

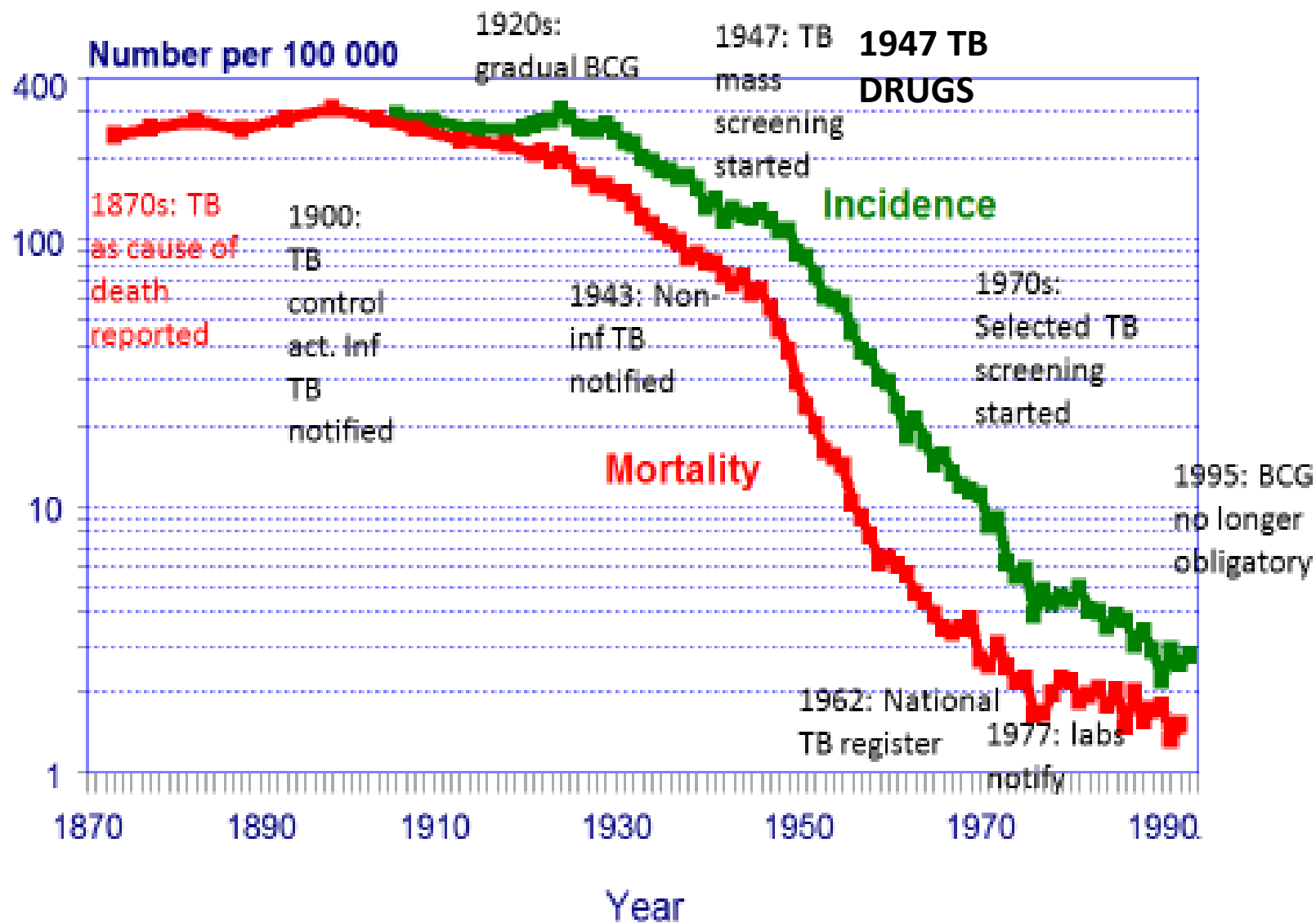
Utfordringer i kampen mot tuberkulose

Tuberkulosedagen 7.september 2023

Folkehelseinstituttet

Einar Heldal

Mortality from TB and incidence from infectious pulmonary TB in Norway



Utfordringer i Norge

- NOU1998:3 Utryddelse av tuberkulose? Strategi for fremtidig tuberkulosekontroll
- Utrydde TB innen 2015 (<1 per 100 000)
- TB-avdeling i SHUS, rådgivningsgruppe
- Kompetansegruppe for TB i regionsykehus/universitetsklinikker
- Helsesøster ved fylkets poliklinikk med tuberkulosekontroll som spesialoppgave.
- TB-medikamenter fortsatt distribueres gjennom Rikshospitalets apotek-Kombinerte tabletter. SHD bør anskaffe TB-medikamenter til en lavere pris enn i dag.
- BCG fortsetter inntil videre (mindretall Waaler, Bjune mente skulle opphøre).

PRIMUM NIL EFFUNDERE

— du skal ikke sløse *1994*

Festskrift til Hans Th. Waaler

A. Bjørndal, T. Iversen, E. Nygaard (red.)



Avdeling for samfunnsmedisin
Seksjon for helsetjenesteforskning

Store endringer

- 2002 SHUS slått sammen med FHI
- Regionale helseforetak
- Norsk forening for lungemedisins Tuberkuloseutvalg erstattet med FHIs tuberkulosekomite (første leder Ole Rysstad)
- Ny Tuberkuloseforskrift og Tuberkuloseveileder (2002, den siste i papir)
- Tuberkulosekoordinatorene opprettet (2003)

Utfordringer

- Papirløse – lang prosess før politi og migrasjonsetater godtok å endre forskriften. »Ifølge Utlendingsforskriftens § 17-14 annet ledd skal utlendinger som er under utredning eller behandling for tuberkulosesykdom, ikke pålegges å forlate riket før mistanke om tuberkulosesykdom er avkrefte, eller behandlingen er fullført.» (2010, siste endring 2016)
- Jfr. TB-unionens statement on undocumented migrants. Heldal E, Kuyvenhoven JV, Wares F, Migliori GB, Ditiu L, Fernandez de la Hoz K, Garcia D. Diagnosis and treatment of tuberculosis in undocumented migrants in low- or intermediate-incidence countries. Int J Tuberc Lung Dis. 2008 Aug;12(8):878-88. PMID: 18647446.

