Supplementary material to accompany:

Evaluating the Effectiveness of Contact Tracing on Tuberculosis Outcomes in Saskatchewan Using Agent-based Modeling

This supplement provides additional analysis and explanation of our agent-based TB CT model, including additional notes on network structure, sensitivity analysis of network on the effectiveness of contact tracing, implementation of the contact tracing priority queue in Java, and supplementary results which we didn't have space to address in the manuscript.

Sensitivity Analysis of Network Structures on Contact Tracing (Tian, 2012)

Scenarios design

1. Baseline Scenarios

Before exploring future policy alternatives, we first establish "Baseline scenarios" reflecting the status quo absent contact tracing. The parameters for these baseline scenarios maintain their default values. The baseline scenarios, serving as the reference scenarios, will be compared with a set of customized scenarios regarding different research questions to evaluate alternative contact tracing strategies.

Table 1. Baseline scenarios settings without CTI

Id	Network Type	CTI	Tracing Target	Lost follow-up	Tracing Fraction
R0	Random	Disabled	N/A	N/A	N/A
W0	Small World	Disabled	N/A	N/A	N/A
S0	Scale-free	Disabled	N/A	N/A	N/A

In our model, the default settings for baseline scenarios are established as different network assumptions (random, small world, scale-free network respectively) without contact tracing investigation program for 20 years' simulation, seen in Table 1. Because of contact tracing program is absent in the baseline scenarios, active diagnosis and treatment for latent TB infection are disabled as well.

2. Scenarios Assuming a Random Network

In addition to the baseline scenario under the assumption of a random network, 5 additional scenarios are simulated in the random network with different assumptions with regards to contact tracing. Table 5.6 exhibits the settings for each scenario. For the "Loss to follow-up" column, a value of "30% to 40%" means that contact tracing is implemented with a loss to follow up given by empirical data from Saskatchewan TB Control; by contrast, a 10% indicates the standard level of lost follow-up required to achieve published guidelines. All the other parameters (i.e. population size, transmission rate, RR) are maintained the same for all the scenarios in the random network except those mentioned in Table 2.

Table 2. Scenario Settings under the Assumption of the Random Network with Fraction of contacts to investigate equal to 90%

Id	CTI	Tracing Target	Lost follow-up	Additional Settings
R0	**Disabled**	**N/A**	**N/A**	**None**
R1	Enabled	Infectious & Primary TB	30%-40%	None
R2	Enabled	Infectious & Primary TB	10%	None
R3	Enabled	Infectious TB	30%-40%	None
R4	Enabled	Infectious TB	10%	None
R5	Enabled	Infectious & Primary TB	10%	Fast CTI (within 30 days)

The set of scenarios with the random network assumption focus primarily on simulating the impact of lost follow-up on TB control outcome. R1 and R2 simulate the effect of different contact loss levels in the contact tracing, with investigation targets on both infectious TB and primary TB cases. In a similar fashion, R3 and R4 also address the issue of loss of contacts, but with the assumption that the investigation only takes place on infectious TB cases.

The final scenario shown is designed to investigate the impact of greater timeliness of contact tracing. Specifically, Scenario R5 is designed to simulate a contact tracing scheme which is to investigate 90% of the contacts within 30 days of the diagnosis of an active case. In the other scenarios besides R0 (baseline) and R5, the mean time of investigating contacts is maintained as that obtained given by empirical data from 2008.

3. Scenarios Assuming a Small World Network

Under the assumption of a small world network, scenarios regarding the impact of follow-up loss are also examined. In addition to the small world baseline scenario without contact tracing, 2 more scenarios are designed and simulated with different level of follow-up loss. The settings of the scenario are depicted in Table 3.

Table 3. Scenarios' Settings under the Assumption of the Small World Network with Fraction of Contacts to Investigate Equal to 90%.

