



Linking TB and the Environment

An Overlooked Mitigation Strategy

One of the world's leading killers, tuberculosis (TB) is nearly as old as humanity itself; fossilized evidence of this lethal infection has been found in a *Homo erectus* skeleton half a million years old. But look to a modern hospital in a developed country, and you'd be hard pressed to find more than a few cases. Historically, TB is a disease of the poor. Most of the 2–3 million people who die of the disease every year come from the developing world or from poor, urban neighborhoods in wealthier nations. For centuries, TB has been linked anecdotally with environmental risk factors that go hand-in-hand with poverty: indoor air pollution, tobacco smoke, malnutrition, overcrowded living conditions, and excessive alcohol use. Now scientists are presenting convincing evidence to back these associations, leading some TB experts to argue that control programs must confront underlying risk factors to limit the spread of the disease.

A man suffering from TB arrives at a hospital in Mymensingh, Bangladesh. Bangladesh has the sixth greatest TB burden in the world.

Tim Diven/Panos Pictures

According to the World Health Organization (WHO), more than 9 million new cases of TB are diagnosed annually, 55% of them in Asia and 31% in Africa, placing TB second only to HIV/AIDS in terms of the global burden of infectious disease. TB control strategies adopted by the WHO and other organizations emphasize clinical solutions in the form of drugs, vaccines, and access to health care. But despite the success of these programs, TB incidence and mortality aren't falling rapidly enough to meet WHO targets, and in some areas, particularly in parts of Asia and throughout sub-Saharan Africa, they continue to climb. "Better treatment is essential, but if we want to affect longer-term trends in the epidemic we will also have to deal with risk factors," asserts Eva Rehfuess, a scientist with the WHO Department of Public Health and Environment. "But doing that won't be easy. Social and environmental interventions aren't usually delivered or funded by the health sector, so that means we all have to work with other sectors, in particular housing, energy, and education, to move them forward."

Emerging evidence suggests such interventions could yield big benefits. In a report published online 3 October 2008 ahead of print in *The Lancet*, Majid Ezzati and colleagues at the Harvard School of

Public Health predict that by 2033 TB incidence rates in parts of China could be 14–52% lower if tobacco smoking and indoor air pollution from traditional cooking stoves are eliminated. These reductions assume that 80% of the population already has access to optimal treatments for TB; the benefits would be even greater among those without such access, says Ezzati, an associate professor of global health and environmental health.

The Current Situation

One-third of the world's population is thought to be infected with various strains of *Mycobacterium tuberculosis*, the microbe that causes TB, but only 5–10% of infected individuals will develop active disease. Among those with latent infections, which are nontransmissible, *M. tuberculosis* exists in a mysterious dormant state. Precisely why the bacterium favors latency is unknown. Immunity appears to play a role, given that dormant TB often converts to active disease when immune systems falter, for instance, as a consequence of HIV/AIDS. But some TB strains might also favor latency as an evolved trait that fosters survival, says Christopher Dye, an epidemiologist in the WHO Stop TB Department and coauthor of "Expanding the Global Tuberculosis Control Paradigm: The Role of TB Risk Factors and

