A dynamical analysis of tuberculosis in the Philippines

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Tuberculosis (TB), an infection obtained from Mycobacterium, is the fourth leading cause of death in the Philippines. It remains to be a problem especially in developing countries, even after following guidelines and achieving some of the targets set by the World Health Organization (WHO) for TB elimination. Inspired by the TB transmission model developed by Trauer et al. (2014), we propose a model for TB transmission in the Philippines and validated it using Philippine-based data for TB incidence and prevalence rates in 2003-2013 (WHO, 2014). Using the Theorem of van den Driessche & Watmough (2002) we show that our proposed Philippine TB model has a locally asymptotically stable endemic equilibrium, with basic reproduction number $R_0 = 0.4516$ and an unstable free-disease equilibrium, with $R_0 = 3.8896$. Moreover, our projected simulations show that improving partial immunity, treatment success, treatment duration and case detection in the Philippines will significantly reduce the TB incidence and prevalence rates. Interestingly, we found that improving vaccine coverage would not significantly reduce the projected TB incidence and prevalence rates. These results can help the Philippines in improving its TB programs and develop new strategies to eliminate tuberculosis in the country.

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INTRODUCTION

Tuberculosis is the infection of *Mycobacterium tuberculosis*, acquired through inhaling and causing infection in the lungs (NIAID, 2009). There are two main kinds of tuberculosis: latent and active. Latent tuberculosis is the inactive infection in which the body's immune system can only control the growth of the bacteria but cannot eradicate them. This makes the infection non-contagious and asymptomatic. After latency, active TB can occur and *M. tuberculosis* can populate, infect and destroy the defense mechanism of the body, making the TB contagious (NIAID, 2009). Treatments and drugs have already been developed, but these drugs have side effects and the treatment can last for at least 6 months thus, costly and open to possibility of failure (WHO, 2010b). Moreover, treatment failure could result in the development of the multi-drug-resistant TB or MDR-TB.

Although the World Health Organization (WHO) and countries affected by TB have set guidelines and targets for TB elimination, some countries are far from achieving them (WHO, 2014a). The Philippines is one of the TB high-burden countries and is listed as the 13th highest TB-related death rate, 8th highest TB incidence, and 7th highest TB prevalence as of 2013 (WHO, 2014a). This paper aims to contribute to the Philippines in its effort to control TB by understanding its dynamics in the country through mathematical modelling.

Mathematical modelling of disease transmission is a tool for studying an epidemic and can be used for designing epidemic control strategies and for predicting the effects of certain strategies (Abu-Raddad et al., 2009). We want to make sense out of the data and provide meaning to the model (Wolkenhauer et

al., 2009). A valid model can be used to project the effects of interventions made on the dynamics of a disease for short or long periods. The long-term effects can be determined by looking at the stability of the system, while the short-term effects are identified by numerically analyzing the model.

Related studies investigated the impact of strategies on eliminating TB such as improving case detection, treatment and vaccination. Trauer et al. (2014) showed that case detection rate is a sensitive parameter of TB prevalence and mortality. Bhunu et al. (2011) highlighted the role of treatment success, arguing that a high case detection rate with low treatment success rate could still result in an endemic situation. Moreover, Dowdy and Chaisson (2009) showed that fixing the treatment success to 85% will stabilize TB incidence if case detection is less than 80% although it will decrease yearly only by an average of 1.5% despite rapid case detection increase. They recommended researchers to continuously put efforts to improve case detection and other factors of TB control, particularly treatment success.

Nainggolan et al. (2013), comparing the TB dynamics with and without vaccination, showed that incorporating vaccination significantly lowers the maximum number of latently and actively infected persons and always reduces the basic reproduction number (average secondary infection caused by an infectious individual, (van den Driessche and Watmough, 2002)). Moreover, Lietman and Blower (2000), analysing the effects of pre-exposure and post-exposure vaccines on TB dynamics, showed that if TB incidence is high (greater than 100 per 100,000 population), then the reduction due to post-exposure vaccine is greater than that due to pre-exposure vaccine; and, if the TB incidence is low, then the reduction due to pre-exposure vaccine is greater. They recommended therefore, that a combination of pre-exposure and post-exposure vaccines be used to aid in eliminating TB in developing countries. Trauer et al. (2014) however, found out that vaccine coverage is not a sensitive parameter of TB prevalence and mortality.

How can these results help the Philippines strategize a more effective TB control in the country? This paper aims to answer this question through mathematical modelling of TB dynamics in the Philippines. We propose a TB transmission model for the Philippine setting by modifying the model formulated by Trauer et al. (2014) based on the TB incidence and prevalence data for the Philippines as reported by the World Health Organization (WHO) for 2003-2013. Our proposed model will be analyzed for stability and used to determine factors which can significantly reduce TB in the country. Conclusions of this study can give important insights for the development and implementation of more effective and efficient TB programs in the Philippines.

THE MODEL

In this study, we propose a TB transmission model for the Philippine setting based on the work of Trauer and colleagues for the Asia Pacific Region (2014). Restricted by the data that is available for validation, we revised the model of Trauer et al. in three ways. First, in order to focus this study only on drug-susceptible TB, we omitted the drug-resistant compartments in the model. This omission could not significantly affect our study since drug-resistant TB in the Philippines is still relatively low – about 4,000 persons or a prevalence of 4 per 100,000 population as of 2013 (WHO, 2014b). Second, while the model of Trauer et al. assumed that birth rate is proportional to the total population, we assumed the birth rate to be constant. This was done in order to focus the cause of changing population on the disease. This method of using constant birth rate was also used by Liu et al. (2011) in their analysis of the TB dynamics in Guangdong, China. Third, because treatment success rate is an important element in TB dynamics, we incorporated it in our model.

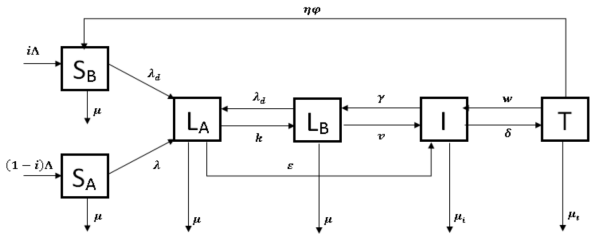

Figure 1. Diagram of our proposed model for TB transmission in the Philippines. The population is assumed to be homogeneous and is divided into 6 compartments (represented by boxes): the susceptible unimmunized group (S_A), the susceptible and partially immunized group (S_B), the "slow" latently infected (L_A), the "fast" latently infected (L_B), the actively infected and undetected group (I), and the actively infected, detected, and treated (T). Individuals transfer from one group to another (represented by arrows) with the corresponding rates of transfer (represented by the parameters indicated on each arrow).

