know that the earlier Cochrane verdict was negative.

D-mannose. Kranjcec and colleagues randomised 308 women after treatment of acute cystitis to 2 g of D-mannose powder in 200 mL of water daily, nitrofurantoin 50 mg daily, or nothing, 103, 103 and 102 respectively, for six months. Recurrence occurred in 14.6 per cent on D-mannose, 20.4 per cent on nitrofurantoin and 60.8 per cent on

nothing, relative risks 0.239 and 0.335, p<0.0001. The trial was open and the control arm received nothing at all, so it cannot separate the sugar from the ritual of taking it.

Hayward and colleagues' MERIT trial, published in JAMA Internal Medicine on 8 April 2024, was placebo-controlled and double blind, across 99 UK primary-care centres, with 2 g of D-mannose powder daily against matched placebo for six months in women with recurrent infection. Of the D-mannose group 51.0 per cent contacted care about a further urinary infection against 55.7 per cent on placebo, relative risk 0.92, CI 0.80 to 1.05, p=0.22. The authors concluded it should not be recommended. The brief's "Kranjcec 2014 against the 2024 randomised trial" is exactly right, and the 2024 trial wins. The difference between a 76 per cent reduction and an 8 per cent non-significant one is the placebo arm.

Bearberry. *Arctostaphylos uva-ursi* (L.) Spreng., the leaf, is the one urinary herb with a regulatory monograph. The European Medicines Agency's Committee on Herbal Medicinal Products specifies 1.5 to 4 g of the comminuted leaf in 150 mL of boiling water as an infusion, or the same amount in cold water as a macerate used immediately, two to four times daily, to a maximum daily dose of 8 g. Its indication is traditional use for symptoms of mild recurrent lower urinary tract infection in women, after serious conditions have been excluded. The duration limit is explicit: **not to be used for more than one week**, and a practitioner should be consulted if symptoms persist beyond four days or worsen. It is not recommended under 18 or in men, it is contraindicated in hypersensitivity and in kidney disorders, it should be avoided in pregnancy and is not recommended in lactation, it may turn the urine greenish-brown, and the reported adverse effects are nausea, vomiting and stomach ache.

The mechanism is arbutin, hydrolysed to hydroquinone and excreted in urine. An in vitro study of urine from volunteers after 800 mg of arbutin found antibacterial activity only when the urine was adjusted to pH 8, not at pH 6, which is the fatal detail: urine is normally acid, and the traditional instruction in some herbals to add bicarbonate is the only way the proposed mechanism works. On safety, EMA notes that genotoxicity tests of uva-ursi extracts are inadequate, that carcinogenicity studies have been negative, that arbutin showed maternal and fetal toxicity in rats at 400 mg/kg/day subcutaneously with no effect at 100, and that hydroquinone itself has shown some evidence of genotoxicity and carcinogenicity, while judging the risk from short-term use minimal. The one-week limit is not caution for its own sake. It is the whole basis on which the preparation is considered acceptable.

The oft-quoted trial in which no woman taking bearberry had cystitis in the following year against 23 per cent on placebo could not be traced to a readable primary source and should not be used [VERIFY].

Water, and methenamine. Hooton and colleagues randomised 140 premenopausal women with at least three cystitis episodes in the prior year who drank less than 1.5 L of fluid a day to an extra 1.5 L of water daily or no change, in Sofia. Intake rose by 1.7 L. Over twelve months the water group had a mean of 1.7 cystitis episodes against 3.2 in the control group, a difference of 1.5, CI 1.2 to 1.8, p<0.001, roughly a halving. The trial was open label, the outcome self-reported, and it was funded by Danone Research, which sells the water. The accompanying editorial observed that any safe water would presumably do. This is the cheapest preventive in the whole report and the one a village can supply without limit, provided the water is clean, for which see the hydration and water reports in this library.

The ALTAR trial randomised 240 women at eight UK sites to methenamine hippurate or daily low-dose antibiotic prophylaxis for twelve months. Episodes per person-year were 1.38, CI 1.05 to 1.72, with methenamine and 0.89, CI 0.65 to 1.12, with antibiotics, within the pre-set non-inferiority margin of one episode per person-year. Only 52 per cent of treated episodes were culture confirmed. Methenamine is a salvageable, non-antibiotic urinary antiseptic that works by releasing formaldehyde in acid urine, and if a chest contains it, it is the right drug for a woman with four infections a year, and it spares the antibiotics.

Chinese and Ayurvedic practice. Flower and colleagues' Cochrane review of Chinese herbal medicine for recurrent urinary infection in women found seven studies and 542 women. Against antibiotics, effectiveness was relative risk 1.24, CI 1.13 to 1.37, from three studies and 282 participants, and recurrence at a mean of five months was relative risk 0.28, CI 0.09 to 0.82, with 550 per 1,000 recurring on antibiotics against 154 per 1,000 on the herbs. Every

one of those estimates was graded very low quality, most participants were post-menopausal, and only two studies even stated that adverse events were to be collected, neither of which reported any. That is a promising signal buried in the kind of evidence that regularly evaporates. For the Ayurvedic diuretics the position is worse. *Tribulus terrestris* showed a dose-dependent diuretic effect in rats comparable to furosemide at the highest dose but no detectable activity against *Escherichia coli*, the organism that causes most urinary infection. *Boerhavia diffusa*, punarnava, has an animal pyelonephritis study and in vitro antibacterial work but no retrievable controlled human trial. No clinical trial could be found for *Crataeva nurvala*, *Plantago* species or *Equisetum* in urinary infection.