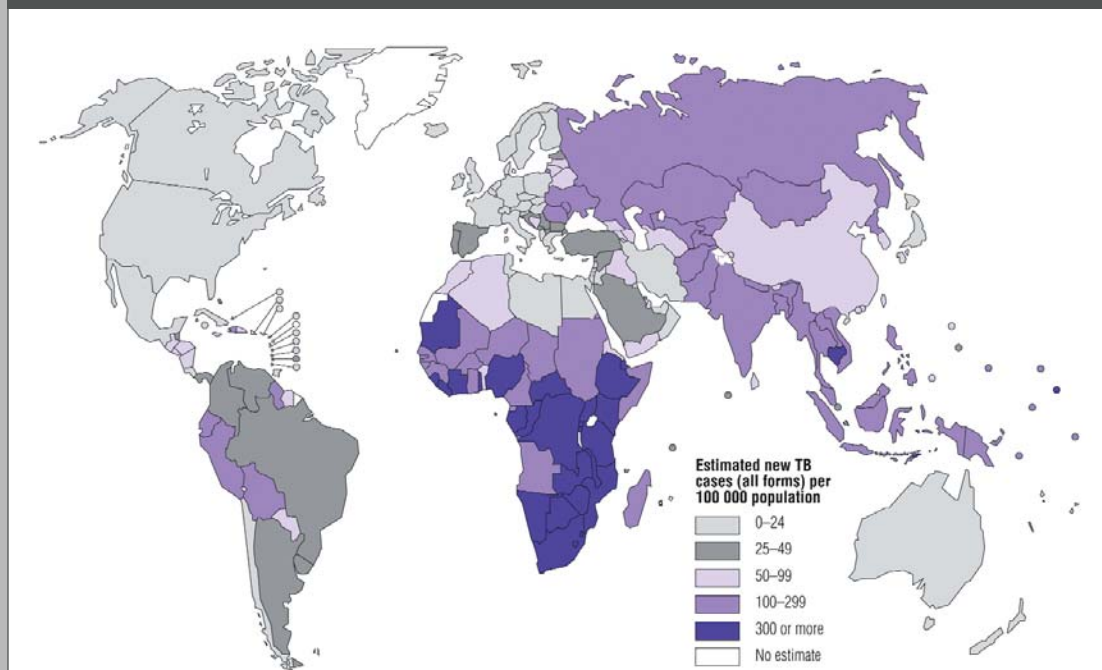
Social Determinants," a chapter in the forthcoming WHO report *Priority Public Health Conditions: From Learning to Action on Social Determinants of Health*. "It's possible that latency evolved as a mechanism to avoid extinction when human populations were small and isolated," he explains. "There are lots of ideas, but our understanding of the bacteria is primitive, and we haven't come close to explaining the basic facts yet."

TB drugs are a two-edged sword, says Tommie Victor, a professor of health sciences at Stellenbosch University in South Africa's Western Cape Province. They destroy the bacterium, but can also select for resistant bacteria against which those drugs are then ineffective. In the 1970s, the drugs had the upper hand, and TB seemed to be in decline. But funding and interest in TB control programs also declined, says Victor, and for the following 20 years no systematic monitoring of drug resistance was carried out. The situation changed dramatically with the arrival of HIV/AIDS in the 1980s, when transmission of TB and outbreaks of multidrug-resistant (MDR) TB increased around the globe.

Drug-susceptible TB cases can be cured with a standardized 6-month regimen of first-line antibiotics administered using the "directly observed treatment, short-course," or DOTS, protocol. Under the DOTS protocol, patients take their daily medication in the presence of a health care worker to ensure compliance. Considered one of the most effective clinical programs ever, DOTS is a cornerstone of the WHO Stop TB Strategy, which by 2015 aims to reduce the incidence of new TB cases to 50% of 1990 levels. (The long-term goal is to reduce annual TB incidence to fewer than 1 case per 1 million people by 2050.)

When TB patients don't comply with treatment, or when they take their drugs intermittently, resistant bacteria survive preferentially while drug-susceptible strains die. Thus, noncompliant

Estimated Incidence of New TB Cases as of 2006



Source: WHO. 2008. Global tuberculosis control 2008: surveillance, planning, financing. Geneva: World Health Organization; p. 20.

patients diagnosed initially with drug-susceptible TB can “acquire” MDR TB over time. MDR TB now accounts for 1 of every 20 new cases, making the global TB epidemic a far more urgent problem.

Studies by the Boston-based Partners In Health, a nonprofit supplier of health care services to developing countries, have shown MDR TB treatments can achieve cure rates of up to 80%. But MDR TB patients who remain noncompliant with treatment can acquire a still more worrisome form of TB—dubbed extensively drug-resistant (XDR) TB—that resists practically every known drug at doctors’ disposal.