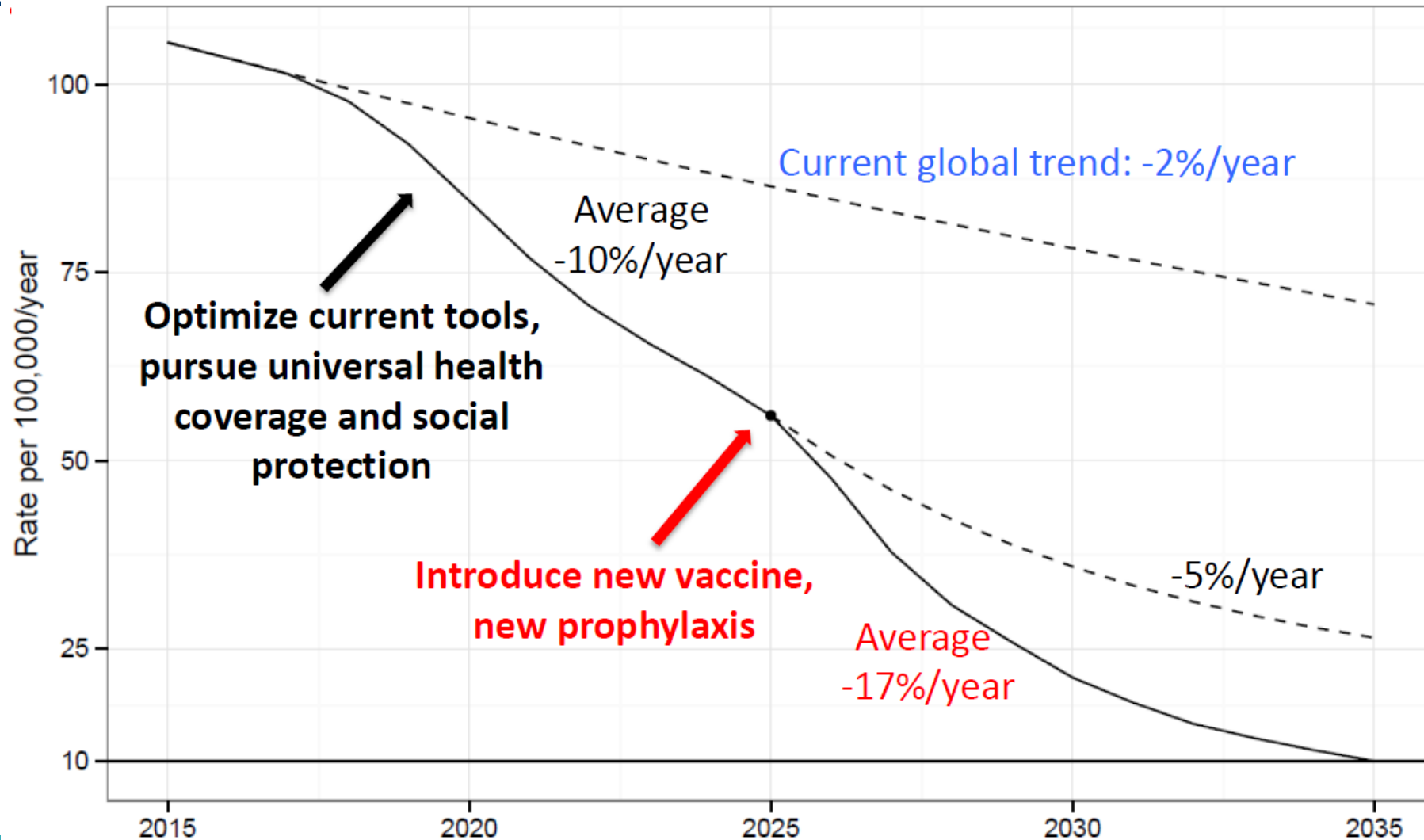
Utfordring: FHIs rolle

- Faggruppen for MDR-TB. Opprettet ca 2003 for å rådgi FHI. Møtested for de regionale spesialistene for å sikre enhetlige diagnostikk, behandling og oppfølging, som beskrevet i TB-veilederen.
- Diskusjon om medikamentregimer som WHO stadig modifierer. FHI har ikke spesialistkompetanse men en nøkkelrolle gjennom referanselab, MSIS, TB-komiteen og TB-koordinatornettverket.

Utfordring: Legemiddelmangel

- TB-koordinatorene har siden tidlig 2022 klaget til FHI over stadig mangel på TB-medikamenter, noe som fører til mye ekstraarbeid.
- Mangelsenteret ved OUS har drevet saken som nå ligger i HDIR/HOD om finansiering av et 6 mnds lager for viktige medikamenter der TB-medisinene vil inngå.
- Problemet har oppstått dels pga internasjonal mangel på enkelte medikamenter (relasjon til covid), dels pga overføring av ansvar for anskaffelse og distribusjon til Alliance Healthcare Norge som er en del av Alliance Healthcare - en av verdens ledende grossister og distributør av legemidler og sykepleieartikler. Det er frustrasjon rundt uklare ansvarsforhold og at problemet visstnok ikke vil bli løst før i 2024.

