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Trade liberalization and tuberculosis incidence: a longitudinal multi-level analysis in 22 high burden countries between 1990 and 2010

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Background Trade liberalization is promoted by the World Trade Organization (WTO) through a complex architecture of binding trade agreements. This type of trade, however, has the potential to modify the upstream and proximate determinants of tuberculosis (TB) infection. We aimed to analyse the association between trade liberalization and TB incidence in 22 high-burden TB countries between 1990 and 2010.

Methods and findings A longitudinal multi-level linear regression analysis was performed using five different measures of trade liberalization as exposure [WTO membership, duration of membership, trade as % of gross domestic product, and components of both the Economic Freedom of the World Index (EFI4) and the KOF Index of Globalization (KOF1)]. We adjusted for a wide range of factors, including differences in human development index (HDI), income inequality, debts, polity patterns, conflict, overcrowding, population stage transition, health system financing, case detection rates and HIV prevalence.

None of the five trade indicators was significantly associated with TB incidence in the crude analysis. Any positive effect of EFI4 on (Log-) TB incidence over time was confounded by differences in socio-economic development (HDI), HIV prevalence and health financing indicators. The adjusted TB incidence rate ratio of WTO member countries was significantly higher [RR: 1.60; 95% confidence interval (CI): 1.12–2.29] when compared with non-member countries.

Conclusion We found no association between specific aggregate indicators of trade liberalization and TB incidence. Our analyses provide evidence of a significant association between WTO membership and higher TB incidence, which suggests a possible conflict between the architecture of WTO agreements and TB-related Millennium Development Goals. Further research is needed, particularly on the relation between the aggregate trade indices used in this study and the hypothesized mediators and also on sector-specific indices, specific trade agreements and other (non-TB) health outcomes.

Keywords Globalization, social epidemiology, social determinants, tuberculosis, health systems research

Introduction

All World Health Organization (WHO) regions are on track to reach the tuberculosis (TB)-related Millennium Development Goals (MDGs) (WHO 2012b), but the progress is slow and the decline in global TB incidence since 2004 has been estimated at <1.0% per year (WHO 2009; Lönnroth *et al*. 2010a). This rate of reduction in TB incidence is much less than the rate of 6% that could be expected under the full implementation of the Global Plan to Stop TB (Lönnroth *et al*. 2009).

Concern has risen about the neglected links between TB and the proximate risk factors of TB infection (Creswell *et al*. 2011) such as diabetes (Stevenson *et al*. 2007; Jeon and Murray 2008; Baker *et al*. 2011; Hall *et al*. 2011; Maurice 2011), smoking (Lin *et al*. 2007; van Zyl-Smit *et al*. 2010), malnutrition (Cegielski and McMurray 2004; Lönnroth *et al*. 2010b) and alcoholism (Lönnroth *et al*. 2008; Rehm *et al*. 2009), which increase the relative risk to acquire, develop or die from TB.

The 'slower-than-expected' rate of decline in global TB incidence (Lönnroth *et al*. 2009) has also shifted the focus towards the upstream or social determinants of health in TB control strategies (Lönnroth *et al*. 2009; Rasanathan *et al*. 2011). These are the factors that affect and modify the proximate risk factors of TB infection, ranging from weak health systems (Atun *et al*. 2010), urbanization (Hargreaves *et al*. 2011), conflict (Drobniewski and Verlander 2000; Gustafson *et al*. 2001; Martins *et al*. 2006), debts and structural adjustments (Stuckler *et al*. 2008) to poverty, migration (Lönnroth *et al*. 2009), inequitable social structures and 'structural violence' (Farmer 1999).

Notably, international trade—an important macro-economic determinant with the potential to modify both upstream (Spiegel *et al*. 2004) and proximate determinants of TB (Labonte *et al*. 2011)—is not explicitly mentioned in recently formulated frameworks on the social determinants of TB (Lönnroth *et al*. 2009).

Linking international trade, liberalization policies and TB

The overarching promise of trade liberalization is well reflected in the following statement of the Director-General of the World Trade Organization (WTO):

> The opening of national markets to international trade [...] will encourage and contribute to sustainable development, raise people's welfare, reduce poverty, and foster peace and stability. (WTO 2012)

Increasing attention has been paid by scholars and researchers within the health community to the potential negative effects of trade liberalization on individual and population health (Blouin 2007; Labonte and Schrecker 2007). Numerous links between multi-lateral trade agreements (MTAs) under the WTO and population health have been outlined in the last decade (Bettcher *et al*. 2000; Ranson *et al*. 2002; WHO and WTO 2002; Labonte 2003; Labonte and Sanger 2006a,b; Lee *et al*. 2009; Blouin *et al*. 2009; MacDonald and Horton 2009; Smith *et al*. 2009a,b). Three potential pathways from international trade to determinants of TB infection deserve particular attention. These pathways might be of particular relevance for the 22 high-burden TB countries (HBCs) that (in absolute terms) accumulated ~81% of all incident cases between 1990 and 2010 (WHO 2012b) (Supplementary Appendix p. 2).

Effects mediated through income, poverty and (in)equality

First, trade policies, including trade liberalization, have a direct impact on income, (in)equality and economic (in)security (Blouin *et al*. 2009). Although the links to all stages of the disease are not yet clear, there is a consensus that these factors affect the vulnerability of individuals and populations to the proximate risk factors of TB (Bates *et al*. 2004; Semenza and Giesecke 2008; Lönnroth *et al*. 2009) and mark TB out as a social disease (Raviglione and Krech 2011).

Effects mediated through the prevalence of diabetes, smoking, alcoholism and malnutrition

Second, there is a link between economic policies and the 'chronic disease pandemic' (Geneau *et al*. 2010) which in turn is associated with the TB epidemic (Stuckler *et al*. 2010; Creswell *et al*. 2011). Labonte and his colleagues reviewed the evidence underlying the first part of this link. They suggested a generic framework that illustrates how tariff reductions and/or increased foreign direct investments (FDIs) in potentially health-damaging industries (such as the food, tobacco and alcohol industry) may fuel the epidemiological transition in low- and middle-income countries (Labonte *et al*. 2011). The key insight is that these mechanisms can increase the supply of potentially health-damaging products, reduce respective prices and (in the case of FDI in the food, alcohol and/or tobacco industry) help transnational corporations to circumvent national regulations (Labonte *et al*. 2011). Merging their framework conceptually with the framework on the social determinants of TB (Lönnroth *et al*. 2009) opens up the insight that there might be an effect of trade liberalization on TB incidence which is—in epidemiological terms—mediated by its effects on the prevalence of chronic conditions such as diabetes, smoking, alcoholism and malnutrition (Figure 1).

Effects mediated through complex interactions between trade agreements and upstream and proximate determinants of TB infection

Third, over and above the effects of income, tariff rates and FDI flows, there are several links between international trade and the upstream and proximate determinants of TB that have their roots in the legal-judicial architecture of MTAs under the WTO (Figure 2).

The General Agreement on Trade in Services (GATS) might affect the epidemiology of TB via effects on important blocks of the health system, such as access to and affordability of health service provisions and/or the availability and distribution of human resources for health (Pollock and Price 2003; Smith *et al*. 2009a; Kanchanachitra *et al*. 2011).

The agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), through its impact on access to essential medicines (Ranson *et al*. 2002; Haakonsson and Richey

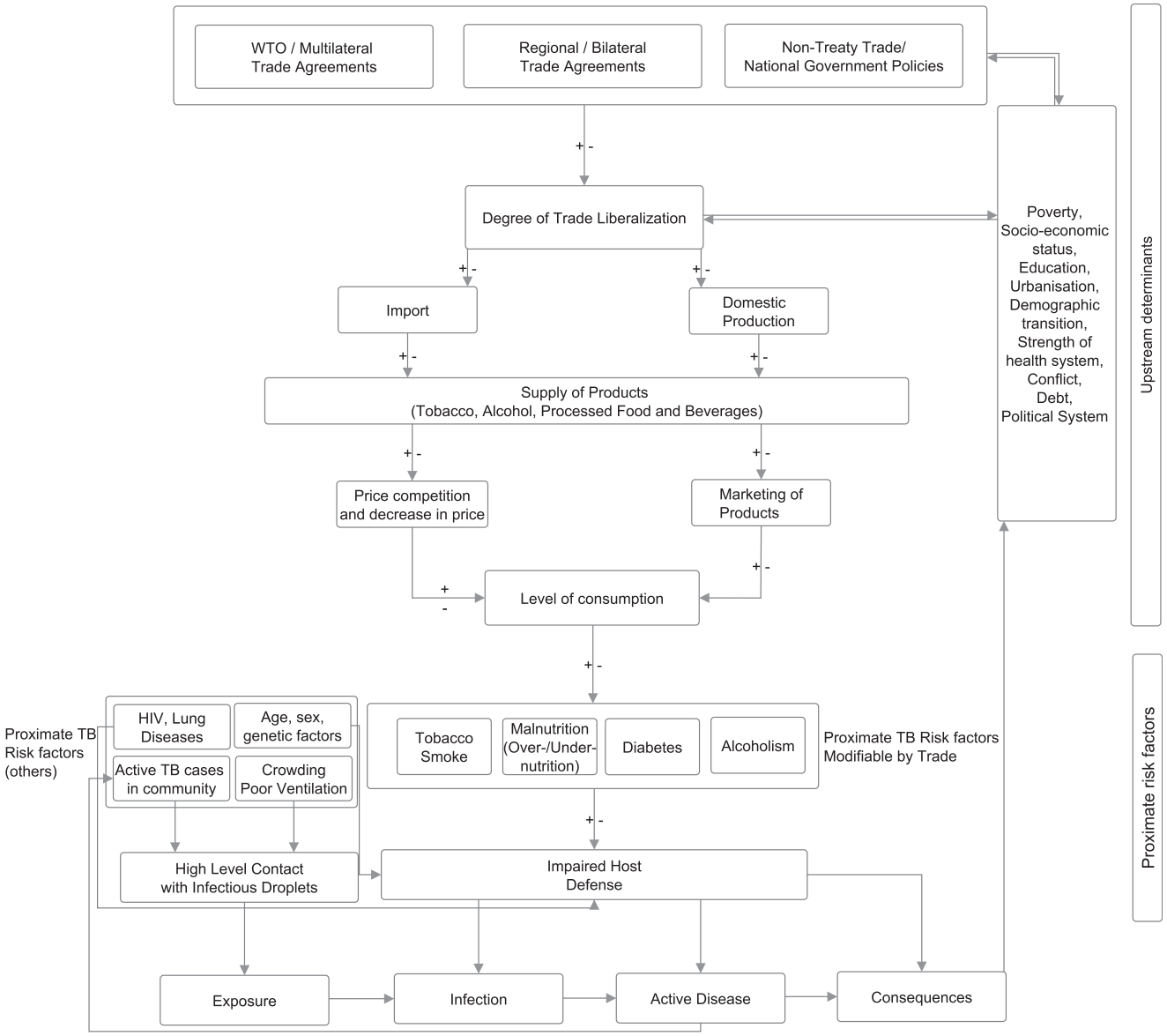

Figure 1 Conceptual framework of the theoretical link between trade liberalization, chronic diseases and TB. Adapted from: Labonte *et al.* (2011) and Lönnroth *et al*. (2009).

2007; Smith *et al.* 2009b), might affect the affordability of drugs for TB treatment, or for the prevention, diagnosis and treatment of important risk factors for TB infection such as HIV/AIDS or diabetes (Commission on Intellectual Property Rights Innovation and Public Health 2006).

Finally, the Agreement on Agriculture (AoA) might affect food security and thereby the prevalence of undernutrition (WHO and WTO 2002; Chand 2006; Gayi 2006; Labonte and Sanger 2006b) which is a proximate risk factor of TB infection (Lönnroth *et al.* 2009) (Figure 2).

The empirical evidence on the links between trade liberalization and TB incidence

Despite the hitherto presented potential power of trade liberalization to modify the upstream and proximate determinants of TB infection (Figures 1 and 2), and thereby influence the epidemiology of TB globally, there is a dearth of evidence regarding this relationship.

A boolean search on Web of Science© and PubMed with very broad search terms [(trade OR 'international trade' OR 'trade lib*') AND tuberculosis] including all databases and all years (i.e. '1945–2012') yielded 141 and 104 articles, respectively (on '13 May 2012'). No single study was identified that explicitly aimed to quantify the effect of any dimension of trade liberalization on TB epidemiology in any country or region of the world.

If any of the suggested pathways (Figures 1 and 2), or the above-mentioned promise of the WTO, hold, it should be possible to quantify any positive or negative effect of trade liberalization on TB control and the progress towards MDG 6.

