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Optimal Control of an Age-structured Tuberculosis Model

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شكر وتقدير

بسم الله الرحمن الرحيم، والحمد لله الذي بنعمته تتم الصالحات، وبفضله تنال الغايات، أحمده سبحانه على ما يسر وأعان، وأسأله أن يجعل هذا العمل خالصاً لوجهه، نافعاً بعلمه، ومباركاً في أثره.

أتقدم بجزيل الشكر وعظيم الامتنان إلى الأستاذ المؤطر الدكتور نابي عبد الرزاق، على ما قدمه لي من توجيه علمي، ونصائح قيمة، ومتابعة مستمرة طويلة فترة إنجاز هذه المذكرة. فقد كان لتوجيهاته وملاحظاته أثر كبير في تحسين هذا العمل وإخراجه في أحسن صورة ممكنة.

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إهداء

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ملخص

تُبرز هذه المذكرة أهمية النماذج الرياضية المنظّمة بالعمر في دراسة ديناميكيات انتشار مرض السل، باعتباره من الأمراض المعدية التي تتميز بفترة كمون وإمكانية الانتكاس بعد الشفاء. ندرس في هذا العمل نموذجاً وبائياً من نوع SEIR منظماً بالعمر، يصف تطوّر المرض عبر إدخال عمر الكمون a وعمر العدوى b ، مع مراعاة الانتكاس بمعدّل δ . ويهدف التحليل الرياضي للنموذج إلى دراسة حسن وضع المسألة، وتحديد التوازن الخالي من المرض E^0 ، واستنتاج عدد التكاثر الأساسي R_0 ، الذي يمثل عتبة وبائية أساسية لفهم سلوك المرض داخل المجتمع. كما ندرس خصائص الاستقرار المحلي والشامل للنموذج، ونوظف نظرية التحكم الأمثل لاقتراح استراتيجيات فعّالة للحدّ من انتشار السل، بالاعتماد على التلقيح وتقليل الانتكاس مع مراعاة تكلفة التدخلات. وتؤكد النتائج أهمية النمذجة الرياضية والتحكم الأمثل في دعم القرارات الصحية المبنية على أسس علمية.

الكلمات المفتاحية: مرض السل؛ نموذج SEIR منظم بالعمر؛ عدد التكاثر الأساسي R_0 ؛ الاستقرار المحلي والشامل؛ التحكم الأمثل.

Résumé

Ce mémoire met en évidence l'importance des modèles mathématiques structurés par âge dans l'étude de la dynamique de transmission de la tuberculose, en tant que maladie infectieuse caractérisée par une période de latence et par la possibilité de rechute après la guérison.

Dans ce travail, nous étudions un modèle épidémique de type SEIR structuré par âge, qui décrit l'évolution de la maladie en introduisant l'âge de latence a et l'âge d'infection b , tout en tenant compte de la rechute au taux δ . L'analyse mathématique du modèle vise à étudier le bon posé du problème, à déterminer l'équilibre sans maladie E^0 et à obtenir le nombre de reproduction de base $\mathcal{R}_0$, qui représente un seuil épidémiologique fondamental pour comprendre le comportement de la maladie au sein de la population. Les propriétés de stabilité locale et globale du modèle sont également étudiées. La théorie du contrôle optimal est utilisée afin de proposer des stratégies efficaces pour réduire la propagation de la tuberculose, fondées sur la vaccination et la réduction de la rechute, tout en tenant compte du coût des interventions. Les résultats confirment l'importance de la modélisation mathématique et du contrôle optimal dans l'appui aux décisions de santé publique fondées sur des bases scientifiques.

Mots-clés : tuberculose ; modèle SEIR structuré par âge ; nombre de reproduction de base $\mathcal{R}_0$; stabilité locale et globale ; contrôle optimal.

Abstract

This dissertation highlights the importance of age-structured mathematical models in studying the transmission dynamics of tuberculosis, as an infectious disease characterized by a latency period and the possibility of relapse after recovery. In this work, we study an age-structured SEIR epidemic model that describes the evolution of the disease by introducing the latency age a and the infection age b , while taking relapse into account through the rate δ . The mathematical analysis of the model aims to study the well-posedness of the problem, determine the disease-free equilibrium E^0 , and derive the basic reproduction number $\mathcal{R}_0$, which represents a fundamental epidemiological threshold for understanding the behavior of the disease within the population. The local and global stability properties of the model are also studied. Optimal control theory is used to propose effective strategies to reduce the spread of tuberculosis, based on vaccination and relapse reduction while taking intervention costs into account. The results confirm the importance of mathematical modeling and optimal control in supporting scientifically based public health decisions.

Keywords: tuberculosis; age-structured SEIR model; basic reproduction number $\mathcal{R}_0$; local and global stability; optimal control.

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Introduction

Infectious diseases are among the main topics studied in epidemiology because of their direct impact on the health of individuals and populations. Understanding how these diseases spread is an essential step in analysing their behaviour and proposing suitable ways to reduce their effects. In this context, mathematical modelling is used as an important tool to study the dynamics of infectious diseases. It allows us to represent the epidemic phenomenon by mathematical equations and to analyse the factors that influence the evolution of the disease in a population [1, 2].

Epidemic models are usually based on dividing the population into different classes according to the health status of individuals. One of the classical models is the SIR model, introduced by Kermack and McKendrick, where the population is divided into susceptible, infectious, and recovered individuals [5]. However, this model is not sufficient for diseases in which an infected individual passes through a stage where he is infected but not yet infectious. For this reason, SEIR-type models were introduced by adding the exposed or latent class in order to describe this epidemiological stage [7, 6].

Tuberculosis is an infectious disease with a particular epidemiological behaviour. After infection, an individual may remain in a latent stage before becoming able to transmit the disease. The duration of this stage may vary from one individual to another according to biological and health-related factors. In addition, the disease may return after recovery, which is known as relapse. Therefore, the study of tuberculosis requires a model that takes into account the latent stage, the infectious stage, and the possibility that recovered individuals return to the infectious class [9, 10].

In classical epidemic models, individuals are often not distinguished according to the time they have spent in each epidemiological class. However, this distinction becomes important for diseases in which individual characteristics change with time, such as the duration of latency or the duration of infection. For this reason, in this dissertation we consider an age-structured model, where the variable a denotes the latency age of latent individuals $e(t, a)$, and the variable b denotes the infection age of infectious individuals $i(t, b)$. This choice gives a more accurate description of the transition from the latent class to the infectious class, and from the infectious class to the recovered class, while also taking into account the effect of relapse [14, 16].