Ethnobotany for the sexual infections. A PRISMA-guided review of South African plants used against gonorrhoea catalogued 28 species in 21 families, of which only 44 per cent have ever been tested against *Neisseria gonorrhoeae*. *Gunnera perpensa*, the rhizome, was the lead species in one screen with a minimum inhibitory concentration of 48.7 micrograms per millilitre. No in vitro work against *Treponema pallidum* could be found at all, which is unsurprising since the organism cannot be routinely cultured. The honest statement for the book is that no plant in the record has ever been shown to cure syphilis or gonorrhoea in a person, that the long history of guaiacum shows how convincingly a useless plant can seem to work against a disease whose signs remit by themselves, and that the convergent-use argument that carries weight elsewhere in this library carries almost none here, because the diseases themselves fluctuate.

8. Barriers, partners and the problem of 300 people

Condoms. Weller and Davis-Beaty's Cochrane review of serodiscordant heterosexual couples found that consistent condom use reduced HIV incidence by about 80 per cent. The reviewers stress that this is effectiveness, not efficacy, because the studies did not measure correctness of use, and that "consistent" meant a condom for every act of penetrative vaginal intercourse. Warner and colleagues' review of 45 studies found most reported reduced risk of gonorrhoea and chlamydia in both sexes, with methodological limits that probably understate the protection. A WHO Bulletin review notes that the 2000 NIH review found the evidence sufficient for HIV and for male gonorrhoea and insufficient for the rest, and that later prospective studies added statistically significant protection against chlamydia, gonorrhoea, HSV-2 and syphilis. The widely quoted figures of about 13 per cent annual pregnancy failure under typical use and about 2 per cent under perfect use could not be traced to an authoritative source in this search and should be checked [VERIFY].

After the Fall, latex condoms are a wasting asset. They degrade with heat, ozone and oil, and nobody is making more. A reasonable plan is to treat the surviving stock as a strategic reserve for the highest-transmission settings rather than as a general supply, and to accept that behaviour, partner notification and treatment will carry most of the prevention burden within a decade.

Partner notification. The Cochrane review by Ferreira, Low and colleagues covered 26 trials and 17,578 participants. Expedited partner therapy, meaning giving the index patient the drugs to pass on, reduced reinfection of the index patient against simple referral, relative risk 0.71, CI 0.56 to 0.89, moderate quality from six trials, but the effect attenuated to 0.80, CI 0.62 to 1.04, when trials with more than 20 per cent attrition were excluded, and to 0.90, CI 0.60 to 1.35, in chlamydia-only trials. Against enhanced patient referral it made no clear difference, 0.96, CI 0.60 to 1.53. It did increase the number of partners treated per index case. The reviewers concluded that no single optimal strategy has been identified for any infection.

The stigma problem. In a population of 300 nobody is anonymous. The clinical consequence is measurable harm: if people will not present, the syndromic flowchart never runs, the pregnant woman is never screened and the infant is born blind. The three mitigations that have the best support from the general literature, rather than from any trial in this setting, are these. Treat partners without requiring a confession, which is what expedited partner therapy is and what both MSF and WHO instruct. Fold the one screening that matters, syphilis in pregnancy, into routine antenatal care so that it is not a test for a shameful disease but a test every pregnant woman has. And keep the healer's record separate and closed, because a register that names who had what, in a village of 300, is an instrument of harm.

Doxycycline after exposure. Luetkemeyer and colleagues found that doxycycline 200 mg taken within 72 hours of condomless sex cut bacterial sexually transmitted infection sharply: in the HIV pre-exposure prophylaxis cohort the incidence was 10.7 per cent against 31.9 per cent, relative risk 0.34, CI 0.24 to 0.46, with chlamydia 0.12, syphilis 0.13 and gonorrhoea 0.45. A 2025 meta-analysis of seven trials and 2,091 participants gave a pooled relative risk of 0.43, with 0.28 for chlamydia, 0.28 for syphilis and 0.56 for gonorrhoea. Tetracycline-resistant gonorrhoea was found in 5 of 13 doxycycline-arm isolates against 2 of 16 in standard care, on very small numbers. This is included for completeness and is recommended against after the Fall. It consumes the one stable, broad, oral antibiotic the village most needs for pneumonia, rickettsial fever and leptospirosis (THRIVING library, IN-05), and it breeds resistance in exactly the organism least able to afford it.