Global projections to 2035



End TB
Strategy

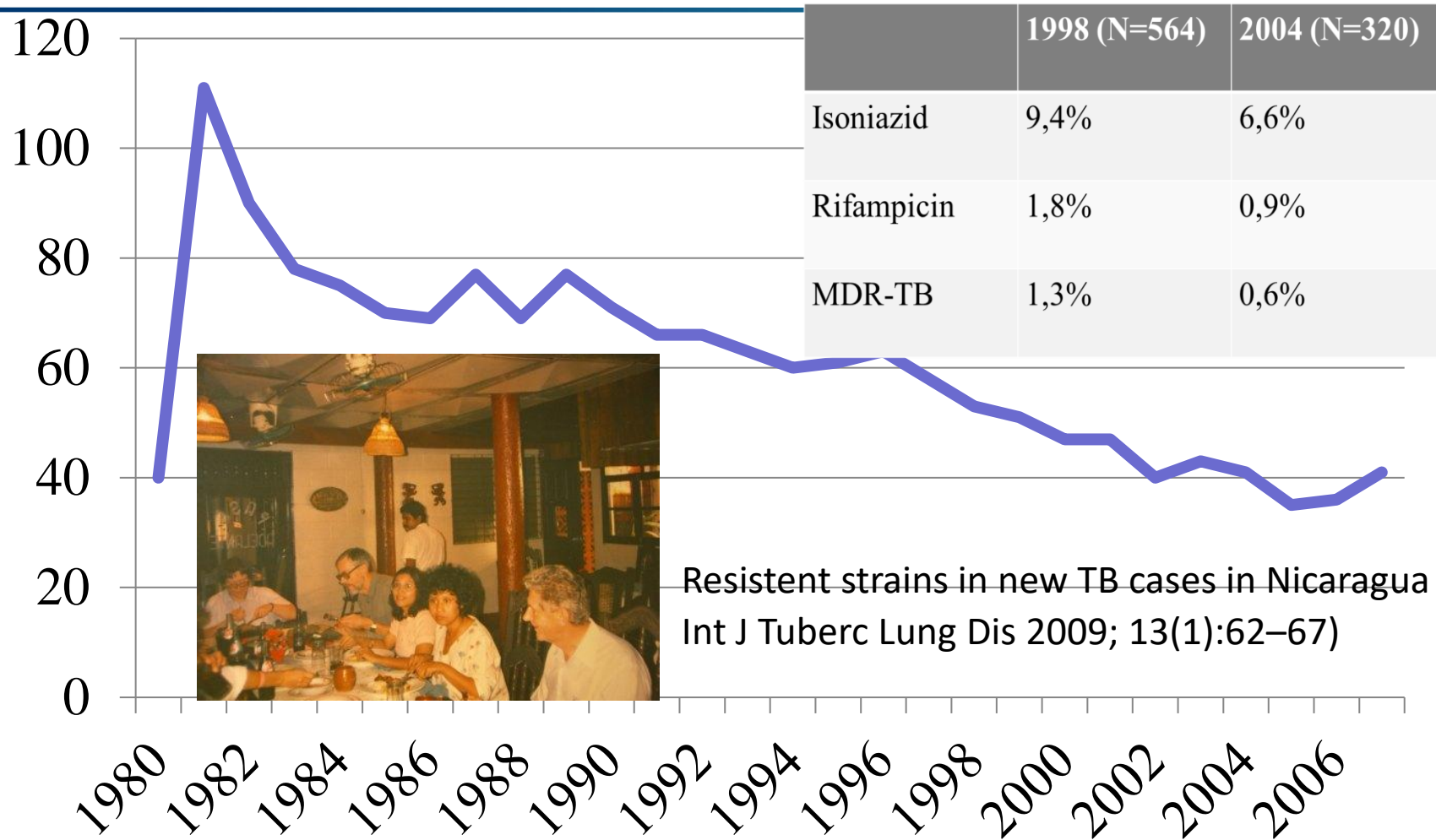
1990: DOTS-strategy (Directly Observed Treatment - Short course)

- Developed by The TB Union (Styblo), adopted and expanded by WHO:
 - Political commitment, budgets
 - Diagnostics based on bacteriology
 - Standardized treatment (2RHZE/4RH) under direct observation (DOT) and patient support
 - Supply of medicines
 - Recording and reporting system

Enarson DA. Principles of IUATLD collaborative tuberculosis programmes. Bull Int Union Tuberc Lung Dis. 1991 Dec;66(4):195-200.