After formulating the model, we study some of its qualitative properties, especially the disease-free equilibrium E_0 and the basic reproduction number R_0 . The equilibrium E_0 represents the situation where the disease is absent from the population, while R_0

allows us to determine the conditions under which the disease disappears or persists. If $R_0 < 1$, then the disease tends to die out, whereas if $R_0 > 1$, the disease may persist in the population and a positive endemic equilibrium may appear [3, 18].

The analysis of the model is not limited to the determination of equilibria. It also requires the study of their stability. Local stability allows us to understand the behaviour of solutions near an equilibrium, while global stability gives a clearer idea about the long-term behaviour of solutions in the biologically feasible region. For this purpose, we use some tools from dynamical systems, such as the linearization method, Lyapunov functionals, and LaSalle's invariance principle, in order to determine the cases where the disease disappears or persists in the population [19, 22].

After completing the qualitative analysis of the model, we study an optimal control problem in order to reduce the spread of tuberculosis over a fixed time interval. For this purpose, two time-dependent controls are introduced into the model. The control $u_1(t)$ represents the vaccination effort applied to susceptible individuals, while the control $u_2(t)$ represents the relapse-prevention effort applied to recovered individuals. The aim of this study is to reduce the number of susceptible, latent, and infectious individuals, while taking into account the costs of applying the vaccination and relapse-prevention strategies [24].

This dissertation is organized as follows. The first chapter is devoted to some mathematical concepts and tools used throughout the study. The second chapter presents the formulation of the age-structured epidemic model, the existence, uniqueness and boundedness of solutions, the determination of the basic reproduction number, and the stability analysis of the disease-free equilibrium. In the third chapter, we study the optimal control problem by introducing two time-dependent controls, where $u_1(t)$ represents vaccination and $u_2(t)$ represents relapse prevention. We also define the objective functional, which combines the reduction of the susceptible, latent, and infectious populations with the costs of the two controls. Then, we prove the existence of an optimal control and use the variational method and the adjoint system to derive the necessary optimality conditions and characterize the optimal controls.

Preliminaries

This chapter collects the functional-analytic and dynamical tools used in the sequel. We first recall the basic spaces and modes of convergence, then the operator- and semigroup-theoretic results underlying the well-posedness of the age-structured model, the stability notions used for the equilibrium analysis, and finally the elements of optimal control invoked in the existence and characterisation of optimal strategies.

1.1 Basic Functional Spaces and Convergence Concepts

Definition 1.1.1 (Normed vector space). *Let X be a vector space over $\mathbb{R}$ or $\mathbb{C}$. A function $\|\cdot\| : X \rightarrow [0, \infty)$ is called a norm if for all $x, y \in X$ and all scalars α ,*

1. $\|x\| = 0$ if and only if $x = 0$;
2. $\|\alpha x\| = |\alpha| \|x\|$;
3. $\|x + y\| \leq \|x\| + \|y\|$.

The pair $(X, \|\cdot\|)$ is called a normed vector space.

Definition 1.1.2 (Inner product). *Let H be a vector space over $\mathbb{R}$ or $\mathbb{C}$. An inner product on H is a mapping $\langle \cdot, \cdot \rangle : H \times H \rightarrow \mathbb{R}$ (or $\mathbb{C}$) satisfying, for all $x, y, z \in H$ and all scalars α ,*

1. $\langle x, x \rangle \geq 0$, and $\langle x, x \rangle = 0$ if and only if $x = 0$;
2. $\langle x, y \rangle = \overline{\langle y, x \rangle}$;
3. $\langle \alpha x + y, z \rangle = \alpha \langle x, z \rangle + \langle y, z \rangle$.

Definition 1.1.3 (Complete space). *A normed space $(X, \|\cdot\|)$ is complete if every Cauchy sequence in X converges to an element of X .*

Definition 1.1.4 (Banach space). *A Banach space is a complete normed vector space.*

Definition 1.1.5 (Hilbert space). *An inner product space H endowed with the norm $\|x\|_H = \sqrt{\langle x, x \rangle}$ is called a Hilbert space if it is complete with respect to this norm.*

Definition 1.1.6 ($L^p(\Omega)$ space). *Let $\Omega \subset \mathbb{R}^n$ be measurable and $1 \leq p < \infty$. The Lebesgue space $L^p(\Omega)$ consists of (equivalence classes, modulo equality almost everywhere, of) measurable functions $f : \Omega \rightarrow \mathbb{R}$ with $\int_{\Omega} |f(x)|^p dx < \infty$, equipped with the norm*

$$\|f\|_{L^p(\Omega)} = \left(\int_{\Omega} |f(x)|^p dx \right)^{1/p}.$$

Definition 1.1.7 ($L^\infty(\Omega)$ space). *The space $L^\infty(\Omega)$ consists of measurable functions $f : \Omega \rightarrow \mathbb{R}$ with $\text{ess sup}_{x \in \Omega} |f(x)| < \infty$, with norm*

$$\|f\|_{L^\infty(\Omega)} = \text{ess sup}_{x \in \Omega} |f(x)|.$$

We write $L_+^\infty(\Omega)$ for its nonnegative elements.

Definition 1.1.8 ($L^2(\Omega)$ space). *The space $L^2(\Omega)$ is the case $p = 2$ above (real-valued functions). It is a Hilbert space with inner product and norm*

$$\langle f, g \rangle_{L^2(\Omega)} = \int_{\Omega} f(x)g(x) dx, \quad \|f\|_{L^2(\Omega)} = \left(\int_{\Omega} |f(x)|^2 dx \right)^{1/2}.$$

Definition 1.1.9 ($C(\overline{\Omega})$ space). *The space $C(\overline{\Omega})$ consists of all continuous functions on the compact set $\overline{\Omega}$, endowed with the supremum norm $\|f\|_\infty = \sup_{x \in \overline{\Omega}} |f(x)|$.*

Definition 1.1.10 (Sobolev spaces $W^{1,p}(\Omega)$ and $W^{1,1}(\Omega)$). *Let $1 \leq p < \infty$. The Sobolev space $W^{1,p}(\Omega)$ is*

$$W^{1,p}(\Omega) = \{u \in L^p(\Omega) : D^\alpha u \in L^p(\Omega), |\alpha| \leq 1\},$$

where $D^\alpha u$ denotes the weak derivative of u , with norm

$$\|u\|_{W^{1,p}(\Omega)} = \left(\|u\|_{L^p(\Omega)}^p + \sum_{i=1}^n \left\| \frac{\partial u}{\partial x_i} \right\|_{L^p(\Omega)}^p \right)^{1/p}.$$

The space $W^{1,1}(\Omega)$ is the particular case $p = 1$, with norm $\|u\|_{W^{1,1}(\Omega)} = \|u\|_{L^1(\Omega)} + \sum_{i=1}^n \|\partial u / \partial x_i\|_{L^1(\Omega)}$. On the half-line ($\Omega = (0, \infty)$, $n = 1$) this reduces to $\|u\|_{W^{1,1}} = \|u\|_{L^1} + \|u'\|_{L^1}$.