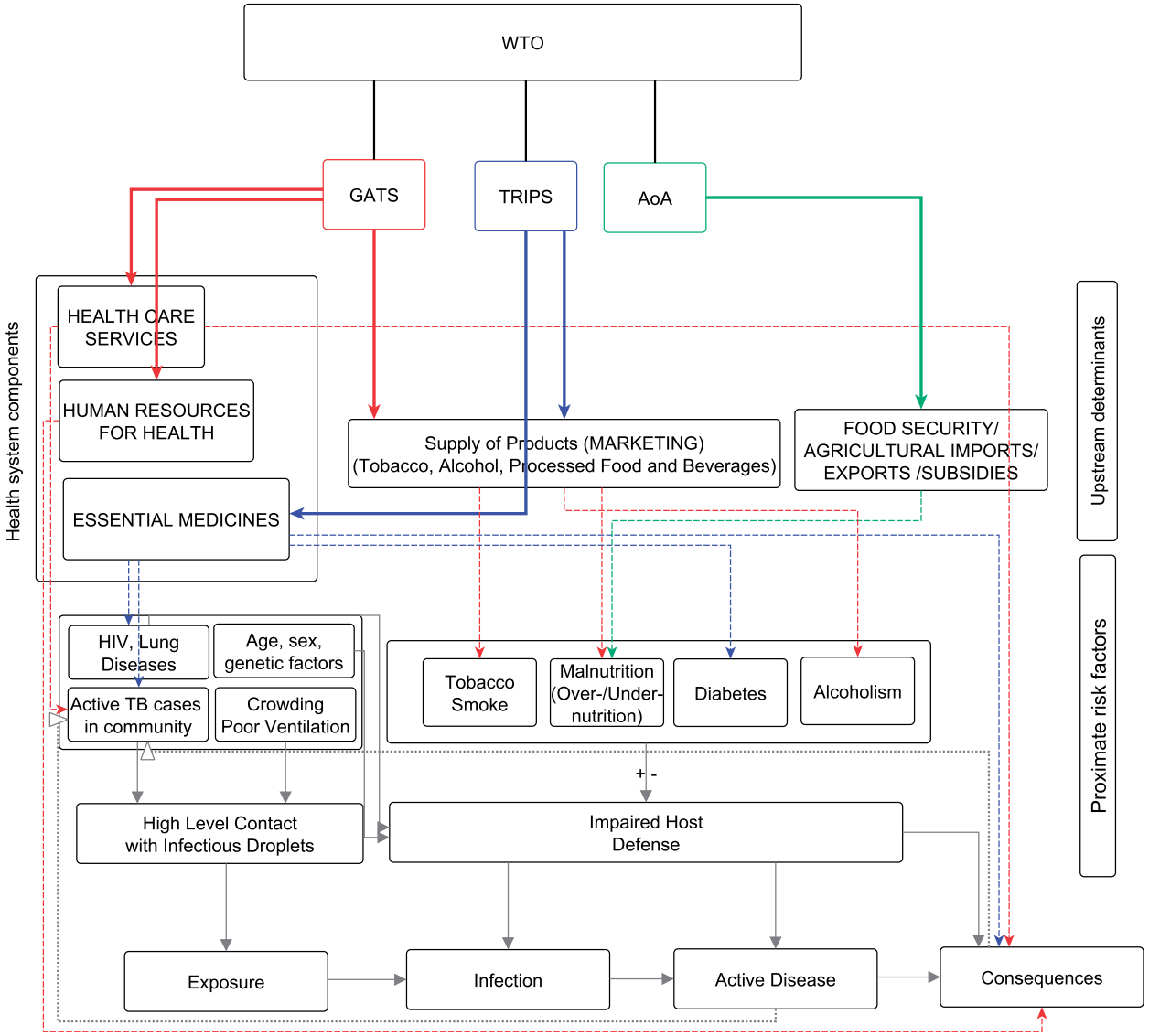

Figure 2 Conceptual framework of the theoretical link between multi-lateral trade agreements under the World Trade Organization and TB incidence. Adapted from: Lönnroth *et al.* (2009). Thick solid arrows theoretical direct links between MTAs and upstream determinants of TB infection. Dashed arrows theoretical indirect links between MTAs and the proximate risk factors of TB infection. Thin solid arrows pathway from proximate risk factors to infection/transmission chain. Dotted arrows feedback effects on prevalence of active TB cases in community. GATS, General Agreement on Trade in Services; TRIPS, Trade-Related Aspects of Intellectual Property Rights; AoA, Agreement on Agriculture.

Purpose of this study

We examined the relationship between trade liberalization, measured by five different indicators, and TB incidence in the 22 HBCs between 1990 and 2010. We further controlled for confounding of the relationship by (1) socio-economic, (2) socio-political and (3) socio-demographic factors and/or (4) differences in health systems performance or HIV prevalence.

Methods

Study design, study sites and observation period

We conducted a longitudinal multi-level linear regression analysis on the association between trade liberalization and TB incidence in the 22 HBCs (Supplementary Appendix p. 2) using publicly available secondary data. The observation period included 21 observations between 1990 and 2010, yielding a total of 462 country-years that fed into the study.

Exposures

We chose five different measures of trade liberalization as exposures (Table 1), of which three particularly qualified for the first pathway (Figure 1). These were Trade Openness; the fourth dimension of the Economic Freedom of the World Index (EFI4) (Gwartney *et al.* 2011); and the first dimension of the KOF index of globalization (KOF1) (ETH 2012). KOF1 draws upon data used to calculate EFI4 (ETH 2012) and has been reported to be similar to EFI4 except for two important aspects

Table 1 Summary overview and definitions of exposures and selected hypothesized confounders

	Variable	Definition
Exposures	Economic Freedom of the World Index (fourth dimension)—EFI4	A composite indicator that measures 'Freedom to Trade Internationally' by drawing upon five dimensions: (A) Taxes on international trade [i. International trade tax revenues (% of trade sector); ii. mean tariff rate; iii. standard deviation of tariff rates]. (B) Regulatory trade barriers (i. Non-tariff trade barriers; ii. compliance cost of importing and exporting). (C) Size of the trade sector relative to expected. (D) Black-market exchange rates. (E) International capital market controls (i. Foreign ownership/investment restriction; ii. Capital controls).
	KOF Index of Globalization (first dimension)—KOF1	A weighted composite measure of 'Economic Globalization' building upon 'Trade Openness' and components of EFI4, but includes additional information on Foreign Direct Investments: (A) Actual flows (weighted 50%): - Trade (% of gross domestic product, GDP); Foreign Direct Investment, stocks (% of GDP); Portfolio Investment (% of GDP); Income Payments to Foreign Nationals (% of GDP). (B) Restrictions (weighted 50%): - Hidden Import Barriers (component of EFI4); Mean Tariff Rate (component of EFI4); Taxes on International Trade (% of current revenue); Capital Account Restrictions (component of EFI4).
	Trade Openness (% of GDP)	The sum of exports and imports of goods and services measured as a share of GDP.
	WTO membership[a]	Dummy for WTO membership (=1) or non-membership (=0) for each year of observation and country.
	WTO duration of membership (WTOcumxp)	The cumulative exposure to WTO membership was used as level 1 variable to account for time effects. The variable is zero as long as a country is not a WTO member, equals 1 after accession and increases in increments of 1 for each additional year of WTO membership.
Selected hypothesized confounders	Age dependency ratio (% of working-age population)	The ratio of dependents (people younger than 15 years or older than 64 years) to the working-age population (those aged 15–64 years).
	Armed conflict	Dummy for presence (=1) or absence (=0) of armed conflict, defined as 'a contested incompatibility [...] where the use of armed force [...] results in at least 25 battle-related deaths'.[a]
	Case detection rate (%)	The number of new and relapse TB cases '[...] that were diagnosed and notified by N[ational] T[uberculosis] P[rograms] [...], divided by the estimated incident cases of TB that year. The CDR [...] gives an approximate indication of the proportion of all incident TB cases that are actually diagnosed, reported to NTPs and started on treatment'.[b]
	Disbursements on external debt, long-term + International Monetary Fund (IMF) (DIS, current US$) in billion US$	'Disbursements are drawings by the borrower on loan commitments during the year specified. This item includes disbursements on long-term debt and IMF purchases. Long-term external debt is defined as debt that has an original or extended maturity of more than 1 year and that is owed to non-residents by residents of an economy and repayable in foreign currency, goods or services. IMF purchases are total drawings on the General Resources Account of the IMF during the year specified, excluding drawings in the reserve tranche'.[c]
	GINI index	Measures the extent to which the distribution of income among individuals or households within an economy deviates from a perfectly equal distribution. 0 represents perfect equality, 100 implies perfect inequality.[c]
	Human Development Index	A composite index measuring average achievement in three basic dimensions of human development: country-level income (GDP), education levels and life-expectancy (range 0–100).
	IMF repurchases and charges (Total debt service, TDS, current US$) in billion US$	'IMF repurchases are total repayments of outstanding drawings from the General Resources Account during the year specified, excluding repayments due in the reserve tranche. IMF charges cover interest payments with respect to all uses of IMF resources, excluding those resulting from drawings in the reserve tranche'.[c]

(continued)

Table 1 Continued

Variable	Definition
Polity2	The Polity IV Project's time-series indicator for democracy/autocracy: A composite measure that specifically focuses on 'institutionalized authority patterns' of states. Ranges from −10 (full autocracy) to 10 (full democracy).
Population density (people per sq. km of land)	Population density is mid-year population divided by land area in square kilometers.[c]
Population in urban agglomerations of more than 1 million (% of total population)	The percentage of a country's population living in metropolitan areas that in 2000 had a population of more than 1 million people.[c]
Regime durability	The number of years since the most recent regime change or the end of a transition period defined by the lack of stable political institutions.
Time since 1990 (period effects)	Continuous (level-1) variable calculated as: YEAR(i)—1990 (Equation 1), where YEAR(i) is the year of the ith measurement occasion.
Use of IMF credit (Debt outstanding and disbursed, DOD, current US$) in billion US$	Use of IMF credit denotes members' drawings on the IMF other than those drawn against the country's reserve tranche position.[c]
WTO cohort (cohort effects)	Variable based on year of accession to WTO. A WTO-cohort variable with seven groups (WTOcoh7) was generated, based on the year of accession to WTO, including the cohorts of the year 1995, 1996, 1997, 2002, 2004, 2007 and those who remained non-members throughout the whole observation period. An additional WTO-cohort variable with three groups (WTOcoh3) contained non-members (1), the cohorts 1995–1997 (2) and the cohorts 2002–2007 (3).

[a]Uppsala Conflict Data Program.

[b]WHO TB Report 2011.

[c]World Bank World Development Indicators Database. See Supplementary Appendix for full list of variables, definitions and calculations.

(Nilsson 2009): it includes additional information on FDIs and relies more on actual flows of trade and less on institutional aspects.

We additionally used WTO membership (dummy) and the cumulative duration of WTO membership as relevant indicators (Table 1) that qualified for both pathways (Figures 1 and 2).

Outcome

The primary outcome of interest was TB incidence, defined as the number of new and relapse cases of all forms of TB that occur in a given year per 100 000 population (WHO 2012b), retrieved from the WHO Global TB database (WHO 2012a).

Confounders and intermediate variables

We identified relevant confounding factors (Table 1) (Stuckler *et al*. 2008; Lönnroth *et al.* 2009) and mediators (Cegielski and McMurray 2004; Lin *et al*. 2007; Stevenson *et al.* 2007; Lönnroth *et al.* 2008, 2010b; Jeon and Murray 2008; Rehm *et al*. 2009; van Zyl-Smit *et al.* 2010; Baker *et al*. 2011; Hall *et al*. 2011; Labonte *et al*. 2011; Maurice 2011) from the literature. All analyses were guided by causal diagrams to distinguish between confounders (Figure 3) and mediators (Figure 4). An exception from these diagrams are EFI4 and WTO membership, which we included in some models together—using one of them as exposure and the other as a confounder, respectively.

To account for confounding by absolute and relative dimensions of health financing (Figure 3), a summary index (HSfinance-Index) was generated based on relevant health financing indicators (Supplementary Appendix p. 2). The measure is sensitive to absolute and compositional changes in health systems financing (Supplementary Appendix p. 3) and was used instead of single indicators to avoid problems caused by multicollinearity.

The Supplementary Appendix (pp. 3–6) contains an overview of exact definitions, calculations and data sources for 'all' variables used in this study.

Statistical analysis

We downloaded all data in MS Excel© format and merged these into a single, strongly balanced panel-dataset for further analysis using Stata® version 11.2.

Descriptive analysis

We analysed continuous variables longitudinally and cross-sectionally. Categorical variables (WTO membership/armed conflict) were analysed cross-sectionally and the % of countries for which the event (WTO membership/armed conflict) was present (1) or absent (0) was calculated in 5-year increments. We analysed descriptive trends by drawing scatterplots of the annual sample mean of TB incidence and the continuous liberalization indicators (Trade Openness, EFI4 and KOF1). We explored the relation between WTO membership and trends in EFI4 by panel data line plots (drawing upon EFI4 data for the period 1970–2009) to assess whether it is justified to use these variables in selected models together (or in other words: to assess whether or not EFI4 is a confounding factor or rather an intermediate variable on the pathway from WTO membership to TB incidence).

