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LONG TERM INTERFERENCE BETWEEN DEMOGRAPHY AND EPIDEMIOLOGY: THE CASE OF TUBERCULOSIS

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Abstract. Recent studies on the population dynamics of tuberculosis (TB) have evidenced that TB is a disease with very long time scales. This makes it of interest to investigate the long term interactions between the disease and the underlying population patterns. This paper studies the properties of two basic models for TB embedding typical patterns of population dynamics. The first model considers TB dynamics within a stably growing population, whereas the second considers the effects of logistic-type population dynamics.

1. Introduction. Patterns of reemergence of tuberculosis in the recent years are well documented for a large part of the western world (Cantwell et al. 1995, Raviglione et al. 1993, 1995). Italy is not an exception in this trend (AAVV 1997). Among the invoked explanations there are increased immigrations, increasing poverty, intravenous drug-abuse and HIV, via the immunodepression in HIV individuals which raises the long term probability of developing TB (Raviglione et al. 1993, 1995). In the italian case a role has been played by the progressive decaying of the surveillance system (AAVV 1997). A further important factor is the development of new strains of the mycobacterium tuberculosis (MB since now on) which are resistent to antibiotic treatment, as a consequence of incomplete treatment. Even if the data are still very poor TB risks to become a dramatic problem in former Soviet Union where poverty and homelessness dramatically increased since 1989.

The re-emergency of tuberculosis in developed countries and its connection with the dynamics of HIV has raised new interest for TB, which remains the world's leading killer among infectious diseases.

This renewed interest has concerned also the area of mathematical models for the population dynamics of TB. Recent contributions by Blower et al. (1995, 1996; Porco and Blower 1998) have thrown new light on the historical dynamics of tuberculosis (TB) in developed areas. It is well known that the lethal incidence of TB in these areas started to decline during the nineteenth century, long before TB became curable. Traditional explanations of the decline are based on exogenous arguments (improvements in standards of living and hygiene) or on possible selection processes, both at the pathogen level (appearance of strains of the pathogen characterized by lower virulence) and the human-host level. The analysis by Blower et al. is based on a model for TB embedding the most relevant features of historical TB, i.e. the coexistence of two main ways of acquiring infection: *fast TB* via direct contact with an infective case, and *slow TB* via endogenous reactivation after a latency period. The model extensively validated on large data-sets on TB, shows how the natural dynamics of TB reaches its long term steady state with a "rise, fall and rise" pattern usually taking several

hundred years. This suggests a fully endogenous explanation of the observed decline as the outcome of the intrinsic dynamics of TB alone.

Castillo-Chavez and Feng (1997) have considered the effects of treatment both in absence and in presence of competing strains of MB. In the latter case they could show that coexistence is quite common in presence of antibiotic resistance. Castillo-Chavez and Feng (1997, 1998) have considered several other issues. In particular they have considered the effects of long and variable (rather than exponentially distributed) latency period. Moreover they have considered the possibility of (exogenous) reinfection, i.e. that latent individuals may become active TB cases acquiring a new infection from other infected individuals. In this case they could show that multiple endemic equilibria may appear through backward bifurcation of the disease free equilibrium when the basic reproduction ratio R_0 equals one. They have also considered (1997, 1998) optimal vaccination strategies against TB in age structured frameworks, by showing that the optimal strategy can be either a one-age strategy or a two-ages strategy.

Finally, the problem of the interaction between HIV and TB has been considered by West and Thompson (1997) by using a simulation model of interaction between the two diseases.

The present paper represents a preliminary report of a larger project aimed to a more systematic investigation of the effects played on the dynamics of TB by more realistic patterns of population dynamics within the model by Blower's et al. The results by Blower et al., as all the other previously mentioned efforts, are based on epidemiological models in which demography is neutral: the pathogen is introduced in a previously stationary population. Our investigation appears of interest both on the purely theoretical side, as "Blower-type" TB models represent a special class of mathematical models of infectious disease which blends features of several classes of models, and the applied side. We investigate the properties of two different Blower-type models, characterised respectively by exponentially stable and logistic population dynamics. The first model appears to be useful to understand recent observed patterns of TB in developing areas, while the second seems useful to better understand the historical dynamics of TB, which suffers, in developed areas, of the massive interference with demographic transition. The aim of the second model is therefore to reconsider the process of "rise, fall and rise" of TB in its natural demographic environment.

The present paper is organised as follows. In the second section the basic model by Blower et al. (1995) is introduced with a brief description of its results, also from a historical perspective. In the third section we review the role of population dynamics within basic epidemiological models. In the fourth section we introduce a general Blower-type model for TB embedding population dynamics. In the fifth section we study in full detail the case of exponentially growing population, while in the sixth section we report the main facts on the model with logistic population dynamics, and we are able to fully characterise a special case with density dependency only in the death rate.

2. The framework model: the intrinsic transmission dynamics of TB. Blower et al. (1995) have considered two basic models for TB transmission dynamics, a simpler one and a more refined one. The simpler model postulates the coexistence of two main ways of acquiring infection: *fast TB* via direct contact with an infective case, and *slow TB* via endogenous reactivation after a usually very long latency period.

The population is subdivided in three classes: i) susceptibles (X), ii) latently infected (L), i.e. those who have been infected with mycob. tuberculosis (MT since now on) but have no clinical illness and hence are noninfectious, and iii) active infectious tuberculosis (T), who are infectious and hence can transmit the infection to others. Once a susceptible has being infected with MB, he either develops active tuberculosis (in a fraction p estimated approximately to be 10%), so directly entering T state, or enter the L state (in a fraction $1-p$) from which they can develop tuberculosis in by the so called endogenous reactivation mechanisms. The structure of the model is the following:

$$
\begin{aligned}
\dot{X}(t) &= \Lambda - (\mu+\lambda)X \\
\dot{L}(t) &= (1-p)\lambda X - (\mu+v)L \\
\dot{T}(t) &= vL + p\lambda X - (\mu+\mu_T)T
\end{aligned} \tag{1}
$$

where Λ is the birth-recruitment term, μ the death rate per unit time, μ_T the extra-mortality rate induced by TB, λ the force of infection (FOI), i.e. the hazard of getting infected, v the rate of developing TB via endogenous reactivation, p and $(1-p)$ are, respectively, the fractions of infected individuals who develop fast TB or enter the latent state. The FOI is modelled via a bilinear mass action (BMA):

$$
\lambda = \beta T \tag{2}
$$

where β is the transmission parameter, representing both the contact and transmission processes. (Castillo-Chavez and Feng (1997,1998) used a true mass action incidence (TMA), with FOI given by: $\lambda = \beta T/N$). The refined model adds more realism by considering further features of TB namely (Blower et al. 1995, 815): i) only a certain fraction of cases are assumed to be infectious; ii) cases may recover (without treatment); iii) recovered cases may relapse TB again.

The common features to both models are: a) they do not consider reinfection, a phenomenon considered quite relevant in presence of immunodepression (for instance in presence of HIV); b) they do not include the effects of treatment (considered in Castillo-Chavez and Feng, 1997a,b, and 1998). From this last point of view they are useful essentially for historical purposes or for the understanding of the epidemiology of TB in developing countries where treatment is not the norm (Porco and Blower, 1998).

