

Developing an effective anti-tuberculosis treatment cascade: from Edinburgh to Bangladesh

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Treatment must be initiated promptly in any patient newly diagnosed with tuberculosis. The choice for initial treatment is a regimen ideally proven in a clinical trial to have high efficacy in preventing treatment failure and relapse. Over time, the choice of this initial regimen has changed with ever increasingly efficacious and effective drug combinations. The regimen is only changed when there is evidence for intolerance or bacteriological failure. Commonly, a fallback regimen in case of bacteriologic failure is again a standardized regimen promising a high probability of success. In industrialized countries and with the increasing access to rapidly available drug susceptibility test results, the fallback regimen's composition is often individualized according to drug susceptibility test results. This may not always be appropriate as there might not be a good clinical correlation with laboratory test results. If a failing standard initial regimen is followed by another standard fallback regimen, we call this sequence the "cascade of treatment regimens". In this presentation, we will delineate the history of the regimen cascade and the often encountered difficulties to find acceptance of new standards by the medical community. In doing so, we will honor individuals who pioneered new paradigms by providing pragmatic and programmatic assistance in moving the concept and implementation of the cascade of regimens forward towards full integration into national tuberculosis control programs.

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As a precedent to the first efficacious and effective treatment regimen we list here the most important clinical trials in the 6-year period up to the introduction of isoniazid, conducted by the British Medical Research Council and the United States Public Health Service. Streptomycin, the first available drug was compared with placebo. The next available was para-aminosalicylic acid, and finally isoniazid (discounting here the thiosemicarbazones which include thioacetazone). All possible combinations of these drugs were tested. Importantly, the researchers saw no advantage of the triple combination over a combination of only two drugs, but they were careful in formulating this interpretation.

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The fourth US Public Health Service trial examined the various combinations of the three drugs. The point estimate for culture conversion after 32 weeks of treatment was best for the 3-drug combination.

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This slide shows the summary of the first seven US Public Health Service trials. The fourth trial had five arms, showing that the 3-drug arm used a relatively high isoniazid dose of 10 mg/kg. As mentioned earlier, this arm did not convince the researchers to be superior to that of any other two-drug combination arms.

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We may note that no attempt was made at that time in the US to actually cure tuberculosis. The first trial to assess curability of tuberculosis had to await the seventies and the introduction of rifampicin

into chemotherapy. The objectives of anti-tuberculosis chemotherapy in the fifties were to achieve clinical and radiographic improvement, superior bacteriologic response, and most notably prevention of emergence of drug resistance which had already been recognized as a serious problem in both the US and the United Kingdom in the very first trial using streptomycin monotherapy.

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In the mid-fifties, John Crofton in Edinburgh used prolonged chemotherapy for 12 months or longer to obtain not just remission but to actually achieve definitive conversion, and to the extent followed up, without subsequent relapse, i.e. attempting curative treatment. Among patients with initially drug-susceptible tuberculosis, all 240 patients achieved conversion with negative cultures by the end of the one-year treatment with a two- or three-drug regimen.

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Several things are notable about Crofton's report. First, it was relegated to the Correspondence section of the then probably most prestigious respiratory disease journal in the world. The defensive tone chosen by Crofton about the veracity of the conversion in every single patient suggests that the reviewers or the editor had actually raised some doubts. We remember that the mindset in the US (and much of the rest of the world) was that tuberculosis was not curable. The editor of the American Review of Tuberculosis and Pulmonary Diseases was Walsh McDermott for the quarter century from 1948 when the journal's name was American Review of Tuberculosis through 1972 when it had long become the American Journal of Respiratory Diseases. McDermott was a pre-eminent expert in tuberculosis and anti-tuberculosis drugs.

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Two years after the publication of Crofton's article in his journal, McDermott published a large review on treatment of pulmonary tuberculosis. Quite apparently, he was neither convinced that bacilli can be eradicated by chemotherapy nor that there was any justification for triple-drug chemotherapy. Crofton had seemingly not convinced him with the observational study from Edinburgh.

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McDermott was influential though and his thinking quite possibly also influenced the World Health Organization's Expert Committee's eighth report published in 1964 being then a member of the organization's Expert Advisory Panel on Tuberculosis from 1958 to 1973. The Committee allowed an intensive phase of two drugs and a continuation phase with a single drug, isoniazid, for the remaining period. From today's perspective, we are aware of the high risk of acquisition of isoniazid resistance with such a regimen.