In our proposed model (shown in Figure 1), we assumed that the population is homogeneously mixed and is divided into six (6) groups or compartments: the susceptible unimmunized group S_A; the susceptible and partially immunized S_B; the "slow" latently infected L_A; the "fast" latently infected L_B; the actively infected and undetected group I; and the actively infected, detected and treated T. The whole population increases by birth with rate $(1 - i)\Lambda + i\Lambda$, where Λ is the constant birth rate and i is the fraction of those who got TB vaccine. The whole population decreases by death: μ is the natural death rate, μ_i is the death rate of actively infected and undetected persons, while μ_t is the death rate of those actively infected and detected.

Similar to the model of Trauer et al., we assumed frequency-dependent transmission. In this case, the unimmunized and immunized susceptible individuals become infected with the respective force of infection $\lambda = \frac{\beta\rho(I + hT)}{N}$ and $\lambda_d = \frac{\chi\beta\rho(I + hT)}{N}$, where β is the effective contact rate, ρ is the fraction of those who are infectious, h is the modification of infectiousness of those who are treated, and χ is partial immunity that is either acquired from vaccination or developed from previous TB disease.

Moreover, our proposed model assumed that the L_A group could undergo fast progression to active TB at rate ε or slow progression and go to L_B group at rate k. Those in L_B could develop active TB with rate ν, or acquire additional infection and go to "slow" latency group L_A with force of infection λ_d. Those who develop active TB but are undetected could be cured without medical treatment at rate γ or be detected by the national TB program at rate δ. Those detected are assumed to be treated immediately. Those who are treated are cured at rate $\eta\varphi$, where η is the treatment success rate and $\frac{1}{\varphi}$ is the duration of TB treatment. They could also miss treatment at rate w (default rate).

All parameters are assumed to be positive since the model only deals with positive rates. The values of i, h and ρ range from 0 to 1 since they represent ratios. Moreover, since the variables represent numbers of individuals, their values are also nonnegative. Given the model in Figure 1, we obtain the following system of equations:

$$\frac{dL_A}{dt} = \lambda S_A + \lambda_d S_B + \lambda_d L_B - \varepsilon L_A - kL_A - \mu L_A \quad \textbf{(Eq. 1)}$$

$$\frac{dL_B}{dt} = kL_A + \gamma I - \lambda_d L_B - vL_B - \mu L_B \quad \textbf{(Eq. 2)}$$

$$\frac{dI}{dt} = \varepsilon L_A + vL_B + wT - \gamma I - \delta I - \mu_i I \quad \textbf{(Eq. 3)}$$

$$\frac{dT}{dt} = \delta I - \eta\varphi T - wT - \mu_t T \quad \textbf{(Eq. 4)}$$

$$\frac{dS_A}{dt} = (1-i)\Lambda - \lambda S_A - \mu S_A \quad \textbf{(Eq. 5)}$$

$$\frac{dS_B}{dt} = i\Lambda + \eta\varphi T - \lambda_d S_B - \mu S_B \quad \textbf{(Eq. 6)}$$

where

$$\lambda = \frac{\beta\rho(I + hT)}{N} \quad \textbf{(Eq. 7)}$$

$$\lambda_d = \frac{\chi\beta\rho(I + hT)}{N} \quad \textbf{(Eq. 8)}$$

$$N = S_A + S_B + L_A + L_B + I + T \quad \textbf{(Eq. 9)}$$

The system has a total of 19 parameters: 13 have fixed values throughout the study, 5 were tested for significance and 1 was subjected to data fitting (β). These are listed in Table 1 with their corresponding values obtained from literature.

Table 1. Summary of model parameters with their corresponding descriptions, values and sources.

PARAMETER	DESCRIPTION	VALUE	SOURCE
Fixed parameters			
ε	Early progression	0.129 over 23 months	(Diel et al., 2011)
k	Transition to late latency	0.821 over 23 months	(Blower et al., 1996)
v	Reactivation	0.075 over 20 years	(Blower et al., 1996)
γ	Spontaneous recovery	0.63 over 3 years	(Tiemersma et al., 2011)
μ_i	TB-specific death rate	0.2647358 per year	(Liu et al., 2011)
μ_t	Treated TB-specific death rate	0.0210358 per year	(Liu et al., 2011)
h	Treatment modification of infectiousness	0.21	(Cox et al., 2007)
Λ	Constant birth rate	2,192,078 per year	
μ	Natural death rate	1 over 67.862 years [average from 2003 to 2012]	("Philippines - Life expectancy at birth 2015," 2015)
ρ	Infectious proportion	0.546 [average from 2003 to 2013]	WHO database (WHO, 2015)
d_i	Death rate due to TB alone	$\mu_i - \mu$	
w	Default rate	0.0225 per year	WHO database (WHO, 2015)
d_t	Death rate due to TB alone during treatment	$\mu_t - \mu$	
Parameters tested for significance			
χ	Partial immunity	0.49	(Colditz et al., 1994)
$\frac{1}{\varphi}$	Duration of treating drug-susceptible TB	6 months or 0.5 year	(WHO, 2010a)
i	BCG vaccination rate	0.8664 [average from 2003 to 2013]	WHO database (WHO, 2015)
η	Treatment success rate	0.7 [average from 1995 to 2012]	(WHO, 2014b)
δ	Case detection rate	0.45 per year	WHO database (WHO, 2015)
Parameter subjected to model fitting			
β	Effective contact rate	11.5	Estimated using MatLab
Initial values of the variables			
$\bar{I}(0)$	Estimated proportion of actively infected and undetected persons as of 2003	0.0053028	WHO database (WHO, 2015)
$\bar{T}(0)$	Estimated proportion of actively infected, detected and treated persons as of 2003	0.0016072	WHO database (WHO, 2015)
$\bar{N}(0)$	Estimated proportion of constant birth rate	(24.24/1000) x 82,604,681 [average from 2003 to 2013]	WHO database (WHO, 2015)
Initial values of the varialbes subject to model fitting			
$\bar{S}_A(0)$	Estimated proportion of susceptible unimmunized persons as of 2003	0.04409	Estimated in MatLab
$\bar{S}_B(0)$	Estimated proportion of susceptible immunized persons as of 2003	0.4	Estimated in MatLab
$\bar{L}_A(0)$	Estimated proportion of 'fast' latently infected persons as of 2003	0.049	Estimated in MatLab
$\bar{L}_B(0)$	Estimated proportion of 'slow' latently infected persons as of 2003	0.5	Estimated in MatLab