Definition 1.1.11 (Dual space). Let $\mathbb{K}$ be $\mathbb{R}$ or $\mathbb{C}$. The space

$$X^* = \mathcal{L}(X, \mathbb{K}) = \{\phi : X \rightarrow \mathbb{K} : \phi \text{ linear and continuous}\}$$

is called the dual space of X .

Definition 1.1.12 (Reflexive space). A Banach space X is reflexive if the canonical embedding $X \hookrightarrow X^{**}$ is surjective. Hilbert spaces and $L^p(\Omega)$ with $1 < p < \infty$ are reflexive.

Definition 1.1.13 (Strong convergence). A sequence (x_n) in a normed space X converges strongly (or in norm) to $x \in X$, written $x_n \rightarrow x$, if $\|x_n - x\|_X \rightarrow 0$ as $n \rightarrow \infty$.

Definition 1.1.14 (Uniform convergence). A sequence of functions (f_n) from a set Ω into $\mathbb{R}$ (or $\mathbb{C}$) converges uniformly to f , written $f_n \xrightarrow{\text{unif}} f$, if $\sup_{x \in \Omega} |f_n(x) - f(x)| \rightarrow 0$ as $n \rightarrow \infty$.

Definition 1.1.15 (Weak convergence). A sequence (x_n) in a normed space X converges weakly to $x \in X$, written $x_n \rightharpoonup x$, if $\phi(x_n) \rightarrow \phi(x)$ for every $\phi \in X^*$.

Definition 1.1.16 (Weak convergence in $L^2(\Omega)$). A sequence (f_n) in $L^2(\Omega)$ converges weakly to $f \in L^2(\Omega)$, written $f_n \rightharpoonup f$, if

$$\langle f_n, g \rangle_{L^2(\Omega)} \longrightarrow \langle f, g \rangle_{L^2(\Omega)}, \quad \forall g \in L^2(\Omega).$$

Definition 1.1.17 (Lipschitz and locally Lipschitz continuity). Let X, Y be normed spaces. A map $f : X \rightarrow Y$ is Lipschitz continuous (equivalently, uniformly or globally Lipschitz) if there is a constant $L > 0$ with

$$\|f(x) - f(y)\| \leq L\|x - y\|, \quad \forall x, y \in X,$$

and L is called a Lipschitz constant. It is locally Lipschitz continuous if for every $x \in X$ there exist a ball $B(x, r)$ and a constant $L_x > 0$ such that $\|f(u) - f(v)\| \leq L_x\|u - v\|$ for all $u, v \in B(x, r)$.

Definition 1.1.18 (Uniform continuity and equicontinuity). A map $f : X \rightarrow Y$ between metric spaces is uniformly continuous if for every $\varepsilon > 0$ there is $\delta > 0$ such that $d_X(x, y) < \delta$ implies $d_Y(f(x), f(y)) < \varepsilon$. A family $\mathcal{F}$ of maps $X \rightarrow Y$ is equicontinuous if for every $\varepsilon > 0$ there is $\delta > 0$ such that $d_X(x, y) < \delta$ implies $d_Y(f(x), f(y)) < \varepsilon$ for all $f \in \mathcal{F}$ simultaneously.

Definition 1.1.19 (Lower and upper semicontinuity). Let X be a topological (or metric) space and $f : X \rightarrow \mathbb{R}$. Then f is lower semicontinuous if $x_n \rightarrow x$ implies $f(x) \leq \liminf_{n \rightarrow \infty} f(x_n)$, and upper semicontinuous if $x_n \rightarrow x$ implies $f(x) \geq \limsup_{n \rightarrow \infty} f(x_n)$.

Definition 1.1.20 (Weak lower semicontinuity). *A functional $J : X \rightarrow \mathbb{R}$ on a Banach space X is weakly lower semicontinuous if, for every sequence with $x_n \rightharpoonup x$,*

$$J(x) \leq \liminf_{n \rightarrow \infty} J(x_n).$$

Definition 1.1.21 (Convex set and convex functional). *Let X be a real vector space. A set $C \subset X$ is convex if $\lambda x + (1 - \lambda)y \in C$ for all $x, y \in C$ and $\lambda \in [0, 1]$; that is, the whole segment joining any two of its points lies in C . A functional $J : C \rightarrow \mathbb{R}$ on a convex set C is convex if*

$$J(\lambda x + (1 - \lambda)y) \leq \lambda J(x) + (1 - \lambda)J(y), \quad \forall x, y \in C, \lambda \in [0, 1].$$

The following compactness and weak-topology results are used repeatedly.

Theorem 1.1.22 (Arzelà–Ascoli). *Let K be a compact metric space and let $\{f_n\} \subset C(K, \mathbb{R}^m)$ be uniformly bounded and equicontinuous. Then $\{f_n\}$ has a subsequence that converges uniformly on K . Equivalently, a subset of $C(K)$ is relatively compact for the supremum norm if and only if it is bounded and equicontinuous.*

Theorem 1.1.23 (Weak compactness in reflexive spaces). *Let X be a reflexive Banach space. Then every bounded sequence in X has a weakly convergent subsequence.*

Theorem 1.1.24 (Mazur). *In a normed space X , a convex set $C \subset X$ is strongly closed if and only if it is weakly closed. In particular, a convex, strongly closed set is weakly closed.*

Theorem 1.1.25 (Convexity implies weak lower semicontinuity). *Let X be a Banach space and $J : X \rightarrow \mathbb{R}$ convex and strongly lower semicontinuous (in particular, convex and continuous). Then J is weakly lower semicontinuous.*

1.2 Linear Operators, Semigroups, and Abstract Cauchy Problems

Definition 1.2.1 (Domain and bounded operators). *Let X, Y be Banach spaces. For an operator $A : D(A) \subset X \rightarrow Y$, the domain is $D(A) = \{x \in X : Ax \text{ is defined}\}$. The space of bounded linear operators is*

$$\mathcal{L}(X, Y) = \{A : X \rightarrow Y : A \text{ linear and continuous}\}, \quad \|A\|_{\mathcal{L}(X, Y)} = \sup_{u \neq 0} \frac{\|Au\|}{\|u\|}.$$

We write $\mathcal{L}(X) := \mathcal{L}(X, X)$.