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It is also recognized that poor policy issued by an expert committee rarely leads to better practice in the field where the execution if anything may tend to be even poorer. This is evidence here in this report from India's National Tuberculosis Institute in Bangalore. The authors report that they did not shy away from giving isoniazid monotherapy for pulmonary tuberculosis from the outset. We also note that the authors include a WHO epidemiologist and a WHO medical officer, functions in the organization that surely required knowledge of the earlier Expert Committee report.

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It was only the ninth report of WHO's Expert Committee in 1974, more than 20 years after the three drugs had become available that established a regimen based on a triple-drug intensive phase followed by a two-drug continuation phase, containing isoniazid as the core drug given throughout. The regimen was difficult though to actually implement in low-income countries, both because of drug costs and the difficulty to provide daily injections. In fact, national tuberculosis control programs rarely reached the population in the entire territory of a country.

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In 1977, a pioneering plan was initiated in Arusha, Tanzania, that defined a new approach to national tuberculosis control, heralding a new era. There would be a national program to provide uniform diagnostic and treatment services throughout the entire territory of the country, serving remote rural areas by adhering to the same principle as urban areas. No patient in the entire country was to be left out from these services wherever he or she may live. The International Union Against Tuberculosis, represented by Karel Styblo, its Director of Scientific Activities, was requested by the Tanzania government to coordinate all external assistance to the national tuberculosis program.

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Tanzania mainland had 20 regions at that time and each was to have a coordinator for tuberculosis and leprosy services. In the early years, some of these regional coordinators were expatriate physicians, largely employed and seconded by various leprosy organizations that contributed to the combined tuberculosis and leprosy program. One among these regional coordinators was Armand Van Deun from the Damien Foundation Belgium. He was to witness and help building the national program following a sound scientific approach laid down in national guidelines for diagnosis, treatment, recording and reporting, and evaluation of treatment results.

The first-line standard regimen for newly diagnosed tuberculosis patients was identical to the regimen recommended in the ninth report by WHO's Expert Committee, except that PAS was replaced by thioacetazone. Because evaluation of treatment outcome results was an integral part of the program from the outset, it was soon recognized how poor the results with this 12-month regimen actually were. From 1982 onwards, a so-called short-course regimen of eight months duration was thus to be tested in a few regions. The 8-month regimen consisted of isoniazid, rifampicin, pyrazinamide, and streptomycin, all drugs given directly observed for two months to patients with new sputum smear-positive tuberculosis hospitalized for the duration of this intensive phase. Upon discharge, patients received monthly supplies for self-administered treatment with isoniazid plus thioacetazone for another six months. This regimen had a solid clinical trial basis in East Africa.

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A cohort analysis of treatment results demonstrated already in 1984 substantially superior effectiveness of the 8-month regimen compared with the standard 12-month regimen with almost 80% cured compared to just over 50% respectively.

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The International Union Against Tuberculosis and Lung Disease started to publish in what became colloquially known as the "Orange guide" the experiences made in Tanzania and the scientific conclusions drawn from these. The first edition of this guide was published in 1986 and defined for

the first time the treatment cascade as then used in Tanzania. Any previously untreated patient was placed on the above 8-month regimen. The regimen delivered a high proportion of bacteriological cure and a very small proportion of bacteriological treatment failures, defined as sputum smear positivity at five months or later. Patients failing were switched to an 8-month rifampicin-throughout regimen that used all available first-line drugs but thioacetazone.

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We digress here to the rationale for defining treatment failure by sputum smear microscopy. It roots in observations from clinical trials with serial smears and cultures throughout treatment. In regimens based on the core drug isoniazid but not using rifampicin, a positive sputum smear microscopy result reliably predicted a positive culture whenever during the treatment the specimen was obtained. Because sputum smear conversion is relatively slow but not as slow as to still not having occurred by 5 months into treatment, the decision in Tanzania was to define treatment failure as a positive sputum smear microscopy result at 5 months or later. From the US Public Health Service trial data shown here, we might infer that a positive smear at this point in treatment strongly predicted a positive culture and had thus a high probability of indicating bacteriological failure. We also note from this graph that the same inference does no more hold with rifampicin-throughout regimens, where culture conversion is faster, but also where a positive sputum smear predicts a positive culture with decreasing likelihood, the further one is into the course of treatment. On a rifampicin-throughout regimen, positive smears increasingly represent bacilli no longer able to reproduce, the longer the patient is already on treatment. Thus, in such a regimen sputum smear microscopy at 5 months or later is not a good predictor for failure attributable to multidrug-resistant tuberculosis, and an alternative method to identify MDR during such a first-line regimen is required.