Evidence grades

Remedy or practice	What tradition says	What the record shows	What science infers	Grade
Benzathine penicillin 2.4 MU single dose, early syphilis	n/a	76 vs 70 per cent serological response vs 3 doses, no relapses, n=249	Cures early syphilis	A
Benzathine penicillin in pregnancy	n/a	97 per cent fewer congenital cases, 82 per cent fewer stillbirths (Blencowe 2011)	Prevents congenital syphilis	B
Ceftriaxone 500 mg IM, gonorrhoea	n/a	Only remaining reliably active single dose (CDC 2020)	Cures	A
Doxycycline 100 mg bd 7 days, chlamydia	n/a	Standard in WHO and MSF guidelines	Cures	A
Metronidazole 500 mg bd 7 days, trichomonas	n/a	Failure 10.9 vs 18.6 per cent against single 2 g, n=623	Better than single dose	A
Povidone-iodine 2.5 per cent eye drop at birth	n/a	Best of three arms, n=3,117, Kenya	Prevents ophthalmia	A
Silver nitrate 1 to 2 per cent at birth (Credé)	n/a	9.8 to 0.5 per cent at Leipzig, 1878 to 1880	Prevents gonococcal ophthalmia, irritant	B
Treating all genital ulcers for syphilis	n/a	Misses none, over-treats 90 to 95 per 100	Right where drug allows	B
Cervical motion tenderness as PID gate	n/a	Sensitivity 99 per cent, specificity 0	Rule-out test only	B
Doing nothing for simple cystitis for 48 to 72 h	“It passes”	52 to 54 per cent symptomatically better on placebo	Most resolve	B

Remedy or practice	What tradition says	What the record shows	What science infers	Grade
Nitrofurantoin 5 days, cystitis	n/a	NNT 1.6 at day 3, 3 at day 7 (bacteriological)	Cures, spares kidney drugs	A
Antibiotics for bacteriuria in pregnancy	n/a	Pyelonephritis 199 to 48 per 1,000, NNT 7	Prevents kidney infection	B
Extra 1.5 L water daily, recurrent cystitis	"Flush it out"	1.7 vs 3.2 episodes a year, n=140	Halves recurrence	B
Cranberry, women with recurrent UTI	"Acidifies urine"	RR 0.74 (0.55 to 0.99), 50 trials	Prevents recurrence in this group only	A
Cranberry in the old, in pregnancy, in neurogenic bladder	Same claim	RR 0.93, 1.06, 0.97, all null	No benefit	X for these groups
Methenamine hippurate prophylaxis	n/a	Non-inferior to antibiotics, n=240	Spares antibiotics	A
D-mannose 2 g daily	"Blocks the bacteria"	RR 0.92 (0.80 to 1.05) vs placebo, n=598	No benefit	X
Uva-ursi leaf infusion, max one week	"The urinary herb"	No usable controlled human trial found	Arbutin active only at alkaline urine pH	D
Chinese herbal medicine, recurrent UTI	Varied	RR 0.28 for recurrence, all very low quality	Unresolved	D
Tribulus, Boerhavia and other Ayurvedic diuretics	"Clears the water"	Animal and in vitro only	Diuretic yes, antibacterial not shown	D
Guaiacum for syphilis	"Holy wood cures it"	No evidence of cure in four centuries	Nothing	X
Mercury for syphilis	"Salivation is the cure"	Tooth loss, ulceration, neuropathy, deaths	Benefit unproven, harm certain at the doses used	X
Malaria fever therapy for general paresis	n/a	27.5 per cent full remission, 2 to 15 per cent died	Historic only	D
Condoms, consistent use	n/a	80 per cent fewer HIV seroconversions	Reduces most STIs	A
Expedited partner therapy	n/a	RR 0.71, attenuating to 0.80 on sensitivity analysis	Modest, worth doing	B

Means ledger

Rung	Syphilis and gonorrhoea	Genital syndromes	Urinary infection	Newborn eyes
Hands and knowledge alone	Recognise the painless ulcer, the rash, the discharge. Abstain while sore. Tell the partner. No cure.	Examine. Feel for cervical motion tenderness. Count the days of fever.	Rest, warmth, more water. About half recover in 3 days.	Wipe the eyes at birth with a clean cloth. Nothing else.
At the hearth	Salt-water sitz baths for comfort. Boiled cloth. Honey on a broken ulcer for cleanliness, not cure.	Pain relief, fluids, a record of who was seen when.	2 to 3 L of clean water a day. Cranberries in season for the woman who keeps getting it. Uva-ursi tea for no more than one week.	Clean water rinse. Watch for pus and swelling from day 1 to day 14.
Garden and still	Nothing that cures either disease.	Alcohol for instrument cleaning. Beeswax ointment for excoriation.	Methenamine if salvaged. Scales to weigh a child.	Povidone-iodine if any salvaged iodine stock survives, diluted on a scale.
Village dispensary (300)	**The rung that changes everything.** Benzathine penicillin 2.4 MU IM for every ulcer and every pregnant woman. Ceftriaxone 500 mg IM for discharge. Doxycycline 7 days. Adrenaline at hand.	Run the four WHO flowcharts. Treat partners without interrogation. Register pregnancies.	Dipsticks while they last. Nitrofurantoin for cystitis, ciprofloxacin or a ceftriaxone dose plus oral for the kidney.	2.5 per cent povidone-iodine, one drop each eye within an hour of birth. Ceftriaxone for established disease.
District infirmary (3,000)	Microscope for Gram stain of urethral pus. RPR cards if any survive. Ten beds for severe PID. Procaine or benzathine for late syphilis, 3 weeks.	Admit the uncertain abdomen, the pelvic abscess, the pregnant woman. Surgery for ruptured ectopic.	IV ampicillin and gentamicin for the septic kidney. Urine culture on a lab bench.	Keep the iodine store. Train every birth attendant in the district.
Hospital before the Fall	NAAT, RPR and treponemal tests, darkfield, lumbar puncture, resistance surveillance, partner services	Point-of-care tests of 80 to 95 per cent sensitivity, laparoscopy	Culture and sensitivities, imaging, dialysis	Universal prophylaxis, antenatal screening of every pregnancy