Definition 1.2.2 (Closed operator). *An operator $A : D(A) \subset X \rightarrow Y$ is closed if, whenever $x_n \rightarrow x$ and $Ax_n \rightarrow y$ with $x_n \in D(A)$, one has $x \in D(A)$ and $Ax = y$.*

Definition 1.2.3 (Compact operator). *A linear operator $A : X \rightarrow Y$ is compact if it maps bounded subsets of X into relatively compact subsets of Y .*

Definition 1.2.4 (Dense subset). *Let X be a normed space and $M \subset X$. The set M is dense in X if $\overline{M} = X$; equivalently, for every $x \in X$ and every $\varepsilon > 0$ there exists $y \in M$ with $\|y - x\| < \varepsilon$.*

Definition 1.2.5 (Resolvent set and resolvent operator). *Let $A : D(A) \subset X \rightarrow X$ be linear. The resolvent set is*

$$\rho(A) = \{\lambda \in \mathbb{C} : (\lambda I - A)^{-1} \text{ exists and is bounded}\},$$

and for $\lambda \in \rho(A)$ the resolvent operator is $R(\lambda, A) = (\lambda I - A)^{-1}$.

Definition 1.2.6 (Hille–Yosida operator). *Let X be a Banach space. A closed linear operator $A : D(A) \subset X \rightarrow X$ is a Hille–Yosida operator if there exist constants $M \geq 1$ and $\omega \in \mathbb{R}$ such that $(\omega, \infty) \subset \rho(A)$ and*

$$\|(\lambda I - A)^{-n}\|_{\mathcal{L}(X)} \leq \frac{M}{(\lambda - \omega)^n}, \quad \forall \lambda > \omega, \forall n \geq 1.$$

The domain $D(A)$ is not required to be dense in X .

Remark 1.2.7 (Part of A in $\overline{D(A)}$). *Set $X_0 := \overline{D(A)}$. The part of A in X_0 is*

$$A_0x = Ax, \quad D(A_0) = \{x \in D(A) : Ax \in X_0\},$$

and A_0 generates a strongly continuous semigroup $\{T_{A_0}(t)\}_{t \geq 0}$ on X_0 . When $\overline{D(A)} = X$ one recovers the classical theory below; when $\overline{D(A)} \subsetneq X$ (as for the age-structured operator A , whose domain is not dense) one works with the integrated semigroup of Definition 1.2.9.

Theorem 1.2.8 (Hille–Yosida, classical C_0 -semigroup case). *A linear operator $A : D(A) \subset X \rightarrow X$ generates a strongly continuous semigroup $\{T(t)\}_{t \geq 0}$ with $\|T(t)\| \leq Me^{\omega t}$ if and only if A is densely defined, closed, and satisfies the resolvent estimates of Definition 1.2.6. In that case*

$$R(\lambda, A)x = \int_0^\infty e^{-\lambda t} T(t)x \, dt, \quad \lambda > \omega, \, x \in X.$$

Definition 1.2.9 (Integrated semigroup). *A strongly continuous family $\{\mathcal{S}(t)\}_{t \geq 0} \subset \mathcal{L}(X)$ with $\mathcal{S}(0) = 0$ is the integrated semigroup generated by A if, for all $x \in X$ and $t \geq 0$, $\int_0^t \mathcal{S}(s)x ds \in D(A)$ and*

$$\mathcal{S}(t)x = A \int_0^t \mathcal{S}(s)x ds + tx.$$

Every Hille–Yosida operator generates a unique integrated semigroup.

Definition 1.2.10 (Integrated (mild) solution). *Let A be a Hille–Yosida operator, $X_0 = \overline{D(A)}$, and $F : X_0 \rightarrow X$. A continuous map $u \in C([0, t_{\max}), X_0)$ is an integrated solution of the abstract Cauchy problem $u'(t) = Au(t) + F(u(t))$, $u(0) = u_0$, if $\int_0^t u(s) ds \in D(A)$ for all $t \in [0, t_{\max})$ and*

$$u(t) = u_0 + A \int_0^t u(s) ds + \int_0^t F(u(s)) ds.$$

Theorem 1.2.11 (Existence and uniqueness of integrated solutions). *Let A be a Hille–Yosida operator on X and let $F : X_0 \rightarrow X$ be locally Lipschitz continuous on $X_0 = \overline{D(A)}$. Then for every $u_0 \in X_0$ there exist $t_{\max} \in (0, \infty]$ and a unique maximal integrated solution $u \in C([0, t_{\max}), X_0)$. Moreover, the blow-up alternative holds: if $t_{\max} < \infty$ then $\limsup_{t \rightarrow t_{\max}^-} \|u(t)\|_X = +\infty$.*

Theorem 1.2.12 (Positivity and invariance). *Under the hypotheses of Theorem 1.2.11, let $X_+ \subset X$ be a closed cone and $X_{0+} = X_0 \cap X_+$. Assume*

1. *A is resolvent positive: $(\lambda I - A)^{-1}X_+ \subset X_+$ for all $\lambda > \omega$;*
2. *for every $r > 0$ there exists $c \geq 0$ (subtangential condition) such that $F(u) + cu \in X_+$ for all $u \in B_X(0, r) \cap X_{0+}$.*

Then X_{0+} is positively invariant: $u_0 \in X_{0+}$ implies $u(t) \in X_{0+}$ for all $t \in [0, t_{\max})$.

1.3 Stability Analysis

Consider an autonomous dynamical system

$$\dot{x}(t) = f(x(t)), \quad x(0) = x_0, \tag{1.1}$$

where $f : D \rightarrow \mathbb{R}^n$ is continuously differentiable on an open domain $D \subset \mathbb{R}^n$. Let $x^* \in D$ be an equilibrium, $f(x^*) = 0$.