2.1. Main mathematical properties. As in this paper we are essentially interested in the model (1) we briefly report here some of its main features. The model is a blend of the basic SI (Susceptible $\rightarrow$ Infectious) and SEI (Susceptible $\rightarrow$ Exposed $\rightarrow$ Infectious) models for the population dynamics of infectious diseases: for $p=1$ all infected individuals become infectious (collapsing in the SI case), whereas for $p=0$ all the infected enter first the latent state (the SEI case). The basic reproduction ratio, i.e. the expected number of new TB cases caused by an initial TB infected seed during his sojour in the T state in presence of a wholly susceptible population, is given by:

$$
R_0 = \frac{\beta}{\mu+\mu_T}\left(p + (1-p)\frac{v}{\mu+v}\right)N
$$

R_0 is the sum of two components: a fast component ($R_0^{Fast} = p\beta N(\mu+\mu_T)^{-1}$) and a slow component ($R_0^{Slow} = (1-p)\beta N v(\mu+v)^{-1}(\mu+\mu_T)^{-1}$)) denoting respectively the number of new fast and slow TB cases caused by the given initial case of TB.

The model (1) has the disease free equilibrium $(\Lambda/\mu, 0, 0)$ which is globally asymptotically stable (GAS) when $R_0 < 1$. When $R_0 > 1$ the disease free equilibrium (DFE) becomes unstable and, at the same time, a unique endemic equilibrium appears which is locally stable (LAS). As shown in fig. 1 the dynamics of the model for historically plausible parameter constellations exhibits the rise-fall-stabilising pattern, which is the outcome of the asynchronous activity of the two separate source of infection embedded in the model. More precisely, when $R_0 > 1$ we have the following effects: i) in the first phase a major part of the population is infected (entering the L state) while at the same time the fast mechanism triggers a fast TB epidemics with exponential growth in the number of cases (which is more or less rapid depending on the magnitude of R_0). ii) Even if the fast TB epidemics cannot be maintained in the long term due to the reduction in susceptibility, which cause the prevalence of fast TB to cases to fall down, the disease becomes endemic in the population via the slow mechanism, by effect of which an increasing number of latent individuals starts to develop TB over time.

2.2. Historical TB: main facts. Extensive uncertainty analysis of the model parameters (aimed to define the more likely parameter constellation) relying on the available historical data-sets on TB, coupled with sensitivity analysis, shows that, for almost all "historically plausible" parameter constellations, the natural dynamics of TB reaches a long term steady state with a "rise, fall and rise" pattern taking from a hundred to several hundred years. This prediction qualitatively fits very well observed historical pattern of TB: "*Major TB epidemics arose in Europe in in the early 1600's, spread for almost 200 hundred years and then peaked at the end of the eighteen century...in Europe and North America these epidemics have been in decline since 1850.*" (Blower et al. 1995, 818). This in turn suggests a fully endogenous explanation of the observed decline of TB as the outcome of the intrinsic dynamics of TB alone, which very well agrees with observed historical facts. The essence of the explanation is the threshold effect of the model. By writing the threshold condition in terms of population we get:

$$N > \left((1-p)\frac{v}{\mu+v} + p\right)^{-1} \frac{\mu+\mu_T}{\beta} = N^* \tag{3}$$

where $N^* = N^*(\beta)$ is the critical community size, which is an inverse function of β. The condition (3) states that for every parameter constellation there exists a critical community size above which the epidemics will spread and below which the epidemics fades out.

It is not difficult to realise that the factors traditionally invoked to explain the blow-up of TB in western countries, namely urbanisation, industrialisation and population growth, not only created the conditions for the satisfaction of the threshold condition but presumably resulted in the threshold conditions being suddenly and dramatically exceeded, generating major epidemics. In fact population growth and urbanisation with the connected crowding effects possibly increased the left member of (3) while increasing poverty and malnutrition, by depressing the immune system of individuals possibly increased the transmission rate β reducing the right member of (3).

3. Population dynamics in infectious disease models. Basic epidemiological models usually assume a stationary population (let us call it *type 1* population dy-

namics) obtained by assuming identical birth and death rates. In this case traditional epidemiological models (SI, SIS, SIR, ...,SEIRS) in which the only nonlinearity is the incidence term (usually assumed BMA or TMA), exhibit a common feature, which is the dichotomy between the disease free equilibrium and a unique endemic equilibrium filtered though the action of a unique threshold parameter, usually denoted by R_0[1]. The assumption of constant population is unsatisfactory in many cases, for instance when disease-related death exists, as the population is necessarily driven to extinction. A formal remedy to this has been to assume a (long term) stationary through immigration population, i.e.e a population that, in absence of the disease is described by:

$$\dot{N} = A - rN$$

where $A > 0$ is the immigration term and $r > 0$ is the internal rate of growth (sometimes A is naively assumed to be a constant natality term, and r the mortality rate). Let us denote the previous model as "*type 2*" population dynamics. For human populations "*type 2*" may result well suited to describe the recent story of developed countries, characterised by below replacement fertility plus immigration.

As long as BMA or TMA are considered, type 2 demography preserves most features of the basic model with stationary population, among which the dichotomy between the DFE and the endemic equilibrium as mediated by R_0 (for instance Mena-Lorca and Hethcote 1992, sec.2,3).

When more realistic assumptions are made on the underlying demography things become more complex. Two common assumptions are, following traditional population theories, malthusian exponential dynamics and density dependent dynamics, usually typified via the logistic curve. Exponential dynamics (*type 3*) is expressed by the ordinary differential equation: $\dot{N} = (b - \mu)N$ where $b > 0, \mu > 0$, are respectively the birth and death rate (when $b = \mu$ we fall in the type 1 case). A general logistic type dynamics (*type 4*) is expressed by: $\dot{N} = (B(N) - D(N))N$ where $B(N), D(N)$ are the *density dependent* birth and death rates.

Epidemic models with type 3 or type 4 population dynamics often exhibit more complex properties. Both these cases are characterised by the appearance of multiple equilibria and/or multiple thresholds needed to keep into account the evolution of both the population and the disease, and the possibility that the disease be weakly or strongly persistent (Busenberg and VandenDriessche 1990). Multiple equilibria follow in the logistic case, by the existence of two equilibria for the population which may be paired with the equilibria of the joint epidemic process.

For what concerns epidemic models with type 3, Anderson et al. (1988) have considered a SI model for HIV in the developing world, and gave the first classification of the effects of the interaction of population growth and infectious diseases. Busenberg and Van den Driessche (1990) have studied in detail the properties of a general SIRS model with TMA incidence and extra-mortality both in the infectious and removed state. They are able to prove the GAS of the endemic state by means of a new negative Bendixson-Dulac type criterion (see also Busenberg and Van den Driessche, 1992). Thieme (1992) has considered a similar SIRS model embedding a nonlinear contact rate defined as a saturating function of population size. Busenberg, Cooke and Thieme (1991) have considered a more refined model for AIDS. Mena-Lorca and

[1] This feature is not necessarily preserved by nonlinear contact rates. For instance Liu et al. (1987)

Hethcote (1992) study SIRS models similar to that considered in Busenberg and Van den Driessche (1990), by systematically comparing the effects of type 2,3 population dynamics crossed with three different assumptions on the FOI mechanism: TMA, BMA and a saturating one. They obtain results similar to Busenberg and Van den Driessche (1990) in the common case, and are able to show the existence of periodic behaviour in the case of exponential population plus saturating FOI. Lin et al. (1993) have considered exponential population evolution within a model for sexual transmission of HIV/AIDS with several stages of infection and TMA, generalising results by Anderson et al. (1988). More general results on multigroup models are given in Busenberg and Van den Driessche (1995).