What each rung changes: the hearth changes comfort and the cystitis half-cure. The dispensary changes congenital syphilis from 15 per cent of affected pregnancies to under one, blindness in the newborn from about 1 in 300 births to near zero, and gonococcal infertility from a sentence to an episode. The district changes the septic kidney and the ruptured ectopic from death to survival. Nothing on any rung touches herpes or late syphilis already established.

Harm test

Benzathine penicillin. The fatal risk is anaphylaxis, pooled at 54 cases in 2,028,982 people given injected benzathine penicillin, 0.002 per cent, with four deaths, about 1 in 500,000, and none among 1,244 pregnant women (Galvão et al 2013, via THRIVING library, IN-05). Never give it to someone with known penicillin anaphylaxis. **Never give benzathine or procaine penicillin into a vein**, which has caused cardiac arrest. Give it deep intramuscularly, 1.2 MU into each buttock for an adult. Keep adrenaline drawn and watch for 30 minutes. Procaine penicillin can cause the Hoigné reaction, 15 to 30 minutes of agitation, hallucination and fear of death, which settles on its own and is not allergy.

The Jarisch-Herxheimer reaction. Up to 40 per cent of people treated for primary or secondary syphilis get fever, chills and worsening rash hours after the first dose. In pregnancy the figures are 45 per cent of 33 women in a prospective study with 24-hour monitoring and 40 per cent of 50 women at 24 weeks or more in a retrospective review. Fever occurred in 73 per cent, uterine contractions in 67 per cent and decreased fetal movement in 67 per cent, with onset 2 to 8 hours, peak at 6 to 12 and settling by 16 to 24 hours. Transient late decelerations were seen in three of eleven monitored fetuses. Preterm labour, preterm delivery and fetal death have been reported, mainly where the fetus was already severely affected. What to do: expect it, warn the woman, give paracetamol 1 g six-hourly, keep her where she can be watched for 24 hours, and **do not let the reaction stop the treatment**, because the untreated alternative is worse.

Ceftriaxone. Never in a jaundiced newborn and never with calcium-containing fluids, which has caused fatal precipitation. The lidocaine-containing solvent for intramuscular use must never be given intravenously (THRIVING library, IN-05).

Doxycycline. Oesophageal ulceration if swallowed dry or lying down, so take it with a full cup of water sitting up. Photosensitivity. Avoid in the second and third trimesters except single doses, and limit courses under age eight to 21 days. No tooth staining was found in 58 children given doxycycline before age eight (Todd et al 2015, via IN-05).

Metronidazole. Nausea and a metallic taste. The disulfiram-like alcohol reaction is poorly evidenced but avoiding alcohol costs nothing. A 2 g single dose is the one most likely to make someone vomit it back.

Nitrofurantoin. Contraindicated in glucose-6-phosphate dehydrogenase deficiency, where it causes haemolysis. Contraindicated on label below a creatinine clearance of 60 mL/min, though short courses appear tolerated at 30 and above. Never in the last month of pregnancy and never in an infant under three months, because of neonatal haemolysis. Chronic pulmonary and hepatic reactions occur with use beyond six months, which is a prophylaxis problem, not a five-day problem. It is useless for pyelonephritis because it does not reach tissue levels, and giving it for a febrile kidney is a lethal error of substitution.

Uva-ursi. The harm is cumulative hydroquinone exposure. The regulatory limit is one week. It is not for men, not for anyone under 18, not in pregnancy or lactation and not in kidney disorder. Because the people most likely to reach for it are the people with recurrent symptoms, the realistic failure mode is weeks of repeated courses. The sign that it is going wrong is persistent symptoms beyond four days, which is also the sign of pyelonephritis or of something that is not infection at all. Stop it and look harder.

Misidentification. *Arctostaphylos uva-ursi* is a prostrate evergreen shrub with small leathery obovate leaves, white to pink urn-shaped flowers and red berries. Its dangerous confusions in the field are with *Vaccinium vitis-idaea*, lingonberry, which has notched leaf tips and dark dotted undersides and is harmless but inactive, and with *Arctostaphylos*

alpina, which is deciduous with toothed leaves and black fruit. The genuinely lethal confusion in any hedgerow gathering is with the glossy-leaved evergreens that are not in this genus at all, above all *Taxus baccata*, yew, whose foliage kills. The rule for the book is that nobody gathers a leaf for internal use on the strength of a description, only on the strength of having been shown the living plant by someone who knows it.

Silver nitrate and povidone-iodine in the eye. Silver nitrate causes a chemical conjunctivitis in a substantial minority and was reduced from 2 to 1 per cent for that reason. Povidone-iodine is less toxic but must be the correct dilution, 2.5 per cent, and must not be the surgical scrub formulation containing detergent, which will damage the cornea. If no scale and no known concentration exist, do not improvise a strength into a newborn's eye.

