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2011: The year in review. Part I: Tuberculosis

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IN THIS YEAR-IN-REVIEW ARTICLE, we summarise 104 articles published on tuberculosis (TB) in the *International Journal of Tuberculosis and Lung Disease* from the January to the August issue in 2011, and arbitrarily categorise them according to three subject areas: active TB, latent TB infection (LTBI), and operational research (see Table).

ACTIVE TB

Epidemiology

Three studies examined trends in TB burden. Chang et al. found that a number of measures based on disability-adjusted life years (DALY) due to TB significantly decreased from 1996 to 2006 for non-aboriginals, with the highest DALY/100 000 among those aged ⩾65 years, but fluctuated for aboriginals, with the highest DALY/case among those aged 35–44 years.[1] In Japan, Hoshino et al. found a decline in the ratio of chronic TB excretors (continuous excretion of TB bacilli in the last 2 years) among all subgroups from 1991–1997 to 1998–2004.[2] Pepperell et al. identified differences in TB incidence, demographics and genotypic clustering between Saskatchewan Aboriginal communities with differing epidemic trajectories over the past 150 years.[3]

Two studies described the epidemiology of TB in Benin, West Africa. Affolabi et al. found that only 22 of 214 smear-negative TB suspects were culture-positive, thereby suggesting a relatively low yield of mycobacterial culture among subjects with chronic cough.[4] Gninafon et al. estimated that the average annual risk of infection in Benin was around 0.5% in the mid 1980s, and reported an average TB notification rate of 35 per 100 000 population, a strong gradient from the north to the south, and an increase by 1% per year from 1995 to 2007.[5]

Two studies corroborated a possible impact of migrants on TB control. Li et al. identified high-rate TB clusters among permanent residents and migrants in 220 towns of Beijing, and found that new migrants contributed considerably to the increased TB caseload in Beijing.[6] Lowenthal et al. showed that implementation of an enhanced pre-immigration screening protocol including sputum cultures for TB suspects immigrating into California from countries with high TB endemicity resulted in reduced importation of infectious TB.[7]

A number of studies reported a high prevalence of multidrug-resistant TB (MDR-TB). Qi et al. found that 6% of new and 32% of previously treated patients in northern China in 2008 had MDR-TB.[8] Guo et al. typed 158 strains from Beijing, Heilongjiang, Inner Mongolia, Tibet and Guangdong, and found that the Beijing genotype was associated with rifampicin (RMP) resistance and was more prevalent in the interior than the southern coastal area.[9] Gler et al. found that MDR-TB was present in 76% of culture-positive patients referred for MDR-TB screening, with decreasing frequency among the following groups: Category II failures (97%) and non-converters (91%), Category I failures (83%), Category II relapses (78%) and returns after default (57%), and Category I relapses (33%) and returns after default (22%).[10] Simpson et al. reported a high prevalence (24.8%) of MDR-TB in the Western Province of Papua New Guinea.[11] Ollé-Goig et al. found that 27 (75%) of 36 chronic patients hospitalised in a TB referral centre in the Horn of Africa had MDR-TB, including four (11%) with extensively drug-resistant TB (XDR-TB).[12]

TB and human immunodeficiency virus (HIV) co-infection is common in Africa. In a retrospective study on intensified TB case finding among 300 HIV-infected patients in Ethiopia, Assefa et al. found 34 TB cases in one year, of whom 27 (79%) were identified in the first 6 months.[13] Among 20 HIV-infected subjects with disseminated TB in Tanzania, von Reyn et al. found that the majority had strongly positive tuberculin skin test (TST) results before developing disease, but that the majority of isolates in blood were clustered, whereas concurrent sputum isolates in 37% represented a different strain.[14]

Two studies evaluated molecular epidemiological tools. Kato-Maeda et al. evaluated the accuracy of strain classification by spoligotyping, and found 95% of *Mycobacterium tuberculosis* isolates could

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Table Classification of 104 articles on TB published in issues 1–8 of volume 15 (2011) of the *International Journal of Tuberculosis and Lung Disease*