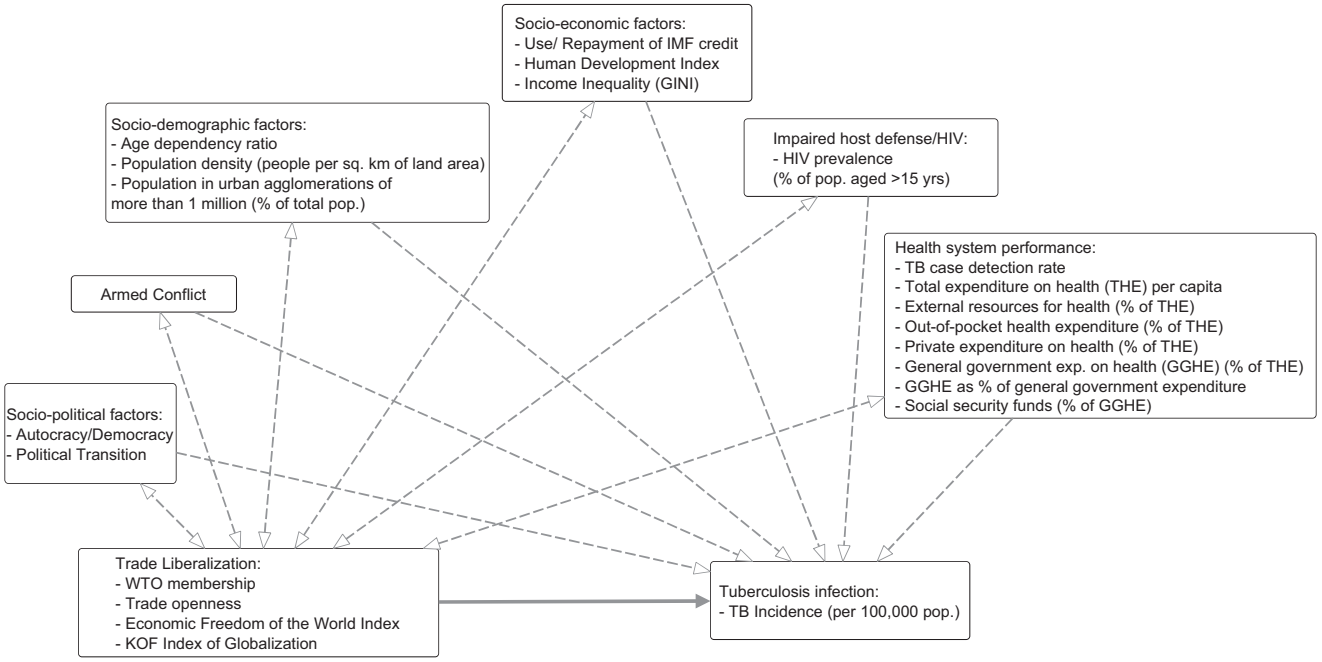

Figure 3 Simplistic causal diagram of the hypothetical causal relation between trade liberalization (exposure) and TB infection (outcome) and the causal or non-causal relations between confounders and exposure or outcome. Potential collinear relationships between confounders are deliberately omitted. Causal relations: one-sided arrows. Non-causal relations: two-sided arrows. Dashed lines: confounding relations.

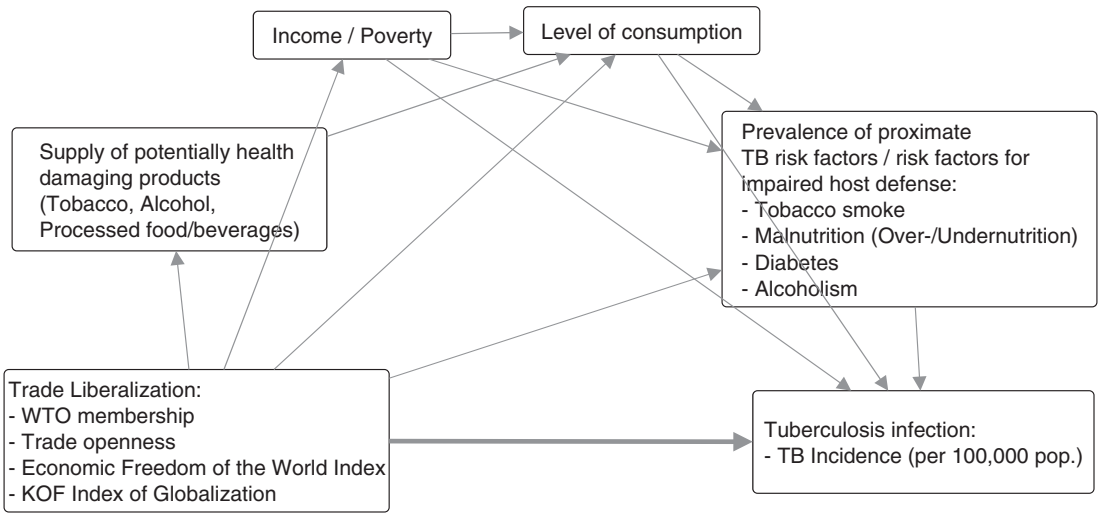

Figure 4 Causal diagram of the hypothetical relation between trade liberalization and TB incidence and mediators of the association.

Regression analysis

We fitted two-level (uni- and multivariate) linear regression models in which observations (level 1) are nested within countries (level 2) according to a repeated measurements design (Supplementary Appendix p. 8).

Regression diagnostics were performed to assess the model assumptions (linearity, normality of residuals, homoscedasticity, multicollinearity, and independence of the error terms, see Supplementary Appendix p. 10). Where the assumptions of linearity and normality of residuals were violated, variables (including the outcome variable) were log-transformed. We calculated robust standard errors (SEs) to account for heteroscedasticity of residuals and serial autocorrelation.

To obtain the fixed effects on Log-TB incidence of a given predictor, we fitted both random effect models (REMs) and fixed-effect models (FEMs) by generalized least squares estimation. An important difference between REMs and FEMs is that the REM can be used to make inferences regarding a

hypothetical population of clusters, while the FEM can be used to make inferences on the clusters in the sample in exactly the given time period (Rabe-Hesketh and Skrondal 2008) (see Supplementary Appendix p. 8 and 9 for further particulars on the statistical models). We present regression coefficients (β) as a measure of association between Log-TB incidence and exposure/confounder. To assess any effects on TB incidence 'on the original scale' when the exposure/confounder was not log-transformed, we present the exponential of the regression coefficients [exp(β)] and interpret these as incidence rate ratios (IRRs) with the respective 95% confidence interval (CI) [exp(β $\pm 1.96 \times SE$)].

We calculated the intra-class correlation (ICC) (Merlo *et al*. 2005a) (a measure of the degree of clustering at the country level) and the proportional change in variance (PCV) (Merlo *et al*. 2005b) for each variable that was added to a respective model using the null model (M0) (a model without predictors) as a reference. We added each trade indicator separately to M0 to retrieve the crude effects on the outcome variable, and added level 1 variables (time since 1990) to control for effects attributable to the mere passage of time. Based on the strength of association of the crude analysis (adjusted for level 1 variables), we chose EFI4 for further analysis and controlled for confounding variables from within the same category (Figure 3). To adjust for variables from different confounding categories, we performed an extended analysis in models containing EFI4, WTO membership and confounders from different categories which had been statistically significant in the previous models. The magnitude of negative/positive confounding was assessed by the % of excess risk explained (Supplementary Appendix p. 8).

To assess whether the use of a REM is reasonable, we performed the Hausman test (with Stata's 'sigmamore' option). Where this test was significant at the 0.05 level (indicating that the estimates of the REM are inconsistent), we interpreted the respective FEM; in all other cases, the estimates of the REM were interpreted. We assessed the goodness-of-fit of a given model by the root mean square error (root MSE), the within/between/overall and adjusted coefficient of determination (R^2).

Sensitivity analysis

We performed several sensitivity analyses for variables for which the linearity assumptions were violated (Sensitivity Analyses 1–3, Supplementary Appendix pp. 13–15). We cross-validated the results of selected models by multi-level poisson regression (ML-PR) and negative binomial regression models for panel data (ML-NBR) (Sensitivity Analysis 4, Supplementary Appendix p. 33).

Missing data

There were no missing data for the outcome variable. Missing data in exposure/confounding variables were categorized as 'intermittent' when missing between data points, or as 'drop out' when missing at the end or at the beginning of the observation period. To increase the sample size, we interpolated between data points and/or carried forward the last value of an observation for selected variables. For an exact documentation of missing proportions, patterns and handling strategies, see Supplementary Appendix p. 16.

Results

Descriptive results

TB incidence (per 100 000) peaked between 2000 and 2005 and declined until 2010 in the 22 high-burden countries (Table 2 and Figure 5). The variability (standard deviation, SD) in TB incidence on both scales was higher between than within countries (Table 2).

On average, the degree of liberalization in the sample (measured by all indicators) was higher in 2010 compared with 1990 (Figure 5). Nineteen of the 22 HBCs became WTO members until 2010, with an average duration of 12.4 years of membership (Table 2).

As measured by EFI4, the 22 HBCs experienced on average the highest increase in trade liberalization between 1990 and 1995, whereas Trade Openness and KOF1 increased steadily until 2007 (Figure 5). Exploring the relationship between trade liberalization measured by EFI4 and WTO membership revealed a non-stationary trend which, for most HBCs (Figure 6), started long before entry to WTO. This finding means that it is unlikely that increases in EFI4 are purely attributable to WTO membership and thus justify using WTO membership as distinct exposure/confounder together with EFI4 later in the same regression model.

During the two decades of the observation, there was on average a 25% increase in human development measured by the human development index (HDI) when compared with 1990, with variations much higher between than within countries (Table 2). Income inequality increased on average by ∼3% until 2005. As for socio-political factors, the average increase of 5.6 points in the Polity2 measure indicates that the sample's institutional authority patterns were characterized by higher levels of 'democracy' at the end of the observation period compared with the baseline. The sample prevalence of armed conflict ranged between 55% and 45% in the observation period.

TB case detection rates (on the original scale) were 19.0% higher in 2010 compared with 1990 indicating improvements in TB control programs. Compared with the baseline, there was a 120% increase in total health expenditures per capita in 2010, as well as a higher share of government expenditures and a lower share of private- and out-of-pocket-expenditures (as % of total health expenditure). These changes translated into a 0.82 increase in the logarithm of the HSfinance-Index (Table 2).

Regression results

Null-model and crude analysis (adjusted for level 1 effects)

Log-TB incidence was significantly ($P < 0.0001$) clustered within countries, as shown by the non-overlapping confidence bands of country-level mean Log-TB incidence rates with the sample mean incidence rate of all 22 HBCs which is illustrated by the red horizontal line (Figure 7). The ICC of the null model (M0) (Table 3) indicates that 90.4% of the variance in Log-TB incidence over time was attributable to differences between countries.

None of the liberalization indicators was significantly associated with Log-TB incidence in the crude analysis.

EFI4 and KOF1 changed significance and were negatively associated with Log-TB incidence (Table 3), when adjusted for effects attributable to the mere passage of time.

Table 2 Descriptive characteristics of empirical sample of HBCs ($n = 22$) between 1990 and 2010 (country-years $N = 462$)

Variable	Statistic	Period 1990–2010 (longitudinal)			Year (cross-sectional)					Change
		Overall	Between	Within	1990	1995	2000	2005	2010	1990/2010
TB Incidence (per 100 000 population)	Mean	283.29			259.55	266.09	291.55	304.59	283.68	24.14
	SD	*176.18*	*160.72*	*79.57*	*143.56*	*142.36*	*168.59*	*215.53*	*212.28*	
Log-TB incidence (per 100 000 population)	Mean	5.47			5.43	5.45	5.51	5.51	5.42	0.00
	SD	*0.60*	*0.58*	*0.19*	*0.52*	*0.55*	*0.60*	*0.67*	*0.70*	
Trade Openness (%)	Mean	57.34			41.96	52.01	57.89	69.25	64.28	22.32
	SD	*32.40*	*29.53*	*15.14*	*21.81*	*25.21*	*33.95*	*37.45*	*36.20*	
EFI4	Mean	5.74			4.66	5.71	5.91	6.02	5.95	1.29
	SD	*1.61*	*1.46*	*0.76*	*1.59*	*1.63*	*1.65*	*1.65*	*1.56*	
KOF1 (Values in last column are for 2008)	Mean	42.34			31.43	37.47	44.51	50.35	50.38	18.96
	SD	*13.39*	*11.35*	*7.54*	*10.74*	*11.54*	*13.61*	*11.83*	*12.02*	(*1990/2008*)
WTO membership*	Freq. (%)				0 (*0.00*)	14 (*63.64*)	16 (*72.73*)	18 (*81.82*)	19 (*86.36*)	19 (*86.36*)
*(*n* and % of countries that are WTO members)	5-years change (%)					*63.64*	*9.09*	*9.09*	*4.54*	
Duration of WTO membership (years)	Mean	4.79			0.00	0.64	4.23	8.14	12.41	12.41
	SD	*5.32*	*2.65*	*4.65*	*0.00*	*0.49*	*2.69*	*4.57*	*6.03*	
Log-population density (people per sq. km land)	Mean	4.34			4.14	4.25	4.35	4.44	4.52	0.38
	SD	*1.08*	*1.10*	*0.13*	*1.10*	*1.10*	*1.10*	*1.11*	*1.11*	
Log-Pop. in urban agglomerations of more than 1 million (% of total pop.)	Mean	2.38			2.27	2.32	2.38	2.45	2.50	0.24
	SD	*0.54*	*0.54*	*0.10*	*0.55*	*0.55*	*0.54*	*0.55*	*0.55*	
Age dependency ratio (%)	Mean	74.29			81.76	79.18	74.22	69.85	66.02	−15.73
	SD	*19.95*	*19.27*	*6.54*	*17.34*	*18.62*	*19.75*	*20.89*	*21.45*	
Human Development Index (HDI)	Mean	46.57			41.58	44.57	45.33	48.61	51.83	10.25
	SD	*13.58*	*13.26*	*3.85*	*12.36*	*13.94*	*14.45*	*13.36*	*13.13*	
Income Inequality (GINI index)	Mean	42.14			40.80	41.78	41.55	42.00	–	1.20
	SD	*8.60*	*8.05*	*2.35*	*9.45*	*8.78*	*8.88*	*10.70*	–	(*1990/2005*)
Log-use of IMF credits (in billion US$)	Mean	−1.16			−1.82	−0.75	−0.52	−1.14	−1.49	0.32
	SD	*2.22*	*1.38*	*1.76*	*2.24*	*1.27*	*1.60*	*1.26*	*1.71*	
Log-disbursements on long-term (external) debt and IMF purchases (in billion US$)	Mean	0.13			−0.11	0.33	−0.04	0.23	0.61	0.72
	SD	*2.36*	*2.18*	*1.02*	*1.73*	*1.78*	*2.05*	*2.63*	*2.74*	
Log-IMF repurchases and charges (TDS, in billion current US$)	Mean	−3.61			−3.04	−3.40	−3.01	−2.70	−5.96	−2.92
	SD	*2.87*	*2.55*	*1.86*	*2.88*	*2.18*	*2.81*	*2.81*	*3.50*	
Log-Case detection rate (%)	Mean	3.71			3.47	3.39	3.52	3.99	4.13	0.66
	SD	*0.65*	*0.45*	*0.48*	*0.75*	*0.75*	*0.75*	*0.31*	*0.25*	
Prevalence of HIV, total (% of population aged 15–49 years)	Mean	4.13			2.04	4.22	4.84	4.46	4.13	2.09
	SD	*5.90*	*5.53*	*2.27*	*3.34*	*6.41*	*6.89*	*6.11*	*5.55*	
Polity2	Mean	1.12			−2.45	0.77	1.32	2.57	3.10	5.55
	SD	*6.00*	*5.12*	*3.33*	*6.23*	*6.19*	*5.97*	*5.91*	*5.09*	
Durability of regimes (years)	Mean	14.93			21.05	12.64	12.32	15.91	18.23	−2.82
	SD	*17.59*	*15.69*	*8.59*	*21.53*	*15.79*	*16.89*	*17.88*	*19.61*	
Armed conflict**	Frequency (%)				12 (*54.55*)	9 (*40.91*)	10 (*45.45*)	10 (*45.45*)	10 (*45.45*)	−2 (*−9.10*)
** (*n* and % of countries in which a conflict occurred)	5-years change (%)					*−13.64*	*4.54*	*0.00*	*0.00*	