Id	CTI	Tracing Target	Lost follow-up	Tracing Fraction
W0	**Disabled**	**N/A**	**N/A**	**N/A**
W1	Enabled	Infectious & Primary TB	30%-40%	90%
W2	Enabled	Infectious & Primary TB	10%	90%

Results

1. Results of Baseline Scenarios

Table 4 shows the cumulative incident cases for a period of 20 years under each of the baseline scenarios in turn. Given assumptions of different underlying network structures for the population, the cumulative incident cases vary significantly. A scale-free network baseline scenario (S0) gives the highest mean of cumulative incident cases with large standard deviation, while the lowest mean of the cumulative incident cases among these 3 baseline scenarios is given by the small world baseline scenario (W0), which also gives the lowest standard deviation.

Table 4. Baseline Scenarios Absence of Contact Tracing with Implementation of Different Network Structures

	Cumulative Incident Cases			
Scenario Id	**Mean**	**Max**	**Min**	**Std. Deviation**
R0	250.633	300	199	25.591
W0	181.433	211	151	14.516
S0	425.633	614	289	74.659

The mean prevalence of TB Infection for baseline scenarios are illustrated in Figure 1. In the absence of any contact tracing protocols, the prevalence increases over time in the scale-free network. In random and small world networks, a declining trend is observed over time, and the prevalence of TB infection in a small world decreases faster compared with that of random network.

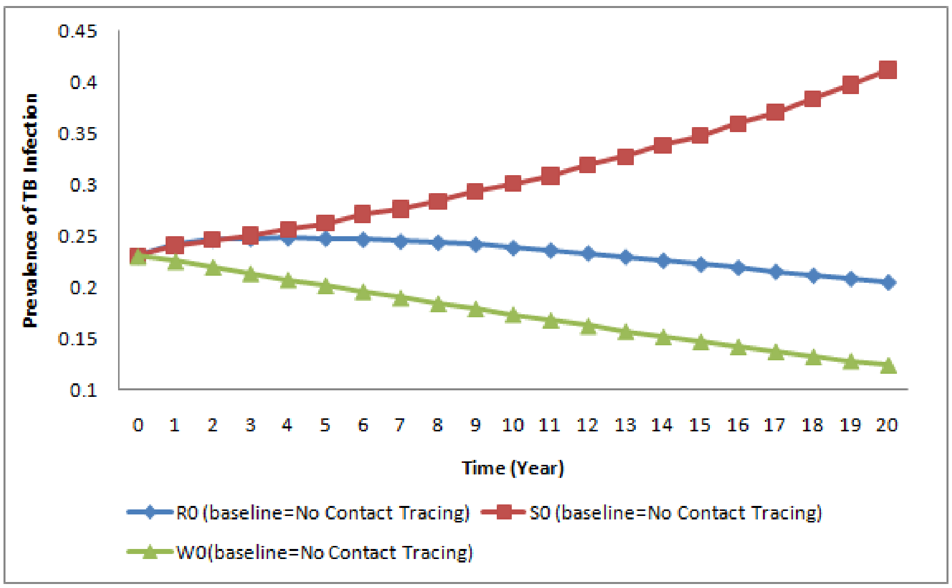

Figure 1: Prevalence of TB Infection in the Baseline Scenarios

2. Results of Scenarios Assuming a Random Network

Table 5 depicts the cumulative incident cases for scenarios with a random network assumption. Different protocols of contact tracing are assessed especially for the issue regarding follow-up loss. Based on the mean of the cumulative TB cases, the baseline scenario gives the highest number of TB cases across all the scenarios. Contact tracing investigation helps reduce the cumulative TB cases, although the average number of reduced TB cases are quite limited. Targeting both infectious and primary TB cases, scenarios R1 and R2 show that lowering the loss of contacts to follow-up to 10% can reduce around 19 cases (8.2%) on average. If we restrict the aim of contact tracing to infectious TB cases only (R3 and R4), maintaining a 10% loss of contacts level can prevent roughly 15.4 active TB cases on average (a reduction of 6.6%).

Comparing scenario R1 with R3 (which differs only in tracing just infective cases), the cumulative incident cases varies little. Scenarios R2 and R4 also do not exhibit significant difference regarding the average count of cumulative incident cases, despite the broader population being traced in *R2*.

Regarding the ideal protocol for contact tracing – having 90% of the contacts skin tested within 30 days of diagnosis of active TB cases as well as maintaining 10% loss of contacts – scenario R5 doesn't show a large difference in cumulative TB cases compared with those of R2 where 90% of the contacts are tested continuously within a year (rather than within 30 days).