Pilot of DOTS strategy: Nicaragua

(TB notifications per 100 000 1980-2007)



Er bedre redskaper nok?

- Finansiering til internasjonalt TB-arbeid knyttet til utvikling av nye medikamenter, diagnostika og vaksiner – skal være lønnsomt
- Nye produkter markedsfører samtidig med kritikk av og kampanjer mot eksisterende metoder:
 - GenXpert erstatter mikroskopi – men etter >10 år er bare 38% av TB-pasienter testet, fordi testen er dyr, teknisk krevende, forsyningsproblemer. Mikroskopi har blitt diskreditert med dårligere kvalitet. De fleste pasienter har fått dårligere tilbud enn tidligere. Unionen argumenterte at dette er komplementære tester.

New tools 1:

Xpert MTB/RIF vs smear microscopy

«Despite individual patient data analysis from 5 RCTs, we were unable to confidently rule in nor rule out an Xpert MTB/RIF-associated reduction in mortality among outpatients tested for TB.»



Ref. Di Tanna GL, et al. Effect of Xpert MTB/RIF on clinical outcomes in routine care settings: individual patient data meta-analysis. *Lancet Glob Health*. 2019 Feb;7(2):e191-e199.

Van Deun A, et al. Sputum smear microscopy in the Xpert(®) MTB/RIF era. *Int J Tuberc Lung Dis*. 2019 Jan 1;23(1):12-18.

New tools 2: Shorter MDR-treatment regimen (9-12 months)

- WHO «Conventional» MDR treatment two years, including 8 months intensive phase with injections with 50% success rate.
- Shorter regimen 9-12 måneder (4+5 months): current medicaments incl. clofazimin. Developed in Bangladesh by Damian Foundation, later used by The Union in West Africa, MSF in Central Asia etc. For patients with strains not resistant to quinolones or injections. Success rate over 80%.
- STREAM1, randomised clinical trial 2019: shorter regimen not inferior to conventional regimen. Included as alternative in WHO treatment guidelines 2019 being used in over 40 countries.

Nunn AJ, et al; STREAM Study Collaborators. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. N Engl J Med. 2019 Mar 13. doi: 10.1056/NEJMoa1811867.

Ref. Aung KJ, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis. 2014; 18:1180-1187.

WHO Treatment guidelines for drug-resistant tuberculosis - 2016 update. Geneva: World Health Organization. 2016.

Prevention vs treatment of drug resistant TB?

The Union vs WHO

- Directly observed treatment (DOT) and adequate regimen in first treatment needed to prevent MDR-TB
- Directly observed treatment (DOT) and adequate regimen in MDR-TB treatment needed to prevent resistance to fluoroquinolones (pre-XDR) and other 2-line drugs (XDR)
- Stop selling TB drugs (including quinolones) in pharmacies without prescriptions - and doctors stop using it for cough without excluding TB
- Ensure infection control in hospitals to stop nosocomial transmission
- TB Union is concerned that BDQ resistance will rapidly spread because of weak follow-up of patients (esp. during COVID), inability to exclude Fluoroquinolone resistance before start and no adequate regimen to treat those resistant

Ref.(1) (2) Trébucq A, et al. Short-Course Regimen for Multidrug-Resistant Tuberculosis: A Decade of Evidence. J Clin Med. 2019 Dec 25;9(1). (3) Schwöebel V, et al. Outcomes of a nine-month regimen for rifampicin-resistant tuberculosis up to 24 months after treatment completion in nine African countries. EClinicalMedicine. 2020 Feb 10;20:100268.