DATA FITTING

We fitted our proposed model with the data of TB incidence and prevalence rates in the Philippines. Incidence and prevalence are two of the key indicators of TB burden in a country. **Prevalence** is the number of TB cases at a given point in time, while **incidence** is the number of new and relapse cases of TB occurring in a given time period, usually in one year (WHO, 2014b). Incidence here is estimated by dividing the number of notified cases by the case detection rate (Glaziou et al., 2009), while prevalence is obtained by adding the notified and undetected cases. Prevalence and incidence data are usually expressed in proportion to the total population, which in this study we shall call **prevalence rate** and **incidence rate**. In order to fit the data into the model therefore, we first converted the system given by equations (**1**) – (**9**) into a dynamical system where the variables are proportions of the total population. Hence,

$$\bar{S}_A = \frac{S_A}{N}, \bar{S}_B = \frac{S_B}{N}, \bar{L}_A = \frac{L_A}{N}, \bar{L}_B = \frac{L_B}{N}, \bar{I} = \frac{I}{N}, \bar{T} = \frac{T}{N}, \bar{N} = \frac{\Lambda}{N} \quad \textbf{(Eq. 10)}$$

By adding equations (**1**) – (**6**), we obtained the time derivative $\frac{dN}{dt}$ of the total population N, which is given by

$$\frac{dN}{dt} = \Lambda - \mu N - d_i I - d_t T, \quad \textbf{(Eq. 11)}$$

where $d_i = \mu_i - \mu$ and $d_t = \mu_t - \mu$. From equation (**10**) we obtained the following non-dimensionalized system of ODEs:

$$\frac{d\overline{L_A}}{dt} = \beta\rho(\overline{I} + h\overline{T})\overline{S_A} + \chi\beta\rho(\overline{I} + h\overline{T})\overline{S_B} + \chi\beta\rho(\overline{I} + h\overline{T})\overline{L_B} - \varepsilon\overline{L_A} - k\overline{L_A} - \mu\overline{L_A} - \overline{L_A}(\overline{N} - \mu - d_i\overline{I} - d_t\overline{T}) \quad \textbf{(Eq. 12)}$$

$$\frac{d\overline{L_B}}{dt} = k\overline{L_A} + \gamma\overline{I} - \chi\beta\rho(\overline{I} + h\overline{T})\overline{L_B} - v\overline{L_B} - \mu\overline{L_B} - \overline{L_B}(\overline{N} - \mu - d_i\overline{I} - d_t\overline{T}) \quad \textbf{(Eq. 13)}$$

$$\frac{d\overline{I}}{dt} = \varepsilon\overline{L_A} + v\overline{L_B} + w\overline{T} - \gamma\overline{I} - \delta\overline{I} - \mu_i\overline{I} - \overline{I}(\overline{N} - \mu - d_i\overline{I} - d_t\overline{T}) \quad \textbf{(Eq. 14)}$$

$$\frac{d\overline{T}}{dt} = \delta\overline{I} - \eta\varphi\overline{T} - w\overline{T} - \mu_t\overline{T} - \overline{T}(\overline{N} - \mu - d_i\overline{I} - d_t\overline{T}) \quad \textbf{(Eq. 15)}$$

$$\frac{d\overline{S_A}}{dt} = (1-i)\overline{N} - \beta\rho(\overline{I} + o\overline{T})\overline{S_A} - \mu\overline{S_A} - \overline{S_A}(\overline{N} - \mu - d_i\overline{I} - d_t\overline{T}) \quad \textbf{(Eq. 16)}$$

$$\frac{d\overline{S_B}}{dt} = i\overline{N} + \eta\varphi\overline{T} - \chi\beta\rho(\overline{I} + h\overline{T})\overline{S_B} - \mu\overline{S_B} - \overline{S_B}(\overline{N} - \mu - d_i\overline{I} - d_t\overline{T}) \quad \textbf{(Eq. 17)}$$

$$\frac{d\overline{N}}{dt} = -\overline{N}(\overline{N} - \mu - d_i\overline{I} - d_t\overline{T}) \quad \textbf{(Eq. 18)}$$

Thus, we have the following formulations for prevalence and incidence rates, respectively

$$prev(t) = \overline{I}(t) + \overline{T}(t) \quad \textbf{(Eq.19)}$$

$$inc(t) = \frac{\overline{T}(t)}{\delta}. \quad \textbf{(Eq. 20)}$$

Using Philippine data for prevalence and incidence rates obtained from the World Health Organization Report for 2003 to 2013 (WHO, 2015), values for parameters obtained from literature, and assuming initial values for $\overline{L_A}, \overline{L_B}, \overline{I}, \overline{T}, \overline{S_A}, \overline{S_B}$ we estimated the effective contact rate β for the model using *Matlab* and found it to be 11.5. All simulations in this paper were also done in *Matlab*.

As shown in Figure 2, the fitted values follow the same decreasing behaviour of the actual values of the incidence and prevalence rates of TB in the Philippines. The discrepancies are within the error bars. Hence, we can say that our model is valid and is able to describe the TB dynamics in the Philippines, particularly the TB incidence and prevalence rates in the country.

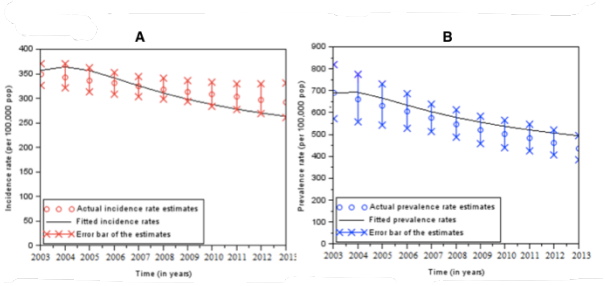

Figure 2. Simulations of actual and fitted values of incidence rate (A) and prevalence rate (B) for the years 2003 to 2013. The fitted values are obtained using the least square method in MatLab. The fitted values follow the same decreasing behaviour as the actual values and are within the error brackets of the actual values.