Subject areas, categories	Number
Active TB	
Epidemiology	16
Risk factors	
TB risk factors	8
Delay in diagnosis	3
Morbidity and mortality	8
Treatment failure and recurrence	3
Diagnosis	
Specimens	3
Phenotypic methods	6
Molecular methods	7
Other methods	2
Treatment	
Standard TB regimens	3
Extra-pulmonary TB	2
MDR-TB	3
New TB drugs	2
TB-related complications	1
Latent TB infection	
Epidemiology	3
Diagnosis	9
Operational research	
Improving programme performance	14
Assessing the impact of TB control strategies	11

TB = tuberculosis; MDR-TB = multidrug-resistant TB.

be classified into a spoligotype family, thereby suggesting that spoligotype families are sub-lineages within the main lineages.[15] Zhou et al. demonstrated that a modified 15-locus mycobacterial interspersed repetitive units-variable number of tandem repeats typing method had a high discriminatory power, and suggested its potential use alongside spoligotyping in routine epidemiological investigations.[16]

Risk factors

TB risk factors

Wu et al. found that cancers of the aerodigestive tract and haematological cancers significantly increased the hazard ratio (HR) of TB in Taiwan to 3.09 and 3.22, respectively.[17] Kik et al. demonstrated that travel to the country of origin was a risk factor for TB among Moroccan immigrants, with an odds ratio (OR) of 3.2 that increased to 17.2 when the cumulative duration of travel exceeded 3 months.[18] Hoa et al. found that the TB prevalence rate in 2006–2007 was 2.5 times higher for those in the lowest household expenditure quintile than those in the highest quintile, thereby corroborating an association between TB and poverty in Viet Nam.[19] In a logistic risk model, Ladefoged et al. demonstrated that Inuit ethnicity (OR 15.3), living in a settlement (OR 5.1), being unemployed (OR 4.1) and frequent alcohol use (OR 3.1) were significantly associated with TB in Greenland.[20] Abebe et al. found that the risk of pulmonary TB in Ethiopian prisons was associated with young age, urban residence, cough $>$ 4 weeks and sharing a cell with a TB patient or a prisoner with a chronic cough.[21] Banda et al. measured 25-hydroxy vitamin D levels in 161 adult TB patients at a central hospital in Malawi, and found that 68 (42%) had vitamin D concentrations $\leqslant$ 50 nmol/l.[22] Massi et al. demonstrated a high prevalence of resistance to isoniazid (INH) among both new (28.3%) and previously treated patients (34.6%), and a significant association between MDR-TB and a history of excess alcohol use (adjusted OR 4.01) and previous TB treatment (adjusted OR 6.28).[23] Tochon et al. demonstrated that MDR-TB disease might be associated with recent TB contact among French children.[24]

Delay in diagnosis

Comparing fluoroquinolone-exposed and non-exposed patients in a South African goldmining community, Jeon et al. found that patients recently exposed to a fluoroquinolone for $\geqslant$5 days were less likely to be smear-positive (OR 0.27), with an increased time to treatment (time ratio 2.02), but that brief fluoroquinolone exposure might not be associated with fluoroquinolone resistance.[25] In British Columbia, Wang et al. found that delays in TB treatment initiation were positively related to the number of courses of antibiotic prescribed rather than the type of antibiotic received.[26] Van Wyk et al. found that consulting health care providers outside the National TB Programme (NTP) and HIV infection were associated with delayed initiation of TB treatment.[27]

Morbidity and mortality

In a retrospective study in Seoul, Ryu et al. found that extensive TB-related lung damage independently predicted shorter survival.[28] Lee et al. documented an all-cause hospital mortality of 61.2% among 67 patients with acute respiratory distress syndrome caused by miliary TB, and a significant association between Sequential Organ Failure Assessment score and mortality.[29] In a Western African case-control study, Rasmussen et al. found that baseline procalcitonin levels were significantly higher among TB patients than controls and positively correlated with disease severity and mortality.[30]