(continued)

Table 2 Continued

	Statistic	Period 1990–2010 (longitudinal)			Year (cross-sectional					Change
		Overall	Between	Within	1990	1995	2000	2005	2009	1990/2009
General Government Health Expenditure (GGHE) (% of General government expenditure)	Mean	8.32			–	7.68	8.48	7.90	7.95	0.27
	SD	*4.89*	*3.74*	*3.21*	–	*3.87*	*5.95*	*3.95*	*4.31*	
Log-External resources on health (% of THE)	Mean	1.01			–	0.38	0.73	1.26	1.71	1.33
	SD	*2.07*	*1.90*	*0.84*	–	*2.02*	*1.93*	*2.27*	*2.08*	
Social security funds (% of GGHE)	Mean	9.39			–	8.28	9.07	10.59	10.49	2.21
	SD	*14.98*	*14.86*	*2.92*	–	*15.27*	*14.90*	*15.58*	*16.91*	
Log-HSFinance-Index	Mean	8.08			–	7.72	7.82	8.29	8.54	0.82
	SD	*1.62*	*1.56*	*0.49*	–	*1.56*	*1.75*	*1.50*	*1.55*	
Total expenditure on health (THE) per capita (PPP, NCU per US$)	Mean	139.25			–	87.21	109.50	166.78	192.36	105.15
	SD	*199.36*	*189.23*	*71.42*	–	*124.71*	*154.00*	*224.78*	*258.33*	
Out-of-pocket health expenditure (% of THE)	Mean	48.96			–	49.90	51.20	49.29	45.29	−4.61
	SD	*19.88*	*19.38*	*6.40*	–	*20.28*	*20.37*	*19.62*	*20.32*	
GGHE (% of THE)	Mean	38.40			–	38.72	38.12	38.23	40.96	2.24
	SD	*16.29*	*15.54*	*5.64*	–	*15.87*	*16.45*	*16.54*	*18.93*	
Private expenditure on health (PvtHE) (% of THE)	Mean	61.60			–	61.28	63.08	61.77	59.04	−2.24
	SD	*16.29*	*15.54*	*5.64*	–	*15.87*	*16.24*	*16.54*	*18.93*	

TB, tuberculosis; EFI4, fourth dimension of the Economic Freedom of the World Index; KOF1, first dimension of the KOF Index of Globalization; WTO, World Trade Organization; IMF, International Monetary Fund; HIV, human immunodeficiency virus; THE, total health expenditure; PPP, Purchaising Power Parity; NCU, National currency unit. Columns 3–5 show period means (SD) of the longitudinal analysis. Columns 6–10 show means (SD) of the cross-sectional analysis. Last column shows the change in respective variables calculated as the baseline value of a given variable minus the value of that variable in the last year for which an observation existed.

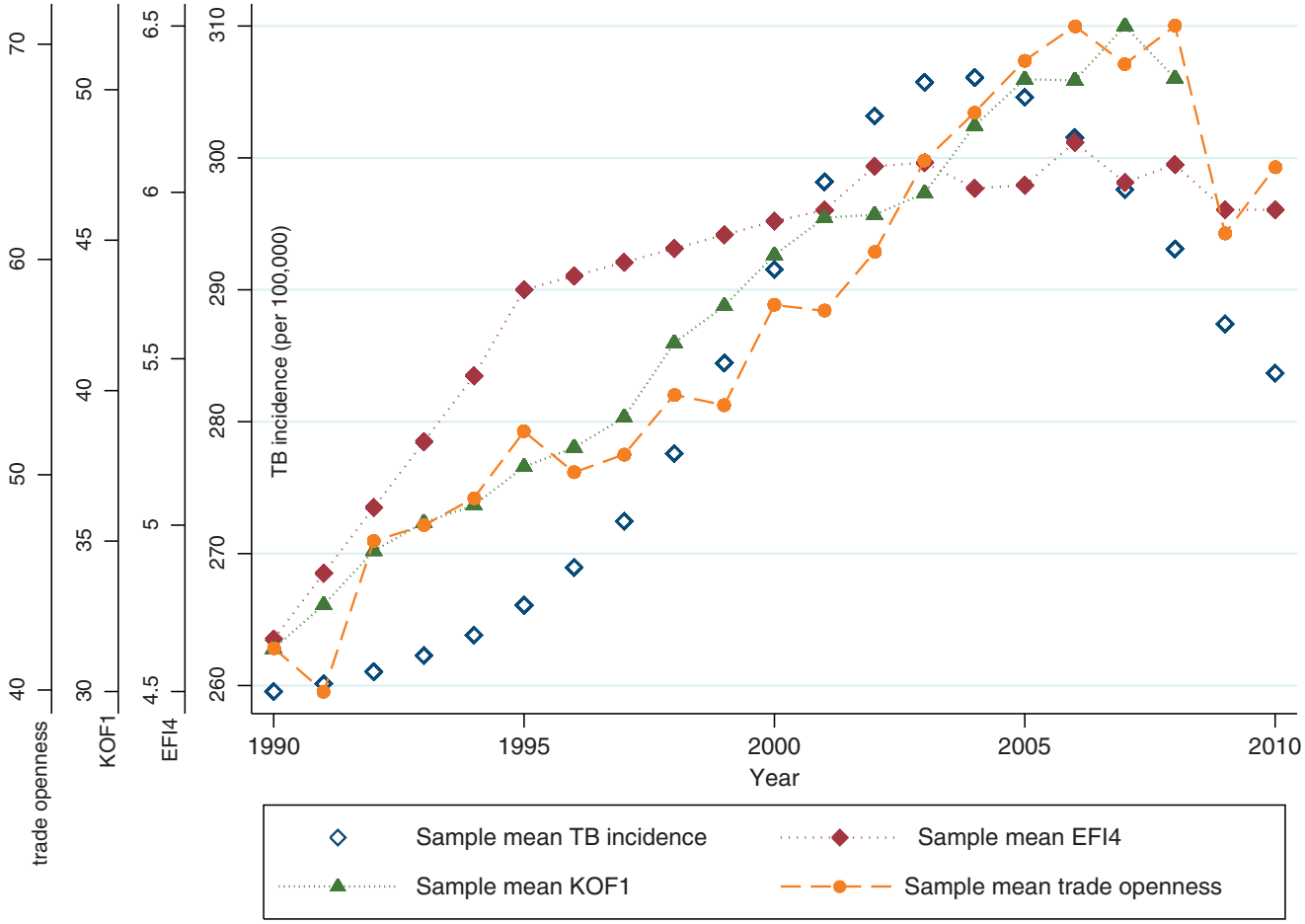

Figure 5 Annual sample averages in TB incidence (per 100 000) and the liberalization indicators Trade Openness, KOF1 and EFI4. Stacked *y*-axis from left to right: trade openness (%), KOF1, EFI4 and TB incidence (per 100 000).

The interpretation of the regression coefficients in REMs is 2-fold. First, per one unit increase in EFI4 within countries over time, there was a 9.61% decrease (95% CI: 1.48–17.06) in TB incidence. Second, comparing two countries, the one with a one unit higher value in EFI4 will have 9.61% (95% CI: 1.48–17.06) lower TB incidence according to M3 (Table 3).

Confounding within and across confounding categories

Socio-economic factors The EFI4 Log-TB incidence association was positively confounded by socio-economic factors (Table 4), which means that not accounting for the effects of these factors leads to an overestimation of the 'true' effect of EFI4 on TB incidence. These variables explained 100% of the excess risk and reduced the coefficient of EFI4 to insignificant levels when included jointly in a model (Table 4). HDI alone in the model accounted for 53% of the excess risk and had the power to reduce the effect of EFI4 to non-significant levels (see M3-crude vs M3a-1 in Supplementary Appendix p. 19). According to the FEM M3a-10 (Table 4), a one unit increase in HDI was significantly associated with an 11% (95% CI: 2.03–19.06) decrease in TB incidence in the 22 HBCs between 1990 and 2010, all other factors in the model—including the degree of liberalization—held constant.

Socio-demographic factors The socio-demographic factors in the model (Table 4) were negative confounders of the relationship between EFI4 and Log-TB incidence, leading to an underestimation of the 'true' effect if they were not taken into account.

Health system performance and HIV prevalence Adjusting for differences in health system financing and HIV prevalence between countries or within countries over time together in a model (Table 4) did not affect the regression coefficient of EFI4 when compared with the crude effect. The coefficient of EFI4 remained statistically non-significant (at the 0.05 level) in all models when controlling for single confounding by factors from within this category [except for (Log-) external resources for health as % of THE (Supplementary Appendix p. 25)].

Differences in (Log-) TB case detection rates, a proxy measure of the coverage of TB control programs, within countries over time or across countries were not significantly associated with Log-TB incidence in any of the models (Supplementary Appendix p. 25).

Socio-political factors The relationship between EFI4 and Log-TB incidence was negatively confounded by socio-political factors (Table 4). The confounding of the relationship was mainly due

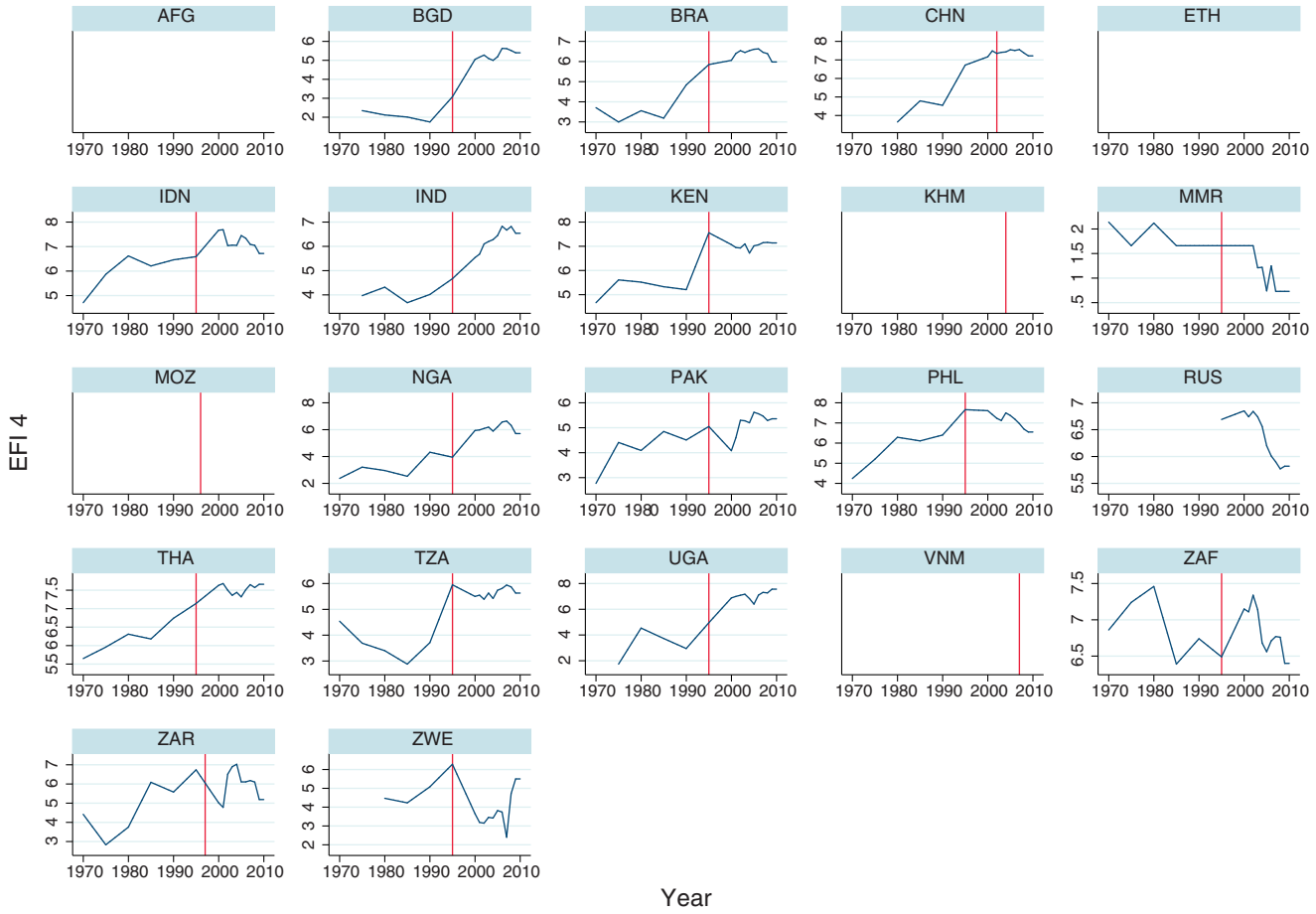

Figure 6 Trends in trade liberalization (1970–2009) measured by EFI4 before and after entry of HBCs to WTO. Vertical lines indicate year of entry to WTO. Blank fields, no data for EFI4. No vertical lines, non-WTO member. Country acronyms, AFG: Afghanistan; BGD, Bangladesh; BRA, Brazil; CHN, China; ETH, Ethiopia; IDN, Indonesia; IND, India; KEN, Kenya; KHM, Cambodia; MMR, Myanmar; MOZ, Mozambique; NGA, Nigeria; PAK, Pakistan; PHL, Philippines; RUS, Russian Federation; THA, Thailand; TZA, United Republic of Tanzania; UGA, Uganda; VNM, Viet Nam; ZAF, South Africa; ZAR, Democratic Republic of the Congo; ZWE, Zimbabwe.

to effects of 'democratization' (measured by Polity2) and/or WTO membership, less due to the effect of regime durability (Supplementary Appendix p. 23).