STABILITY ANALYSIS OF THE MODEL

We determined the free-disease and endemic equilibrium points and analyzed their stability. To calculate an equilibrium point $\mathbf{x}_0$, we equated each of the differential equations (**1**) – (**6**) to zero and solved for the respective variables. Thus we have,

$$L_A = \frac{\lambda S_A + \lambda\chi(S_B + L_B)}{\varepsilon + k + \mu} \quad \textbf{(Eq. 21)}$$

$$L_B = \frac{kL_A + \gamma I}{\lambda\chi + v + \mu} \quad \textbf{(Eq. 22)}$$

$$I = \frac{\varepsilon L_A + vL_B + wT}{\gamma + \delta + \mu_i} \quad \textbf{(Eq. 23)}$$

$$T = \frac{\delta I}{\eta\varphi + w + \mu_t} \quad \textbf{(Eq. 24)}$$

$$S_A = \frac{(1-i)\Lambda}{\lambda + \mu} \quad \textbf{(Eq. 25)}$$

$$S_B = \frac{i\Lambda + \eta\varphi T}{\lambda\chi + \mu} \quad \textbf{(Eq. 26)}$$

The exact expressions for L_A, L_B, I, T, S_A, S_B, in terms only of the parameters were computed using Mathematica and are found in Appendix A.

Free-disease Equilibrium

We denoted the free-disease equilibrium as $\mathbf{x}^o = (L_A^o, L_B^o, I^o, T^o, S_A^o, S_B^o)$. In the free-disease state, the system has no infection. Thus, we have

$$L_A^o = L_B^o = I^o = T^o = \lambda = \lambda_d = 0. \quad \textbf{(Eq. 27)}$$

Solving for S_A^o and S_B^o, we arrived at the free-disease equilibrium:

$$\mathbf{x}^o = \left(0,0,0,0,\frac{(1-i)\Lambda}{\mu} + \frac{i\Lambda}{\mu}\right). \quad \textbf{(Eq. 28)}$$

Endemic Equilibrium

We denoted the endemic equilibrium as $\mathbf{x}^* = (L_A^*, L_B^*, I^*, T^*, S_A^*, S_B^*)$. To describe the endemic state of the system, we considered the force of infection

$$\lambda^* = \frac{\beta\rho(I^* + hT^*)}{N}. \quad \textbf{(Eq. 29)}$$

Since $N = S_A^* + S_B^* + L_A^* + L_B^* + I^* + T^*$, equation (**29**) can be expressed as

$$\lambda^*S_A^* + \lambda^*S_B^* + \lambda^*L_A^* + \lambda^*L_B^* + \lambda^*I^* + \lambda^*T^* - \beta\rho I^* - \beta\rho hT^* = 0. \quad \textbf{(Eq. 30)}$$

Substituting the expressions for S_A^*, S_B^*, L_A^*, L_B^*, I^* and T^* in terms of λ^* and the parameters, equation (**30**) resulted into a polynomial equation of the form

$$\lambda^{*n} + a_1\lambda^{*n-1} + a_2\lambda^{*n-2} + \cdots + a_{n-1}\lambda^* + a_n = 0, \quad \textbf{(Eq.31)}$$

where $n = 4$ since we found four (4) roots using *Mathematica*. Two of those roots are imaginary, one is zero and one is real. Please see Appendix B for their exact expressions. Since λ^* is the force of infection during spread of tuberculosis, we only considered its nonzero real value in the computation of the endemic equilibrium, found in Appendix C.

In this paper, the analysis of an equilibrium point $\mathbf{x}_0$, whether the free-disease equilibrium or the endemic equilibrium, is based on the basic reproduction number following the method of van den Driessche & Watmough (2002).

Basic Reproduction number R_0

The basic reproduction number R_0 is the average secondary infection produced by an infectious individual in a fully susceptible population.

Let $\mathbf{x} = [L_A\ L_B\ I\ T\ S_A\ S_B]^T$ be the 6 × 1 matrix containing the number of individuals x_i in compartment i. Moreover, let $F(\mathbf{x})$ be the 6 × 1 matrix whose entries $F_i(\mathbf{x})$ are the rates of

appearance of new infectious individuals in the compartment i, and $V(\mathbf{x})$ is the 6 × 1 matrix whose entries $V_i(\mathbf{x})$ are the rates of transfer of individuals into and out of compartment i. Thus, $V_i(\mathbf{x}) = V_i^-(\mathbf{x}) - V_i^+(\mathbf{x})$, where $V_i^+(\mathbf{x})$ is the rate of transfer of individuals into compartment i and $V_i^-(\mathbf{x})$ is the rate of transfer of individuals out of compartment i. Hence,

$$F(\mathbf{x}) = \begin{bmatrix} \lambda S_A + \lambda_d S_B \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} \frac{\beta\rho(I+hT)}{N} S_A + \frac{\chi\beta\rho(I+hT)}{N} S_B \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

and

$$V(\mathbf{x}) = \begin{bmatrix} \varepsilon L_A + kL_A + \mu L_A \\ \lambda_d L_B + \nu L_B + \mu L_B \\ \gamma I + \delta I + \mu_i I \\ \eta\varphi T + wT + \mu_t T \\ \lambda S_A + \mu S_A \\ \lambda_d S_B + \mu S_B \end{bmatrix} - \begin{bmatrix} \lambda_d L_B \\ kL_A + \gamma I \\ wT + \varepsilon L_A + \nu L_B \\ \delta I \\ (1-i)\mathbf{\Lambda} \\ i\mathbf{\Lambda} + \eta\varphi T \end{bmatrix} =$$

$$\begin{bmatrix} \varepsilon L_A + kL_A + \mu L_A - \frac{\chi\beta\rho(I+hT)}{(S_A+S_B+L_A+L_B+I+T)} L_B \\ \frac{\chi\beta\rho(I+hT)}{(S_A+S_B+L_A+L_B+I+T)} L_B + \nu L_B + \mu L_B - kL_A - \gamma I \\ \gamma I + \delta I + \mu_i I - wT - \varepsilon L_A - \nu L_B \\ \eta\varphi T + wT + \mu_t T - \delta I \\ \frac{\beta\rho(I+hT)}{(S_A+S_B+L_A+L_B+I+T)} S_A + \mu S_A - (1-i)\mathbf{\Lambda} \\ \frac{\chi\beta\rho(I+hT)}{(S_A+S_B+L_A+L_B+I+T)} S_B + \mu S_B - i\mathbf{\Lambda} - \eta\varphi T \end{bmatrix}.$$

For any equilibrium point of the system $\mathbf{x}_0$, we defined matrices F and **V** to be the respective Jacobian of matrices $F(\mathbf{x})$ and V($\mathbf{x}$). That is, $\mathbf{F} = \left[\frac{\partial F_i(\mathbf{x}_0)}{\partial x_i}\right]$ and $\mathbf{V} = \left[\frac{\partial V_i(\mathbf{x}_0)}{\partial x_i}\right]$.