HIV co-infection increases the risk of morbidity and mortality among TB patients. HIV co-infection was independently associated with severe anaemia (haemoglobin $<$ 8.5 g/dl) in Tanzanian TB patients.[31] High rates of advanced disease and high mortality were found in a retrospective, hospital-based study of HIV-infected infants with TB in South Africa.[32] Marks et al. found that, after controlling for age, HIV remained the strongest risk factor for TB diagnosed at death (adjusted OR 4–11), and for death during TB treatment (adjusted OR 3–19).[33] A retrospective cohort analysis of 5311 TB patients reported in North Carolina from 1993 to 2003 also showed a significant association between mortality (before or during TB

treatment) and HIV infection, as well as increasing age, miliary/meningeal disease, excess alcohol use and residence in a nursing home.[34] A retrospective cohort study in Barcelona showed that survival at 10 years, which was 47.4%, was significantly lower among patients diagnosed with acquired immune-deficiency syndrome (AIDS) prior to their TB episode (HR 1.8) after controlling for age > 30 years (HR 1.5), inner-city residence (HR 1.3), injecting drug use (HR 1.5), non-cavitary disease (HR 1.6), and CD4 ⩽ 200/μl (HR 1.7).[35]

Treatment failure and recurrence

Tachfouti et al. demonstrated that smoking was independently associated with treatment failure in Morocco.[36] Uwizeye et al. found that female sex in Rwanda was associated with a higher risk of treatment failure and death due to smear-positive pulmonary TB, a higher frequency of smear-negative pulmonary and extra-pulmonary TB, and a higher prevalence of HIV co-infection.[37] Pettit et al. found that TB recurrence was significantly associated with chronic lung disease and HIV infection, while HIV infection was significantly associated with TB re-infection.[38]

Diagnosis

Specimens

Bhat et al. demonstrated that refrigeration of sputum specimens for respectively 0–3, 4–7 and ⩾8 days until they were transported for processing at a reference laboratory for culture did not seem to significantly affect the recovery of *M. tuberculosis* complex isolates.[39]

Kranzer et al. found that induced sputum obtained with a human-powered nebuliser might be of higher quality than that obtained with an electric nebuliser.[40]

A prospective, hospital-based paediatric study showed that bone marrow biopsy was valuable in the diagnosis of suspected disseminated mycobacterial disease.[41] Of 25 children with confirmed or probable disseminated TB, the diagnosis was ascertained in 5 (20%) only by bone marrow histology and/or culture, which was frequently collected after initiation of TB treatment.

Phenotypic methods

Aung et al. found that use of hydrochloric acid for Ziehl-Neelsen (ZN) staining was associated with fewer false-positive results than with sulphuric acid, with the additional advantages of being cheaper, easier and safer to use.[42] Shenai et al. found that, given adequate training and detailed standard operating procedures, using light emitting diode (LED) fluorescence microscopy (FM) instead of ZN microscopy and conventional FM can be beneficial in view of its sensitivity and specificity (78.3% and 92.0% in pulmonary specimens, 34.0% and 88.8% in extra-pulmonary specimens) and the mean time per smear examination (1.41 min for LED FM vs. 2.48 min for ZN).[43]

A study by Hepple et al. in a remote area in southern Sudan showed that liquid culture was usually not clinically useful, owing to the long delays involved in obtaining culture results and the confusion created by high rates of isolation of non-tuberculous mycobacteria.[44]

Peres et al. demonstrated that the use of BACTEC™ MGIT™ with a double concentration of PANTA (supplemental polymyxin B, amphotericin B, nalidixic acid, trimethoprim and azlocillin) may significantly reduce culture contamination without affecting the diagnostic yield.[45]

Schön et al. determined wild-type minimum inhibitory concentration (MIC) distributions of *M. tuberculosis* for ethionamide, prothionamide, thioacetazone, cycloserine, rifabutin, clofazimine and linezolid in consecutive susceptible clinical isolates, and proposed this approach for defining clinical breakpoints against second-line drugs.[46]

Mendoza et al. demonstrated the feasibility of delivering rapid INH and RMP drug susceptibility testing (DST) close to the point of care by decentralising the use of microscopic observation drug susceptibility in Peru.[47] The sensitivity and specificity for detecting MDR-TB were >90%, with a low contamination rate of 1.0–2.3%, and a mean turnaround time of 9.9–12.9 days.[47]