Definition 1.3.1 (Stability). *The equilibrium x^* is stable (in the sense of Lyapunov) if for every $\epsilon > 0$ there exists $\delta = \delta(\epsilon) > 0$ such that $\|x(0) - x^*\| < \delta$ implies that $x(t)$ exists for all $t \geq 0$ and $\|x(t) - x^*\| < \epsilon$ for all $t \geq 0$.*

Definition 1.3.2 (Local and global asymptotic stability). *The equilibrium x^* is locally asymptotically stable (LAS) if it is stable and there exists $\delta_0 > 0$ such that $\|x(0) - x^*\| < \delta_0$ implies $\lim_{t \rightarrow \infty} x(t) = x^*$. It is globally asymptotically stable (GAS) on D if it is stable and $\lim_{t \rightarrow \infty} x(t) = x^*$ for every $x(0) \in D$.*

Theorem 1.3.3 (Hartman–Grobman). *Let x^* be an equilibrium of (1.1) and $A = Df(x^*)$ the Jacobian at x^* . If x^* is hyperbolic, i.e. $\Re(\lambda) \neq 0$ for every eigenvalue λ of A , then there exist neighborhoods U of x^* and V of the origin and a homeomorphism $h : U \rightarrow V$ such that (1.1) is topologically conjugate to its linearization $\dot{y} = Ay$: if $x(t)$ is a trajectory of the nonlinear system, then $y(t) = h(x(t))$ is a trajectory of the linear one, and conversely.*

Remark 1.3.4. *Consequently, the nonlinear system and its linearization have the same qualitative behaviour in a neighborhood of x^* .*

Corollary 1.3.5 (Local stability via linearization). *Let x^* be a hyperbolic equilibrium of (1.1) and $A = Df(x^*)$.*

1. *If $\Re(\lambda) < 0$ for every eigenvalue λ of A , then x^* is locally asymptotically stable.*
2. *If $\Re(\lambda) > 0$ for some eigenvalue λ of A , then x^* is unstable.*

Definition 1.3.6 (Definiteness). *Let $V \in C^0(S)$ on a region $S \subset \mathbb{R}^n$ containing x^* , with $V(x^*) = 0$. Then V is positive definite on S if $V(x) > 0$ for all $x \in S$, $x \neq x^*$, and negative definite if $V(x) < 0$ for all $x \neq x^*$. If the inequalities are non-strict, V is positive (resp. negative) semi-definite.*

Definition 1.3.7 (Derivative along trajectories). *For $V \in C^1(\mathbb{R}^n)$, the total derivative of V along solutions of (1.1) is*

$$\dot{V} = \frac{d}{dt}V(x(t)) = \sum_{i=1}^n \frac{\partial V}{\partial x_i}(x) \dot{x}_i(t) = \nabla V(x)^T f(x).$$

Theorem 1.3.8 (Lyapunov). *Suppose there is a function V with (i) $V(x^*) = 0$, (ii) V positive definite, and (iii) $\dot{V}$ negative semi-definite along the trajectories of (1.1). Then V is a Lyapunov function and x^* is stable.*

Remark 1.3.9. *If, moreover, $\dot{V}$ is negative definite, then x^* is asymptotically stable.*

In many models—including age-structured epidemic systems—the strict inequality $\dot{V} < 0$ fails: one only has $\dot{V} \leq 0$, with equality on a whole set. LaSalle’s principle recovers asymptotic stability in this situation.

Definition 1.3.10 (Invariant and largest invariant set). *A set $M \subseteq D$ is invariant for (1.1) if every trajectory starting in M remains in M for all $t \in \mathbb{R}$, and positively invariant if this holds for all $t \geq 0$. Given $E \subseteq D$, the largest invariant set contained in E is the union of all complete trajectories lying entirely in E (equivalently: discard from E every point whose trajectory eventually leaves E).*

Theorem 1.3.11 (LaSalle’s invariance principle). *Let $\Omega \subseteq D$ be a compact positively invariant set and $V \in C^1(\Omega, \mathbb{R})$ with $\dot{V}(x) \leq 0$ on Ω . Set $E = \{x \in \Omega : \dot{V}(x) = 0\}$ and let M be the largest invariant set in E . Then every solution starting in Ω approaches M : $\text{dist}(x(t), M) \rightarrow 0$ as $t \rightarrow \infty$.*

Remark 1.3.12 (LaSalle in infinite dimensions). *For the age-structured model the state space is infinite dimensional, so the above principle applies only after one verifies that the bounded orbits are precompact (i.e. the semiflow is asymptotically smooth). Under the boundedness established in the well-posedness chapter this holds, and the infinite-dimensional version of LaSalle’s principle yields convergence to the largest invariant set contained in $\{\dot{V} = 0\}$.*

1.4 Elements of Optimal Control

Finite-dimensional optimization problems read $\inf_{u \in U} \Phi(u)$ with $\Phi : U \rightarrow \mathbb{R}$ and U a subset of a Euclidean space, whereas a calculus-of-variations problem minimizes a functional J over an infinite-dimensional set,

$$\inf_{u \in \mathcal{U}} J[u], \quad J : \mathcal{U} \rightarrow \mathbb{R}.$$

A frequent instance is the integral functional $J[x] = \int_a^b L(u, x(u), x'(u)) du$, where L is the *Lagrangian*.

Definition 1.4.1 (Local and global minima). *Let X be a normed space, $K \subset X$, and $J : K \rightarrow \mathbb{R}$. A point $u \in K$ is a local minimum of J on K if there is $\delta > 0$ such that $\|v - u\| < \delta$, $v \in K$, implies $J(v) \geq J(u)$; it is a global minimum if $J(v) \geq J(u)$ for all $v \in K$.*

Definition 1.4.2 (Infimum and minimizing sequence). *The infimum $\inf_{v \in K} J(v)$ is the greatest lower bound of the values of J on K (equal to $-\infty$ if J is unbounded below, and to $+\infty$ by convention if $K = \emptyset$). A sequence $(u_n) \subset K$ is a minimizing sequence for J on K if $\lim_{n \rightarrow \infty} J(u_n) = \inf_{v \in K} J(v)$. By the definition of the infimum, at least one minimizing sequence always exists; note that this says nothing about convergence of (u_n) itself.*

Definition 1.4.3 (Gâteaux derivative). *A map $F : \Omega \subset X \rightarrow Y$ is Gâteaux differentiable at $u \in \Omega$ if there exists $DF(u) \in \mathcal{L}(X, Y)$ such that*

$$DF(u)v = \lim_{\varepsilon \rightarrow 0} \frac{F(u + \varepsilon v) - F(u)}{\varepsilon}, \quad \forall v \in X.$$

For a real functional J we also write $J'(u)(v) := DJ(u)v$.