A one unit increase in EFI4 in a country over time (or comparing two countries with a unit difference in EFI4) was significantly ($P = 0.011$) associated with a 10.4% (95% CI: 2.50–17.69) decrease in TB incidence, regardless of polity characteristics, regime durability, WTO membership and time effects.

Not accounting for the (negative) effects of WTO membership alone (0.128, SE 0.09, $P = 0.15$) in the model led to an underestimation of the effect of EFI4 on Log-TB incidence by 38% (see M3-crude vs M3c-3 in Supplementary Appendix p. 23).

Assuming that this coefficient for WTO membership is the 'true' estimate at the 0.15 level, TB incidence (per 100 000) in WTO-member countries (or in a given country after accession to WTO) was 1.14 (95 % CI: 0.95–1.35) times the incidence in non-member countries (or times the incidence prior to accession) regardless of their level of liberalization as measured by EFI4 (Figures 8 and 9).

The WTO Log-TB incidence association was negatively confounded by differences in HIV prevalence, HDI and health financing indicators between countries or within countries over time (i.e. not accounting for the effects of these factors leads to an underestimation of the effect of WTO membership on TB incidence). Controlling in addition to EFI4 for differences in HDI increased the strength of the association between Log-TB incidence and WTO membership (Figures 10 and 11) and explained 71.4% of the excess risk. The IRR of this association rose up to 1.60 (95% CI: 1.17–2.30) when controlling for differences in HIV prevalence and health financing indicators (M3c-3.7 in Table 5).

WTO membership was thus consistently associated with higher Log-TB incidence in 9 out of 10 models, of which 6 were significant below the 0.05 level (Table 5). Sensitivity Analysis 4 confirmed the significantly positive association between WTO membership and Log-TB incidence, regardless of the degree of liberalization measured by EFI4, by means of non-linear regression models (ML-PR: IRR = 1.22; 95% CI: 1.20–1.24; ML-NBR: IRR = 1.14; 95% CI: 1.09–1.20) (Supplementary Appendix pp. 33–35).

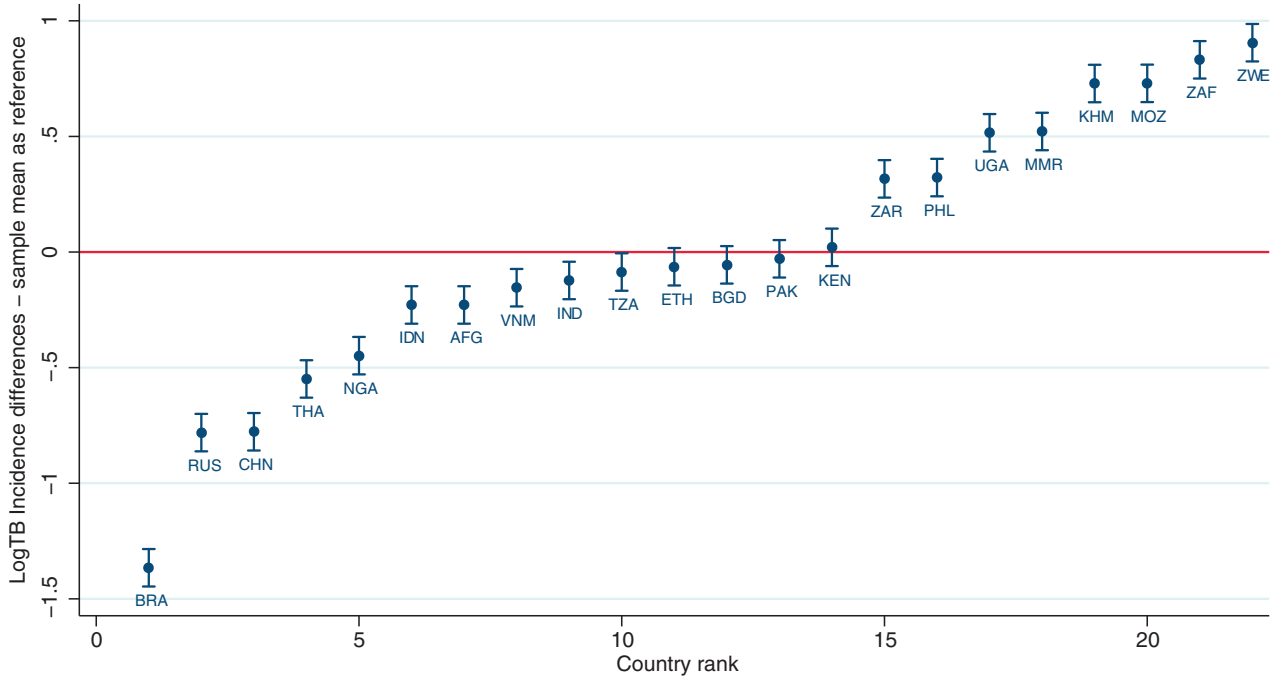

Figure 7 Caterpillar plot of Log-TB incidence differences (per 100 000) from the sample mean ranked by country-level mean (with 95% CIs). Country acronyms: AFG, Afghanistan; BGD, Bangladesh; BRA, Brazil; CHN, China; ETH, Ethiopia; IDN, Indonesia; IND, India; KEN, Kenya; KHM, Cambodia; MMR, Myanmar; MOZ, Mozambique; NGA, Nigeria; PAK, Pakistan; PHL, Philippines; RUS, Russian Federation; THA, Thailand; TZA, United Republic of Tanzania; UGA, Uganda; VNM, Viet Nam; ZAF, South Africa; ZAR, Democratic Republic of the Congo; ZWE, Zimbabwe.

Controlling additionally for (Log-) case detection rates as a proxy for differences in TB control programs between countries or improvements within countries over time did not affect the above-mentioned relationship between WTO membership and Log-TB incidence in any of the models.

It is important to note that until now the presented effects on TB incidence (per 100 000) expressed as IRR would be considerably different for different countries in absolute terms depending on their burden of TB (Supplementary Appendix p. 2).

Discussion

Our aim was to assess whether trade liberalization is associated with TB incidence in HBCs between 1990 and 2010, while controlling for confounding by differences in socio-economic, -political and -demographic factors, and/or health system performance and HIV prevalence.

We found that none of the five different measures of trade liberalization was significantly associated with Log-TB incidence in the crude analysis. If, according to the WTO, liberalization had indeed led to '[...] sustainable development, raise[d] people's welfare, [and] reduce[d] poverty [...]' (WTO 2012) in the last two decades, the effect should have been reflected in reduced TB incidence in the crude analysis if we accept that TB is not only an infectious disease but at the same time also an indicator of socio-economic development (Rasanathan *et al.* 2011).

KOF1 and EFI4 were significantly and negatively associated with the outcome when adjusting for time effects (Table 3). The estimate for KOF1 (−0.013, SE 0.006) was one-tenth of the estimate for EFI4 (−0.101, SE 0.044), indicating that the time-adjusted decrease in Log-TB incidence was much less when the additional dimensions of liberalization such as FDIs were taken into account by KOF1.

This finding supports the argument that FDIs are key in the suggested pathway in Figure 1. It is important to note that KOF1 captures actual FDI flows in 'all' trade sectors (Dreher 2006). The measure is thus not specific to FDIs in potentially health-damaging products. This might explain why the relationship with Log-TB incidence (when compared with EFI4) was considerably weaker, but did not change signs as would be expected according to the pathway in Figure 1. Future research in this area should assess the relationship between FDI flows, or ideally sector-specific FDIs in potentially health-damaging industries, and the mediators of the suggested pathway (i.e the prevalence of chronic diseases) (Figure 4). Data on sector-specific FDIs in the food, alcohol and tobacco industries are collected by the United Nations Conference on Trade and Development. The data required for this study (i.e for the 22 HBCs and the last two decades) were however not sufficiently available at the time when this research was conducted (February 2012).

The relationship between EFI4 and Log-TB incidence was substantially confounded by economic, demographic and political factors, as well as by differences in health system financing and HIV prevalence within countries over time or between countries (Table 4).

Table 3 REMs for Log-TB incidence and liberalization indicators: crude level-2 effects adjusted for level-1 effects

	(M0) Null model	**(M1)** Period effects	**(M2)** Trade openness	**(M3)** EFI4	**(M4)** KOF1	**(M5)** WTO member	**(M6)** Duration of WTO member	**(M5.1)** M5 and cohort effects	**(M5.2)** M5 and cohort effects
				Fixed effects (SE)					
Level 2 variables									
Trade openness			−0.001 (*0.0009*)						
EFI4				**−0.101*** (*0.0439*)					
KOF1					**−0.0133*** (*0.0060*)				
WTO membership (ref: non-membership)						0.0205 (*0.0457*)		0.0177 (*0.0427*)	0.0179[a] (*0.0428*)
Level 1 variables									
Period-effects (time since 1990)		0.002 (*0.0062*)	0.004 (*0.0068*)	0.007 (*0.0079*)	0.021 (*0.0112*)	0.001 (*0.0020*)	0.002 (*0.0071*)	0.001 (*0.0074*)	0.001 (*0.0074*)
Duration of WTO membership							0.001 (*0.0117*)	0.000 (*0.0117*)	0.000[a] (*0.0117*)
Cohort-effects (ref: non-membership)									
1995–1997 cohorts								**0.424*** (*0.207*)	
2002–2007 cohorts								0.286 (*0.407*)	
1995 cohort									0.36 (*0.214*)
1996 cohort									**1.078***** (*0.171*)
1997 cohort									**0.664***** (*0.170*)
2002 cohort									**−0.430*** (*0.174*)
2004 cohort									**1.086***** (*0.177*)
2007 cohort									0.201 (*0.180*)
Mean log-TB incidence ß0	**5.472***** (*0.124*)	**5.447***** (*0.116*)	**5.469***** (*0.124*)	**5.919***** (*0.305*)	**5.818***** (*0.249*)	**5.445***** (*0.115*)	**5.449***** (*0.117*)	**5.099***** (*0.159*)	**5.099***** (*0.160*)
Country-years (*N*)	462	462	447	352	361	462	462	462	462
Countries (*n*)	22	22	22	17	19	22	22	22	22
				Random effects					
Level-2 variance	0.338	0.338	0.368	0.350	0.381	0.336	0.341	0.358	0.327
Level-1 variance	0.338	0.036	0.037	0.040	0.035	0.036	0.036	0.036	0.036
ICC (%)	90.4	90.4	90.9	89.8	91.6	90.4	90.4	90.8	90.1
PCV (%)	Reference	0.00	0.55	−0.66	1.33	0.00	0.00	0.44	−0.33
Within R2	0.00	0.00	0.01	0.11	0.11	0.01	0.01	0.01	0.01
Between R2	0.00	0.00	0.01	0.09	0.00	0.05	0.04	0.07	0.31
Overall R2	0.00	0.00	0.00	0.09	0.00	0.01	0.00	0.06	0.28

(continued)

Table 3 Continued

	(M0) Null model	(M1) Period effects	(M2) Trade openness	(M3) EFI4	(M4) KOF1	(M5) WTO member	(M6) Duration of WTO member	(M5.1) M5 and cohort effects	(M5.2) M5 and cohort effects
Model characteristics									
Wald chi-square (df)	3737.37 (0/1)	0.156 (1)	0.556 (2)	5.25 (2)	4.911 (2)	0.258 (2)	0.171 (2)	4.676 (5)	391.74 (5)
Sig	***	0.693	0.757	0.072	0.086	0.879	0.235	0.457	***
Root MSE	0.190	0.190	0.192	0.199	0.187	0.190	0.190	0.190	0.190
Hausman test	–	[b]	0.8769	0.5039	0.2978	0.3217	0.369	0.4804	[b]

Robust standard errors in parentheses; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; [o]test statistic of Breusch-Pagan Lagrangian multiplier test for random effects; df, degrees of freedom; § excluding WTO membership and duration of WTO membership from Model 5.2 did not change the magnitude, the significance or the direction of the estimates of the cohort effects considerably, therefore the variables are presented together in one model; # Hausman specification test failed to meet asymptotic assumptions due to collinearity/time-invariance of variables in FEM. None of the trade variables was significantly associated with Log-TB incidence in the crude analysis ($0.5 < p < 0.9$) not adjusted for time, with exception of EFI4 which was marginally significant ($p = 0.077$). EFI4: Economic Freedom of the World Index (4th dimension). KOF1: KOF Index of Globalisation (1st dimension). WTO: World Trade Organization. ICC: Intra-class correlation. PCV: Proportional change in variance. R2: coefficient of determination. MSE: Mean squared error. The outcome variable in all models is Log-TB incidence (per 100.000 pop.). M0: Model without predictors. M1: contains ''time since 1990'' as predictor, assesses the effects attributable to the passage of time (period effects). M2: contains Trade Openness as predictor. M3: contains EFI4 as predictor. M4: contains KOF1 as predictor. M5: contains WTO membership as predictor. M6: contains duration of WTO membership as predictor. M1–M6: all adjust for period effects. M5.1 / M5.2: contain the same variables as M5, but additionally adjust for the duration of WTO membership and cohort-effects based on different group-categories of the year of accession to WTO.