Mathematically, the basic reproduction number R_0 is given by $R_0 = r(\mathbf{FV}^{-1})$, where r is the ***spectral radius*** of the ***next generation matrix***, $\mathbf{FV}^{-1}$ (that is, the greatest eigenvalue of the matrix $\mathbf{FV}^{-1}$, in absolute value).

Stability of the Equilibrium Points

To determine the local asymptotic stability of the equilibrium points, we used the following theorem:

> ***Theorem of van den Driessche and Watmough***
> *Let $\mathbf{x}_0$ be an equilibrium point of a system $\dot{\mathbf{x}} = f(\mathbf{x})$ and $X_s = \{\mathbf{x} \geq 0 \,|\, x_i = 0, i = 1, 2, \ldots, m\}$ be the set of all disease-free states.*
>
> *Moreover, let $F(\mathbf{x})$, $V(\mathbf{x})$, $V^-(\mathbf{x})$ and $V^+(\mathbf{x})$, as defined above, satisfy the following assumptions:*
> 1. *If $\mathbf{x} \geq 0$, then $F_i(\mathbf{x})$, $V_i^-(\mathbf{x})$, $V_i^+(\mathbf{x}) \geq 0$, for $i = 1, 2, \ldots, n$.*
> 2. *If $x_i = 0$, $V_i^-(\mathbf{x}) = 0$ for $i = 1, 2, \ldots, n$. In particular, if $\mathbf{x} \in X_s$ then $V_i^-(\mathbf{x}) = 0$ for $i = 1, 2, \ldots, m$.*
> 3. *$F_i(\mathbf{x}) = 0$ if $i > m$.*
> 4. *Both $F_i(\mathbf{x}) = 0$ and $V_i^+(\mathbf{x}) = 0$ if $\mathbf{x} \in X_s$ for $i = 1, 2, \ldots, m$.*
> 5. *If $F_i = 0$ for all i, then all the eigenvalues of the Jacobian matrix $J(\mathbf{x}_0)$ at $\mathbf{x}_0$ have negative real parts.*
>
> *Then the equilibrium $\mathbf{x}_0$ is locally asymptotically stable when $R_0 \leq 1$ and unstable when $R_0 > 1$.*

In our model, $X_s = \{S_A, S_B\}$. Our computations of $F(\mathbf{x})$, $V(\mathbf{x})$, $V^-(\mathbf{x})$ and $V^+(\mathbf{x})$ showed that conditions 1 to 4 of the Theorem are satisfied. Therefore, in order to determine the stability of the free-disease and endemic equilibrium points, we only needed to check the respective Jacobian matrices of the original ODE system given by equations (**1**) – (**6**), evaluated at each equilibrium point, namely $\boldsymbol{J}(\mathbf{x}^0)$ and $\boldsymbol{J}(\mathbf{x}^*)$. Details of computations in this section are found in Appendices D, E and F.

For the free-disease equilibrium $\mathbf{x}^0 = \left(0, 0, 0, 0, \frac{(1-i)\mathbf{\Lambda}}{\mu}, \frac{i\mathbf{\Lambda}}{\mu}\right)$, the corresponding Jacobian of the ODE system of equations (**1**) – (**6**) is

$$J(\mathbf{x}^0) = \begin{bmatrix} -k-\varepsilon-\mu & 0 & 0 & 0 & 0 & 0 \\ k & -\mu-\nu & \gamma & 0 & 0 & 0 \\ \varepsilon & \nu & -\gamma-\delta-\mu_i & w & 0 & 0 \\ 0 & 0 & \delta & -\mu_t-\eta\varphi-w & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu & 0 \\ 0 & 0 & 0 & \eta\varphi & 0 & -\mu \end{bmatrix}$$

and this gave eigenvalues which all have negative real parts. Moreover, computing for the basic reproduction number we obtained $R_0 = 3.8896 > 1$. By the *van den Driessche and Watmough Theorem*, this implies that the free-disease equilibrium point is locally asymptotically unstable.

Similarly, we computed the Jacobian matrix of the system of ODEs for equations (**1**) – (**6**) for the endemic equilibrium $\mathbf{x}^*$, $\boldsymbol{J}(\mathbf{x}^*)$ and obtained eigenvalues which all have negative real parts. Calculating the basic reproduction number we obtained $R_0 = 0.4516 < 1$. By the *van den Driessche and Watmough Theorem*, this implies that the endemic equilibrium point is locally asymptotically stable.

These results – that free-disease equilibrium point is unstable and the endemic equilibrium point is locally asymptotically stable – are consistent with the fact that the Philippines continues to be a TB high-burden country and therefore, its population is highly susceptible to tuberculosis. Hence, there has to be an aggressive program to combat the disease in the country. And the model proposed in this paper can be used to formulate strategies for the nation's TB programs.

SIMULATIONS

Projected simulations of the incidence and prevalence rates were based on our proposed TB model for the Philippines in terms of case detection rate, vaccination coverage, partial immunity, duration of treatment and treatment success rate for the years 2013 to 2023. Assuming the initial conditions $L_{A_{2013}}(0)$, $L_{B_{2013}}(0)$, $I_{2013}(0)$, $T_{2013}(0)$, $S_{A_{2013}}(0)$, $S_{B_{2013}}(0)$, and $N_{2013}(0)$ to be the 2013 projected values of the system, we calibrated the case detection rate, vaccination coverage, partial immunity, duration of treatment and treatment success rate and simulated the projected incidence and prevalence rates using default parameter values without any adjustments. These were compared with simulations of projected incidence and prevalence rates made using the calibrated values of each parameter (as shown in Figures 3 and 4).