Several results are available also for what concerns models for endemic diseases in presence of density dependent effects and/or logistic-type population dynamics. Greenhalg (1990,1992a,1992b,1992c) has analysed the effects of a density dependent death rates within SIR,SIS,SEIS,SEIR and SEIRS models with BMA. Pugliese (1990) has considered a SI model embedding general density dependent mortality and a nonlinear contact rate. Greenhalg and Das (1995a, 1995b) have considered SIR and SIRS models with density dependence both in the death and the contact rates.

The first study of the effects of type 4 demography is Gao and Hethcote (1992) who considered SIS and SIRS models with TMA and "classical" logistic population dynamics (type 4). The SIS cases is fully characterised and all results found hold globally. In the more complex SIRS case they identify all the relevant thresholds but the global stability of the "main" endemic equilibrium is still an open question. Zhou and Hethcote (1994) have investigated a SIS model combining logistic demography with a nonlinear incidence obtaining global results.

A central question in applied sciences is the identification of mechanisms leading to persistent oscillations. This question is even more important in epidemiology where traditional models with standard nonlinearities (BMA or TMA) unavoidably lead to global stability. The routes to oscillations that have been found for epidemiological models are: i) periodic forcing; ii) time delays (both these aspect will not be of interest here); iii) more nonlinearities. The two types of nonlinearities considered in epidemiological models regard essentially: i)the incidence rate, ii)the underlying demography, through density dependent effects of the aforementioned type. At present there are no clear-cut results on which are the minimal nonlinear ingredients needed to excite persistent oscillations in epidemiological models without resorting to external forcing or time delays. For instance, in the case of constant population, i.e. working only on the side of the incidence rates, SEIRS type models may exhibit Hopf bifurcations (Hethcote and Van den Driessche 1991) only through very strong nonlinearities in the contact rates, i.e. nonlinearities generating a downturn in transmission leading to multiple endemic states.

Hence an important point is: to what extent may population effects force the appearance of persistent oscillations in epidemiological models? For SIRS models Mena-Lorca and Hethcote (1992) have shown that a special type of saturating contact rate may be able to generate persistent oscillations provided the population is exponentially evolving. Anderson et al. (1981) found numerically that SEI models with BMA, linear density-dependent mortality and zero fertility of exposed and infectious are responsible for persistent oscillations. A proof of the existence of at least a stable limit cycle in their model by is given in Swart (1988). This leads to the confidence that for SEI models BMA plus (linear) density-dependent mortality plus differential fer-

tility could be "true" minimal nonlinear ingredients for the generation of oscillations. Pugliese (1992) has considered a SEI model with a density dependent mortality rate, a density dependent incidence and differential fertility among the three classes. Analysis of selected subcases shows again the appearance of persistent oscillations and of other complications as well, such as multiple endemic states. In particular the following facts are ascertained: i) density-dependent effects plus the nonlinearity in the FOI are the main responsible for persistent oscillations; ii) differential fertility causes the lost of the simple DFE-EE dichotomy, with the appearance of multiple equilibria. Roberts and Jovett (1996) have considered a quite similar model, with density dependence also on the birth rate, vertical transmission, and incidence $B(t) = N^{-1}C(N)XZ$, where the contact rate $C(N)$ satisfies $C'(N) \geq 0$. They remark that by ruling out the assumption of differential fertility, they may avoid the problem of multiple endemic states while maintaining the existence, for some parameter window, of periodic behaviours. Gao et al. (1995) have considered several SEI models with type 4 demography and both BMA and TMA, vertical transmission and disease related death. They have been able to show that type 4 plus BMA may cause the appearance of a Hopf bifurcation (this is not true for TMA). Gao et al. (1997) have also been able to show that, still for SEI models, even *type 3* demography may cause persistent oscillations with TMA.

The TB models we will consider in this work are mixed models blending features of both SI and SEI models. Existence or nonexistence of periodic behaviours for this class of models is still an open question.

4. A general model for TB with population dynamics. The general model we will consider here is

$$
\begin{aligned}
\dot{X}(t) &= B(N)N - (D(N) + \lambda(T,N))\,X \\
\dot{L}(t) &= (1-p)\lambda X - (D(N) + v)L \\
\dot{T}(t) &= vL + p\lambda X - (D(N) + \mu_T)T
\end{aligned}
\tag{4}
$$

The main news with respect to the basic model of the previous section concern:

- The dynamics of the total population $N = X+L+T$ in absence of the disease ($\mu_T = 0$) is:

$$\dot{N}(t) = (B(N) - D(N))\,N \tag{5}$$

where $B(N), D(N)$ are nonnegative, continuously differentiable functions denoting respectively the birth and death rates. Standard assumptions are:

$$i)\ B' \leq 0, D' \geq 0\ ;\ \ ii)\ B(0) > D(0);\ \ iii)\ B(\infty) < D(\infty)$$

The (5) is a general model for population dynamics embedding as special subcases the traditional malthusian model ($B(N) = b$; $D(N) = \mu$) and the logistic model ($B(N) = b - k_1 N\ ;\ D(N) = \mu + k_2 N$). In this last case we have the equation:

$$\dot{N}(t) = [(b-\mu) - (k_1 + k_2)N] \qquad b, \mu, k_1, k_2 > 0 \tag{6}$$

sometimes written as:

$$\dot{N}(t) = r(1 - \frac{N}{K})N \tag{7}$$

where $r = b - \mu$ is the initial malthusian rate of growth and $K = r/(k_1 + k_2)$ is the carrying capacity of the system, which is the (GAS) long term equilibrium of the model.[2]

The previous set of assumptions is the most general preserving for (5) the main features of (7), i.e. the existence of a unique (GAS) nonzero long term equilibrium for the population.

- The force of infection term follows a general density dependent pattern of the form: $\lambda = \lambda(T, N)$. Noteworthy subcases are the bilinear mass action (BMA) used by Blower et al: $\lambda(T, N) = \beta T$, and the true mass action (TMA), used by Castillo-Chavez and Feng (1997,1998): $\lambda(T, N) = \beta T/N$. In this paper we consider only TMA; the effects of BMA and more general FOI's with nonlinear contact rate $\lambda(T, N) = \beta(T, N)T/N$ will be considered in a forthcoming paper (Salinelli et al. 1998).

5. TB in an exponentially varying population. Here we consider the model (4) under malthusian population dynamics and TMA-type force of infection. The final form of the model is:

$$\begin{aligned} \dot{X}(t) &= bN - \mu X - \beta\frac{XT}{N} \\ \dot{L}(t) &= (1-p)\beta\frac{XT}{N} - (\mu + v)L \\ \dot{T}(t) &= vL + p\beta\frac{XT}{N} - (\mu + \mu_T)T \end{aligned} \tag{8}$$

where all the parameters are strictly positive. In particular $b \neq \mu$. The most interesting case is $b > \mu$ (malthusian growing populations).