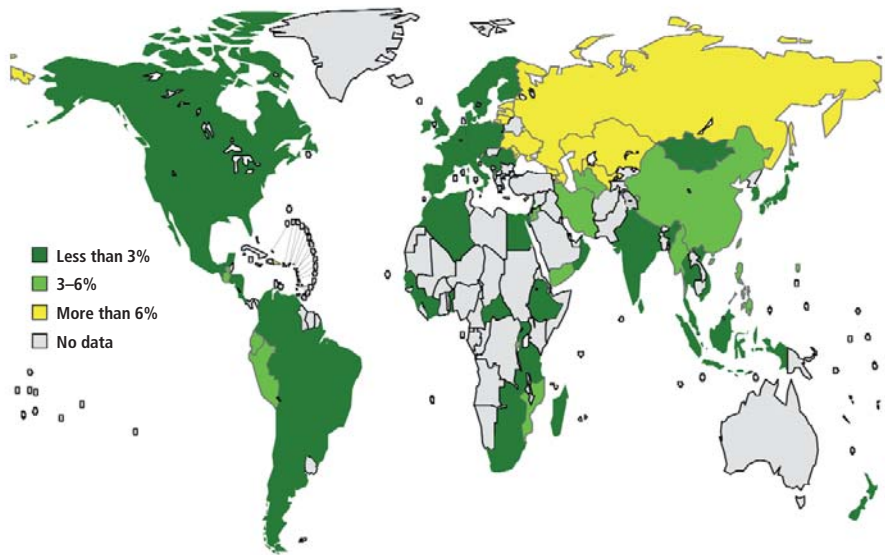
This lethal disease, discovered for the first time in 2005 in South Africa’s KwaZulu-Natal Province, has a far worse prognosis. This is especially true for patients coinfecting with HIV/AIDS, which blunts the immune response and severely exacerbates the downward spiral for those sickened by TB. A study published in the 7 August 2008 *New England Journal of Medicine* found that among 48 XDR TB patients in Peru, daily supervised treatment at community control centers achieved cure rates of 60%. However, none of these patients were HIV-positive. In comparison, all but 1 of 53 HIV-infected individuals stricken with XDR TB in KwaZulu-Natal Province in 2005 and 2006 died within several weeks of developing TB symptoms.

Other researchers have produced particularly dire assessments of XDR TB’s lethality. Citing results from his survey of 4,000 TB cases across several European countries, published in the May 2007 issue of *Emerging Infectious Diseases*, Giovanni Battista Migliori, director of the WHO Collaborating Centre for TB and Lung Diseases, says XDR TB’s mortality rate is up to 5 times greater than that of MDR TB.

It was previously thought that XDR TB, once acquired, might not be infectious beyond hospitals and other clinical settings. XDR TB bacteria were believed to be too weak to be broadly transmissible, presumably because the bacteria are so mutated that they’re generally unhealthy.

Scientists have begun questioning that assumption. Ted Cohen, an epidemiologist and assistant professor at Harvard Medical School, believes

Percentage of MDR TB among New TB Cases, 1994–2007



Source: WHO Stop TB Department. Available: http://www.who.int/tb/features_archive/mdr_map_new_cases.pdf.

Countries with the Most MDR TB among New TB Cases

	ESTIMATED CASES, 2006		NOTIFIED		EXPECTED TO BE TREATED	
	% OF ALL TB CASES WITH MDR-TB	NUMBER OF MDR-TB CASES	2006	2007	2008	
1 China	8.3	130 548	2	165	388	
2 India	4.9	110 132	21	100	450	
3 Russian Federation	19	36 037	3 949	24 100	24 000	
4 Pakistan	5.0	15 233	–	0	0	
5 Bangladesh	4.0	14 583	–	50	150	
6 South Africa	2.6	14 034	6 716	4 843	5 252	
7 Ukraine	22	13 429	–	–	–	
8 Indonesia	2.2	12 142	59	–	100	
9 Philippines	4.6	11 848	403	170	340	
10 Nigeria	2.3	11 171	–	0	500	
11 Uzbekistan	24	9 829	83	60	395	
12 DR Congo	2.8	7 044	1	–	–	
13 Kazakhstan	25	6 608	4 117	–	–	
14 Viet Nam	4.0	6 421	–	100	–	
15 Ethiopia	1.9	5 825	–	50	50	
16 Myanmar	4.8	4 251	666	75	75	
17 Tajikistan	20	3 204	0	0	–	
18 Azerbaijan	29	2 397	398	50	150	
19 Republic of Moldova	27	2 035	1 040	290	–	
20 Kyrgyzstan	18	1 368	336	–	–	
21 Belarus	16	1 096	651	–	–	
22 Georgia	12	652	266	155	225	
23 Bulgaria	13	451	53	50	50	
24 Lithuania	17	425	332	–	–	
25 Armenia	14	381	215	30	–	
26 Latvia	14	218	143	130	115	
27 Estonia	20	128	52	67	–	
Global priority countries	5.6	421 490	19 503	30 485	32 240	
AFR	2.2	66 711	7 074	7 673	7 993	
AMR	3.4	12 254	2 088	6 736	5 301	
EMR	4.2	25 475	295	901	928	
EUR	16	82 042	12 498	27 243	27 358	
SEAR	4.3	149 615	767	2 587	3 004	
WPR	6.9	153 042	631	1 397	1 643	
Global	4.8	489 139	23 353	46 537	46 227	