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Returning to the first-line 8-month regimen using isoniazid plus thioacetazone in the continuation phase, there will be patients with initial isoniazid resistance not usually known and will actually never be known in countries with limited resources. In some of these patients, the regimen will nevertheless work because the initial bacillary load is substantially reduced during the intensive phase due to the action of the other three still effective drugs. Thus, even weak effective monotherapy with thioacetazone in the continuation phase did not result in failures in the majority of patients in the clinical trial. However, some of these patients do fail and will by definition have acquired thioacetazone resistance at the point of failure. The chosen fallback regimen in such cases consisted of an 8-month rifampicin-throughout regimen also using ethambutol throughout. Thus, at all times during treatment with this regimen, patients received effectively two drugs (rifampicin plus ethambutol) to which the organism was likely still susceptible and more effective drugs in the initial assault. This cascade from first- to second-line regimen did thus not require any drug susceptibility testing and yet each of these sequential regimens was likely to be effective in a very high proportion of patients.

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The vast experience in Tanzania and subsequently in other Union collaborative programs provided a substantial database upon which an analysis of the World Bank concluded on the cost effectiveness of the approach. Between 1991 and 1993 the Union cascade of regimens became international standard by making it into the WHO treatment guidelines.

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In the mid-1990s, the WHO asked Sir John Crofton to lead an expert group to draft recommendations on how to best treat emerging rifampicin resistance. This group included some of the then most prominent experts in mycobacteriology and clinical practice in the management of complex and drug-resistant tuberculosis.

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One of the prominent proposed possible regimens for the treatment of MDR tuberculosis was based on the core drug ofloxacin, a second-generation fluoroquinolone. Key companion drugs in the full-assault intensive phase included an aminoglycoside other than streptomycin and a thioamide. It was supplemented by the essential first-line drugs pyrazinamide and ethambutol which may not yet had been lost during the two prior treatment courses. This proposed regimen was solidly based on efficacy information about then available drugs.

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The fifth edition of the Union guide from the year 2000 in addressing MDR tuberculosis basically stated that after the cascade had run through the fallback 8-month rifampicin-throughout regimen, there wasn't any more option on offer, if that regimen ended in treatment failure. This was a rather pessimistic view with no attempt to consider the options proposed in the WHO guide on drug resistance. The "Orange guide" was to summarize the Union's experience in national programs, yet there was no experience with "failures of failures" in its collaborative programs.

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In contrast, three years earlier than the Union guide and following virtually immediately the publication of the WHO guidelines on treatment of drug resistance, Armand Van Deun initiated in the Damien Foundation projects in Bangladesh treatment for the small proportion of "failures of failures", i.e. of patients who had failed on the rifampicin-throughout second-line regimen used after failure and other retreatment cases on or after the first-line regimen. The regimen followed very closely the MDR regimen presented above in the WHO guidelines elaborated by Crofton and collaborators.

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The results in Bangladesh among the first cohort of 58 patients enrolled in the two-year period from April 1997 through March 1999, expected to have completed this standard 21-month regimen plus a 2-year follow-up period after treatment cessation, were published in 2004, with a reported proportion cured of 70%. Notably, all patients who absconded from treatment did so because of intolerance of the prescribed treatment. Bacteriologically, there were 3 failures and 1 relapse, thus the microbiological efficacy of the regimen largely delivered what had been anticipated.

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The temporal sequence and the number of patients enrolled in each of the six regimens is summarized here. Typically, each of the regimens before the last enrolled about 35 to 60 patients, sufficient for clinically judging which next adaptation was indicated. The final 9-month regimen which satisfied the criteria of effectiveness and efficacy had over 500 patients enrolled by the time of the publication of results in 2014.

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This table gives a summary overview of the six sequential MDR treatment regimens, the major problem encountered with each, and the adaptation made to address it. The first regimen of 21 months duration was clearly too long as then emerging information suggested that shortening it to 15 months retained efficacy while the shorter duration of thioamide use might reduce absconding due to adverse drug events and other factors. Critique was raised about the use of isoniazid despite laboratory-demonstrated resistance to that drug. It was thus removed in the third regimen with the seeming drawback of an increase in treatment failures yet a persisting high frequency of adverse drug events. In the fourth regimen, isoniazid was thus re-introduced and prothionamide was dropped from the continuation phase. However, treatment failures increased, presumably because of the dropping of the thioamide in the continuation phase. The fifth regimen contained clofazimine throughout rather than only in the intensive phase as in all earlier regimens, and failure frequency decreased substantially. Several bold changes were then made in the final and sixth regimen: 1) the fourth generation fluoroquinolone gatifloxacin had become generically available and had substantially more anti-tuberculosis activity on a weight basis than ofloxacin. It likely permitted reducing the total treatment duration without increasing the risk of relapse. The regimen was thus shortened to a minimum duration of 9 months; 2) isoniazid was dropped from the continuation phase, and 3) the intensive phase was strengthened by prolonging it to a minimum of 4 months, to be prolonged if sputum smears were still positive at its flexible intensive phase endpoint.