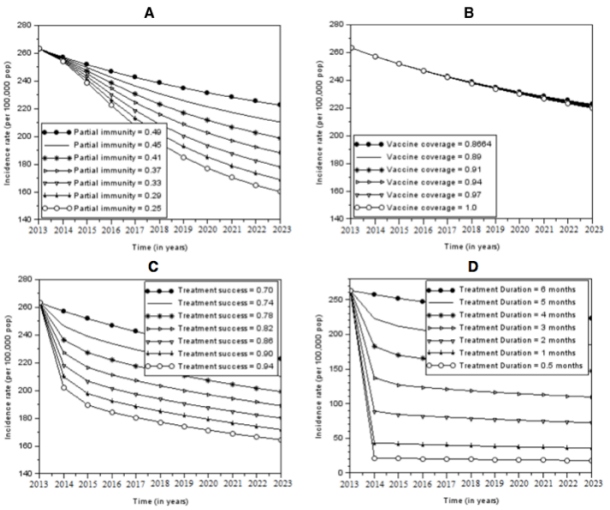

Figure 3. Projected incidence rates from year 2013 to 2023 with the calibrations of partial immunity (A), vaccine coverage (B), treatment success rate (C) and treatment duration (D). Graphs show that improving partial immunity, treatment success and treatment duration will significantly reduce incidence rate while improving vaccine coverage will not.

Figure 3 shows the simulations of projected incidence rates for 2013-2023 with the corresponding calibration. It can be observed that partial immunity (Figure 3A), treatment success (Figure 3C) and treatment duration (Figure 3D) are parameters that have significant effects on the projected TB incidence rates. In Figure 3A, adjusting partial immunity reduces the projected TB incidence rate very minimally in the first few years, but the reduction increases in the long run up to 2023. By improving treatment success, significant reduction on the projection can be seen for the first years in Figure 3C. The same behavior can be observed for the adjustments of treatment duration shown in Figure 3D. In this case, the difference from the default projection is enormously greater, causing the TB incidence rate to be close to zero. However, TB incidence rate suddenly becomes stable in the next years up to 2023. This implies that the annual decline in the TB incidence rates in the long run will become low. Still, the effects of treatment success and duration on the projected TB incidence rate are significant.

In Figure 3B, we observe that improving vaccine coverage does not significantly reduce the projected TB incidence but this does not mean that vaccine coverage is not a relevant factor for TB elimination. Decreasing vaccine coverage down to zero would significantly increase the projected incidence rate. The results only mean that further increase in vaccine coverage would not result in a significant change on the projected TB incidence.

Figure 4 shows simulations of the effects on prevalence rate. In Figure 4A, we observe that the difference of the projected prevalence rate with partial immunity adjustments from the default projection is small in the first years, but gradually becomes greater in the next years. Figure 4C shows that adjustments of treatment success rate cause a small difference, while adjustments of vaccine coverage cause insignificant difference in Figure 4B. Projections from case detection rate adjustments shown in Figure 4E, follow the same behavior as the projections from the partial immunity, but the effect caused by case detection is greater than by partial immunity. Lastly, improving treatment duration causes drastic decrease of TB prevalence in the first two years, and maintains slower but significant decrease in the next years, as shown in Figure 4D.

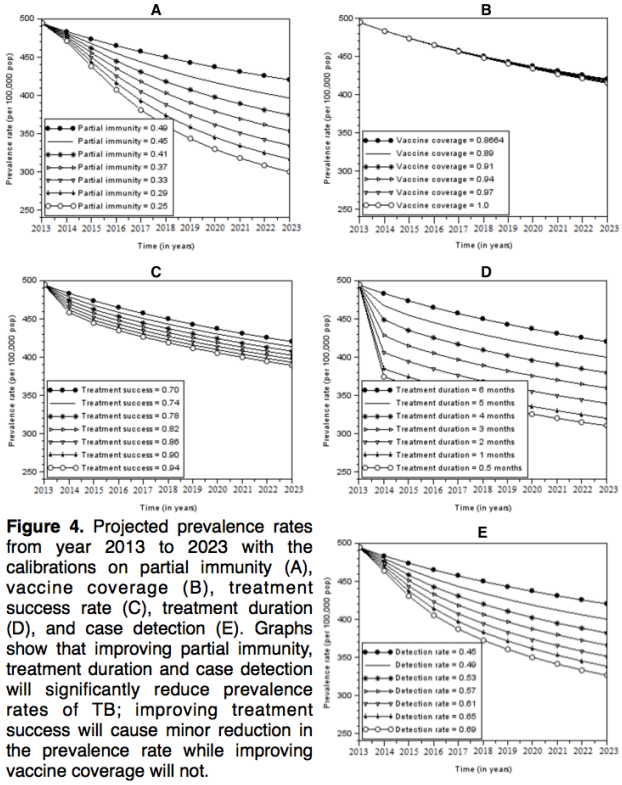

Figure 4. Projected prevalence rates from year 2013 to 2023 with the calibrations on partial immunity (A), vaccine coverage (B), treatment success rate (C), treatment duration (D), and case detection (E). Graphs show that improving partial immunity, treatment duration and case detection will significantly reduce prevalence rates of TB; improving treatment success will cause minor reduction in the prevalence rate while improving vaccine coverage will not.

Through the projected simulations therefore, we have shown that improving the five parameters results in a decline in the projected TB incidence and prevalence rates in varying degrees. However, the projected TB incidence and prevalence rates are far from zero even up to 2023. This implies a continuing challenge for eliminating tuberculosis in the Philippines.

We have shown in our study that the effect of improving partial immunity would only be felt in a distant future. Since improving partial immunity will provide TB resistance to more individuals who do not have the active disease yet, this will reduce the number of active TB cases in the future. Our results also suggest that the relevant effect of partial immunity may not be solely due to vaccination (Figures 3B and 4B), because the partial immunity in our model does not only include acquired immunity from vaccination but also developed immunity from previous acquisition of infection.

The simulations of prevalence rate with different case detection rate (Figure 4) are consistent with what Trauer et al. (2014), Bhunu et al. (2011), Dowdy and Chaisson (2009) have shown in their studies. That is, improving case detection rate means lowering the number of contagious individuals infecting the population.

CONCLUSIONS

In this study, we proposed a TB transmission model for the Philippines based on the work of Trauer et al. (2014) and validated it by fitting the model in the data of the incidence and prevalence rates for the Philippines obtained from WHO Report (2014). Using the Theorem of van den Driessche & Watmough (2002), we analysed the dynamics of the model based on the basic reproduction number R_0. We obtained a free-disease equilibrium which is unstable and an endemic equilibrium which is locally and asymptotically stable. This implies a continued challenge to control TB in the Philippines.