Table 5. Results of the Scenarios under the assumption of random network. The statistical tests are Mann-Whitney U tests (two tailed).

	Cumulative Incident Cases				
Scenario Id	**Mean**	**Max**	**Min**	**Std. Deviation**	**P-value**
R0	250.633	300	199	25.591	
R1	231.5	299	197	29.821	<0.05
R2	212.667	262	184	17.149	<0.05
R3	232.333	285	187	26.259	<0.05
R4	216.933	266	181	21.284	<0.05
R5	213.3667	277	167	22.51	<0.05

Figure 2 gives the realization-mean prevalence of TB infection among the population over time. All trajectories demonstrate the declining trend over time. The prevalence of TB infection in baseline R0 is above that of other scenarios where contact tracing is enabled. Lower level of follow-up loss ultimately gives lower prevalence, seen in R2, R4 and R5. Having reverse contact tracing (which targets on primary TB cases to assess the source of infection) enabled doesn't appear to bring observable difference in TB infection prevalence; the TB infection prevalence in R1 and R3 are almost overlapped; R2 and R4 are also overlapped in prevalence of TB infection.

In addition, maintaining a faster speed of contact tracing (mean time of contact tracing of 30 days) in R5 doesn't produce significant improvement in prevalence compared with the current speed of contact tracing (R2).

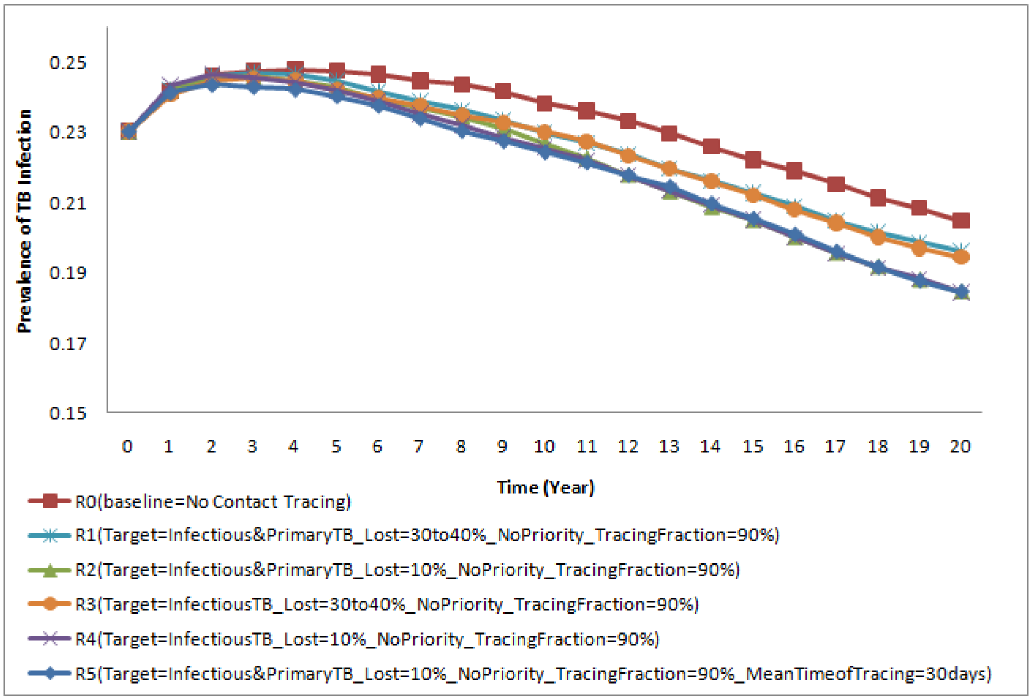

Figure 2: Prevalence of TB infection for Scenarios regarding Random Network

3. Results of Scenarios Assuming a Small World Network

Table 6 shows the results of small world network scenarios regarding cumulative incident cases. Regarding the loss of contacts, the mean of cumulative TB cases does not vary dramatically across scenarios W0, W1 and W2. On average, a small number of active TB cases can be prevented by having contact tracing enabled (W0 versus W1). The improvement in reducing active TB cases is also small (only 6 cases) when a 10% of loss of contacts is maintained (see W1 versus W2).