Molecular methods

Two studies evaluated the use of molecular methods for detecting *M. tuberculosis* complex. Hur et al. demonstrated comparable performance of the *artus*® *M. tuberculosis* PCR Kit and the widely used COBAS® AMPLICOR™ *Mycobacterium tuberculosis* Test using clinical respiratory specimens from Korea.[48] Malbruny et al. demonstrated that Xpert® MTB/RIF, a commercial real-time polymerase chain reaction (PCR) assay, could be useful for the diagnosis of extrapulmonary as well as pulmonary TB.[49]

A number of studies examined the use of multiplex allele-specific polymerase chain reaction (MAS-PCR) and Genotype® MTBDR*plus* for DST. Using clinical isolates of *M. tuberculosis*, Imperiale et al. found concordance in the detection of mutations in *kat*G, the *inh*A promoter and *rpo*B between MAS-PCR and DNA sequencing in 100%, 94.1%, and 97.8% of cases, respectively.[50] Tho et al. found that the sensitivity and specificity for INH resistance among culture isolates of *M. tuberculosis* were 90% and 100%, respectively, for both MAS-PCR and the MTBDR*plus* assay.[51] Al-Mutairi et al. found that GenoType MTBDR*plus* used in clinical isolates accurately detected RMP resistance in 78 of 82 MDR-TB strains, INH resistance in 76 of 82 MDR-TB strains, and that it detected approximately 88% of the 82 MDR-TB strains.[52] Using data from a South African population sample, which demonstrated a significant increase in the proportion of *inh*A promoter mutations

from MDR-TB isolates to XDR-TB isolates, Müller et al. suggested that GenoType MTBDR*plus* might be useful in the management of XDR-TB.[53] Rigouts et al. found that GenoType MTBDR*plus* performed directly on sputum specimens was highly accurate in identifying RMP resistance and MDR-TB, despite underestimating INH resistance by roughly 50% in comparison with phenotypic DST.[54]

Other methods

Kim et al. demonstrated that previous TB had a long-term effect on T-SPOT®.*TB* results even after TB treatment, thereby limiting the role of T-SPOT.*TB* in differentiating between inactive and active TB.[55] Van Beek et al. found that exhaled nitric oxide (eNO) measured with a validated handheld analyser had a sensitivity of 78% and specificity of 62% for active pulmonary TB.[56]

Treatment

Standard TB regimens

Nunn et al. reported the 30-month results of a randomised trial of two 8-month regimens with 6-month INH+ethambutol (EMB) continuation phases (one with a daily and the other with a thrice-weekly standard initial phase) compared with the standard 6-month regimen. Unfavourable outcomes occurred in 11.7% and 15.3%, respectively, of subjects receiving the 8-month regimens and 6.0% of those receiving the 6-month regimen. INH-resistant cases fared worse with the 8-month regimens. HIV roughly doubled the risk of an unfavourable outcome in all regimens.[57] In two urban areas of the Central African Republic that predominantly used the 8-month regimen, Minime-Lingoupou et al. reported resistance to RMP (and MDR) in only 0.4%, in contrast to primary resistance to INH in 9.3% and streptomycin in 8.4%.[58] Wells et al. found that many TB high-burden countries are moving towards a single standard 6-month, RMP-throughout regimen, which should facilitate the comparison of new regimens with a single control arm in clinical trials.[59]

Extra-pulmonary TB

Findings from a retrospective cohort analysis by Blaikley et al. corroborated the effectiveness of standard 6-month regimens for treating drug-susceptible TB lymphadenitis.[60] Jacob et al. evaluated a UK cohort of 160 patients with mediastinal TB, and suggested that mediastinal TB could be managed by initiating empirical TB treatment of adult asymptomatic immigrants presenting with mediastinal adenopathy and a strongly positive Heaf test.[61]

MDR-TB

Feasey et al. demonstrated in a case report the possiblity of treating MDR-TB with additional resistance to fluoroquinolones and pyrazinamide (PZA) using high-dose moxifloxacin.[62] Tabarsi et al. reported safety during pregnancy and delivery for both mothers and neonates with an acceptable rate of treatment success in the use of standardised second-line anti-tuberculosis medications among five MDR-TB patients.[63]