Theorem 1.4.4 (First-order necessary condition on a convex set). *Let X be a normed space, $\mathcal{U} \subset X$ convex, and $J : \mathcal{U} \rightarrow \mathbb{R}$ Gâteaux differentiable. If $u^* \in \mathcal{U}$ minimizes J over $\mathcal{U}$, then*

$$J'(u^*)(u - u^*) \geq 0, \quad \forall u \in \mathcal{U}.$$

In $\mathbb{R}^n$ this is $\langle \nabla f(x^*), y - x^* \rangle \geq 0$ for all $y \in \Omega$.

Remark 1.4.5. *The direct method of the calculus of variations combines these tools as follows: a minimizing sequence in a bounded, convex, closed admissible set is weakly compact (Theorems 1.1.23 and 1.1.24); the associated states are uniformly bounded and equicontinuous, hence uniformly convergent along a subsequence (Theorem 1.1.22); and weak lower semicontinuity of the cost (Theorem 1.1.25) passes the limit through the functional, yielding the existence of a minimizer.*

Stability Analysis of the Age-Structured SEIR Model

In this chapter, we study the main stability properties of the proposed age-structured SEIR epidemic model, which describes the transmission dynamics of an infectious disease using partial differential equations and age-dependent epidemiological parameters. We begin by formulating the model and presenting the main biological assumptions, then we establish the positivity and boundedness of solutions and prove the existence and uniqueness of global solution in order to ensure the mathematical and biological relevance of the system. Next, we derive the disease-free equilibrium and compute the basic reproduction number $\mathcal{R}_0$, which represents the epidemic threshold. Finally, we investigate the local and global stability of the disease-free equilibrium according to the values of $\mathcal{R}_0$.

2.1 Model Formulation

We consider an age-structured SEIR epidemic model describing the transmission dynamics of TB infectious disease. The total population is divided into four epidemiological compartments: susceptible individuals, exposed individuals, infectious individuals, and recovered individuals. The susceptible population at time t is denoted by $S(t)$. The latent and infectious populations are structured with respect to age variables. More precisely, $e(t, a)$ denotes the density of latency individuals having latency-age a , whereas $i(t, b)$ denotes the density of infectious individuals having infection age b . Finally, $R(t)$ represents the number of recovered individuals at time t . In order to describe the dynamic of the TB infectious in this work, we assume that our model satisfies the following biological assumptions:

The disease transmission process depends on the infection age through the transmission function rate $\beta(b)$. Therefore, the incidence function rate is defined by

$$S(t)M(t), \quad M(t) = \int_0^\infty \beta(b) i(t, b) db,$$

where $M(t)$ represents the global infection pressure generated by all infectious individuals at time t .

Moreover, new susceptible individuals enter the population at a constant recruitment rate Π , all individuals experience natural mortality at rate μ , latent individuals progress toward the infectious class at rate $\varphi(a)$, infectious individuals recover at rate $\psi(b)$, recovered individuals may relapse into the infectious class at rate δ , a proportion $p \in [0, 1)$ of newly infected individuals enters directly into the infectious class, while the remaining proportion enters the latent class. Finally, under the previous assumptions, the epidemic dynamics are governed by the following system:

$$\left\{ \begin{array}{l} \frac{dS(t)}{dt} = \Pi - \mu S(t) - M(t)S(t), \\ \frac{\partial e(t, a)}{\partial t} + \frac{\partial e(t, a)}{\partial a} = -(\mu + \varphi(a)) e(t, a), \\ \frac{\partial i(t, b)}{\partial t} + \frac{\partial i(t, b)}{\partial b} = -(\mu + \psi(b)) i(t, b), \\ \frac{dR(t)}{dt} = \int_0^\infty \psi(b) i(t, b) db - (\mu + \delta)R(t). \end{array} \right. \quad (2.1)$$

The associated boundary conditions are given by

$$\left\{ \begin{array}{l} e(t, 0) = (1 - p) M(t) S(t), \\ i(t, 0) = p M(t) S(t) + \int_0^\infty \varphi(a) e(t, a) da + \delta R(t). \end{array} \right. \quad (2.2)$$

The initial conditions are

$$S(0) = S_0, \quad e(0, a) = e_0(a), \quad i(0, b) = i_0(b), \quad R(0) = R_0. \quad (2.3)$$

Assumption 1. *Throughout this chapter, we assume the following hypotheses:*

- (H1) *The model parameters satisfy: $\Pi > 0$, $\mu > 0$, $\delta \geq 0$, $0 \leq p < 1$.*
- (H2) *The transmission, progression and recovery function rates satisfy: $\beta, \varphi, \psi \in L_+^\infty(0, \infty)$.*
- (H3) *The initial conditions are nonnegative and satisfy:*

$$S_0 \geq 0, \quad R_0 \geq 0, \quad e_0, i_0 \in L_+^1(0, \infty).$$

2.2 Well-posedness of solution

This section focuses on the existence, uniqueness, positivity, and boundedness of solutions to the proposed age-structured epidemic model (2.1)-(2.3). To this end, we employ the integrated semigroup approach. We begin by introducing the Banach space $\widehat{X} = \mathbb{R} \times L^1(0, \infty)$, equipped with the norm

$$\left\| \begin{pmatrix} \phi_1 \\ \phi_2 \end{pmatrix} \right\|_{\widehat{X}} = |\phi_1| + \|\phi_2\|_{L^1(0, \infty)}.$$

For the latent and infectious classes, we define the linear operators

$$A_e : D(A_e) \subset \widehat{X} \rightarrow \widehat{X}, \quad A_i : D(A_i) \subset \widehat{X} \rightarrow \widehat{X}$$

by

$$A_e \begin{pmatrix} 0 \\ f \end{pmatrix} = \begin{pmatrix} -f(0) \\ -f'(a) - (\mu + \varphi(a))f(a) \end{pmatrix},$$

and

$$A_i \begin{pmatrix} 0 \\ g \end{pmatrix} = \begin{pmatrix} -g(0) \\ -g'(b) - (\mu + \psi(b))g(b) \end{pmatrix},$$

with $D(A_e) = D(A_i) = \{0\} \times W^{1,1}(0, \infty)$. Next, for $\lambda \in \rho(A_e)$, where $\rho(A_e)$ denotes the resolvent set of A_e , let

$$(\lambda I - A_e)^{-1} \begin{pmatrix} w_1 \\ w_2 \end{pmatrix} = \begin{pmatrix} 0 \\ w \end{pmatrix}, \quad \begin{pmatrix} w_1 \\ w_2 \end{pmatrix} \in \widehat{X}.$$

Then, we have $\begin{pmatrix} 0 \\ w \end{pmatrix} \in D(A_e)$ and $(\lambda I - A_e) \begin{pmatrix} 0 \\ w \end{pmatrix} = \begin{pmatrix} w_1 \\ w_2 \end{pmatrix}$.