Notice that (8) admits a unique solution for every initial datum, which is also meaningful, i.e. solutions originating from positive initial conditions remain positive. The dynamics of the total population is:

$$\dot{N} = (b - \mu - \mu_T R)\, N \tag{9}$$

As (8) is first degree homogeneous it is convenient to work on the proportions, by considering the new variables[3]: $S = X/N$; $I = L/N$; $R = T/N$. This leads to the system:

$$\begin{aligned} \dot{S}(t) &= b(1 - S) - \beta SR + \mu_T SR \\ \dot{I}(t) &= (1-p)\beta SR - (b + v)I + \mu_T IR \\ \dot{R}(t) &= vI + p\beta SR - (b + \mu_T)R + \mu_T \end{aligned} \tag{10}$$

[2] The linear assumption (6) is at best an approximation, as the birth rate may become negative for higher N. This restricts the study to the case $N < b/k_1 = N_A$ which preserves the meaningfuness of the carrying capacity, as $K = \frac{b-\mu}{k_1+k_2} < N_A$.

[3] A more deep resort to homogeneous equations, following for instance Busenberg and Hadeler (1990), is possible.

The system (10), which is two-dimensional, as $S+I+R=1$, is defined on the feasible region: $\mathcal{D}=\{S\geq 0,\ I\geq 0,\ R\geq 0,\ S+I+R=1\}$. The (9) and (10) show that the epidemiological part of the system decouples from its demographical part, as a consequence of homogeneity. This permits, as in Anderson et. al. (1988) and Busenberg and Vanden Driessche (1990), to study first the dynamics of the epidemiological part and then using the dynamics of R as an input to study the dynamics of the overall population given by (9). The population dynamics would then be given by the equation:

$$N(t)=N_0\exp\left\{(b-\mu)t-\mu_T\int_0^t R(u)du\right\} \tag{11}$$

For instance if the epidemiological part of the system reaches a positive equilibrium R^* then, unless in the very special case $(b-\mu)-\mu_T R^*=0$, the population would experience exponential growth or decay:

$$N(t)=N_0\exp\left\{(b-\mu-\mu_T R^*)t\right\} \tag{12}$$

It is possible to show that for the epidemiological system (10) there exists a threshold parameter R_0 defined as:

$$R_0=\frac{\beta}{b+\mu_T}\left(p+(1-p)\frac{v}{b+v}\right) \tag{13}$$

which governs whether the endemic proportion can exist and be locally stable. These facts are summarised by the following theorem which gives the main mathematical results concerning system (10):

THEOREM 5.1. *The system (10) always has the disease free (DFE) equilibrium $E_0=(1,0,0)$, which is GAS whenever $R_0<1$. Viceversa, when $R_0>1$ a unique endemic equilibrium $E_1=(S^*,I^*,R^*)$ appears which is GAS.*

We only sketch the proof of the previous theorem (short details are postponed to the appendix; the more technical aspects will be discussed elsewhere). To check the existence of the DFE is trivial matter. The investigation of its local stability leads to the jacobian:

$$J(1,0,0)=\begin{pmatrix} -b & 0 & -(\beta-\mu_T) \\ 0 & -(b+v) & (1-p)\beta \\ 0 & v & p\beta-(b+\mu_T) \end{pmatrix} \tag{14}$$

from which the threshold R_0 is determined.

As the DFE is LAS for $R_0<1$ and unstable for $R_0>1$, R_0 is the relevant threshold which governs whether the endemic proportion can exist and be locally stable.

By studying the equilibrium system:

$$\begin{aligned} (1-p)\beta(1-I-R)R-(b+v)I+\mu_T IR &= 0 \\ vI+p\beta(1-I-R)R-(b+\mu_T)R+\mu_T R^2 &= 0 \end{aligned}$$

on the set

$$\mathcal{D}_0=\{I>0,R>0,I+R<1\}.$$

it is possible to check that the DFE remains the unique equilibrium for $R_0 < 1$ and that a unique locally stable endemic E_1 equilibrium appears for $R_0 > 1$ (see the appendix).

To prove that the DFE is also GAS for $R_0 < 1$ we use a Poincaré-Bendixson-type argument. The argument goes as follows: a) for $R_0 < 1$ the DFE is the unique equilibrium in the feasible region, and it is LAS; b) $\mathcal{D}$ is positively invariant: trajectories initiating in $\mathcal{D}$ stay in $\mathcal{D}$ forever; c) there exist no periodic orbits which could attract trajectories in $\mathcal{D}$, as a periodic orbit should necessarily enclose an equilibrium point, and this is excluded by the fact that the DFE is the unique equilibrium in $\mathcal{D}$ for $R_0 < 1$ (and by the positivity of the trajectories). Hence the DFE is the only attracting point in $\mathcal{D}$ and is necessarily GAS. Finally the proof of the GAS of the endemic equilibrium for $R_0 < 1$ is obtained by the generalisation of the Dulac criterion proposed by Busenberg and Vanden Driessche (1990).

5.1. Behaviour of the model. In the more interesting case of exponential population growth ($b > \mu$) the overall long term behaviour of the model is the outcome of the complex interplay between several thresholds[4] (notice that the present discussion holds thanks to the fact that our results are global). These thresholds are:

$$R_B = \frac{\beta}{\mu + \mu_T}\left(p + (1-p)\frac{v}{\mu + v}\right) \tag{15}$$

which governs whether the disease is capable to persist in absolute terms in a constant population ($b = \mu$). Then we have:

$$R_0 = \frac{\beta}{b + \mu_T}\left(p + (1-p)\frac{v}{b + v}\right)$$

which governs the persistence of the disease in relative terms.
For $b > \mu$ we have $R_0 < R_B$ which implies the obvious fact that persistence in relative terms is more difficult than absolute persistence, as the growth in numbers could be more than counterbalanced by a faster growth in the total population. Finally we have:

$$R^1 = \frac{b - \mu}{\mu_T R^*} \tag{16}$$

which follows from the "long term" dynamics of the population:

$$\dot{N} = N\left[(b - \mu) - \mu_T R^*\right] \tag{17}$$

The threshold (16) governs whether in the long term the disease is capable of regulating the growth of the population by converting population growth ($R^1 > 1$) into population decay ($R^1 < 1$). Notice that it any case the presence of the extra mortality of the disease slowers population growth. Population decay will intervene when (remember $b - \mu > 0$): $R^* > (b - \mu)/\mu_T$ i.e. when TB (relative) endemicity exceed a prescribed threshold.