– Indicates information not provided.

AFR=Africa; AMR=Americas; EMR=Eastern Mediterranean; EUR=Europe; SEAR=Southeast Asia; WPR=Western Pacific. “Notified” refers to notification of public health officials of new TB cases for tracking purposes.

Source: WHO. 2008. Global tuberculosis control 2008: surveillance, planning, financing. Geneva: World Health Organization; p. 51.

When considering these factors, it's important to distinguish infection risks (i.e., situations that bring people who have TB in close contact with others) from those that accelerate disease progression among people who are already infected. For 40 years, crowding has been cited as a crucial infection threat in both industrialized and nonindustrialized countries. But this factor's unique contribution to TB risk is hard to quantify, concedes Lönnroth. "The relative risks [from crowding] vary with housing quality, TB prevalence in the community, and also with access to health care, which is associated with chance of early cure of infectious cases," he says.

Recent findings on crowding and TB infection risk were published by Michael Baker and colleagues at the He Kainga Oranga/Housing and Health Research Programme, University of Otago, New Zealand, in the August 2008 *Journal of Epidemiology and Community Health*. The study revealed that among those aged 40 years or younger, every 1% increase in the proportion of overcrowded households in a given census block led to an 8% increase in TB incidence in that block, holding other variables constant.

Those results support more general findings from India, which show that compared with rural areas, TB prevalence rates are consistently higher among urban children aged 9 years or younger. Vineet Chadha, a senior epidemiologist at the National Tuberculosis Institute in Bangalore, who published those findings in the May 2004 issue of the *International Journal of Tuberculosis and Lung Disease*, says two factors explain the urban/rural discrepancy: first, slum conditions facilitate TB transmission; and second, many urban health practitioners don't adhere to the DOTS protocol for TB detection and treatment.

The WHO agrees that poverty and urbanization create the perfect conditions for TB transmission. Urbanization leads to higher population densities, crowded living conditions, and increased mobility among migrants seeking temporary work.



Arkadiy Yusev, age 23, is a Russian prisoner and TB patient. The disease is rampant in the overcrowded prisons of the Russian Federation, which has the eleventh greatest TB burden in the world.

A report on crowding and TB, created by researchers at the University of Otago under contract with the WHO, is expected by the end of the year, Rehfuess says. "My sense is that crowding is an important risk factor, but the exposure measures used in epidemiological studies so far haven't been very reliable," she says. "So we cannot claim to have conclusive evidence for a causal effect yet." She points out that many studies show an association—the issue is whether the association is causal or not, as crowding tends to be associated with many other poor socioeconomic and living conditions that could confound the observed relationship.

The links between cigarette smoking and TB, on the other hand, are well documented. Worldwide approximately 1.1 billion people smoke cigarettes, including 930 million in developing or middle-income countries, according to the WHO. At the same time, half the world's population cooks on open fires or traditional

stoves fueled by coal or biomass (wood, animal dung, crop residues, or charcoal), often indoors in poorly ventilated spaces. These stoves produce smoke with chemical constituents—for example, carbon monoxide—similar to those in cigarette smoke. Rehfuess points out that in the developing world most women do not smoke, and most men do not cook for their families. Therefore, in these settings, smoking is one of the greatest TB risk factors for men, whereas indoor air pollution from solid fuel use is likely to be one of the greatest for women. However, a meta-analysis published by Ezzati's doctoral student Hsien-Ho Lin in the January 2007 *PLoS Medicine* suggests exposure to second-hand tobacco smoke—not just active smoking—also elevates TB risk, making cigarette smoke exposure a risk factor for both sexes.