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This figure summarizes the results with the regimens. Because the sample size in each arm was relatively small, the confidence intervals were accordingly wide, yet the point estimates spoke a clear message. The poorest results among all were obtained with Regimen 3 that used prothionamide throughout but no isoniazid ever. Subsequently, the results improved with each regimen and the fifth actually gave results quite similar to the final 9-month regimen, interestingly the only two regimens containing also clofazimine throughout.

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The intensive phase of the final regimen lasts a minimum of four months. The bacteriologic response in sputum smear microscopy results defines the action taken at end of the fourth month. If sputum smear results are still positive, the intensive phase is extended until sputum smears become negative or the patient is declared to have treatment failure. The continuation phase is of a fixed five months duration.

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The cumulative proportion of patients without an adverse outcome actually completing treatment shows that 75% completed treatment within 10, 90% within 11, and 95% within about 12 months.

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Bacteriologic response was swift and culture conversion was faster than microscopic conversion. Not unexpectedly, the initial bacillary load predicted the speed at which sputum smear examinations became negative. For instance, 50% of patients with initially low-grade positivity had already converted by the end of the first month of treatment, while it was less than 10% among those with the highest initial bacillary load.

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There were 515 patients for analysis. Of these, 501 had an initial fluoroquinolone drug susceptibility test result. Among the 62 with an initially resistant strain, the gatifloxacin minimum inhibitory concentration (MIC) distribution was determined. Of the 62, 33 had low-level, and 29 high-level gatifloxacin resistance. The Kaplan-Meier probability for a successful treatment outcome is stratified here by initial fluoroquinolone susceptibility test result. Of the 439 patients with an initially fluoroquinolone-susceptible strain, there was only 1 failure and 1 relapse or 0.5% bacteriologically poor outcomes. The prolonged follow-up of two or more years in more than 80% of the patients is a strong argument that bacteriological failures during treatment had not been missed and cure was definitive beyond treatment cessation. The outcome among patients with low-level gatifloxacin resistance was very similar, suggesting that high-dose gatifloxacin successfully overcame low-level fluoroquinolone resistance, mostly classified as ofloxacin-resistant in laboratories still using the latter drug in fluoroquinolone susceptibility testing. It is less surprising that 8 of the 29 patients with initial high-level fluoroquinolone resistance failed or relapsed as one might expect if the core drug of a regimen is no more effective. Nevertheless, still a remarkable half of these patients had a successful outcome.

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It was therefore examined what the predictors for a bacteriologically adverse outcome (failure or relapse) were. While the association was strong but the confidence interval wide due to the small sample size, pyrazinamide resistance increase the risk of a non-successful outcome if there was high-level fluoroquinolone resistance. Thus, one might conclude that in the presence of initial high-level gatifloxacin resistance, pyrazinamide improved the chance for success in the absence of genotypic resistance to the latter.

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Efficacy, effectiveness, and efficiency are all key attributes that must be considered in the choice of a treatment regimen for MDR. It is a prerequisite that drugs are efficacious. Yet proven efficacy alone does not necessarily also make for an effective regimen. This was shown in the first regimen in the series in Bangladesh when bacteriologic results were reasonably good but the outcome of treatment was nevertheless poor because patients absconded to an important extent due to drug intolerance.

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Only a clinical trial can provide a direct unbiased estimate of regimen efficacy. One may submit nevertheless that the observational study in Bangladesh provides internally an indirect and unbiased estimator of relative drug efficacy. Drug susceptibility test results for any fluoroquinolone result, and most notably gatifloxacin MIC distributions for ofloxacin-resistant strains, became available only after treatment completion. In no case could the initial detailed fluoroquinolone drug susceptibility test result thus possibly have influenced management or ascertainment of bacteriologic response to treatment as the assessment was blind to these results. The difference in the frequency of and the odds for an adverse bacteriologic outcome (i.e. failure or relapse) are huge. This finding testifies to the validity of bacteriologic ascertainment and the efficacy of the fluoroquinolone against susceptible strains.