The relations:

$$\frac{\dot{X}}{X} = \frac{\dot{S}}{S} + \frac{\dot{N}}{N} \;;\; \frac{\dot{L}}{L} = \frac{\dot{I}}{I} + \frac{\dot{N}}{N} \;;\; \frac{\dot{T}}{T} = \frac{\dot{R}}{R} + \frac{\dot{N}}{N}$$

[4] From this point of view the discussion is similar to Busenberg and Vanden Driessche (1990).

permit to understand the interplay between the existence of a globally asymptotically stable equilibrium in the system (S, I, R) and the long term dynamics of the original system. It holds for instance:

$$\left(\frac{\dot{T}}{T}\right)_{E_1} = \left(\frac{\dot{S}}{S}\right)_{E_1} + \left(\frac{\dot{N}}{N}\right)_{E_1} = \left(\frac{\dot{N}}{N}\right)_{E_1} = b - \mu - \mu_T R^*$$

The last result shows that when $R_0 > 1$, so that the system reaches E_1 in the long term, then the long term growth of population and disease will be aligned.[5]

Definitively the behaviour of the model is as follows (full mathematical details will be provided elsewhere). Let us consider the case, more interesting from the demographic point of view, of a population growing exponentially at the positive rate $r = b - \mu$ in which an initial seed of the disease is introduced. If $R_B < 1$ the disease is unable to survive in absolute terms and goes extinct (hence it cannot persist in relative terms in a growing population).[6]

If $R_B > 1$ the disease is able to invade the host population in absolute terms and the number of cases of TB will start grow. This does not mean that the disease will be able to persist in relative terms as the population is growing: as long as population grows faster the incidence figures of TB will be decreasing (in fact $R_B > 1$ may coexist with $R_0 < 1$). Relative persistence needs something more, i.e. $R_0 > 1$: in this event the potentiality of the disease are strong enough to permit the emergence of an endemic equilibrium in relative terms: population and the disease will enter in a regime of stable growth (so that the incidences figures will tend to remain constant over time). The intrinsic rate of growth of the system will not be r, but something less due to the presence of the extra-mortality caused by TB. The reduced intrinsic rate of growth will be exactly:$r^* = r - \mu_T R^*$. There is a further possibility, namely that r^* is forced to become negative: in this event population growth would be converted to population decline until extinction. The interplay between μ_T and R_0 in reducing r^* is not trivial as very large values of μ_T would reduce R_0 and therefore R^*.

6. Logistic population dynamics. Let us now assume that in the general model (4) population dynamics follows the standard verhulstian form (6):

$$\dot{N}(t) = [r - (k_1 + k_2)N] \tag{18}$$

with equilibrium at $K = r/(k_1 + k_2)$, $r = b - \mu$. By assuming that the FOI is of the TMA type we get the final model

$$\begin{aligned} \dot{X}(t) &= (b - k_1 N)N - (\mu + k_2 N)X - \beta\frac{XT}{N} \\ \dot{L}(t) &= (1-p)\beta\frac{XT}{N} - ((\mu + k_2 N) + v)L \\ \dot{T}(t) &= vL + p\beta\frac{XT}{N} - ((\mu + k_2 N) + \mu_T)T \end{aligned} \tag{19}$$

[5] Notice that synchronous growth between population and epidemics appears only when $R_0 > 1$ and the GAS equilibrium in the proportions appears. When this is not the case ($R_0 < 1$) then the disease could even grow in absolute terms but without any synchronicity with population growth. In this case the discrimination between growth and decay of the disease is governed by R_B.

[6] A trivial observation is that this happens whatever be the size of of the population: TMA models are not sentitive to population size.

The total population satisfies:

$$\dot{N}(t) = (r - (k_1 + k_2)N)\, N - \mu_T T$$

As in the exponential case it is convenient to pass to the fractions: S, I, R. We get:

$$\begin{aligned} \dot{S} &= (b - k_1 N)(1 - S) - \beta SR + \mu_T SR \\ \dot{I} &= (1-p)\beta SR - ((b - k_1 N) + v)I + \mu_T IR \\ \dot{R} &= vI + p\beta SR - ((b - k_1 N) + \mu_T)R + \mu_T R^2 \end{aligned} \tag{20}$$

where $S + I + R = 1$ so that one equation can be dropped and substituted by the population equation. We definitively consider the system

$$\begin{aligned} \dot{I} &= (1-p)\beta(1 - I - R)\, R - ((b - k_1 N) + v)I + \mu_T IR \\ \dot{R} &= vI + p\beta(1 - I - R)\, R - ((b - k_1 N) + \mu_T)R + \mu_T R^2 \\ \dot{N} &= N\,[r - (k_1 + k_2)N - \mu_T R] \end{aligned} \tag{21}$$

Here we only report results for the case $r = b - \mu > 0$, which implies a true underlying process of logistic growth of the population (the reversed case of population extinction under the accelerating effect of density dependence is less interesting).

6.1. Equilibria and thresholds. The system may have (as it happens for similar cases) up to four equilibria. In particular it always has two disease free equilibria which are found by posing $I = R = 0$ in (21). This leads to the disease free population equation:

$$\dot{N} = (r - (k_1 + k_2 N))\, N$$

which has the equilibria $N = 0$, $N = K$. Let us denote these equilibria as E_0 and E_1:

$$E_0 = (1,\, 0,\, 0,\, 0) \qquad E_1 = (1,\, 0,\, 0,\, K)$$

Moreover, for $N \to 0$ in (20) we obtain the system:

$$\begin{aligned} \dot{S} &= b(1 - S) - \beta SR + \mu_T SR \\ \dot{I} &= (1-p)\beta SR - (b + v)I + \mu_T IR \\ \dot{R} &= vI + p\beta SR - (b + \mu_T)R + \mu_T R^2 \end{aligned} \tag{22}$$

The nonzero equilibria of (22) represent (provided be feasible) endemic states in the proportions with population lead to extinction. The system (22) is identical to the system (10) defining the equilibria of the TB system with exponentially evolving population and therefore leads to the same equilibria and thresholds. Hence, by defining with R_E the basic threshold parameter of the exponential model (previously defined as R_0):

$$R_E = \frac{\beta}{b + \mu_T}\left(p + (1-p)\frac{v}{b+v}\right) \tag{23}$$

when $R_E < 1$ we only have the already found E_0 equilibrium, while when $R_E > 1$ the E_2 equilibrium:

$$E_2 = (S_2, I_2, R_2, 0)$$

will appear. E_2 is exactly the endemic equilibrium of the exponential case, and satisfies the same properties. In particular for $R_E > 1$ it will be GAS. The corresponding asymptotic dynamics of the population is given by[7]:

$$\dot{N}(t) = [(r - \mu_T R_2) - (k_1 + k_2)N]\, N(t)$$

the ultimate outcome of which will be extinction when $r - \mu_T R_2 < 0$. Local stability analysis shows that this actually happens if and only if $R_E > 1$.