Historical harm. Mercury maimed and killed for four hundred years because a visible physiological effect was read as a therapeutic one. Salvarsan killed about one in 2,000 to one in 7,000 of those injected, partly from mishandling of a drug that demanded clean water and careful dissolution. Malaria therapy killed between 2 and 15 per cent of those treated. The pattern in all three is the same: a desperate disease licensed a dangerous treatment, and the danger was accepted without being measured.

Red flags

These are the signs that mean death or permanent disability without something the village may not have. Each is paired with what to do anyway.

- **Fever with unilateral flank pain, especially in pregnancy.** This is pyelonephritis. Bacteraemic cases carry 10 to 20 per cent mortality. If an injectable is held, give it. If not, give the best oral drug, force fluids, and carry her to the district. Honest comfort if nothing is held: fluids, warmth, paracetamol, and someone with her.
- **Lower abdominal pain in a woman of childbearing age with a missed period, faintness or shoulder-tip pain.** This is ectopic pregnancy until proved otherwise, and it is the error the brief names. It is not PID and antibiotics will not touch it. A ruptured ectopic bleeds to death in hours. Lie her flat, raise the legs, carry her to the district infirmary at once. WHO lists inability to exclude ectopic pregnancy as a reason to hospitalise.
- **A newborn with red, swollen lids and pus in the first five days.** Gonococcal ophthalmia perforates the eye within days. Irrigate with clean saline every hour, give ceftriaxone if held, and send. Without ceftriaxone the eye will usually be lost, and saying so is better than pretending.
- **A pregnant woman with a genital ulcer, a rash on palms and soles, or a previous stillbirth.** Untreated syphilis in pregnancy ends about two pregnancies in three badly. One injection prevents nineteen of twenty congenital cases. If no penicillin exists, erythromycin 500 mg four times daily for 14 days is the fallback, and the newborn must then be treated too because erythromycin does not fully cross the placenta.
- **Lower abdominal pain with high fever, vomiting and a tender mass.** Pelvic abscess. Needs drainage and intravenous antibiotics. Carry her. Oral metronidazole and doxycycline are worth starting on the road.
- **Painless genital ulcer that healed, followed years later by chest pain, a tearing pain through to the back, or a collapsing pulse.** Syphilitic aortitis or aneurysm. Nothing can be done at any rung below a cardiac surgeon. Give opiate if held, keep her still and propped up, and tell the family what is happening.
- **Unsteady gait, lightning pains in the legs, urinary retention, a change of personality in a middle-aged person with old syphilis.** Tabes dorsalis or general paresis. Penicillin will not reverse established damage. Nurse, prevent falls, catheterise intermittently for retention, and do not let a family be told it is madness or drink.
- **A man or woman with urinary retention and a distended bladder.** Catheterise, by intermittent clean technique if possible. Failure to pass urine kills kidneys in days. This is one of the few genuinely reversible emergencies a village can fix with a tube and courage.

The case against

Against treating syndromes as diagnoses. This is WHO's own warning, written into the 2021 guidelines, and the strongest single criticism of the approach this report recommends. Syndromic management for lower abdominal pain finds 30 per cent of gonococcal or chlamydial infection and wrongly flags 27 per cent of the uninfected. Clinical diagnosis of a genital ulcer is wrong more than half the time. A healer who writes "gonorrhoea" in a register on the basis of a discharge has recorded a guess. The consequence is not only wasted drug but a false epidemiology that will steer the next decade's decisions. The mitigation is to record syndromes, not organisms, and to say so out loud.

Against treating everyone. The counter-case to the "treat all ulcers for syphilis" rule is that 90 to 95 per 100 of those treated do not have syphilis, that each dose is an injection with a one in 500,000 chance of killing, and that an irreplaceable stock of benzathine penicillin is being spent at twenty doses per true case. In a world with no resupply this is a real argument, and the honest answer is that it depends on how much penicillin there is and how much syphilis. The decision belongs to the district, not to the book.

Against the romance of the herbal. Guaiacum is the case that should settle it. For a century the most respected physicians in Europe believed a wood decoction cured syphilis, because the chancre heals by itself and the rash fades by itself and a third of patients recover entirely without anything. No herb in the record cures syphilis, gonorrhoea or chlamydia. D-mannose is the modern instance: an open trial showed a 76 per cent reduction, a placebo-controlled trial showed 8 per cent and no significance, and the 2024 authors concluded it should not be recommended. Cranberry survives that test only because it was tested fifty times and only in the groups where it was tested does it hold.

Against the romance of the hospital. The counter-weight is Tuskegee, and the fact that the single most valuable intervention in this entire report is an injection that costs pennies and was available from 1943, yet remains undelivered to millions of pregnant women today for reasons of organisation rather than science. The gap between what the record knows and what reaches a person is where almost all preventable harm lives.

Against the cranberry evidence. The named criticism is that the field has been funded largely by cranberry producers, that Jepson's 2012 Cochrane review concluded cranberry juice could not be recommended, and that the 2023 reversal rests partly on a narrowed outcome definition, culture-verified symptomatic infection, which excludes the symptomatic episodes most patients actually care about. The reviewers themselves note that no proanthocyanidin dose has been established and that the products are unregulated. The verdict in this report, that it works in women with recurrent infection and in children and in nobody else, should be read as provisional.