In the model simulations of the projected TB incidence and prevalence rates, we found that improving partial immunity, treatment success and treatment duration will significantly

reduce the projected TB incidence in the Philippines. Whereas, improving partial immunity, treatment success, treatment duration and case detection will significantly reduce the projected TB prevalence in the Philippines. Interestingly, our model simulations suggest that improving vaccine coverage will not significantly reduce both the TB incidence and prevalence rates.

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CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

CONTRIBUTIONS OF INDIVIDUAL AUTHORS

KJV performed the modeling and wrote the first draft of the manuscript. AL and ER supervised the work and contributed to the writing and editing of the manuscript.

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Appendix A: Equilibrium points for the system of ODEs given by Eqns (1) – (6)

Solve $x_0 = [L_{A0}, L_{B0}, I_0, T_0, S_{A0}, S_{B0}]$

To solve for the equilibrium points x_0, we set each of the differential equations (1) – (6) to 0 and compute for $[L_{A0}, L_{B0}, I_0, T_0, S_{A0}, S_{B0}]$. In the following computations, these are expressed as [L1, L2, I1, T, S1, S2] respectively. Also, $\mu 1$ and $\mu 2$ corresponds to μ_i and μ_t, respectively.

$$\text{Solve}[\lambda*\text{S1} + \chi*\lambda*\text{S2} + \chi*\lambda*\text{L2} - \epsilon*\text{L1} - k*\text{L1} - \mu*\text{L1} = 0 \;\&\&\; k*\text{L1} + \gamma*\text{I1} - \chi*\lambda*\text{L2} - v*\text{L2} - \mu*\text{L2} = 0 \;\&\&$$
$$\epsilon*\text{L1} + v*\text{L2} + w*T - \text{I1}*(\gamma + \delta + \mu 1) = 0 \;\&\&\; \delta*\text{I1} - T*(\eta*\phi + \text{w} + \mu 2) = 0 \;\&\&$$
$$(1 - i)*\Lambda - \lambda*\text{S1} - \mu*\text{S1} == 0 \;\&\&\; i*\Lambda + \eta*\phi*T - \chi*\lambda*\text{S2} - \mu*\text{S2} == 0, \{\text{L1}, \text{L2}, \text{I1}, T, \text{S1}, \text{S2}\}].$$

We arrive at the following solutions:

$$\left\{\left\{ \text{S1} \to -\frac{-\Lambda + i\Lambda}{\lambda + \mu},\right.\right.$$