Since the 1940s, epidemiologists have tried to isolate the unique contributions of tobacco and biomass smoke to TB risk, but early studies did not control adequately for confounders including socioeconomic status, nutrition, alcohol use, housing, and crowding. A turning point came in 2003, when Vendhan Gajalakshmi, a scientist with the Epidemiological Research Center in Chennai, India, and colleagues published a large retrospective investigation that concluded half the TB mortality among Indian men is triggered by active tobacco smoking. This case-control study of 43,000 male deaths and 35,000 controls was published in the 16 August 2003 issue of *The Lancet* and sparked a flurry of new investigations.

Lin's meta-analysis in the January 2007 *PLoS Medicine* and another by epidemiology professor Michael Bates in the 26 February 2007 *Archives of Internal Medicine* helped to confirm that smoke and TB are causally linked. By combining data from dozens of existing studies, meta-analyses reinforce shared conclusions, Ezzati explains. "The findings of any single study could be produced by chance, or it could show an effect whose magnitude is smaller or larger than the true one," he says. "But when you combine many studies that look at the same question and they all point in the

Countries with the Greatest TB Burden as of 2006

	POPULATION 1000s	INCIDENCE ^a				PREVALENCE ALL FORMS		MORTALITY ALL FORMS		HIV PREV. IN INCIDENT TB CASES ^b
		ALL FORMS		SMEAR-POSITIVE		NUMBER 1000s	PER 100 000 POP PER YEAR	NUMBER 1000s	PER 100 000 POP PER YEAR	
		NUMBER 1000s	PER 100 000 POP PER YEAR	NUMBER 1000s	PER 100 000 POP PER YEAR					
1 India	1 151 751	1 933	168	867	75	3 445	299	325	28	1.2
2 China	1 320 864	1 311	99	590	45	2 658	201	201	15	0.3
3 Indonesia	228 864	534	234	240	105	578	253	88	38	0.6
4 South Africa	48 282	454	940	184	382	482	998	105	218	44
5 Nigeria	144 720	450	311	198	137	890	615	117	81	9.6
6 Bangladesh	155 991	351	225	158	101	610	391	70	45	0.0
7 Ethiopia	81 021	306	378	136	168	520	641	68	83	6.3
8 Pakistan	160 943	292	181	131	82	423	263	55	34	0.3
9 Philippines	86 264	248	287	111	129	373	432	39	45	0.1
10 DR Congo	60 644	237	392	105	173	391	645	51	84	9.2
11 Russian Federation	143 221	153	107	68	48	179	125	24	17	3.8
12 Viet Nam	86 206	149	173	66	77	194	225	20	23	5.0
13 Kenya	36 553	141	384	56	153	122	334	26	72	52
14 UR Tanzania	39 459	123	312	53	135	181	459	26	66	18
15 Uganda	29 899	106	355	46	154	168	561	25	84	16
16 Brazil	189 323	94	50	59	31	104	55	7.6	4.0	12
17 Mozambique	20 971	93	443	39	186	131	624	24	117	30
18 Thailand	63 444	90	142	40	62	125	197	13	20	11
19 Myanmar	48 379	83	171	37	76	82	169	6.1	13	2.6
20 Zimbabwe	13 228	74	557	30	227	79	597	17	131	43
21 Cambodia	14 197	71	500	31	220	94	665	13	92	9.6
22 Afghanistan	26 088	42	161	19	73	60	231	8.3	32	0.0
High-burden countries	4 150 313	7 334	177	3 265	79	11 889	286	1 330	32	11
AFR	773 792	2 808	363	1 203	155	4 234	547	639	83	22
AMR	899 388	331	37	165	18	398	44	41	4.5	6.4
EMR	544 173	570	105	256	47	826	152	108	20	1.1
EUR	887 455	433	49	194	22	478	54	62	7.0	3.0
SEAR	1 721 049	3 100	180	1 391	81	4 975	289	515	30	1.3
WPR	1 764 231	1 915	109	860	49	3 513	199	291	17	1.2
Global	6 590 088	9 157	139	4 068	62	14 424	219	1 656	25	7.7

^a All estimates include TB in people with HIV. Estimates of incidence, prevalence and mortality in people with HIV are given by country and region in Annex 3, Table A3.1.