Against the Oslo numbers themselves. A Wellcome Collection catalogue critique argues that the 1955 re-study understates the morbidity of untreated syphilis because many patients were lost during the middle years of infection and the design was retrospective. If that is right, the true tertiary fraction is higher than a third, not lower.

10-line summary

1. Untreated syphilis clears in about 28 per cent, stays harmlessly latent in about a third, and produces late disease in about a third, with neurosyphilis in roughly 6.5 and cardiovascular disease in roughly 10.4 per cent of all infected.
2. One intramuscular dose of benzathine penicillin, 2.4 million units, cures early syphilis as well as three doses do.
3. Treating syphilis in pregnancy prevents about 97 per cent of congenital syphilis and about 82 per cent of syphilis stillbirths.
4. Untreated maternal syphilis ruins about two pregnancies in three.
5. Laparoscopically confirmed pelvic inflammatory disease leaves 10.8 per cent of women with proven tubal infertility and raises first-pregnancy ectopic risk from 1.4 to 9.1 per cent.
6. Gonorrhoea has defeated sulfonamides, penicillin, tetracycline, fluoroquinolones and cefixime in turn, leaving ceftriaxone 500 mg intramuscularly as the only reliable single dose.

7. Credé's silver nitrate cut ophthalmia neonatorum at Leipzig from about 9.8 to 0.5 per cent, and 2.5 per cent povidone-iodine beat both silver nitrate and erythromycin in 3,117 Kenyan infants.
8. Clinical diagnosis of genital ulcers is wrong in over half of cases, and syndromic management of pelvic pain finds only 30 per cent of infections, so treating the syndrome is a bet, not a diagnosis.
9. About half of women with simple cystitis are symptomatically better in three days on placebo, and about 41 per cent are bacteriologically cured in a week on nothing.
10. Cranberry prevents recurrence in women and children who get repeated infections and does nothing in the old or in pregnancy, D-mannose failed against placebo, and uva-ursi must never be taken for more than one week.

Open questions

- What is the true untreated tertiary fraction once loss to follow-up in the Oslo cohort is accounted for?
- Does gonococcal susceptibility to penicillin, tetracycline and ciprofloxacin return in a population cut off from those drugs, and over what timescale? Nothing in the record answers this, and the answer would change the whole chest calculation.
- What are the per-arm placebo percentages in the Falagas meta-analysis, which this agent could not retrieve?
- Is the 2023 cranberry reversal robust to the choice of outcome definition, and does it survive exclusion of industry-funded trials?
- Can a village make a usable eye antiseptic once salvaged povidone-iodine runs out? This report found no answer and does not recommend improvising one.
- What dose of erythromycin, if any, is a usable substitute for benzathine penicillin in a pregnant woman with no penicillin, given that it does not fully cross the placenta?
- Does treating all genital ulcers for syphilis remain net-beneficial at low syphilis prevalence and finite drug stock, and where is the threshold?
- What is the real breakage and slippage rate of latex condoms stored for a decade without climate control?

Sources to read in full

1. **WHO (2021), Guidelines for the management of symptomatic sexually transmitted infections.** The whole basis of the syndromic chapters. Tables 3, 5, 6, 7 and 8 give every dose, and the evidence summaries give the sensitivity and specificity figures that make the flowcharts honest.
2. **Gjestland T (1955), The Oslo study of untreated syphilis.** The natural history of untreated syphilis exists in one document and this is it.
3. **Weström L et al (1992), Pelvic inflammatory disease and fertility.** 1,844 laparoscopically verified cases against 657 controls. The cost of untreated upper genital infection, quantified.
4. **Isenberg SJ, Apt L, Wood M (1995), N Engl J Med 332:562-566.** The povidone-iodine trial, 3,117 infants.
5. **Blencowe H et al (2011), BMC Public Health.** The effect of antenatal syphilis screening and penicillin on congenital syphilis, stillbirth and neonatal death.
6. **Williams G et al (2023), Cochrane CD001321, Cranberries for preventing urinary tract infections.** Fifty trials, and the subgroup table that decides who should bother.
7. **MSF, Clinical Guidelines, Chapter 9, Genito-urinary diseases.** The most usable field dosing in existence for cystitis, pyelonephritis, urethral discharge, genital ulcers and upper genital tract infection.
8. **Christiaens TCM et al (2002), Br J Gen Pract 52:729-734.** The placebo arm that settles the cystitis self-cure question.
9. **Hayward G et al (2024), JAMA Intern Med.** The MERIT trial, and the clearest modern lesson in why an open trial is not evidence.
10. **Smaill FM, Vazquez JC (2019), Cochrane CD000490.** Asymptomatic bacteriuria in pregnancy, with the

numbers needed to treat.