Finally, let us look for endemic equilibria with nonzero population. From the population equation we find:

$$N = \frac{r - \mu_T R}{k_1 + k_2} < K \tag{24}$$

Obviously we seek $N > 0$, implying:

$$R < \frac{r}{\mu_T} \tag{25}$$

which provides a bound on the endemic proportion of TB cases.
Let us write $B(N) = C + DR$ where:

$$C = \frac{k_2 b + k_1 \mu}{k_1 + k_2};\ D = \mu_T \frac{k_1}{k_1 + k_2} \tag{26}$$

From the $\dot{I} + \dot{R} = 0$ we get (as $(\beta + D - \mu_T)R + C < 0$ at equilibrium):

$$I + R = \left(\frac{\beta - \mu_T}{(\beta + D - \mu_T)R + C}\right) R \tag{27}$$

The equilibria with nonzero population may then be found as solutions to the system:

$$\begin{aligned} &(1-p)\beta(1 - I - R)\, R - ((C + DR) + v)I + \mu_T IR = 0 \\ &I - \left(\frac{\beta - \mu_T - ((\beta + D - \mu_T)R + C)}{(\beta + D - \mu_T)R + C}\right) R = 0 \end{aligned} \tag{28}$$

defined on the set $\mathcal{D}_0$. Let us define:

$$R_0 = \frac{\beta}{C + \mu_T}\left(p + \frac{v}{C + v}(1 - p)\right) \tag{29}$$

where $C = B(K)$ is the birth rate at the carrying capacity. It is possible to show that R_0 is the threshold that governs: i) the instability of the "large" DFE $E_1 = (1, 0, 0, K)$; ii) the existence of a (unique) meaningful endemic equilibrium with positive population. The following theorem holds:

THEOREM 6.1. *When $R_0 < 1$ no equilibria with positive population may exist in $\mathcal{D}_0$. When $R_0 > 1$ a unique meaningful endemic equilibrium $E_3 = (S_3, I_3, R_3, N_3)$ exists. The endemic proportion of TB cases R_3 satisfies $R < \overline{R}$, where:*

$$\overline{R} = \frac{\beta - \mu_T - C}{\beta - \mu_T + D}$$

Moreover E_3 is locally stable whenever it exists.

[7] See the lemma of the next section.

6.2. Behaviour of the model. As in the exponential case, the behaviour of the system is governed by an articulated set of thresholds. Among these R_B (governing whether the disease is capable to persist in absolute terms in a constant population) and R_E (governing the existence and stability of the equilibrium E_2) are inherited from the exponential model. Moreover we have:

$$R_0 = \frac{\beta}{B(K)+\mu_T}\left(p + \frac{v}{B(K)+v}(1-p)\right)$$

governing existence and local stability of the large DFE and the existence of the endemic equilibrium E_3. Notice that, as $B(K) < B(0) = b$, it follows $R_0 > R_E$, which permits a nice graduation of the mutual effects of R_0, R_E. R_E is the reproduction rate of TB cases when the population is characterised by its maximal birth rate, for $N = 0$, while R_0 is the reproduction rate corresponding to the carrying capacity of the population, which is characterised by a lower birth rate $B(K)$.

Even if our mathematical analysis of the model (21) is not yet complete, we still lack some global result, the behaviour of the model is roughly as follows. Let us assume, as in the exponential case, that $r > 0$, so that in absence of the disease the population would reach its long term logistic equilibrium K. Let us moreover assume that the population starts from very low initial levels (to emulate the possible phenomenological effects of the process of demographic transition). In this population initial seeds of TB are introduced. If $R_B < 1$ the disease is unable to survive. If $R_B > 1$ the number of cases will grow in absolute terms. In this case, provided $R_0 > 1$ also holds, the disease can persist in relative terms and will synchronise with population growth reaching a long term equilibrium which will be somewhat lower of K due to the existence of the disease induced mortality.

Let us consider the extreme case $R_E > 1$. In this case the disease is very strong (remember that as: $R_B > R_0 > R_E$ it follows $R_0 > 1$ even more so, and $R_B > 1$ as well). In this case the equilibrium E_2 becomes GAS corresponding to the fact that the action of the disease has been so strong so to lead the population to extinction despite its intrinsic growth message.

6.3. The case of density-independent fertility. If fertility is density independent ($B(N) = b$) the system (20) reduces to:

$$\begin{aligned} \dot{S} &= b(1-S) - \beta SR + \mu_T SR \\ \dot{I} &= (1-p)\beta SR - (b+v)I + \mu_T IR \\ \dot{R} &= vI + p\beta SR - (b+\mu_T)R + \mu_T R^2 \end{aligned} \tag{30}$$

and:

$$\dot{N} = N\left[r - k_2 N - \mu_T R\right] \tag{31}$$

In sum: as the system in the proportions is not affected by the general mortality rate of the population, (30) results identical to the exponential case, the only difference being in the population equation. Hence, the epidemic and the demographic subsystems decouple. This permits to use "in toto" results from section 4 for the subsystem (30) and then, once the solution $R(t)$ for the proportion of TB cases is available, it can be used as an input for the population equation. Hence this case is completely characterised. In particular, the basic threshold is once more:

$$R_0 = \frac{\beta}{b+\mu_T}\left(p + (1-p)\frac{v}{b+v}\right) \tag{32}$$

which governs the persistence of the endemic proportion. When $R_0 < 1$ the DFE equilibrium in the proportions is GAS and the population follows a disease free logistic pattern:

$$\dot{N} = N\,[r - k_2 N] \tag{33}$$

When $R_0 > 1$ the exponential endemic equilibrium E_2 is GAS and the population follows the reduced logistic pattern:

$$\dot{N} = N\,[g - k_2 N] \tag{34}$$

where $g(t)$ depends on the dynamics of R from (30):

$$g(t) = r - \mu_T R(t)$$

The equation (34) is quite common in these type of models. The following lemma (Gao and Hethcote, 1992) holds:

LEMMA 6.2. *Provided the function g be continuous and its limit $g(\infty)$ exists, then the true long term behaviour of (34) is equal to that of the ODE:*

$$\dot{N} = N\,[g(\infty) - k_2 N]$$

Hence, as $R(t)$ reaches the long term equilibrium R_2, the true long term dynamics of the population is given by:

$$\dot{N} = N\,[(r - \mu_T R_2) - k_2 N] \tag{35}$$

The (35) is a logistic equation with long term equilibrium given by the reduced carrying capacity:

$$N_2 = \frac{r - \mu_T R_2}{k_2} \tag{36}$$

From (36) we see that, exactly as in the previous cases, when $\mu_T R_2$ exceeds r population growth may be converted into population decay up to extinction.

7. Conclusions. It is our intention to expand this preliminary work in the future along two directions. On the theoretical side our next step will consist in the study of the dynamical effects of bilinear mass action (BMA) incidence terms (with and without exogenous reinfection), in both the exponential and logistic models. As shown by Gao et al. (1997) BMA may be responsible for the appearance of persistent oscillations in SEI models with type3 or type 4 population dynamics. As the Blower-type TB models considered here are mixed SI-SEI models not yet studied in the literature, the fact to prove or disprove the existence of oscillations appears to be an important result for the ongoing debate on ingredients needed to generate oscillations in basic epidemiological models.

On the applied side we intend to deep the analysis by Blower et al. by investigating with uncertainty/sensitivity analysis the behaviour of TB models with population dynamics. Moreover we aim to investigate the processes of modernisation, urbanisation, and definitively of demographic transition, which defined the environment in which historical TB developed, by adding further realism, i.e. by considering reinfection and explicit spatial structures which be able to more directly connect the actual transmission dynamics of TB with specified geographical contexts.