^b Prevalence of HIV in incident TB cases of all ages.

AFR=Africa; AMR=Americas; EMR=Eastern Mediterranean; EUR=Europe; SEAR=Southeast Asia; WPR=Western Pacific.

Source: WHO. 2008. Global tuberculosis control 2008: surveillance, planning, financing. Geneva: World Health Organization; p. 19.

same general direction, then you can have more confidence that the conclusion you're getting is correct."

Although proposed links between smoke exposure and TB might be more defensible now, the underlying mechanisms remain unclear, Ezzati concedes. According to Lin, some scientists speculate that cigarette smoke boosts TB infection risk by impairing the ability of lung cilia to clear bacteria from the respiratory tract.

But exposure might also raise progression risk, adds Adrie Steyn, an assistant professor of microbiology at The University of Alabama at Birmingham, by flooding the body with carbon monoxide. This gas, produced naturally by the body, helps regulate a type of programmed cell death called apoptosis. Evidence suggests apoptosis might account for TB latency. But under high carbon monoxide exposure conditions, such as those induced by cigarette smoking and indoor burning of biomass, apoptosis dramatically declines, Steyn says. And that, he concludes, might allow TB-infected cells to survive and flourish.

More than a matter of medical intrigue, the effects of smoking on the infection/progression continuum pose a real concern for the public health response, Lin says. "DOTS treatment acts on decreasing the probability of infection in the population," he explains. "If you find that smoking acts more on progression than infection, then DOTS treatment and smoking cessation might complement each other. But if smoking is related more to infection, then the beneficial effect of combining DOTS with smoking cessation is smaller."

Excessive alcohol use, meanwhile, appears to raise progression and infection risks alike, the former by impairing immune responses, and the latter by inviting risky social interactions that foster transmission of the disease. Smoking and drinking tend to go hand-in-hand, which makes it hard to tease out the effect of one from the other, says Lönnroth. He is lead author of a new meta-analysis of 3 cohort and 18 case-control studies, produced by the WHO Stop TB Department and published 14 August 2008 in *BMC Public Health*, that strives to

isolate alcohol's role in TB. According to that analysis, TB risk is elevated among people who consume more than 40 grams of alcohol per day (the amount found in roughly three 12-oz glasses of beer, 5-oz glasses of wine, or 1.5-oz shots of hard liquor). "Smoking was controlled for in many but not all of the studies in our review, and when we separated out the studies that controlled for smoking, the relative risk [associated with alcohol] tended to be even higher," Lönnroth says. "The bottom line is that both are independent risk factors, and together they might be particularly strong risk factors."

On a population basis, malnutrition ranks as the risk factor most commonly linked with TB, according to the forthcoming "Expanding the Global Tuberculosis Control Paradigm." Still, "the evidence [for that association] in humans is surprisingly thin from the perspective of scientific rigor," write J. Peter Cegielski and David N. McMurray in a review of human and animal studies published in the March 2004 issue of the *International Journal of Tuberculosis and Lung Disease*. Citing evidence from observations in humans, work in experimental animals, and inferences from related studies in other fields, the authors note that a "wealth of ecological associations link TB with malnutrition in populations affected by famine, war, natural disasters, poverty, mass migration, and confinement in prisons or ghettos."

Still, human studies are problematic, they concede, because TB itself causes wasting, immune system depression, and other symptoms resembling malnutrition. Given that it's usually impossible to retrospectively discern nutritional status in patients before their TB disease, it's hard to determine whether malnutrition led to TB or vice versa. This can only be done reliably through cohort studies that follow healthy subjects over time after determining nutrition status at baseline, says Lönnroth.