At the bedside after the Fall

A household. The minimum viable version is recognition and honesty. Learn the four syndromes: discharge, ulcer, lower abdominal pain with fever, and burning on passing water. Learn that a painless ulcer that heals by itself is the dangerous one. For burning water with no fever and no back pain, give 2 to 3 litres of clean water a day, warmth, and three days. For anything with fever, flank pain, a swollen tender belly or a newborn with pus in the eyes, go for help. **What it needs to start:** clean water, a clean cloth, a way to boil, and the knowledge of what the four syndromes look like. **The first failure to expect:** someone will treat a febrile kidney as a bladder and wait too long, or a woman with an ectopic pregnancy will be given antibiotics for pelvic infection and die of bleeding.

A village of 300. The minimum viable version is one trained lay healer, four laminated flowcharts, and a locked box holding benzathine penicillin, ceftriaxone, doxycycline, metronidazole, nitrofurantoin and dilute povidone-iodine, with adrenaline beside it. Every pregnancy is registered. Every newborn gets a drop in each eye within the hour. Every genital ulcer gets benzathine penicillin while stock allows. Every partner is treated without being asked to explain. **What it needs to start:** the drugs, a scale, a 5 mL syringe and 21 gauge needles for deep intramuscular injection, a way to sterilise them, a kettle, a written register kept closed, and a healer trained to feel for cervical motion tenderness and to recognise a pregnant abdomen. **The first failure to expect:** stigma. People will not come, or will come alone and refuse to name a partner, and the chain will not break. The second failure is running out of benzathine penicillin and having to choose between pregnant women and everyone else, which is a decision that should be made in advance and in public.

A district of 3,000. The minimum viable version adds ten beds, a sterile room, someone who can open an abdomen for a ruptured ectopic, intravenous ampicillin and gentamicin for the septic kidney, and a microscope for Gram-stained urethral pus, which turns a guess into an answer for the commonest male syndrome. It also adds the only sustainable thing: training. One birth attendant in every hamlet who knows the eye drop and the antenatal injection prevents more disability than the ten beds do. **What it needs to start:** the beds, a surgeon or someone taught one operation, a cold store that never fails, a microscope and a slide stain, and a district register of drug stock reviewed monthly. **The first failure to expect:** the ceftriaxone will be spent on things other than gonorrhoea, meningitis and the septic newborn, and will be gone when it is needed.

Protocols

Protocol 1. Newborn eye prophylaxis, every birth, no exceptions 1. Within one hour of birth, before the infant is bathed. 2. Wipe each closed eyelid with a clean cloth and clean water, outer corner to inner. 3. Part the lids gently. Instil **one drop of 2.5 per cent povidone-iodine** into each conjunctival sac. Tolerance: 2 to 3 per cent. Never the surgical scrub formulation with detergent. 4. If only silver nitrate exists, use **one drop of 1 per cent** in each eye. Expect redness for 24 to 48 hours. 5. Do not rinse the eye out afterwards. 6. Record it. Tell the mother to come back at once if the lids swell or pus appears in the first 14 days.

Protocol 2. The newborn with red lids and pus, day 0 to day 14 1. Treat as gonococcal until the fifth day has passed. After day 5, chlamydia becomes likelier but treat both. 2. Irrigate both eyes with clean saline, 1 level teaspoon of salt in 1 litre of boiled cooled water, every hour while discharge is heavy, then four-hourly. 3. Give **ceftriaxone 50 mg/kg as a single intramuscular dose, maximum 125 mg**. Never in a jaundiced newborn. Never with calcium fluids. Never the lidocaine solvent intravenously. 4. Give the mother and her partner treatment for gonorrhoea and chlamydia the same day. 5. Review at 24 and 48 hours. Carry to the district if not improving, or if the cornea looks grey or hazy.

Protocol 3. Genital ulcer, any adult 1. Look. Painless, single, firm-edged suggests syphilis. Painful, multiple, ragged suggests chancroid. Grouped blisters or shallow erosions, especially recurring, suggest herpes. **You will be**

wrong more than half the time, so treat by rule, not by appearance. 2. Give **benzathine penicillin 2.4 million units deep intramuscularly, 1.2 MU into each buttock**, in a single sitting. Substitute doxycycline 100 mg twice daily for 14 days if penicillin is refused or unavailable, never in pregnancy. 3. If chancroid is common locally, add **azithromycin 1 g orally once** or erythromycin 500 mg four times daily for 7 days. 4. If the lesion is blistering or recurrent, add aciclovir 400 mg three times daily, 10 days for a first attack, 5 days for a recurrence started within 24 hours. 5. Warn about the Herxheimer reaction. Give paracetamol 1 g six-hourly. Watch a pregnant woman for 24 hours. 6. Treat the partner the same way. Advise no sex until the ulcer has healed and 7 days have passed. 7. Review at 7 days. If not healing, refer.

Protocol 4. Urethral discharge in a man 1. Treat for both gonorrhoea and chlamydia. Do not try to tell them apart without a microscope. 2. **Ceftriaxone 500 mg intramuscularly as a single dose.** If none, cefixime 400 mg orally once. 3. Plus **doxycycline 100 mg twice daily for 7 days**, or azithromycin 1 g orally once. 4. Treat every partner with the same regimen, symptoms or not. 5. No sex for 7 days after both have been treated. 6. If discharge persists at 7 days and the regimen was correct, give metronidazole or tinidazole 2 g orally once for trichomoniasis, and consider reinfection.