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0.1. Equilibria and local stability analysis of the exponential model. The equilibria are the solutions of the system:

$$\begin{aligned} \dot{I} &= 0 \\ \dot{R} &= 0 \end{aligned} \tag{37}$$

i.e.:

$$\begin{cases} -(b+v)\,I + (\mu_T - (1-p)\,\beta)\,RI + (1-p)\,\beta R - (1-p)\,\beta R^2 = 0 \\ vI - p\beta RI + (p\beta - b - \mu_T)\,R + (\mu_T - p\beta)\,R^2 = 0 \end{cases} \tag{38}$$

on the feasible region:

$$\mathcal{D} = \{I \geq 0, R \geq 0, I + R \leq 1\}\,.$$

It is immediate to check that $E_0 = (1,0,0)$ is a solution, and it is the only solution on the boundary of $\mathcal{D}$. At the DFE we find the jacobian:

$$J(E_0) = \begin{pmatrix} -b & 0 & -(\beta - \mu_T) \\ 0 & -(b+v) & (1-p)\beta \\ 0 & v & p\beta - (b+\mu_T) \end{pmatrix}$$

An eigenvalue is given by $-b$. The other are solutions of:

$$\lambda^2 + P\lambda + Q = 0$$

where:

$$P = (b+v) + (b + \mu_T - p\beta) \quad ; \quad Q = (b+v)(b + \mu_T - p\beta) - (1-p)\beta v$$

The definition of R_0 ((13) of the main text) permits to write:

$$Q = (b+v)(b+\mu_T)(1 - R_0) \quad ; \quad P = \varepsilon + \omega(1 - R_0)$$

where ε, ω are strictly positive. This shows that a dominant eigenvalue exists and is positive if and only if $R_0 > 1$.

Let us now look for endemic equilibria, i.e. solutions located in the region $\mathcal{D}_0$. By adding the two equations (37) we get:

$$(R+I)\left((\mu_T-\beta)R-b\right)=(\mu_T-\beta)R.$$

Notice that if $(\mu_T-\beta)R-b=0$ the last relation is not meaningful; for $(\mu_T-\beta)R-b\neq 0$ the system (37) is equivalent to:

$$\begin{aligned}\dot{I}&=0\\ \dot{I}+\dot{R}&=0\end{aligned}$$

which may be written as:

$$\begin{aligned}&I\left[(\mu_T-(1-p)\beta)R-(b+v)\right]=(1-p)\beta R(R-1)\\ &I=R\frac{(\beta-\mu_T)(1-R)-b}{(\beta-\mu_T)R+b}\end{aligned}\tag{39}$$

LEMMA 0.1. *Let us suppose (I^*,R^*) is a solution of (39) on $\mathcal{D}_0$; then R^* satisfies*

$$R^*<\frac{\beta-\mu_T-b}{\beta-\mu_T}\tag{40}$$

with $\beta-\mu_T-b>0$.

Proof. As it must hold $0<I^*+R^*<1$ with $R^*>0$, the second equation of (39) implies $\beta-\mu_T>0$. Under this assumption, and remembering $I^*>0$, $R^*>0$, we find:

$$R^*<\frac{\beta-\mu_T-b}{\beta-\mu_T}<1$$

But $R^*>0$, leading to $\beta-\mu_T-b>0$. □

After some algebra (39) leads to the equation:

$$f(R)=a_0R^2+a_1R+a_2=0\tag{41}$$

where:

$$\begin{aligned}a_0&=\mu_T(\beta-\mu_T)\\ a_1&=-\left[(\beta-\mu_T-b)\mu_T+(\beta-\mu_T)(b+v)\right]\\ a_2&=(R_0-1)(b+v)(\mu_T+b)\end{aligned}$$

Keeping in mind that $\beta-\mu_T-b>0$ means $(\beta-\mu_T)/b>1$, it holds:

$$R_0=\frac{\beta}{b+\mu_T}\left(p+(1-p)\frac{v}{b+v}\right)<\frac{\beta}{b+\mu_T}\tag{42}$$

implying that when $\beta-\mu_T-b>0$, R_0 may lie on both sides of unity.

The following theorem holds:

THEOREM 0.2. *When $R_0>1$ system (39) admits one and (only one) solution in $\mathcal{D}_0$. No solutions exist in $\mathcal{D}_0$ for $R_0<1$.*

Proof. Thanks to Lemma 1 we only need to solve (39) for $\beta - \mu_T > b > 0$ on the set $\mathcal{D}_1 = \{I > 0, 0 < R < \overline{R}, I + R < 1\}$, where $\overline{R} = (\beta - \mu_T - b) / (\beta - \mu_T)$. Hence $a_0 > 0$, $a_1 < 0$ implying that the parabola $f(R)$ is convex and has a positive vertex. Moreover

$$\begin{aligned} f(0) &= (R_0 - 1)(b + v)(b + \mu_T) \\ f(\overline{R}) &= (p - 1) b\beta \end{aligned}$$

Since $p \in (0,1)$ it follows $f(\overline{R}) < 0$; hence one (and only one) solution exists in $\mathcal{D}_1$ iff $f(0) > 0$ i.e. iff $R_0 > 1$. Viceversa, when $R_0 < 1$, provided $\beta - \mu_T > b > 0$ the parabola $f(R)$ has a negative intercept showing that no endemic equilibria exist for $R_0 < 1$. Finally, for $R_0 = 1$ the parabola $f(R)$ takes the form:

$$f(R) = \mu_T (\beta - \mu_T) R^2 - [(\beta - \mu_T)(\mu_T + b + v) - b\mu_T] R$$

from which, apart the uninteresting solution $R = 0$, it follows:

$$R = \frac{\mu_T + b + v}{\mu_T} - \frac{b}{\beta - \mu_T}$$

which is not acceptable as it does not satisfy $R < \overline{R}$.□

0.2. Local stability analysis of the endemic equilibrium. Let us consider the reduced jacobian in correspondence of the endemic equilibrium E_1:

$$\tilde{J}(E_1) = \begin{bmatrix} (\mu_T - (1-p)\beta) R_1 - b - v & -(1-p)\beta R_1 + (b+v)\dfrac{I_1}{R_1} \\ v - p\beta R_1 & -v\dfrac{I_1}{R_1} - (p\beta - \mu_T) R_1 \end{bmatrix}$$

Hence:

$$\operatorname{Tr} \tilde{J}(E_1) = -(\beta - \mu_T) R - (b + v) + \mu_T R - v\frac{I}{R}$$

Let us now consider the equation $\dot{I} = 0$; solving for S we get:

$$S = I\frac{(b+v) - \mu_T R}{(1-p)\beta S R}$$

As $S > 0$, by definition it necessarily holds: $(b + v) - \mu_T R > 0$. Hence:

$$\operatorname{Tr} \tilde{J}(E_1) = -(\beta - \mu_T) R - ((b + v) - \mu_T R) - v\frac{I}{R} < 0$$

Let us now consider $\det J$:

$$\det \tilde{J}(E_1) = \mu_T (\mu_T - \beta) R^2 + [b(p\beta - \mu_T) + v(\beta - \mu_T)] R + I[v(\beta - \mu_T) + bp\beta.]$$

Let:

$$g(R) = \mu_T (\mu_T - \beta) R^2 + [b(p\beta - \mu_T) + v(\beta - \mu_T)] R \qquad R \in [0,1]$$

with $g(0) = 0$. We now prove that there exists $\tilde{R}$ such that $g\left(\tilde{R}\right) > 0$ and $R_1 < \tilde{R}$ (where R_1 is the endemic solution for R) implying, thanks to $\mu_T - \beta < 0$, that $g(R) > 0$

for all $R \in \left(0, \tilde{R}\right)$. Recalling that the equilibrium equation $f(R) = 0$, has two roots of which only the smaller one R_1 was acceptable (in that lies in $(0,1)$), while the larger R^* is greater than $\overline{R} = (\beta - \mu_T - b)/(\beta - \mu_T)$, from the product

$$R_1 R^* = \frac{v(\beta - \mu_T - b) + b(p\beta - \mu_T - b)}{\mu_T(\beta - \mu_T)}$$

we find:

$$R_1 < \frac{v(\beta - \mu_T - b) + b(p\beta - \mu_T - b)}{\mu_T(\beta - \mu_T - b)} = \tilde{R}$$

Hence:

$$g\left(\tilde{R}\right) = \frac{b^2\beta(1-p)}{\beta - \mu_T - b} > 0.$$

showing definitively that $\det \tilde{J}(E_1) > 0$, thanks to $\beta > \mu_T$.