In particular, adjusting for differences in HDI, HIV prevalence and health financing indicators (Supplementary Appendix p. 25), respectively, in the models diminished any positive effect of EFI4 on Log-TB incidence. Adjusting, on the other hand, for differences in TB incidence that were attributable to repayments of IMF credits (M3a-5, Supplementary Appendix p. 19), socio-demographic factors (Table 4, Supplementary Appendix p. 21), regime characteristics or WTO membership (Supplementary Appendix p. 23) increased the effect of EFI4 on Log-TB incidence. In other words, trade liberalization as measured by EFI4 could 'unfold' a positive effect on (i.e. decrease in) Log-TB incidence when adjusting for differences in TB epidemiology that were attributable to differences in these variables (within countries over time or between countries). This finding points out that an increased openness in the dimensions of trade, captured by EFI4, can significantly decrease TB incidence at the population level, but only if we disregard the effects of e.g. WTO membership and repayment of IMF credits, and at the same time neglect the confounding effects of HDI, HIV prevalence and health financing indicators, which diminish the effect of EFI4 on Log-TB incidence.

The relationship between WTO membership and Log-TB incidence was also substantially 'negatively' confounded. Adjusting for differences in EFI4 and HDI (Figures 10 and 11) or HIV prevalence and health system financing characteristics (Table 5) within countries over time or between countries 'dismantled' an increase in Log-TB incidence depending on countries' membership status in the WTO. When comparing non-member countries with WTO member countries or changing status from non-membership to membership within countries, the effect ranged from no significant difference in TB incidence (per 100 000) in the crude analysis (0.036, SE 0.08, $P = 0.64$) to an IRR = 1.60 (95% CI: 1.17–2.30) in models controlling for HIV prevalence, EFI4 and Log-HSfinance-Index (see M3c-3.7 in Table 5). The model fit across this range was better for the adjusted models compared with the unadjusted or 'less' adjusted as judged by the root MSE (Table 5). The overall R^2 (Supplementary Appendix p. 27) ranged between 11.8% in less adjusted models (M3c-3) and 60.6% in models accounting for EFI4, HIV and health financing indicators that reflect a government's commitment to invest in the health sector (M3c-3.9). In light of the range of higher estimates for the effects of WTO membership in models with better model fit which adjusted for additional confounders, it should be noted that the estimates presented in Figures 8 and 9 are clearly conservative. We could cross-validate the estimates for the relationship between WTO membership and Log-TB incidence, adjusted for EFI4, by methods that did not assume a linear relationship between exposure and outcome (ML-PR) and accounted for the overdispersion (ML-NBR) in our data (Supplementary Appendix pp. 33–35).

The significantly positive association between WTO membership and Log-TB incidence backs the hypothesis that there is a potential conflict between the legal-judicial architecture of binding MTAs and TB control strategies. The specific pathways that might lead to this association [such as those suggested in Figure 2 and discussed elsewhere (WHO and WTO 2002; Ranson *et al.* 2002; Pollock and Price 2003; Chand 2006; Gayi 2006; Labonte and Sanger 2006b; Haakonsson and Richey 2007;

Table 4 Summary overview of full models (M3a-d): relationship between Log-TB incidence and EFI4 adjusted for confounding by variables within confounding categories

Summary of full models M3a-d				
	Fixed-effect model M3a-10	Fixed-effect model M3b-6	Random effect model M3c-6	Random effect model M3d-11
Fixed effects (*SE*)	Socio-economic factors	Socio-demographic factors	Socio-political factors[a]	Health system performance and HIV
Level 1 variables				
Time since 1990	0.0554 (*0.0268*)	**−0.0409*** (*0.0166*)	0.00195 (*0.00663*)	0.0138 (*0.0129*)
Level 2 variables				
EFI4	−0.0223 (*0.0535*)	**−0.109**** (*0.0326*)	**−0.110*** (*0.0432*)	−0.0751 (*0.0456*)
HDI	**−0.116*** (*0.0487*)			
GINI	0.00390 (*0.00774*)			
Log-Use of IMF credits (*in billion US$*)	0.0137 (*0.00664*)			
Log-Disbursements on external debt, long-term and IMF (*in billion US$*)	−0.0681 (*0.0334*)			
Log-IMF repurchases (*in billion US$*)	−0.00904 (*0.0139*)			
Age dependency ratio		**−0.0341**** (*0.0109*)		
Log-population in urban agglomerations (%)		0.140 (*0.425*)		
Log-population density (*people/sq. km of land*)		1.095 (*0.633*)		
Polity2			0.00739 (*0.00668*)	
Regime durability (years)			**−0.00641**** (*0.00238*)	
WTO membership			0.0827 (*0.0517*)	
HIV prevalence (%)				**0.0605*** (*0.0252*)
Log-Case detection rate (%)				−0.0797 (*0.0561*)
General Government Health Exp. (GGHE) (% *of General Gov. expenditure*)				−0.0151 (*0.00816*)
Social security funds (% *of GGHE*)				−0.00980 (*0.00614*)
Log-external resources on health (% *of THE*)				**0.0483*** (*0.0229*)
Log-HSfinance-Index				−0.0656 (*0.0630*)
Mean Log-TB incidence ß0	**10.58***** (*1.849*)	3.701 (*2.187*)	**6.050***** (*0.294*)	**6.530***** (*0.623*)
Country-years (*N*)	140	352	352	192
Countries (*n*)	13	17	17	14
Model characteristics				
Within R2	0.630	0.323	0.235	0.473
Between R2	0.341	0.0177	0.130	0.579
Overall R2	0.372	0.0172	0.139	0.487
Adjusted R^2	0.611	0.313	–	–
Wald chi-square (df)	–	–	22.92 (5)	387.6 (8)
F statistic (df)	11.96 (7,12)	3.350 (5,16)	–	–
Sig	***	***	***	***
Root MSE	0.113	0.170	0.185	0.127
Hausman test	***	***	0.7549	0.403

Robust SEs in parentheses (adjusted for *n* clusters); *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; Random part omitted, see Models 3a-d in Supplementary Appendix pp. 19–26 for details on the random effects.

The 'outcome variable' in all models is Log-TB incidence (per 100 000 pop.). The 'predictor' in all Models is EFI4. All Models are adjusted for period-effects (time since 1990). M3a-10 adjusts additionally for socio-economic indicators (HDI, GINI and IMF indicators). M3b-6 adjusts additionally for socio-demographic factors (age dependency ratio, Log-population in urban agglomerations and Log-population density). M3c-6 adjusts additionally for socio-political factors (Polity2, regime durability and WTO membership). M3d-11 adjusts additionally for health system performance (Log-case detection rates and health financing indicators) and HIV prevalence.

[a]The occurrence of armed conflict (dummy) had no significant effect on Log-TB Incidence, neither as a single predictor in a FEM (0.00246, SE 0.028, $P = 0.93$) nor in a REM (0.00362, SE 0.027, $P = 0.90$). Including the dummy variable for the occurrence of armed conflict in models with other covariates in Model 3c-6 (as FEM/REM) did not change the strength of the association or direction of any of the variables significantly, which is why the variable is not explicitly listed in the summary table.

EFI4, Economic Freedom of the World Index (fourth dimension). HDI, Human Development Index; GINI, Index of Income Inequality; IMF, International Monetary Fund; GGHE, General Government Health Expenditure; WTO, World Trade Organization; R2, coefficient of determination; df, degrees of freedom; MSE, mean squared error.

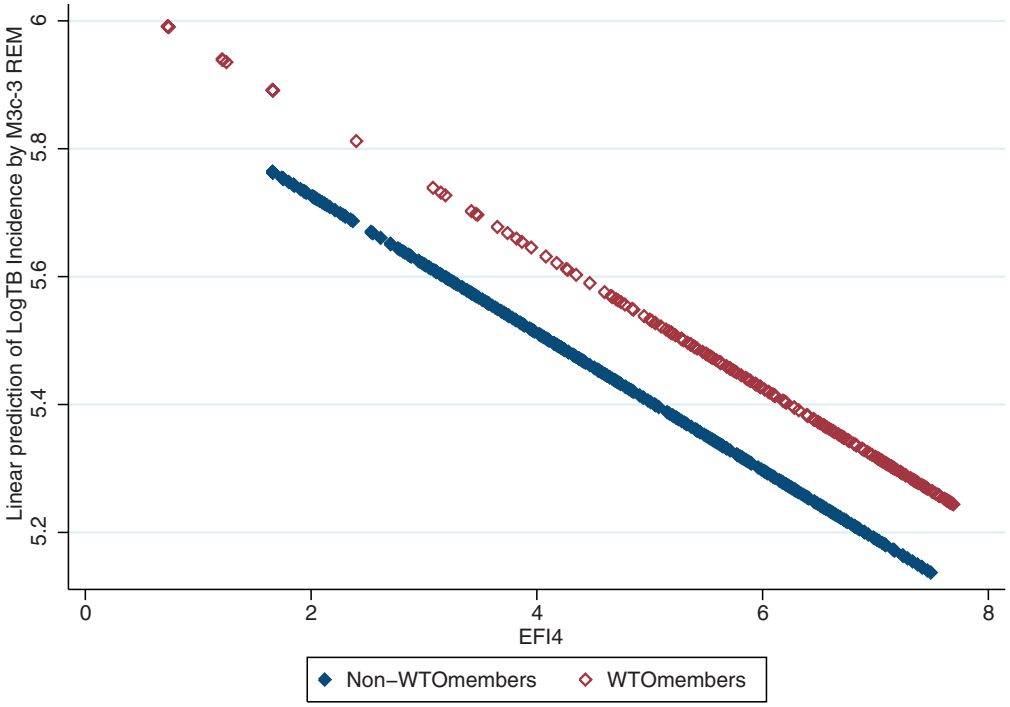

Figure 8 Scatterplot of the relationship between Log-TB incidence (per 100 000) and EFI4 by WTO membership. IRR (WTO-member vs non-member countries) adjusted for EFI4: 1.14 (95% CI: 0.95–1.35). EFI4, Economic Freedom of the World Index (fourth dimension). Model 3c-3, see Supplementary Appendix p. 23 for further details of the model.

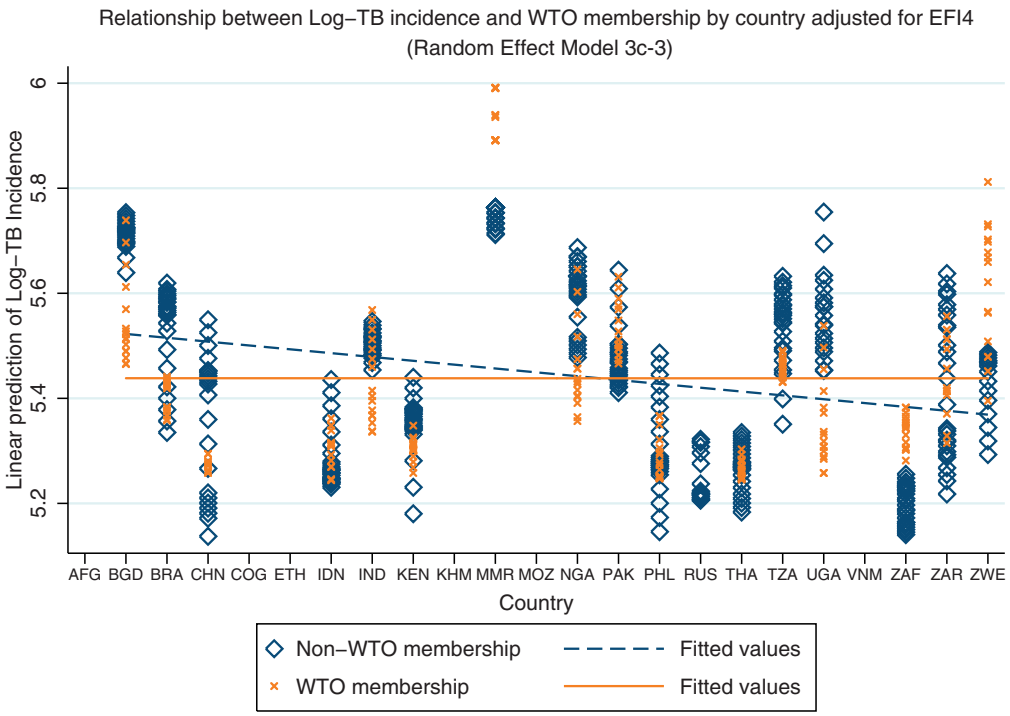

Figure 9 Scatterplot of predicted values of Log-TB incidence (per 100 000) by WTO membership and country adjusted for the degree of liberalization measured by EFI4. IRR (WTO-member vs non-member countries) adjusted for EFI4: 1.14 (95% CI: 0.95–1.35). Model 3c-3: see Supplementary Appendix p. 23 for further details of the model. Country acronyms: AFG, Afghanistan; BGD, Bangladesh; BRA, Brazil; CHN, China; ETH, Ethiopia; IDN, Indonesia; IND, India; KEN, Kenya; KHM, Cambodia; MMR, Myanmar; MOZ, Mozambique; NGA, Nigeria; PAK, Pakistan; PHL, Philippines; RUS, Russian Federation; THA, Thailand; TZA, United Republic of Tanzania; UGA, Uganda; VNM, Viet Nam; ZAF, South Africa; ZAR, Democratic Republic of the Congo; ZWE, Zimbabwe.