Human neutrophil peptides 1, 2 and 3 (HNP1-3) are involved in innate and acquired immune response. Zhu et al. found that, compared with patients with drug-susceptible post-primary pulmonary TB and healthy controls, MDR-TB patients had lower plasma HNP1-3 levels both before and after treatment, and that HNP1-3 was negatively correlated with the time during which *M. tuberculosis* was detected in sputum, but positively correlated with peripheral blood neutrophil counts.[64]

New TB drugs

Six new drug candidates from four different classes are currently in clinical trials for TB. Diacon et al. reported the results of a 14-day early bactericidal activity (EBA) study of delamanid (OPC-67683) in patients with smear-positive pulmonary TB. Daily doses of 200 and 300 mg appeared more active than 100 mg.[65] The overall EBA was modest, lower than that of the Rifafour® control (comprising INH, RMP, EMB and PZA), and also somewhat lower than results observed with PA-824 in a separate study performed at the same site.[66]

TB-related complications

Shin et al. reviewed 169 cases and found a 96.4% initial success rate in using bronchial artery embolisation to manage haemoptysis in patients with pulmonary TB, but recurrence in 29.4%. Recurrence was more likely with TB reactivation and mycetoma, and when aortography was not performed.[67]

LATENT TB INFECTION

Epidemiology

Using a time trend analysis of TB incidence with age-cohort modelling in Sweden, Winqvist et al. estimated that reactivation disease rates fell to below 2% after 1967, thereby suggesting that spontaneous clearance of LTBI may be more common than currently assumed when TB transmission has been largely interrupted.[68]

In a retrospective cohort study at an academic tertiary care hospital in Israel, Sherman et al. found that, of all hospital employees, housekeeping staff and those working in areas with high patient turnover had the greatest risk of TST conversion.[69]

The TB Research Centre in Chennai, India, found that contacts of INH-resistant TB patients were more likely to be infected than contacts of INH-susceptible cases, but that the incidence of TB disease was similar in both groups.[70]

Diagnosis

Diagnostic tools for LTBI can only be as useful as the compliance with targeted testing recommendations. Guh et al. found that, among foreign-born persons developing TB in Connecticut in 2005–2008, more than two thirds did not recall being tested for LTBI after arrival, even though the majority entered as permanent residents, had an established provider or had HIV infection.[71]

A number of studies examined the performance of TST and interferon-gamma release assays (IGRA) in the diagnosis of LTBI. In Taiwan, Ling et al. found a 200–300-fold higher risk of developing TB disease among contacts aged < 15 years relative to the general population, and a significant hazard of developing TB that was 12 times higher among contacts with TST > 15 mm than those with TST < 5 mm.[72] In a prevalence study of adolescents aged 12–18 years in South Africa, Mahomed et al. reported that 55.2% had TST $\geqslant 5$ mm, while 50.9% were QuantiFERON®-TB Gold In-Tube (QFT-GIT) positive.[73] Black/mixed race racial groups, male sex, older age, household TB contact, low income and low education level were independent predictive factors for both TST- and QFT-positive results.[73] By evaluating the sensitivity of QFT-GIT and T-SPOT.*TB* among specimens from newly diagnosed adults with microbiologically confirmed TB with and without diabetes, Walsh et al. found that the sensitivity of IGRA was not compromised by diabetes mellitus in TB patients.[74] By evaluating 316 bacille Calmette-Guérin (BCG) vaccinated foreign-born individuals with a positive TST followed by QFT-GIT, Mahan et al. found that increasing age, male sex, origin from a country with a high prevalence of TB, shorter time since arrival in the United States, and increasing TST size were all independently associated with a positive IGRA,[75] and proposed that a positive TST followed by IGRA might be a preferred and cost-effective alternative to TST alone for screening for LTBI among BCG-vaccinated foreign-born persons.