0.3. Global stability of the endemic equilibrium. To prove that the endemic equilibrium E_1 is GAS we use the negative criterion developed in Busenberg and VanDenDriessche (1990) to exclude the existence of periodic solutions of the proportion system. This criterion constitutes an extension of the classical negative criteria Bendixson-Dulac-type. Given a vector field $\mathbf{v} = (v_1(x,y,z), v_2(x,y,z), v_3(x,y,z))$ which is C^1 on an open set $A \subset \mathbb{R}^3$ the curl of the field is defined as:

$$\operatorname{curl}(\mathbf{v}) = \left(\frac{\partial v_3}{\partial y} - \frac{\partial v_2}{\partial z}, \frac{\partial v_1}{\partial z} - \frac{\partial v_3}{\partial x}, \frac{\partial v_2}{\partial x} - \frac{\partial v_1}{\partial y}\right)$$

Let us now consider the following field in $\mathbb{R}^3$:

$$\mathbf{g}(S,I,R) = \left(\frac{f_3(S,R)}{SR} - \frac{f_2(S,I)}{SI}, \frac{f_1(S,I)}{SI} - \frac{f_3(I,R)}{IR}, \frac{f_2(I,R)}{IR} - \frac{f_1(S,R)}{SR}\right)$$

where:

$$\begin{aligned}
f_1(S,R) &= b - (\beta - \mu_T) RS - bS \\
f_1(S,I) &= b - (\beta - \mu_T)(1 - S - I) S - bS \\
f_2(I,R) &= -(b+v) I + (\mu_T - (1-p)\beta) RI + (1-p)\beta R - (1-p)\beta R^2 \\
f_2(S,I) &= -(b+v) I + \mu_T (1 - I - S) I + (1-p)\beta(1 - S - I) S \\
f_3(I,R) &= vI - p\beta RI + (p\beta - b - \mu_T) R + (\mu_T - p\beta) R^2 \\
f_3(S,R) &= -(v+b) R + \mu_T R^2 + v(1 - S - R) + p\beta RS
\end{aligned}$$

As

$$\begin{aligned}
\frac{\partial}{\partial S}\left(\frac{f_1(S,R)}{SR} + \frac{f_1(S,I)}{SI}\right) &= -\frac{b}{RS^2} - \frac{b}{IS^2} + \frac{\beta - \mu_T}{I} \\
\frac{\partial}{\partial I}\left(\frac{f_2(I,R)}{IR} + \frac{f_2(S.I)}{SI}\right) &= -\frac{\mu_T}{S} - \frac{(1-p)\beta(1+I)}{I^2} \\
\frac{\partial}{\partial R}\left(\frac{f_3(I,R)}{IR} + \frac{f_3(S,R)}{SR}\right) &= \frac{\mu_T - p\beta}{I} + \frac{\mu_T}{S} - \frac{v}{SR^2}
\end{aligned}$$

we find

$$\operatorname{curl}(\mathbf{g}) \cdot (1,1,1) = -\frac{\beta(1-p) S^2R^2 + vI^2S + bI^2R + bIR^2}{I^2S^2R^2} < 0$$

This definitively proves that the E_1 is GAS whenever it exists.

1. **Equilibria in the logistic model.** Inspection of (28) shows that meaningful equilibria may exist only provided $\beta - \mu_T > 0$.
By writing $D = \mu_T q_2$ where $q_2 = K_2/(K_1 + K_2)$, the second equation of (28) gives:

$$I = R\frac{\beta - \mu_T - R(\beta - q_2\mu_T) - C}{R(\beta - q_2\mu_T) + C}$$

As $\beta - \mu_T > 0$, the denominator of the last expression is positive at equilibrium implying that the numerator as well must be positive; this leads to:

$$R < \frac{\beta - \mu_T - C}{\beta - q_2\mu_T} = \overline{R}$$

which is meaningful provided $\beta > \mu_T + C$. Tedious but simple algebra on the system (28) of the main text leads to the following quadratic equation for the determination of endemic equilibria with nonzero population:

$$f(R) = a_0R^2 + a_1R + a_2 = 0$$

where:

$$\begin{aligned}
a_0 &= q_2\mu_T(\beta - q_2\mu_T)\\
a_1 &= -[q_2\mu_T(\beta - \mu_T - C) + (\beta - q_2\mu_T)(v + C) + (1-p)(1-q_2)\beta\mu_T]\\
a_2 &= C(p\beta - \mu_T - C) + v(\beta - \mu_T - C) = (R_0 - 1)(C + v)(C + \mu_T)
\end{aligned}$$

Notice now that $a_0 > 0$ (as $\beta > \mu_T$ and $q_2 \in (0,1)$), $a_1 < 0$, and moreover:

$$f(\overline{R}) = -\frac{(1-p)\beta[C(\beta - q_2\mu_T) + (1-q_2)\mu_T(\beta - \mu_T - C)]}{\beta - q_2\mu_T} < 0$$

Hence, as in equilibrium it must hold $R < \overline{R}$, a meaningful equilibrium will exists if and only if $f(0) = a_2 > 0$, i.e. if and only if $R_0 > 1$.

1.0.1. Local stability analysis of the equilibrium $E_1 = (1, 0, 0, K)$. We find:

$$J(E_1) = \begin{pmatrix} -(b - k_1K + v) & (1-p)\beta & 0\\ v & p\beta - (b - k_1K + \mu_T) & 0\\ 0 & -\mu_TK & -(k_1 + k_2)K \end{pmatrix}$$

Therefore $-(k_1 + k_2)K$ is an eigenvalue. The remaining eigenvalues belong to the reduced matrix:

$$\tilde{J}(E_1) = \begin{pmatrix} -(B(K) + v) & (1-p)\beta\\ v & p\beta - (B(K) + \mu_T) \end{pmatrix}$$

which is identical to the matrix ascertaining stability of the DFE in the exponential model, with the constant birth rate b replaced by the state dependent birth rate $B(K)$. Hence the invasion parameter is :

$$R_0 = \frac{\beta}{B(K) + \mu_T}\left(p + \frac{v}{B(K) + v}(1-p)\right)$$

where:

$$B(K) = \frac{bk_2 + \mu k_1}{k_1 + k_2} = C$$

Hence:

$$R_0 = \frac{\beta}{C + \mu_T}\left(p + \frac{v}{C + v}(1-p)\right)$$