Figure 3 illustrates the TB infection prevalence in the small world network. The difference in scenarios W0 and W1 are not significant, which suggests that increasing the contact investigation level did not make explicit contribution to the prevalence of TB infection. Comparing W0 with W2 shows a significant reduction (7%; P=0.005) in mean cumulative incident TB cases.

Table 6. Results of Scenarios under the Assumption of Small World Network. The statistical tests are Mann-Whitney U tests (two tailed).

	Cumulative Incident Cases				
Scenario Id	**Mean**	**Max**	**Min**	**Std. Deviation**	**P-value**
W0	181.433	211	151	14.516	
W1	174.267	199	136	15.0	0.09
W2	168.867	197	137	16.033	0.005

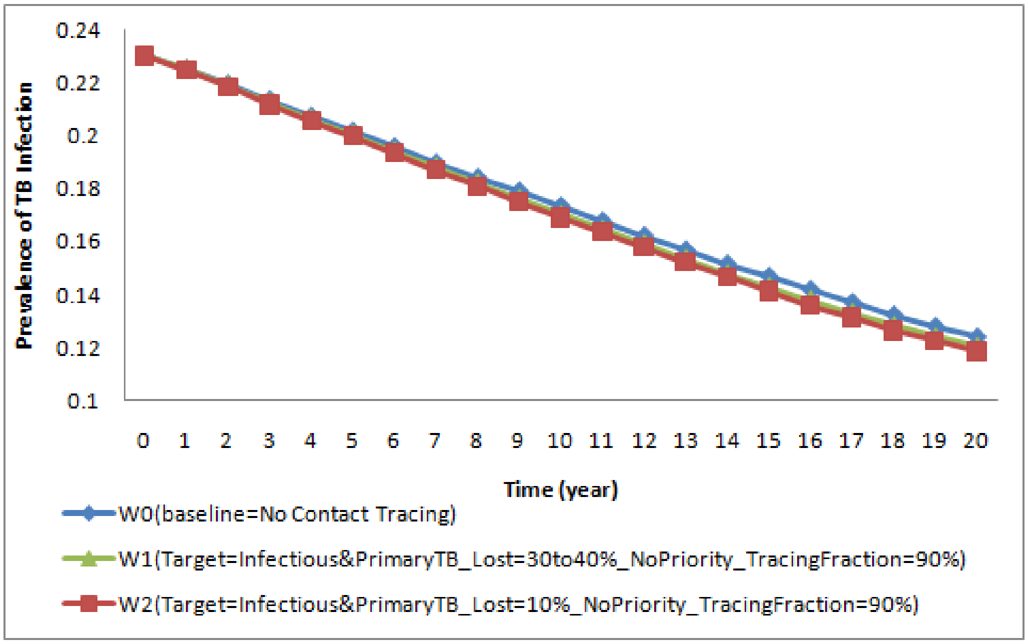

Figure 3: Prevalence of TB infection for Scenarios regarding Small World Network

Prioritized Contact Tracing with Priority Queue

The priority Queue for CT is implemented as a PriorityQueue in Java platform SE 6 Library(Oracle, 2012). Here I provide a snapshot of the Java code of the priority Queue implementation for the Contact Tracing for those who are interested. The following codes are taken from the CT function implemented in diagnosis related transitions in TB transmission statechart. A higher calculated priority score refers to higher estimated risk and a position closer to the front of the queued list of the contacts to be notified. The most important RR values implemented in our model are included in Table 2 of the manuscript. The first five are taken from an updated (but not yet published) calibration of the aggregate SD model (Osgood et al., 2011), and affect both TB diffusion and contact tracing prioritization. The balance are calculated from social network analysis (SNA) by a research team member of our (Al-Azem, 2007), and only affect contact tracing prioritization.