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There is virtually no HIV infection among Bangladeshi tuberculosis patients. A modified 12-month regimen was used in Cameroon where 20% of patients had HIV infection which did not affect regimen effectiveness. Only one among the 150 patients failed and none relapsed.

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A multi-center study using the Bangladesh regimen (modified only by replacing gatifloxacin with moxifloxacin) is being conducted in nine francophone African countries. The preliminary results during treatment have been presented at the 2016 Union World Conference in Liverpool. Over 1,000 patients were in the cohort that should have completed the treatment by the time of the analysis. About 20% of the patients were infected with HIV. The proportion with a successful outcome differed between HIV-infected and not -infected patients, with respectively 72% versus 83% success. There was no difference in the frequency of treatment failures, the difference was entirely attributable to the frequency of deaths between the two groups. Thus, the 9-month regimen has proven sturdy in multiple settings which sometimes had even difficult to implement national programs and that are affected by HIV infection. Its shorter duration and safety profile promises to be a giant leap towards improved control of MDR tuberculosis in many countries.

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Not surprisingly then that WHO followed suit and published revised guidelines in 2016 that provides room for countries to implement the “9-month Bangladesh regimen” in its treatment strategy for MDR tuberculosis.

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Accepting that the “9-month Bangladesh regimen” is an excellent addition to the treatment cascade, we have nevertheless two very practical current challenges. A serious drawback in MDR tuberculosis treatment is the need for prolonged use of an injectable drug, be it an aminoglycoside (like streptomycin, kanamycin or amikacin) or the polypeptide capreomycin, associated with vestibulo-cochlear and renal toxicity, often causing irreversible damage. In many countries, the first fallback regimen after the initial first-line regimen uses streptomycin for two months before MDR is detected when the regimen fails. Even while the 4-month (plus) intensive phase with kanamycin in the 9-month MDR regimen is by far shorter than what had been previously recommended by WHO, such patients will thus receive cumulatively 6 and more months of an injectable drug, not infrequently resulting in permanent hearing loss or even deafness. As at this point in time there is no established way out of the injectable drug in the MDR regimen, diagnostic modalities must thus be developed to avoid at least the streptomycin-containing first fallback regimen if there is actually MDR tuberculosis.

The second and more complex challenge is to develop a fallback regimen for the patients who fail on the 9-month MDR regimen. This would be important for two reasons, first providing assurance that there is a further possibility if the regimen fails, and secondly, thereby automatically widen the indication for the “9-month Bangladesh regimen” to less restriction than currently imposed by the WHO recommendations.

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To address the first challenge mentioned above, a key to resolving it will be the early diagnosis of MDR during the first-line regimen. We mentioned early on in this presentation that a positive sputum smear at five months in a rifampicin-throughout regimen is far from providing definitive evidence for MDR tuberculosis. The Xpert® MTB/RIF assay has been largely discussed as a diagnostic tool prior to initiation of chemotherapy, but it can play a critical role in assessment of putative

microscopic treatment failure during the first-line regimen. As non-viable bacilli can also give a positive test result, the importance of the test is not whether it is positive or not at, say, 5 months, but of whether there is rifampicin resistance or not. If the Xpert® MTB/RIF assay is positive but there is no rifampicin resistance, then treatment should be continued without alteration. In contrast, if there is rifampicin resistance, the patient should be switched immediately to the MDR regimen, bypassing a second-line streptomycin-containing regimen.

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One can argue whether the Xpert® MTB/RIF assay should already be used as early as the end of the second month if sputum smears have not yet converted to negative. One should keep in mind, however, that this is a common occurrence in patients with a diagnostic high-positive smear microscopy result as shown here. Thus, at what point in time during treatment the use of the Xpert® MTB/RIF assay is efficiently optimized will yet have to be determined.