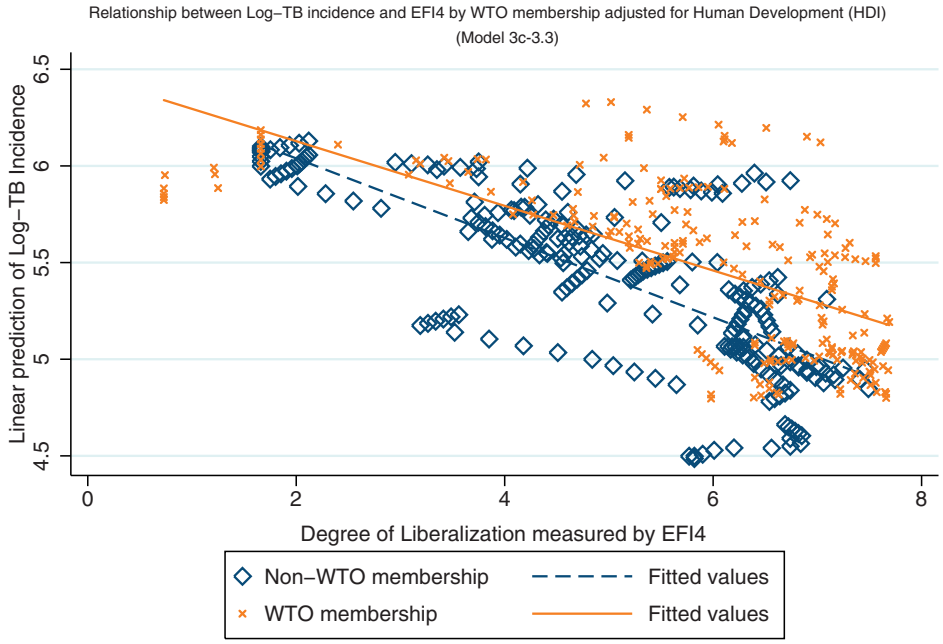

Figure 10 Scatterplot of the relationship between Log-TB incidence (per 100 000) and EFI4 by WTO membership adjusted for human development (HDI). IRR (WTO-member vs non-member countries) adjusted for EFI4 and HDI: 1.24 (95% CI: 1.04–1.48). EFI4, Economic Freedom of the World Index (fourth dimension).

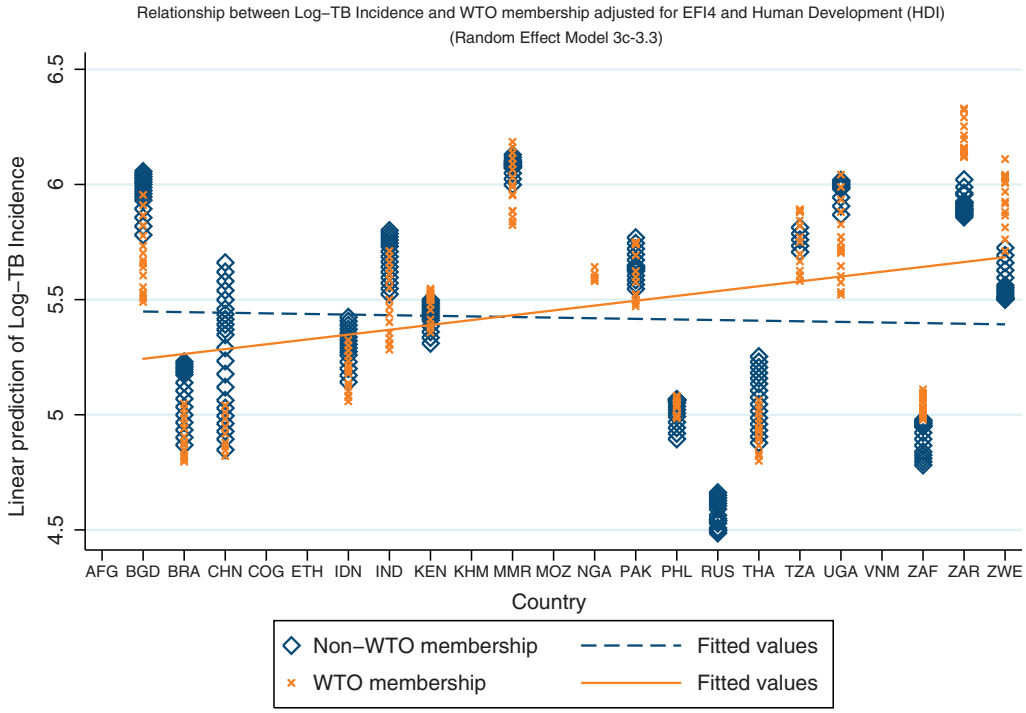

Figure 11 Scatterplot of predicted values of Log-TB incidence (per 100 000) by WTO membership and country adjusted for the degree of liberalization measured by EFI4 and human development (HDI). IRR (WTO-member vs non-member countries) adjusted for EFI4: 1.24 (95% CI: 1.04–1.48). Country acronyms: AFG, Afghanistan; BGD, Bangladesh; BRA, Brazil; CHN, China; ETH, Ethiopia; IDN, Indonesia; IND, India; KEN, Kenya; KHM, Cambodia; MMR, Myanmar; MOZ, Mozambique; NGA, Nigeria; PAK, Pakistan; PHL, Philippines; RUS, Russian Federation; THA, Thailand; TZA, United Republic of Tanzania; UGA, Uganda; VNM, Viet Nam; ZAF, South Africa; ZAR, Democratic Republic of the Congo; ZWE, Zimbabwe.

Table 5 REMs of the relationship between WTO membership, EFI4 and Log-TB incidence (per 100 000) adjusted for different counfounding categories

	(M0) Null model	**(M3crude)** Crude EFI4	**(M3c-3)** WTO membership	**(M3c-3.1)** M3c-3 and HIV	**(M3c-3.2)** M3c-3 and age dependency ratio	**(M3c-3.3)** M3c-3 and HDI	**(M3c-3.4)** M3c-3 and Social Security Funds	**(M3c-3.5)** M3c-3 and HIV + HDI	**(M3c-3.6)** M3c-3 and HIV + Social Security Funds	**(M3c-3.7)** M3c-3 and HIV + HS Finance Index	**(M3c-3.8)** M3c-3 and HIV + external resources	**(M3c-3.9)** M3c-3 and HIV + GGHE
Fixed effects (SE)												
Level 2 variables												
EFI4		−0.0763 (*0.0431*)	**−0.107*** (*0.0440*)	**−0.0899*** (*0.0439*)	**−0.110**** (*0.0372*)	−0.0606 (*0.0352*)	−0.0722 (*0.0427*)	**−0.0703*** (*0.0309*)	−0.0659 (*0.0421*)	−0.0615 (*0.0473*)	−0.0807 (*0.0439*)	−0.0602 (*0.0413*)
WTO membership (ref.: non-membership)			0.128 (*0.0892*)	0.131 (*0.0937*)	0.0365 (*0.0395*)	**0.212*** (*0.0903*)	**−0.155**** (*0.0553*)	**0.199*** (*0.0937*)	**0.340*** (*0.146*)	**0.471*** (*0.184*)	**0.420**** (*0.162*)	**0.467**** (*0.153*)
HIV prevalence (%)				**0.0469**** (*0.0179*)				**0.0398*** (*0.0178*)	**0.0643*** (*0.0324*)	**0.0666*** (*0.0333*)	**0.0618*** (*0.0288*)	**0.0668*** (*0.0327*)
Age Dependency Ratio (%)					−0.0107 (*0.00713*)							
HDI						**−0.0300***** (*0.00841*)		**−0.0202**** (*0.00661*)				
Social security funds (% of GGHE)							**−0.00802**** (*0.00268*)		**−0.00641*** (*0.00321*)			
Log-HSfinance-Index										−0.0137 (*0.0434*)		
Log-External resources on health (% of THE)											0.0496 (*0.0327*)	
GGHE (% of General Government expenditure)												−0.0128 (*0.00678*)
Mean Log-TB incidence ß0	**5.472***** (*0.124*)	**5.851***** (*0.308*)	**5.942***** (*0.302*)	**5.684***** (*0.278*)	**6.784***** (*0.722*)	**7.096***** (*0.509*)	**6.078***** (*0.332*)	**6.567***** (*0.472*)	**5.330***** (*0.303*)	**5.208***** (*0.428*)	**5.285***** (*0.324*)	**5.187***** (*0.282*)
Country-years (*N*)	462	352	352	291	352	337	247	276	203	202	192	203
Countries (*n*)	22	17	17	15	17	17	17	15	15	15	14	15
Model characteristics												
Wald chi-square (df)	3737.37°	3.127 (1)	6.260 (2)	38.08 (3)	8.968 (3)	14.74 (3)	16.38 (3)	59.00 (4)	79.27 (4)	71.15 (4)	107.4 (4)	86.21 (4)
Sig	***	0.077	*	***	*	**	***	***	***	***	***	***
Root MSE	**0.190**	**0.202**	**0.196**	**0.167**	**0.191**	**0.175**	**0.153**	**0.156**	**0.139**	**0.139**	**0.136**	**0.138**
Hausman test	–	0.6149	0.44	0.7686	**	0.8773	0.6739	0.7806	0.3911	0.6717	0.4293	0.5141

Robust SEs in parentheses (adjusted for *n* clusters); *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; the test statistic of Breusch–Pagan Lagrangian multiplier test for random effects. Random part: omitted, see Supplementary Appendix p. 27 for details on the random effects.

The 'outcome variable' in all models is Log-TB incidence (per 100 000 pop.). EFI4 and WTO membership are used in all models as exposure and confounder adjusted for one another, respectively. M0 contains no predictors. M3crude contains EFI4 as single predictor. M3c-3 contains EFI4 as predictor (confounder) and WTO membership as confounder (predictor) and builds the basis for all following models. M3c-3.1 adjusts additionally for HIV prevalence. M3c-3.2 adjusts additionally for age dependency ratio. M3c-3.3 adjusts additionally for HDI. M3c-3.4 adjusts additionally for social security funds (SSFs) (as % of GGHE). M3c-3.5 adjusts simultaneously for HIV and HDI. M3c-3.6 adjusts simultaneously for HIV and SSFs (as % of GGHE). M3c-3.7 adjusts simultaneously for HIV and Log-HSfinance-Index. M3c-3.8 adjusts simultaneously for HIV and Log-External resources on health (as % of THE). M3c-3.9 adjusts simultaneously for HIV and GGHE (as % of general Gov. expenditure). Adjusting for Log-case detection rates (not listed in table) did not change the sign, significance or the magnitude of any of the relationships.

EFI4, Economic Freedom of the World Index (fourth dimension); HDI, Human Development Index; GINI, Index of Income Inequality; IMF, International Monetary Fund; GGHE, General Government Health Expenditure; THE, Total health expenditure; WTO, World Trade Organization; df, degrees of freedom; MSE, mean squared error.

Kanchanachitra *et al.* 2011; Smith *et al.* 2009a,b)] need further elucidation by case studies and/or additional country-level and sub-national analysis.

Relating the findings on trade liberalization and TB as operationalized in this study to other research is difficult due to the previously mentioned dearth of quantitative studies that analysed this relationship. It is however possible to put the findings into context with the literature on the social determinants of TB (Box 1).

Strengths and limitations

The main shortcoming of our study relates to the use of aggregate indicators to assess the link between trade liberalization and TB incidence. These aggregate indicators do not necessarily directly relate to the suggested mediators (Figure 4) of the hypothesized pathway (Figures 1 and 2). Further analyses at this level of aggregation would be justified if it could be shown that these indicators relate directly to the above pathways and mediators. More focused sector-/tariff-specific indicators would be the best choice for assessing the links between trade and TB as suggested by the pathway in Figure 1. The second pathway (Figure 2) rather focuses on non-tariff barriers to trade. Indicators qualifying for this pathway would ideally capture the degree to which the specific sectors (Figure 2) are deregulated as well as regulated in favour of economic freedom. EFI4 captures the prevalence of non-tariff-barriers to trade (Table 1) by drawing upon survey data of the World Economic Forum's Global Competitiveness Report, in which respondents judge the degree to which tariff and non-tariff barriers reduce the ability of imported goods to compete in the domestic market on a seven-point Likert scale. In our opinion, the reliance on survey data to capture this dimension of trade liberalization disqualifies EFI4 (and other survey-based measures) as suitable indicator for the second pathway. Although WTO membership is a high-level indicator, we think that it is more objective for inter-country comparisons over time. It is important to note that WTO agreements are negotiated altogether as part of an indivisible package and—in case of accession to WTO—adopted by countries as a whole. This means that the indicator of membership status in a longitudinal design, although crude at the first glance, is an arguably appropriate measure to capture the exposure to WTO's binding and enforceable trade architecture. In the absence of a world without WTO to compare with as counterfactual (Rose 2003), a country's accession (or non-accession) to WTO over time in a longitudinal design constitutes a natural experiment (Petticrew *et al.* 2005) which we have exploited in this study. An exception to the 'all-or-nothing' principle in the adoption of WTO agreements are e.g. commitments under GATS. These are different from commitments under other MTAs in that countries can make commitments to different degrees in different service sectors. This exception theoretically allows to assess the relationship between health system-related commitments under GATS and health outcomes according to a dose–response relationship, provided that the complex system of commitments under GATS is translated into a valid indicator. We are not aware of any such indicator for the health sector, although similar measures have been developed to assess the degree of liberalization under GATS to the education sector (Verger 2008). Such a measure would be of high relevance for the health sector as well, since it would allow a more differentiated assessment of the effects of WTO agreements than the dummy variable approach applied in this study. Nevertheless, the absence of empirical studies that quantitatively assess the effects of WTO agreements on health outcomes merits our approach of using membership status over time as an indicator to assess the effects on TB incidence.