$$\text{S2} \to - \quad -i\,k\,w\,\gamma\,\lambda\,\Lambda\,\mu - i\,w\,\gamma\,\epsilon\,\lambda\,\Lambda\,\mu - i\,k\,w\,\gamma\,\Lambda\,\mu^2 - i\,w\,\gamma\,\epsilon\,\Lambda\,\mu^2 - i\,w\,\gamma\,\lambda\,\Lambda\,\mu^2 - i\,w\,\gamma\,\Lambda\,\mu^3 - i\,k\,v\,w\,\lambda\,\Lambda\,\mu 1 -$$
$$i\,v\,w\,\epsilon\,\lambda\,\Lambda\,\mu 1 - i\,k\,v\,w\,\Lambda\,\mu\,\mu 1 - i\,v\,w\,\epsilon\,\Lambda\,\mu\,\mu 1 - i\,k\,w\,\lambda\,\Lambda\,\mu\,\mu 1 - i\,v\,w\,\lambda\,\Lambda\,\mu\,\mu 1 - i\,w\,\epsilon\,\lambda\,\Lambda\,\mu\,\mu 1 -$$
$$i\,k\,w\,\Lambda\,\mu^2\,\mu 1 - i\,v\,w\,\Lambda\,\mu^2\,\mu 1 - i\,w\,\epsilon\,\Lambda\,\mu^2\,\mu 1 - i\,w\,\lambda\,\Lambda\,\mu^2\,\mu 1 - i\,w\,\Lambda\,\mu^3\,\mu 1 - i\,k\,v\,\delta\,\lambda\,\Lambda\,\mu 2 - i\,v\,\delta\,\epsilon\,\lambda\,\Lambda\,\mu 2 -$$
$$i\,k\,v\,\delta\,\Lambda\,\mu\,\mu 2 - i\,v\,\delta\,\epsilon\,\Lambda\,\mu\,\mu 2 - i\,k\,\gamma\,\lambda\,\Lambda\,\mu\,\mu 2 - i\,v\,\delta\,\lambda\,\Lambda\,\mu\,\mu 2 - \text{i}\,\gamma\,\epsilon\,\lambda\,\Lambda\,\mu\,\mu 2 -$$
$$i\,\delta\,\epsilon\,\lambda\,\Lambda\,\mu\,\mu 2 - i\,k\,\gamma\,\Lambda\,\mu^2\,\mu 2 - i\,k\,\delta\,\Lambda\,\mu^2\,\mu 2 - i\,v\,\delta\,\Lambda\,\mu^2\,\mu 2 - i\,\gamma\,\epsilon\,\Lambda\,\mu^2\,\mu 2 - i\,\delta\,\epsilon\,\Lambda\,\mu^2\,\mu 2 - i\,\gamma\,\lambda\,\Lambda\,\mu^2\,\mu 2 -$$
$$i\,\delta\,\lambda\,\Lambda\,\mu^2\,\mu 2 - i\,\gamma\,\Lambda\,\mu^3\,\mu 2 - i\,\delta\,\Lambda\,\mu^3\,\mu 2 - i\,k\,v\,\lambda\,\Lambda\,\mu 1\,\mu 2 - i\,v\,\epsilon\,\lambda\,\Lambda\,\mu 1\,\mu 2 - i\,k\,v\,\Lambda\,\mu\,\mu 1\,\mu 2 -$$
$$i\,v\,\epsilon\,\Lambda\,\mu\,\mu 1\,\mu 2 - i\,k\,\lambda\,\Lambda\,\mu\,\mu 1\,\mu 2 - i\,v\,\lambda\,\Lambda\,\mu\,\mu 1\,\mu 2 - i\,\epsilon\,\lambda\,\Lambda\,\mu\,\mu 1\,\mu 2 - i\,k\,\Lambda\,\square\mu 1\,\mu 2 - i\,v\,\Lambda\,\mu^2\,\mu 1\,\mu 2 -$$
$$i\,\epsilon\,\Lambda\,\mu^2\,\mu 1\,\mu 2 - i\,\lambda\,\Lambda\,\mu^2\,\mu 1\,\mu 2 - i\,\Lambda\,\mu^3\,\mu 1\,\mu 2 - k\,v\,\delta\,\eta\,\lambda\,\Lambda\,\phi - v\,\delta\,\epsilon\,\eta\,\lambda\,\Lambda\,\phi - i\,k\,v\,\delta\,\eta\,\Lambda\,\mu\,\phi -$$
$$i\,v\,\delta\,\epsilon\,\eta\,\Lambda\,\mu\,\phi - i\,k\,\gamma\,\eta\,\lambda\,\Lambda\,\mu\,\phi - i\,k\,\delta\,\eta\,\lambda\,\Lambda\,\mu\,\phi - i\,v\,\delta\,\eta\,\lambda\,\Lambda\,\mu\,\phi - i\,\gamma\,\epsilon\,\eta\,\lambda\,\Lambda\,\mu\,\phi - \delta\,\epsilon\,\eta\,\lambda\,\Lambda\,\mu\,\phi -$$
$$i\,k\,\gamma\,\eta\,\Lambda\,\mu^2\,\phi - i\,k\,\delta\,\eta\,\Lambda\,\mu^2\,\phi - i\,v\,\delta\,\eta\,\Lambda\,\mu^2\,\phi - i\,\gamma\,\epsilon\,\eta\,\Lambda\,\mu^2\,\phi - i\,\delta\,\epsilon\,\eta\,\Lambda\,\mu^2\,\phi - i\,\gamma\,\eta\,\lambda\,\Lambda\,\mu^2\,\phi -$$
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$$(\lambda + \mu)\;\; k\,w\,\gamma\,\mu^2 + w\,\gamma\,\epsilon\,\mu^2 + w\,\gamma\,\mu^3 + k\,v\,w\,\mu\,\mu 1 + v\,w\,\epsilon\,\mu\,\mu 1 + k\,w\,\mu^2\,\mu 1 + v\,w\,\mu^2\,\mu 1 + w\,\epsilon\,\mu^2\,\mu 1 +$$
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$$\text{L1} \to \quad \lambda\,\Lambda\,\mu - i\,\lambda\,\Lambda\,\mu + \lambda^2\,\Lambda\,\chi + i\,\lambda\,\Lambda\,\mu\,\chi\;\; (w\,\gamma\,\mu + v\,w\,\mu 1 + w\,\mu\,\mu 1 + v\,\delta\,\mu 2 + \gamma\,\mu\,\mu 2 + \delta\,\mu\,\mu 2 +$$
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$$k\,v\,w\,\lambda\,\mu 1\,\chi + v\,w\,\epsilon\,\lambda\,\mu 1\,\chi + k\,w\,\lambda\,\mu\,\mu 1\,\chi + v\,w\,\lambda\,\mu\,\mu 1\,\chi + 2\,w\,\epsilon\,\lambda\,\mu\,\mu 1\,\chi + 2\,w\,\lambda\,\mu^2\,\mu 1\,\chi + k\,v\,\delta\,\lambda\,\mu 2\,\chi +$$
$$v\,\delta\,\epsilon\,\lambda\,\mu^2\,\chi + k\,\gamma\,\lambda\,\mu\,\mu 2\,\chi + k\,\delta\,\lambda\,\mu\,\mu 2\,\chi + v\,\delta\,\lambda\,\mu\,\mu 2\,\chi + \gamma\,\epsilon\,\lambda\,\mu\,\mu 2\,\chi + 2\,\delta\,\epsilon\,\lambda\,\mu\,\mu 2\,\chi + 2\,\gamma\,\lambda\,\mu^2\,\mu 2\,\chi +$$
$$2\,\delta\,\lambda\,\mu^2\,\mu 2\,\chi + k\,v\,\lambda\,\mu 1\,\mu 2\,\chi + v\,\epsilon\,\lambda\,\mu 1\,\mu 2\,\chi + k\,\lambda\,\mu\,\mu 1\,\mu 2\,\chi + v\,\lambda\,\mu\,\mu 1\,\mu 2\,\chi + 2\,\epsilon\,\lambda\,\mu\,\mu 1\,\mu 2\,\chi +$$
$$2\,\lambda\,\mu^2\,\mu 1\,\mu 2\,\chi + k\,\gamma\,\eta\,\lambda\,\mu\,\phi\,\chi + k\,\delta\,\eta\,\lambda\,\mu\,\phi\,\chi + v\,\delta\,\eta\,\lambda\,\mu\,\phi\,\chi + \gamma\,\epsilon\,\eta\,\lambda\,\mu\,\phi\,\chi + \delta\,\epsilon\,\square\mu\,\phi\,\chi + 2\,\gamma\,\eta\,\lambda\,\mu^2\,\phi\,\chi +$$
$$2\,\delta\,\eta\,\lambda\,\mu^2\,\phi\,\chi + k\,v\,\eta\,\lambda\,\mu 1\,\phi\,\chi + v\,\epsilon\,\eta\,\lambda\,\mu 1\,\phi\,\chi + k\,\eta\,\lambda\,\mu\,\mu 1\,\phi\,\chi + v\,\eta\,\lambda\,\mu\,\mu 1\,\phi\,\chi + 2\,\epsilon\,\eta\,\lambda\,\mu\,\mu 1\,\phi\,\chi +$$
$$2\,\eta\,\lambda\,\mu^2\,\mu 1\,\phi\,\chi + w\,\gamma\,\lambda^2\,\mu\,\chi^2 + w\,\epsilon\,\lambda^2\,\mu 1\,\chi^2 + w\,\lambda^2\,\mu\,\mu 1\,\chi^2 + \delta\,\epsilon\,\lambda^2\,\mu 2\,\chi^2 + \gamma\,\lambda^2\,\mu\,\mu 2\,\chi^2 + \delta\,\lambda^2\,\mu\,\mu 2\,\chi^2 +$$
$$\epsilon\,\lambda^2\,\mu 1\,\mu 2\,\chi^2 + \lambda^2\,\mu\,\mu 1\,\mu 2\,\chi^2 + \gamma\,\eta\,\lambda^2\,\mu\,\phi\,\chi^2 + \delta\,\eta\,\lambda^2\,\mu\,\phi\,\chi^2 + \epsilon\,\eta\,\lambda^2\,\mu 1\,\phi\,\chi^2 + \eta\,\lambda^2\,\mu\,\mu 1\,\phi\,\chi^2 \quad ,$$