A number of studies compared the performance of TST and IGRA. Kasambira et al. compared TST and QFT-GIT among children with an adult household contact with pulmonary TB in South Africa, and found that each test indicated a high prevalence (28–29%) of LTBI, with 81% agreement between tests, and that children under 2 years of age were more likely to have discordant results, with neither test being optimal in this subgroup.[76] Weinfurter et al. observed moderate concordance between TST and QFT-GIT for the diagnosis of LTBI among high-risk patients in the United States. Analysis of discordant results suggested that QFT-GIT outperformed TST in BCG-vaccinated, foreign-born persons and older persons, while appearing as useful as TST in HIV-infected subjects, who showed reduced sensitivity to both tests.[77] Zhao et al. demonstrated low agreement between TST and T-SPOT.*TB* among 899 Chinese college students, which was lower among those with a BCG scar ($\kappa = 0.118$) than those without a BCG scar ($\kappa = 0.179$).[78]

In a study involving 56 patients with rheumatoid arthritis receiving anti-tumour necrosis factor-alpha treatment and 18 patients with active TB, Chen et al. demonstrated that interferon-inducible protein 10 (IP-10) was superior to interferon-gamma (IFN-γ) as a biomarker for detecting LTBI (defined by a positive TST) and active TB.[79] Compared with baseline IFN-γ, baseline IP-10 was more sensitive (83.3% vs. 50.0%) and similarly specific (67.9% vs. 67.9%) in detecting LTBI, and similarly sensitive (100% vs. 94.4%) and more specific (59.6% vs. 17.3%) in detecting active TB. Compared with baseline IP-10, early secreted antigenic target 6-stimulated IP-10 showed similar sensitivity (87.5% vs. 83.3%) and higher specificity (85.7% vs. 67.9%) for LTBI, and similar sensitivity (100% vs. 100%) and higher specificity (71.2% vs. 59.6%) for active TB.

OPERATIONAL RESEARCH

Research that aims at improving programme performance

A number of studies suggested room for improvement regarding diagnosis. Noeske et al. showed that 1.2% of patients identified with pulmonary TB in the Central Prison of Yaounde in Cameroon had been missed; risk factors included severe crowding, low body mass index and previous TB treatment.[80] Bailey et al. showed a median delay of 26 days from first presentation to diagnosis of TB, thereby suggesting that using sputum smear microscopy as the mainstay of diagnosis might have caused a delay in diagnosis.[81] In a cohort study in Guinea-Bissau involving 212 former TB suspects, Porskrog et al. found that 89 (42%) were still symptomatic $\geqslant 1$ month later, including five subsequently diagnosed with TB and a subgroup of 44 symptomatic patients with HIV infection in 17 (39%).[82] Wilson et al. demonstrated that the World Health Organization algorithm for diagnosis of smear-negative TB in HIV-infected patients had a low positive predictive value of 34% among ambulatory suspects in KwaZulu-Natal, despite a relatively high negative predictive value of 86%.[83]

Several studies exposed problems associated with unreliable drug supplies. In a survey of national TB drug policies of 100 countries, including 17 of the 22 high-burden countries, Paydar et al. found that a higher prevalence of MDR-TB was associated with a longer period of availability of RMP from providers or pharmacies outside the NTP and shorter availability of free TB drugs from the NTP.[84] In a survey of pharmacists at centres treating TB in the United Kingdom, Capstick et al. revealed that nearly two thirds of those responding had experienced difficulty obtaining TB drugs, 27% had had to interrupt treatment at

least once, 19% had had to alter the regimen, and 26% had used locally prepared formulations of unknown stability to treat children owing to lack of licensed formulations.[85]

The performance of laboratory diagnostic services was examined by a few studies. In a survey of TB-related services at 15 antiretroviral therapy (ART) programmes in Africa, Asia and Latin America, Fenner et al. found that mycobacterial culture was freely available in only 50% of the programmes, and that only 8% of patients received INH preventive therapy.[86] The network of supranational tuberculosis reference laboratories compared the proficiency of 27 participating laboratories in the use of their preferred phenotypic DST, and suggested the need to consider genotypic and treatment outcome information to ultimately improve the clinical relevance of DST.[87] Otero et al. demonstrated that external quality assessment with stratified lot sampling of treatment follow-up smears proved very efficient and effective for identifying laboratories with substandard performance in a setting with low positivity rates in routine diagnostic smears.[88]