Protocol 5. Lower abdominal pain in a woman 1. **First, exclude the surgical emergency.** Ask about the last menstrual period. If a period is missed or late, if she is faint, pale or has shoulder-tip pain, or if the belly is rigid, this may be a ruptured ectopic pregnancy. Lie her flat, raise the legs, and carry her to the district. Do not give antibiotics and wait. 2. If no emergency, examine. Feel for tenderness when the cervix is moved. If there is none, pelvic infection is very unlikely. 3. If cervical motion tenderness is present, treat for pelvic inflammatory disease: **ceftriaxone 500 mg intramuscularly once, plus doxycycline 100 mg twice daily for 14 days, plus metronidazole 500 mg twice daily for 14 days.** In pregnancy or lactation, substitute erythromycin 500 mg four times daily for 14 days for the doxycycline, and refer. 4. Remove any intrauterine device and offer another method. 5. Treat the partner for gonorrhoea and chlamydia. 6. Review at 48 to 72 hours. Refer if fever persists, if vomiting prevents oral drugs, if a mass is felt, or if she is pregnant.

Protocol 6. Burning on passing water, woman, no fever, no flank pain 1. Confirm there is no fever above 38 degrees and no tenderness over either kidney. If either is present, go to Protocol 7. 2. If a dipstick exists and both nitrites and leukocytes are negative, this is not a urinary infection. Look elsewhere. 3. **Hold the antibiotic.** Give 2 to 3 litres of clean water a day, warmth over the lower belly, and paracetamol. Expect about half to be substantially better by day 3. 4. Review at 48 to 72 hours. If no better, give **nitrofurantoin 100 mg three times daily for 5 days** (MSF) or 100 mg twice daily for 5 days (guideline dose). Never in the last month of pregnancy, never under 3 months of age, never in known G6PD deficiency. 5. If pregnant, do not wait. Treat at the first visit: nitrofurantoin 100 mg three times daily for 7 days, stopping at 36 weeks, or cefixime 200 mg twice daily for 5 days. 6. For more than three or four episodes a year: an extra 1.5 litres of water daily, cranberries in season, methenamine hippurate if any exists. Uva-ursi infusion, 1.5 to 4 g of leaf in 150 mL of boiling water, two to four times daily, maximum 8 g a day, **for no more than seven days, once**, and never in a man, a child, a pregnant woman or anyone with kidney disease.

Protocol 7. Fever with flank pain, any age 1. Treat as pyelonephritis. This can kill. 2. Adult woman, not pregnant, able to drink, no vomiting: single dose of **ceftriaxone 1 g intramuscularly** or gentamicin 5 mg/kg intramuscularly, then **ciprofloxacin 500 mg twice daily for 7 days**. Alternatives: co-amoxiclav or cefixime 200 mg twice daily for 10 to 14 days. 3. Child from 1 month: **ceftriaxone 50 mg/kg once daily for at least 3 days**, then oral co-amoxiclav to complete 10 days. 4. **Carry to the district** if the patient is a child, a pregnant woman, a man, anyone vomiting, anyone with shock, or anyone not improving at 24 hours. 5. Keep the adult drinking about 1.5 litres a day. Do not give non-steroidal anti-inflammatories. 6. Suspect it in any infant with unexplained fever, and in any neonate who is cold, grey, floppy or feeding poorly, even without fever.

Protocol 8. The pregnant woman, once, at the first visit 1. Ask about genital ulcers, rashes, previous stillbirths and previous infants who died early. 2. If any of those, or if a test exists and is reactive, give **benzathine penicillin 2.4 million units deep intramuscularly as a single dose**. Substitute erythromycin 500 mg four times daily for

14 days only if there is no penicillin, and plan to treat the newborn. 3. Watch for 30 minutes for anaphylaxis, with adrenaline at hand. Then watch for 24 hours for the Herxheimer reaction. 4. Treat her partner with the same single dose. 5. Record the pregnancy, the treatment and the date. Ensure the birth attendant knows to give the eye drop.

Numbers to carry

1. **2.4 million units.** One intramuscular dose of benzathine penicillin, split 1.2 million units into each buttock, cures early syphilis.
2. **97 and 82.** Per cent reduction in congenital syphilis and in syphilis stillbirth from treating a pregnant woman with that one dose.
3. **500 mg.** Ceftriaxone intramuscularly, single dose, for gonorrhoea. It is the last drug that reliably works.
4. **1 in 3.** The share of untreated syphilitics who develop late disease, split roughly half gummatous, a third cardiovascular, a fifth neurological.
5. **30 to 50 per cent.** The chance that an infant born to a mother with gonorrhoea gets eye infection without prophylaxis, and the reason for one drop in each eye at every birth.
6. **0 and 99.** The specificity and sensitivity of cervical motion tenderness for pelvic infection. It rules out, it never rules in.
7. **About half.** The share of women with simple cystitis who are symptomatically better in three days with no drug at all.
8. **7.** The number of pregnant women with silent bacteriuria you must treat to prevent one kidney infection.
9. **One week.** The absolute maximum duration of any course of uva-ursi leaf, and never in men, children or pregnancy.
10. **1 in 500,000.** The risk of death from anaphylaxis after an injection of benzathine penicillin. It is the number that justifies giving it, and the number that justifies the adrenaline and the thirty minutes of watching.

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