Another limitation worth being mentioned is that we did not account for time delays in the relationship between trade and TB. Our approach would have considerably benefited from additional analysis by means of auto-regressive models and lagged variables to assess the effects of trade liberalization of previous years on current TB incidence. However, it is difficult to determine what constitutes an 'appropriate' time-lag for the suggested pathways (Figures 1 and 2). Stuckler *et al.* have recently discussed the problem of determining 'appropriate' time-lags in the analysis on aid effectiveness. They conclude that there is an insufficient theoretical or an empirical basis to determine what lags are appropriate for studying the effects of aid (Stuckler *et al*. 2012). We dare to argue that this situation applies to the analysis of trade effects on health as well, let alone the specific effects on chronic diseases or TB. Notably, what constitutes an 'appropriate' time-lag would strongly depend on the pathway of question. Even within pathways, e.g. from WTO membership to TB incidence (Figure 2), time-lags would arguably differ by the MTA under question. While effects of GATS might take longer to filter through the upstream determinants, effects of TRIPS that affect access (or non-access) to essential medicines might have a more immediate effect. The above-mentioned simultaneity of exposure to MTAs makes the choice of time-lags even more difficult, especially if we additionally take into account the simultaneity in the massive proliferation of regional trade agreements (Fiorentino *et al*. 2007) which we completely disregarded in our study to reduce complexity. Nevertheless, future research should assess whether the findings of our study hold or are discarded when accounting for any kind of time-lags, regardless of their theoretical or empirical foundation.

On a conceptual level, one could argue that we sought to analyse the impact of very broad indicators of globalization (e.g. WTO membership) on a relatively narrow indicator of health. Two arguments justify our approach. First, TB as a social disease (Paluzzi 2004; Rasanathan *et al.* 2011; Raviglione and Krech 2011) can be regarded as an indicator of socio-economic development and is more than a 'narrow indicator of health'. Second, if 'globalization' is postulated as an upstream determinant of TB (Lönnroth *et al.* 2009) and if the TB community is interested in the causes of TB incidence, then it is more than legitimate to analyse this relationship at the level of populations. To borrow the words of Geoffrey Rose: 'To find the determinants of [...] incidence rates, we need to study characteristics of populations [...]' (Rose 2001). If we seek for the causes of TB incidence at the population level, it would not be appropriate to limit the level at which trade liberalization is assessed to an intermediate level only.

The study was limited by the uncertainty involved in the estimates of TB incidence, especially at the beginning of the observation period (Supplementary Appendix p. 36).

Box 1 The findings in context with the literature on the social determinants of TB

Socio-economic factors

Socio-economic development as measured by HDI was the strongest confounder of the EFI4 Log-TB incidence relationship, indicating that national income, investments in education and overall life improvements (with higher life expectancy as proxy) reduced TB incidence rather than liberalization measures. These findings reinforce previous knowledge that socio-economic development (Lönnroth *et al.* 2009) is key to reductions in TB incidence. The reductions in TB incidence associated with higher HDI (within countries over time or between countries) were even larger when adjusting, in addition to EFI4, for income inequality measured by the GINI index (see M3a-6 vs M3a-1 in Supplementary Appendix p. 19). The finding that country-level TB incidence is lower when additionally adjusting for relative socio-economic disadvantage measured by GINI is in accordance with a study that found a significantly positive association between income inequality and TB incidence in the European Region (Ploubidis *et al.* 2012). This provides evidence for an effect on country-level TB incidence of the level of egalitarianism. However, the effects of the GINI index found in this study (Supplementary Appendix p. 19) should be interpreted with caution (not only due to its non-significant coefficients which changed directions in different models but also due to the large proportion of missing data for this variable (81% before and 44% after interpolation).

The effects of the use and repayments of IMF credits (Supplementary Appendix p. 19) indicated consistency with the findings of Stuckler and colleagues, who found a positive association between participation in IMF lending programs and TB incidence in post-Soviet countries (Stuckler *et al.* 2008). The 1.5- to 6-fold increase in magnitude of regression coefficients and the changing significance of the IMF and debt indicators in Sensitivity Analysis 1 (Supplementary Appendix p. 29) indicate that it would be worthwhile to further explore the relationship between IMF programs and TB epidemiology in the 22 HBCs.

Socio-demographic factors

Differences in the % of populations living in urban agglomerations and in country-level population density were negative confounders of the EFI4 Log-TB incidence relationship. However, these proxy measures of overcrowding were not significantly associated with Log-TB incidence when adjusting for differences in EFI4 within countries in respective FEMs (Supplementary Appendix p. 21), indicating that calls for action on overcrowding/urbanization (Hargreaves *et al.* 2011) might overestimate the relative importance on TB epidemiology (at least at country-level in the 22 HBCs between 1990 and 2010).

Socio-political factors

Structural violence and inequitable social structures can affect TB epidemiology (Farmer 1999). The polity structures in our sample were (on average) more democratic as measured by Polity2 in 2010 compared with 1990, and differences in Polity2 (between countries or within countries over time) negatively confounded the EFI4 Log-TB incidence relationship (see M3c-1 in Supplementary Appendix p. 23). Notably, Polity2 itself had no significant effect on Log-TB incidence in any of the models adjusted for the respective covariates, including the level of liberalization (Supplementary Appendix p. 23). We are not aware of any other studies that quantified the effect of democratization on TB epidemiology. We can only speculate that the increased level of 'democratization' in polity structures has apparently not translated into benefits for the most vulnerable parts of society, if we believe that TB is an indicator of inequitable social structures (Farmer 1999). The finding that formal democratization did not translate into measurable benefits for the population (in terms of reduced TB incidence) would support Collin Crouch's notion of the post-democracy (Crouch 2004). This notion refers to a situation in which the political institutions function only formally 'democratically' with routine elections being held, which however are a 'tightly controlled spectacle'. The real decisions in the post-democracy are 'shaped in private by interaction between elected governments and elites that overwhelmingly represent business interests' (Crouch 2004) and thus rather serve these instead of the public interest.

Regime durability, on the other hand, was weakly but negatively associated with Log-TB incidence (regardless of polity structures, level of liberalization or WTO membership), indicating that stability in government is a negative predictor of TB incidence.

Our findings related to the non-significant effects of armed conflict on TB epidemiology were in concordance with some (Drobniewski and Verlander 2000) but not with other studies (Gustafson *et al.* 2001). We assume that our approach to measure armed conflict by a dummy variable (Supplementary Appendix p. 4) was too crude to distinguish between different levels of conflict intensity in our sample.

Health system performance

Dependency on external funds (measured by external resources for health as % of THE) was significantly and positively associated with Log-TB incidence, adjusted for differences in EFI4, HIV prevalence, case detection rates, government expenditures on health as % of global government expenditures, and the Log-HSfinance-Index (Supplementary Appendix p. 25) within countries or between countries over time. The plausible explanation that external resources for health as % of THE were 'per se' higher in HBCs with higher TB incidence did not hold descriptively (Supplementary Appendix p. 37). Another possible explanation is that external funds led to reduced government expenditures on health as observed elsewhere (Lu *et al.* 2010). However, the association was still significant when adjusting for differences in government expenditures on health as % of global government expenditures and the Log-HSfinance-Index (Supplementary Appendix p. 25), which captured differences in absolute and relative composition of health financing (Supplementary Appendix p. 2). A third explanation, that dependency on external funds led to fragmentation of the health system with negative effects on TB epidemiology, was beyond the scope of our study to assess.

A recent World Report in *The Lancet* asked whether social protection measures can effectively reduce TB incidence and concluded that more evidence on this relationship is needed (Das 2012). We found a significantly negative association between SSFs as % of GGHE and Log-TB incidence, regardless of the level of liberalization measured by EFI4, or additionally adjusted for the size of GGHE as % general government expenditures (M3d-4/M3d-8 Supplementary Appendix p. 25). Although the effect was very modest, the findings indicate that social protection measures are effective in reducing TB incidence, regardless of the level of liberalization.

Nevertheless, the data from the Global TB database (WHO 2012a) used in this study are the best available TB data source.

Uncertainty was also involved in the measurements and estimates for the covariables over 20 years and for countries with weak data collection and measurement systems. However, again the best available data (Supplementary Appendix pp. 4–7) were used for all variables that fed into the study.

The way we handled missing data might have influenced the estimates or inflated the effects for variables with only few data points and long periods of interpolation (Supplementary Appendix pp. 16–18). However, we manipulated only variables for which high fluctuations from one year to another were not to be expected (e.g. HDI or GINI). Overall, the data manipulation was handled very conservatively, probably at the cost of a

lower sample size and lack of statistical significance for certain variables, but with the benefit of having point estimates and results which were 'more rooted' in the original data.

The study sites in the sample were very heterogeneous in regional, economical, political, demographical and social aspects which ensured sufficient variation between the units of analysis towards the ecological exposures used in this study. This heterogeneity minimized the possibility of bias in the study design that may affect the estimates between exposures and outcome if sufficient variation is not given (Blakely and Woodward 2000).

Another strength is the multi-level methodology applied to assess the association between exposures and outcomes. The method ensures that the non-independence of observations is taken into account, minimizing the possibility of bias in SEs and statistical significance that could arise if the clustered nature of the data (Figure 7) was not accounted for. The analysis performed was relatively robust regarding the violation of the linearity assumption by some variables (Supplementary Appendix pp. 13–15). Another benefit of the applied regression models and the longitudinal approach is that each country serves as their own control (in particular in FEMs) minimizing the possibility of bias due to lack of controls. The FEMs particularly accounted for unobserved, time-invariant factors that would be expected to have an effect on the outcome but were not captured by our co-variables (such as culture or religion). However, it should be noted that the random intercept models (REMs) assume that the effect of exposure on outcome is the same for every country, while the countries are only allowed to differ in their starting points (intercepts) regarding the outcome variable TB incidence. Future research should also assess how random slope models perform, which explicitly allow for differentiated effects of exposure on outcome for different groups of countries. These models would be the closest approximation to 'reality', since the assumption that the effects of the aggregate indices of liberalization are the same for all HBCs in the sample is admittedly a strong one.

Our study design controlled for the influence of a wide range of social determinants of TB (Figure 3) so that the possibility of omitted-variable bias was reduced as far as possible to be handled in one single study. Including a wide range of potential confounders in the study design also ensured to control for potential indirect effects of trade on our outcome variable through changes in these sectors. As a positive 'side effect' of this approach, our study provides a comprehensive empirical analysis of the effects and relative importance of different social determinants of TB at the population level (Box 1). The findings could be useful to identify entry-points in TB control strategies at the structural level.

Areas for further research

In addition to the hitherto presented areas for further research, we suggest that future studies should explore to which extent and in which direction the relationship between KOF1 and TB incidence is confounded by the various social determinants of TB (Figure 3). The role of the hypothesized mediators in the pathway from trade to chronic diseases to TB (Figure 4) should be scrutinized analytically allowing for the conclusions on the effects of liberalization on a more intermediate level. The pathways from specific MTAs under the WTO to higher TB incidence (Figure 2) found in this study deserve further attention in the research agenda on TB. Such research should be multi-disciplinary and build upon a wide array of approaches, ideally including multiple case studies, multi-sited ethnographies and quantitative studies of prospective nature with both individual- and macro-level data. Future research on the topic might particularly include a more detailed analysis of the effects of specific agreements, such as GATS, on TB or on other (non-TB) outcomes that are more inclusive like under-five mortality rates or overall mortality. The identification or development of measures relevant to the health sector at levels lower than 'WTO membership status' should be given a high priority in attempts to assess the effects of trade agreements quantitatively. Finally, taking a different approach to the definition of HBCs, e.g. as countries that accumulate about 80% of 'population standardized' incidence (instead of absolute incidence as used by WHO) between 1990 and 2010, could yield further interesting insights since this approach would increase the number of eligible countries to 75.

Conclusion

We found no association between specific aggregate indicators of trade liberalization and TB incidence in the crude analysis. The time-adjusted positive effect of EFI4 on Log-TB incidence vanished when adjusting for differences in socio-economic development (HDI), HIV prevalence and/or differences in the absolute and relative composition of health financing indicators between countries or within countries over time. Our study provided insufficient evidence to support the pathway outlined in Figure 1. This does not necessarily mean that trade liberalization has no effect on chronic diseases. It rather means that (i) either the aggregated indices do not relate to the suggested mediators or (ii) if there is an effect on chronic diseases, this effect was not (or not yet) measurable at the population level by differences in TB incidence. Notably, trade liberalization measured by EFI4 could unfold positive effects on TB incidence when adjusting for the negative effects of WTO membership. WTO membership turned out to be consistently associated with significantly higher levels of TB incidence between countries or within countries over time. This finding provides support for the pathway from MTAs to the proximate and upstream determinants of TB (Figure 2). Our findings point out to a potential conflict between the achievement of TB-related MDGs (MDG 6c) and the binding and enforceable trade agreements under the WTO that form the global trade architecture since 1995. Further research is needed, particularly on the relation between the aggregate trade indices used in this study and the hypothesized mediators, but also on sector-specific indices, specific trade agreements and other (non-TB) health outcomes.

Supplementary data

Supplementary data are available at *Health Policy and Planning* online

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