Studies from animal models focus on the role of micronutrients, such as proteins and vitamins. The results of such studies, Cegielski and McMurray claim, suggest that protein deficiency in particular impedes both innate and vaccine-induced resistance to TB, although precisely how it does so remains unclear. The two authors conclude that in the aggregate, evidence suggests that malnutrition and TB are related; therefore, “nutritional support of undernourished populations at high risk of TB may reduce the incidence of TB in such groups.”

Keshavjee agrees with that conclusion. “When you’re not eating well, you’re probably not producing collagen and immune proteins properly, and that leads to problems with lung parenchyma [i.e., the integrity of the lung tissue itself] and also with immune function,” he says. “We could be talking about something as simple as vitamin D deficiency. Vitamin D helps with macrophage function, and macrophages help to clear TB bacteria. So if you don’t have enough [vitamin D], you could be at higher risk.”

Adding to a link with nutrition is growing evidence that diabetes exacerbates TB risk. A meta-analysis by Christie Jeon and Megan Murray, published 15 July 2008 in *PLoS Medicine*, concluded “diabetes is associated with TB risk regardless of study design and population.” Indeed, says Enarson, with an increase in high-fat/low-nutrition diets with and lack of exercise, the combination of diabetes and smoking will probably cause more TB worldwide in the next 2 to 3 years than any other factor.

Applying Risk Factors to TB Control

With accumulating evidence showing that environmental factors exacerbate TB risk, health experts are contemplating how to incorporate these findings into TB control programs. For a start, says Rehfuess, health professionals should inform patients and their families of the potential harm resulting from excessive drinking, smoking, indoor biomass burning, and other practices. “Raising awareness and creating demand for solutions

will not solve the problem,” she says, “but it could be a stepping stone. And even that is not happening.”

Murray and others suggest that high-risk populations, including smokers and diabetic patients, might be targeted for active case finding. Locating patients with TB remains a difficult challenge. The disease can take weeks to diagnose; meanwhile, untreated patients pose infection risks to their communities. Looking within high-risk populations might make those efforts more efficient. Moreover, tying case detection to enticements such as improved cooking stoves might also make for good strategy, Ezzati proposes. “Those who agree to be tested for TB regularly, along with those who agree to quit smoking, might be entitled to a clean stove benefit,” Ezzati says. “And that would have benefits

beyond TB, because these pollutants also increase risks for other lung diseases.”

Partners In Health has already incorporated risk factors into their treatment approach, Keshavjee says. The organization supports community treatment programs and helps families pay to build an additional room to house the infected patient, thereby reducing the risk of crowding, while also supplying clean fuels such as kerosene to reduce indoor air pollution. Keshavjee concedes these measures come at a cost to the organization, but he emphasizes the downstream expenses posed by inadequately treated TB are far higher.

Thus far, the WHO hasn’t integrated risk factors into its TB control efforts. The problem, Dye points out, is that changes in the risk factor trends that have traditionally accompanied TB fluctuations occur slowly—

over decades or even centuries. “Smoke exposure and other factors heighten TB risk, but it’s difficult to imagine how we could manipulate these things to bring down TB incidence quickly,” he says. “It would be beneficial if these risk factors didn’t exist, but they’re not going to replace prompt drug treatment, which is still the most powerful way to save lives quickly and reduce transmission. Risk factor interventions are useful, but they’re supplementary.”

Still, the authors of “Expanding the Global Tuberculosis Control Paradigm” acknowledge that “even if the Stop TB strategy is successfully implemented . . . the global incidence rate by 2050 would be about 100 times greater than the elimination target. Interventions to reduce progression to disease may include preventive treatment with anti-TB drugs, a new vaccine that prevents progression from infection to disease, as well as reducing exposure to various social, environmental, and biological risk factors for TB.” Adds Keshavjee, “[Environmental] risk factor controls have not typically been under the purview of the TB community. To address them, we have to think outside the box.”

Charles W. Schmidt

A typographic error in the original version of this article miscited the duration of the DOTS regimen. The error has been corrected here.



For many TB patients, such as this terminally ill woman in Kinshasa, DR Congo, effective drugs are prohibitively expensive. DR Congo has the tenth greatest TB burden in the world.