By the definition of A_e , this is equivalent to

$$\lambda \begin{pmatrix} 0 \\ w \end{pmatrix} - \begin{pmatrix} -w(0) \\ -w'(a) - (\mu + \varphi(a))w(a) \end{pmatrix} = \begin{pmatrix} w_1 \\ w_2 \end{pmatrix}.$$

That is,

$$\begin{pmatrix} w(0) \\ \lambda w + w'(a) + (\mu + \varphi(a))w(a) \end{pmatrix} = \begin{pmatrix} w_1 \\ w_2 \end{pmatrix}.$$

Hence,

$$w(0) = w_1, \quad w'(a) + (\lambda + \mu + \varphi(a))w(a) = w_2(a).$$

Therefore, we can write

$$w(a) = w_1 e^{-(\lambda + \mu)a} e^{-\int_0^a \varphi(s) ds} + \int_0^a e^{-(\lambda + \mu)(a-s)} e^{-\int_s^a \varphi(\tau) d\tau} w_2(s) ds. \quad (2.4)$$

Similarly, for $\lambda \in \rho(A_i)$, let

$$(\lambda I - A_i)^{-1} \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} = \begin{pmatrix} 0 \\ v \end{pmatrix}, \quad \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} \in \widehat{X}.$$

Then $\begin{pmatrix} 0 \\ v \end{pmatrix} \in D(A_i)$ and

$$v(b) = v_1 e^{-(\lambda+\mu)b} e^{-\int_0^b \psi(s) ds} + \int_0^b e^{-(\lambda+\mu)(b-s)} e^{-\int_s^b \psi(\tau) d\tau} v_2(s) ds. \quad (2.5)$$

Now define $\widehat{e}(t) = \begin{pmatrix} 0 \\ e(t, \cdot) \end{pmatrix}$, $\widehat{i}(t) = \begin{pmatrix} 0 \\ i(t, \cdot) \end{pmatrix}$.

Then the system can be written in the form

$$\begin{cases} \frac{dS}{dt} = -\mu S + F_1(S, \widehat{e}, \widehat{i}, R), \\ \frac{d\widehat{e}}{dt} = A_e \widehat{e} + F_2(S, \widehat{e}, \widehat{i}, R), \\ \frac{d\widehat{i}}{dt} = A_i \widehat{i} + F_3(S, \widehat{e}, \widehat{i}, R), \\ \frac{dR}{dt} = -(\mu + \delta)R + F_4(S, \widehat{e}, \widehat{i}, R), \end{cases} \quad (2.6)$$

where

$$\begin{cases} F_1(S, \widehat{e}, \widehat{i}, R) = \Pi - SM, \\ F_2(S, \widehat{e}, \widehat{i}, R) = \begin{pmatrix} (1-p)SM \\ 0 \end{pmatrix}, \\ F_3(S, \widehat{e}, \widehat{i}, R) = \begin{pmatrix} pSM + \int_0^\infty \varphi(a)e(a) da + \delta R \\ 0 \end{pmatrix}, \\ F_4(S, \widehat{e}, \widehat{i}, R) = \int_0^\infty \psi(b)i(b) db. \end{cases} \quad (2.7)$$

Now, let us introduce $X = \mathbb{R} \times \widehat{X} \times \widehat{X} \times \mathbb{R}$,

$$X_+ = \mathbb{R}_+ \times (\mathbb{R}_+ \times L_+^1(0, \infty)) \times (\mathbb{R}_+ \times L_+^1(0, \infty)) \times \mathbb{R}_+,$$

$$X_0 = \mathbb{R} \times (\{0\} \times L^1(0, \infty)) \times (\{0\} \times L^1(0, \infty)) \times \mathbb{R},$$

and $X_{0+} = X_0 \cap X_+$.

For

$$u = \begin{pmatrix} S \\ \begin{pmatrix} 0 \\ e \end{pmatrix} \\ \begin{pmatrix} 0 \\ i \end{pmatrix} \\ R \end{pmatrix} \in X_0,$$

we use the norm $\|u\|_X = |S| + \|e\|_{L^1(0, \infty)} + \|i\|_{L^1(0, \infty)} + |R|$.

Moreover, we define the linear operator $A : D(A) \subset X \rightarrow X$

by

$$A \begin{pmatrix} S \\ \begin{pmatrix} 0 \\ e \end{pmatrix} \\ \begin{pmatrix} 0 \\ i \end{pmatrix} \\ R \end{pmatrix} = \begin{pmatrix} -\mu S \\ A_e \begin{pmatrix} 0 \\ e \end{pmatrix} \\ A_i \begin{pmatrix} 0 \\ i \end{pmatrix} \\ -(\mu + \delta)R \end{pmatrix},$$

with $D(A) = \mathbb{R} \times D(A_e) \times D(A_i) \times \mathbb{R}$.

Define also the nonlinear map $F : X_0 \rightarrow X$

by

$$F \begin{pmatrix} S \\ \binom{0}{e} \\ \binom{0}{i} \\ R \end{pmatrix} = \begin{pmatrix} F_1(S, \widehat{e}, \widehat{i}, R) \\ F_2(S, \widehat{e}, \widehat{i}, R) \\ F_3(S, \widehat{e}, \widehat{i}, R) \\ F_4(S, \widehat{e}, \widehat{i}, R) \end{pmatrix}.$$

Hence, the system can be written as

$$\begin{cases} \frac{du}{dt}(t) = Au(t) + F(u(t)), & t \geq 0, \\ u(0) = u_0 \in X_0, \end{cases} \quad (2.8)$$

where $u(t) = \left(S(t), \widehat{e}(t), \widehat{i}(t), R(t) \right)^T$ and $u_0 = \left(S_0, \binom{0}{e_0}, \binom{0}{i_0}, R_0 \right)^T$.

We are now in a position to prove the following result.