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Summarizing the cascade of regimens, we focus on the susceptibility of the strain to the core drug in each sequential regimen as the primary question. Isoniazid was the first core drug and resistance to it was thus also the historically first to emerge. As a result of being the drug longest in use for every new patient, isoniazid resistance is the most frequent resistance type among drugs routinely in use. If the strain is susceptible to isoniazid, a regimen based on it works very well even without rifampicin in the continuation phase and an effectiveness of 80% and more is achievable under program conditions. If there is isoniazid resistance, a rifampicin-throughout regimen will overcome it in again 80% or more, be it in the form of the 8-month fallback regimen in the Union collaborative programs in the past or the WHO treatment recommendations of the mid-90s. Rifampicin resistance develops most frequently if isoniazid resistance is already present, and rifampicin mono-resistance is thus relatively infrequent. Furthermore, if rifampicin is lost, a regimen based on it as a core drug gives poor results. Thus, in the presence of rifampicin resistance, the next regimen in the cascade is indicated. Over the 14-year period of development for an improved regimen for MDR tuberculosis in Bangladesh as well as evaluations elsewhere both in the field and the laboratory, the fourth generation of fluoroquinolones (gatifloxacin and moxifloxacin) has been firmly established as a new core drug in a fallback regimen for MDR tuberculosis. In the “9-month Bangladesh regimen” the drug is supplemented by three first-line drugs (high-dose isoniazid, ethambutol, and pyrazinamide) whose contribution is likely to vary from one patient to another. There is strong evidence that both isoniazid and pyrazinamide very likely play an important role. There is little doubt that prothionamide plus the aminoglycoside kanamycin are critical drugs while at the same time they are also the drugs with the highest potential of serious adverse drug events. The anti-leprosy drug clofazimine has more recently become recognized as an anti-tuberculosis drug with a large potential in accelerating conversion and preventing relapses both in animal models and humans. Thus, a new regimen with very high effectiveness in a relatively short treatment duration has been identified.

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The cascade of regimens has moved by one regimen. The 8-month first-line regimen with thioacetazone in the continuation phase has now been removed from all national tuberculosis control programs. The 6-month regimen first evaluated in Singapore and published in 1979 (the only subsequent modification being substituting ethambutol for streptomycin in the intensive phase) is the currently recommended first-line regimen for any new patient presenting anywhere in the world, unless there is pre-treatment information that the patient has MDR or rifampicin-resistant tuberculosis. This 6-month regimen is more efficacious in terms of failure and relapse than any other first-line regimen, and it is also more effective as it is the shortest possible regimen. It has the best

safety profile and it also works in most patients with initial isoniazid resistance without requiring modification. In case of true bacteriologic failure, the patient has by definition MDR tuberculosis. In case of failure, if there is no additional resistance to fluoroquinolones of the fourth generation or second-line injectable drugs, then the fallback regimen of choice is the “9-month Bangladesh regimen”. If there is high-level fourth-generation fluoroquinolone resistance, then there is a high probability of failure or relapse (8 among 29 patients in Bangladesh), even if the strain is still susceptible to the injectable drug. There is evidence that, conversely, susceptibility to the injectable drug is also critical for a high success probability. Thus, if either of the two (fluoroquinolone or second-line injectable drug) has been lost, bacteriologic results will be substantially poorer. If there is resistance to both, i.e. extensive drug resistance, the regimen is unlikely to cure a patient and an entirely different regimen must be composed, likely also requiring some one or more of the newer drugs (bedaquiline, delamanid, oxazolidinones).

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This presentation delineated some key events and developments in the history of standardized anti-tuberculosis treatment regimens in national tuberculosis control programs and the core drugs of these regimens. Isoniazid was the first core drug in the triple regimen used in Edinburgh by Sir John Crofton in the 1950s and 1960s. It became the standard recommended regimen by WHO only in 1974. Tanzania pioneered the cascade of treatment regimens in low-income countries with two rifampicin-based regimens formulated by Karel Styblo of The Union, a student of John Crofton. A student of Karel Styblo, Armand Van Deun, then implemented a series of sequentially adaptive regimens for MDR tuberculosis in Bangladesh until arriving at the now internationally recognized regimen of nine months minimum duration. This regimen will have huge repercussions in some of the poorest countries in the world. It has yet to be resolved what the next regimen in the treatment cascade will be when the 9-month regimen fails because of resistance to fourth-generation fluoroquinolones and / or second-line injectable drugs.

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I am indebted to Armand Van Deun for taking me on board of his endeavor to communicate the findings of the carefully conducted observational studies in Bangladesh. Kya Jai Maug Aung coordinated the scientific activities in the Damien Foundation projects in Bangladesh and helped assuring the quality of the database. Etienne Declercq of the Damien Foundation provided continuous support for the project and gave intellectual input into analysis and communication of the study results. The staff of the Mycobacteriology Unit at the Institute of Tropical Medicine in Antwerp provided incredible laboratory support with detailed and comprehensive phenotypic and genotypic drug susceptibility test results and strain genotyping for a much improved understanding of the observed study results.