Scand. J. resp. Dis. (1974) **55**, 218-228

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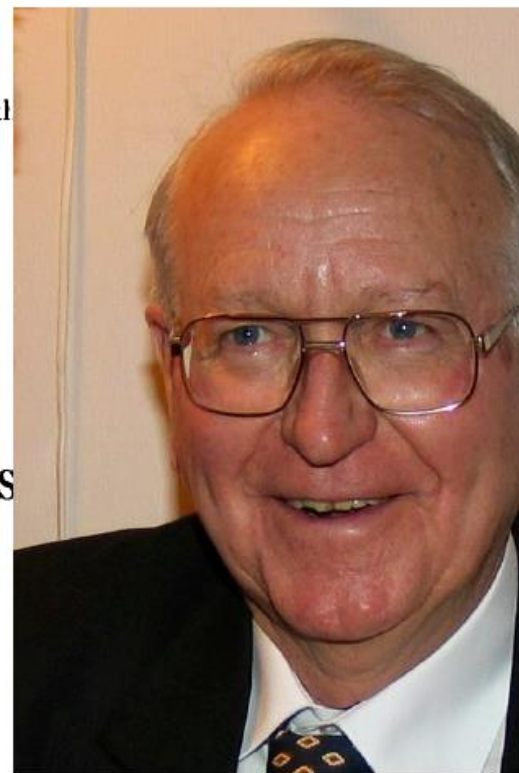
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A National Therapy Project for Drug Resistant Pulmonary Tuberculosis

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The simultaneous introduction of ethambutol, capreomycin and rifampicin into the Norwegian market gave rise to a national coordinated therapy project of a residual of drug resistant cases of pulmonary tuberculosis. Eight sanatoria/lung departments participated in the project, which was organized by the Ministry of Health. Cases were traced through the Central Tuberculosis Register, and were admitted to the project during the calendar year 1968.

Twenty-five cases were admitted to the project. Sputum conversion was obtained in all cases and no bacteriological relapse occurred during the 4 years from the start of treatment. There was a high frequency of side effects. During the follow-up period (4 years) eight patients died of causes other than tuberculosis. Only four cases lead a social life normal for their age.

Key words: capreomycin – central tuberculosis register – chronic tuberculosis –

Diagnosis and treatment of latent TB

- «About a quarter of the world's population is infected with M.tub and thus at risk of developing TB disease» (Global TB Report 2019)
- Controversy: Positive tuberculin/IGRA-test does not necessarily mean live bacilli and risk of reactivation (ref. Behr)
- The risk is mainly seen during the first two years after infection
- Preventive treatment is therefore most useful in newly infected persons: contacts and hiv infected
- WHO plan: 40 mill LTBI to be started on preventive treatment, mainly contacts and HIV infected persons

Ref. Behr MA, et al. Revisiting the timetable of tuberculosis. BMJ. 2018 Aug 23;362:k2738.

WHO operational handbook on tuberculosis. Module 1: prevention - tuberculosis preventive treatment. Geneva: World Health Organization; 2020. (<https://apps.who.int/iris/bitstream/handle/10665/331525/9789240002906-eng.pdf>)

New tools 3: Drugs: Bedaquilin

- 2012 Bedaquilin first new TB drugs in many decades. Producer/WHO made available «on compassionate grounds» for MDR-TB all over the world.
- Rapid development of drug resistance (ref. Mallick 2022)
- Part of WHO new recommended oral MDR-TB regimen (A,B,C-drugs) (2019)
- Free as introduction to low income countries until March 2019, expensive.
- WHO recommendations June 2020: BDQ containing short regimen first choice for RR-TB, and injectible-containing shorter regimen no longer recommended -and no longer supported by Global Fund. Short regimen replacing injection with BDQ.

Ref. Decroo T, et al. Tuberculosis treatment: one-shot approach or cascade of regimens? *Lancet Respir Med.* 2020 Feb;8(2):e4-e5. Mallick JS, et al. Acquired bedaquiline resistance during the treatment of drug-resistant tuberculosis: a systematic review. *JAC Antimicrob Resist.* 2022 Mar 29;4(2):dlac029.