You can observe the key code related to scenarios on tracing fraction and target.

```
if (enableTracing==0) return;
//target=0: tracing ONLY infectious cases
//infectious: whether this case is infectious or not
//1st Con: tracing infectious only; 2nd: tracing all TB cases; 3rd: tracing infectious and primary TB case.
if((targets==0 && infectious)||(targets == 1)||(targets==2 && (infectious || isPrimary))){
    //initialize a Priority queue based on different prioritization or non
    PriorityQueue<Person> queueofCase=new PriorityQueue<Person>(this.getConnectionsNumber());
        //get the contacts of this case
        LinkedList<Agent> contacts=getConnections();
         if(contacts!=null){
```

```
					for(Agent a: contacts){
					//iterate through the contacts to save those available for contact, information lost here is the 3416/4015;
						//the lost here doesn't include death during this process.
						if(randomTrue(get_Main().contactsInvestigatedFraction))
						//queueofCase saved those who are available for contact.
							queueofCase.offer((Person) a);
					}//end for(Agent a: contacts)
				}//if(contacts!=null)
		//apply the percentage to investigate, could be 45%, 90%.
				int tracedNum=(int) (this.getConnectionsNumber()*get_Main().percentageToTrace);
				int investigated=0;
				while(investigated<=tracedNum && !queueofCase.isEmpty()){
					//the investigated include all kinds of contacts, such as PrevPos, skin negative and PrevActiveTB.
					investigated++;
					Person tempContact=queueofCase.poll();
					//save the number times a contact been reported as contact.(If a person is never investigated, then the count won't increase.)
					tempContact.count_tracing++;

					if(tempContact.contactTracing.isStateActive(potentialContact)){
					//send message to the CT message contact
						this.deliver(get_Main().letterForContactMsg,tempContact);
									}
					if(targets==2 && this.isPrimary && tempContact.contactTracing.isStateActive(PreviousPositive)){
					//if this is a primary TB case, then we investigate his/her contacts too, even his/her contacts are previously investigated.
						this.deliver(get_Main().letterForContactMsg,tempContact);
									}

				}//end while
}
```

The prioritization mechanism is internally incorporated within the priorityQueue. In order to compare the agents based on the relative risks (e.g. age, ethnicity), the Agent class (a Java term) need to implement the **Comparable** interface in java, thereby providing rules for such comparison(Oracle, 2012).

Supplementary Results

The results relative to the no CT case using two-sample Kolmogorov–Smirnov tests are shown in Table 7, and the p-values shows statistical significant results which are the same as those of the Mann-Whitney test in the manuscript.

Table 7. Scenario results applying two-sample Kolmogorov-Smirnov tests.

Scenario Id	Cumulative Incident Cases (Active TB)			
	Median	*Mean*	*Std. Deviation*	*P-value*
S0	411	411.08	76.5	
S1	288	292	47.1	<0.0001
S2	277	276.3	44.6	<0.0001
S3	328	326.79	53.4	<0.0001
S4	294	294.52	50.6	<0.0001
S5	295	304.56	57.7	<0.0001

S6	344.5	353.01	67.1	<0.0001
S7	286	291.04	48.7	<0.0001
S8	265	265.7	41.9	<0.0001

Table 8 shows the U statistics of the Mann-Whitney U test (see Table 5 in the manuscript).

Table 8. U statistics of Mann-Whitney U tests applied on scale free network scenarios.

Scenario Id	Cumulative Incident Cases (Active TB)	
	U statistics	*P-value*
S0		
S1	830.5	<0.0001
S2	536	<0.0001
S3	1825	<0.0001
S4	934	<0.0001
S5	1258	<0.0001
S6	2748.5	<0.0001
S7	841.5	<0.0001
S8	360.5	<0.0001

Reference

Al-Azem, A. (2007). Social Network Analysis in Tuberculosis Control Among the Aboriginal Population of Manitoba. (Ph.D.), University of Manitoba.

Oracle. (2012). Priority Queue. Retrieved from http://docs.oracle.com/javase/6/docs/api/java/util/PriorityQueue.html

Osgood, N. D., Mahamoud, A., Lich, K. H., Tian, Y., Al-Azem, A., & Hoeppner, V. H. (2011). Estimating the Relative Impact of Early-Life Infection Exposure on Later-Life Tuberculosis Outcomes in a Canadian Sample. *Research in Human Development, 8*(1), 26-47.

Tian, Y. (2012). *Agent-based Modeling and System Dynamics Modeling on Transmission of Tuberculosis in Saskatchewan.* (M.Sc.), University of Saskatchewan.