Four studies suggested that health education might improve health-seeking behaviour and hence programme performance. Khandoker et al. found that correct knowledge about TB transmission was low among ever-married women aged 15–49 years in Bangladesh, and significantly associated with education, district and access to media.[89] Abebe et al. found that prisoners in three prisons in eastern Ethiopia had a modest level of biomedical knowledge.[90] Buregyeya et al. showed that barriers to seeking care in health facilities in rural Uganda included fears about HIV testing and the heavy pill burden, and belief in instant healing by traditional healers and the incurable nature of HIV-associated TB.[91] Luis et al. showed that knowledge about TB and TB services was associated with appropriate health-seeking behaviour in Angola.[92]

By establishing record linkage, Dunbar et al. found that a total of 102 bacteriologically confirmed cases were missed by the TB registers, which initially recorded 204 bacteriologically confirmed cases.[93]

Research that aims at assessing the impact of TB control strategies

A number of studies evaluated the impact of the DOTS strategy. Lal et al. described how India's Revised National Tuberculosis Control Programme (RNTCP) implemented an intensified scale-up of public-private mix DOTS that resulted in a 12% increase in notification of new smear-positive pulmonary TB cases and a treatment success rate above the 85% target for all sectors combined.[94] Goodchild et al. measured the economic costs and benefits of scaling up TB control under the RNTCP in India from 1997 to 2006, and concluded that it was cost-effective.[95] In contrast, TB patients seeking care from non-NTP health care providers in South Africa and informal practitioners in Bangladesh experienced delayed diagnosis and treatment, respectively.[27,96] Blöndal et al. retrospectively analysed notification rates and treatment outcomes of TB and MDR-TB in Estonia, and found that annual notification rates fell from 1998 to 2006 alongside countrywide implementation of DOTS and access to second-line drugs.[97] A cohort analysis among 582 sputum smear-positive TB patients in urban Pakistan found that clinic directly observed treatment (DOT) nearly doubled the proportion of cured patients compared with family DOT, while patient satisfaction with health care worker's attitude also increased the chance of cure (adjusted relative risk 5.73).[98] Yumo et al. found that the Global Fund Grant Round 3 markedly improved NTP outcome indicators at the district level in North-West Cameroon.[99]

DOTS interplays with other interventions. A comparison of six different interventions (social mobilisation and information, education and communication; engagement of the private sector; innovative approaches for microscopy services; enhanced or semi-active case finding; health systems strengthening; and use of incentives) employed in 51 FIDELIS projects implemented in 18 high TB burden countries between 2003 and 2007 demonstrated a substantial increase in cases, by 85 267, for a median cost of US$103 per additional case, with comparable importance for each intervention.[100]

Some studies assessed the impact of ART in the management of TB-HIV co-infection. Comparing a community-based support programme and standard care in two health districts in Peru in a matched case-control study, Cerda et al. found that patients in the support programme had a lower hazard of dying or defaulting from treatment (adjusted HR 0.34), experienced fewer hospital days (adjusted incidence rate ratio [IRR] 0.37), had fewer out-patient visits (adjusted IRR 0.75), and significantly offset cost over 2 years of follow-up.[101] In a retrospective cohort study of HIV-infected Ugandan children and adolescents initiating ART, Bakeera-Kitaka et al. found that the risk of a new diagnosis of TB was 2.7-fold higher during the first 100 days of ART than it was before ART, and the incidence rate fell significantly below the pre-ART rate afterwards (rate ratio 0.41).[102] Zachariah et al. found that scale-up of ART in Malawi was associated with significant cumulative reductions of 33% and 25% in case notifications for both new and recurrent TB, respectively, after an initial increase.[103] On the other hand, Atkins et al. showed no significant difference in cure or treatment success rates for new TB patients between standard care and TB treatment intervention modelled on the community ART support programme in South Africa, although intervention slightly improved sputum smear conversion rates.[104]

CONCLUSIONS

By providing a glimpse of the meticulous efforts made by many ardent researchers in the combat against TB, it is hoped that this article may help health care workers and policy makers grasp essential scientific messages and translate them into quality clinical care and effective public health actions for a global health threat that still affects many.

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