Fra solidaritet til lønnsomhet

- DOTS-strategien utviklet på 1980-tallet fra nordiske land (samt Nederland, Sveits, Canada, etc) da styrking av offentlige helsetjenester stod i fokus. WHO's «Helse for alle»-strategi med fokus på primærhelse.
- Nå «the future is private» - vestlige givere har stor tillit til private løsninger, også i lavinntektsland. Nasjonale TB-programmer satt til side av utenlandske organisasjoner som bygger parallelle strukturer for å «hjelp» med GF-støtte etc.

Massescreening - Baklengs inn i fremtiden?

- Etter 2.verdenskrig startet store TB-massescreeningsprogrammer både i industri- og lavinntektsland, i regi av bl.a. WHO med skjermbilde, tuberkulintest og BCG-vaksinering
- Studier i ulike land på 1960-70-tallet viste at slik omfattende screening bare oppdaget ca 20% av mikroskopi-positive pasienter mens rundt 60% ble oppdaget pga symptomer. (Toman. Tuberculosis case finding and chemotherapy. Questions and answers, WHO 1979)
- WHO konkluderte i 1974 at slik screening burde opphøre og erstattes av permanente helseinstitusjoner dit pasienter skal gå når de får symptomer.

1947: Statens skjermbildefotografering 1952: tilbudt over hele landet



Nye screeningbusser med digital rtg og xpert-tester

- Elegante mobile enheter har de siste årene kommet på markedet og blitt tatt i bruk for screening i «høyrisiko» befolkninger med støtte av GF og andre givere, blant annet til slumbyer, lansbygdbefolkning, venterom i helseinstitusjoner. «Yield» (hvor mange som blir funnet med testene) varierer svært.
- Studier i Vietnam har tydet på at gjentatt screening av hele befolkningen førte til redusert TB insidens men dataene er **omdiskutert** (Marks GB et al. Epidemiological approach to ending tuberculosis in high-burden countries. Lancet. 2022 Nov 19;400(10365):1750-1752.)

Challenges: Recording and reporting/ Monitoring and evaluation

- Electronic systems (incl DHIS2) replacing paper-based Quarterly TB reports with aggregated data from districts to province and central but often lack of data competence and low quality of basic data.
- Case based electronic systems are being introduced, but advisable also to keep paper-based (sub)district TB-registers for validation and easy access in case interruptions of electronic system.
- TB data are submitted to the central level but weak feedback to provinces and districts
- Too much focus on reaching targets and incentives may lead to manipulation of routine data and data in drug resistance and prevalence studies

Noen inspirerende aktiviteter som peker framover

- Riitta Dlodlo fra TB-unionen– vil snakke om hvordan lokalt helsepersonell inkl TB-koordinatorer kan bruke egne rutinedata til å se hvordan de jobber og hvordan prioritere bedre.
- Sven Gudmund Hinderaker, Universitetet i Bergen: hvordan personell i TB-programmer kan bruke egne data til operasjonell forskning som de selv har nytte av.

Takk til alle for godt samarbeide gjennom mange år.
Lykke til videre!



Første TB-
koordinator-
samling 2003

ekstra

TB vaccines

- BCG developed in 1920s, mass scale used since 1940s
- Newborn BCG vaccination protects small children from miliary TB and TB meningitis, and still recommended in countries with high rates of TB. But has limited impact on adult TB
- BCG vaccination at 12-14 years in UK and Norway high protection for decades (Nguipdop-Djomo P et al. Duration of BCG protection against tuberculosis and change in effectiveness with time since vaccination in Norway: a retrospective population-based cohort study. Lancet Infect Dis. 2016 Feb;16(2):219-26).
- New promising recombinant vaccine in IGRA-positive persons (3 African countries)(Tait DR et al. Final Analysis of a Trial of M72/AS01(E) Vaccine to Prevent Tuberculosis. N Engl J Med. 2019 Dec 19;381(25):2429-2439.)
- Moderate optimism if and when break-through for new TB vaccine.
- See pipeline Oct 2021 next slide (<https://www.tbvi.eu/what-we-do/pipeline-of-vaccines/>)