Proposition 2.2.1. *Assume that the assumptions of the model hold. Then, for every $u_0 \in X_{0+}$, there exist $t_{\max} \in (0, \infty]$ and a unique continuous map $u \in C([0, t_{\max}), X_{0+})$ which is an integrated solution of problem (2.8), that is,*

$$\int_0^t u(s) ds \in D(A), \quad \forall t \in [0, t_{\max}),$$

and

$$u(t) = u_0 + A \int_0^t u(s) ds + \int_0^t F(u(s)) ds, \quad \forall t \in [0, t_{\max}).$$

Proof. We divide the proof into three steps:

- Assume that $\lambda \in \mathbb{C}, \operatorname{Re}(\lambda) > -\mu$. Then, by using (2.4), we could obtain

$$|w(a)| \leq |w_1| e^{-(\operatorname{Re}(\lambda) + \mu)a} + \int_0^a e^{-(\operatorname{Re}(\lambda) + \mu)(a-s)} |w_2(s)| ds.$$

Thus,

$$\|w\|_{L^1} \leq |w_1| \int_0^\infty e^{-(\operatorname{Re}(\lambda) + \mu)a} da + \int_0^\infty \int_0^a e^{-(\operatorname{Re}(\lambda) + \mu)(a-s)} |w_2(s)| ds da.$$

Therefore,

$$\|w\|_{L^1} \leq \frac{1}{\operatorname{Re}(\lambda) + \mu} (|w_1| + \|w_2\|_{L^1}). \quad (2.9)$$

Hence,

$$\left\| (\lambda I - A_e)^{-1} \begin{pmatrix} w_1 \\ w_2 \end{pmatrix} \right\|_{\widehat{X}} \leq \frac{1}{\operatorname{Re}(\lambda) + \mu} \left\| \begin{pmatrix} w_1 \\ w_2 \end{pmatrix} \right\|_{\widehat{X}}, \quad (2.10)$$

and therefore

$$\|(\lambda I - A_e)^{-1}\|_{\mathcal{L}(\widehat{X})} \leq \frac{1}{\operatorname{Re}(\lambda) + \mu}. \quad (2.11)$$

Exactly the same argument gives

$$\|(\lambda I - A_i)^{-1}\|_{\mathcal{L}(\widehat{X})} \leq \frac{1}{\operatorname{Re}(\lambda) + \mu}. \quad (2.12)$$

Now, since A is block diagonal, we have

$$(\lambda I - A)^{-1} = \begin{pmatrix} (\lambda + \mu)^{-1} & 0 & 0 & 0 \\ 0 & (\lambda I - A_e)^{-1} & 0 & 0 \\ 0 & 0 & (\lambda I - A_i)^{-1} & 0 \\ 0 & 0 & 0 & (\lambda + \mu + \delta)^{-1} \end{pmatrix}.$$

Therefore, using (2.5) and (2.7), we obtain

$$\|(\lambda I - A)^{-1}\|_{\mathcal{L}(X)} \leq \frac{1}{\operatorname{Re}(\lambda) + \mu}, \quad \forall \lambda \in \mathbb{C}, \quad \operatorname{Re}(\lambda) > -\mu.$$

More generally, we get

$$\|(\lambda I - A)^{-n}\|_{\mathcal{L}(X)} \leq \frac{1}{(\operatorname{Re}(\lambda) + \mu)^n}, \quad \forall n \geq 1, \quad \operatorname{Re}(\lambda) > -\mu.$$

Thus, A is a Hille–Yosida operator on X .

• Let $u = (S, \binom{0}{e}, \binom{0}{i}, R)^T$ and $\tilde{u} = (\tilde{S}, \binom{0}{\tilde{e}}, \binom{0}{\tilde{i}}, \tilde{R})^T$ be two elements of X_0 . Assume that both belong to a bounded ball $B_X(0, C) \cap X_0$. Then, we will show that there exists $K_C > 0$ such that

$$\|F(u) - F(\tilde{u})\|_X \leq K_C \|u - \tilde{u}\|_X, \quad \forall u, \tilde{u} \in B_X(0, C) \cap X_0.$$

Recall that

$$M = \int_0^\infty \beta(b) i(b) db, \quad \widetilde{M} = \int_0^\infty \beta(b) \tilde{i}(b) db.$$

Then,

$$|M - \widetilde{M}| \leq \int_0^\infty \beta(b) |i(b) - \tilde{i}(b)| db \leq \|\beta\|_{L^\infty} \|i - \tilde{i}\|_{L^1}. \quad (2.13)$$

Similarly,

$$\left| \int_0^\infty \varphi(a) e(a) da - \int_0^\infty \varphi(a) \tilde{e}(a) da \right| \leq \|\varphi\|_{L^\infty} \|e - \tilde{e}\|_{L^1}, \quad (2.14)$$

and

$$\left| \int_0^\infty \psi(b) i(b) db - \int_0^\infty \psi(b) \tilde{i}(b) db \right| \leq \|\psi\|_{L^\infty} \|i - \tilde{i}\|_{L^1}. \quad (2.15)$$

Since $u, \tilde{u} \in B_X(0, C) \cap X_0$, we have $|S| \leq C$, $\|i\|_{L^1} \leq C$. Thus, $|\widetilde{M}| \leq \|\beta\|_{L^\infty} \|\tilde{i}\|_{L^1} \leq C \|\beta\|_{L^\infty}$. Moreover, $SM - \widetilde{S}\widetilde{M} = S(M - \widetilde{M}) + \widetilde{M}(S - \widetilde{S})$. Hence, by using (2.13), we obtain

$$|SM - \widetilde{S}\widetilde{M}| \leq C \|\beta\|_{L^\infty} (|S - \widetilde{S}| + \|i - \tilde{i}\|_{L^1}). \quad (2.16)$$

Now, for the first component, we get

$$F_1(u) - F_1(\tilde{u}) = -SM + \tilde{S}\tilde{M}.$$

Hence, by (2.16),

$$|F_1(u) - F_1(\tilde{u})| \leq C\|\beta\|_{L^\infty} \left(|S - \tilde{S}| + \|i - \tilde{i}\|_{L^1} \right). \quad (2.17)$$

For the second component, we have

$$F_2(u) - F_2(\tilde{u}) = \begin{pmatrix} (1-p)(SM - \tilde{S}\tilde{M}) \\ 0 \end{pmatrix}.$$

Thus,

$$\|F_2(u) - F_2(\tilde{u})\|_{\hat{X}} \leq |SM - \tilde{S}\tilde{M}|.$$

Therefore, by (2.16),

$$\|F_2(u) - F_2(\tilde{u})\|_{\hat{X}} \leq C\|\beta\|_{L^\infty} \left(|S - \tilde{S}| + \|i - \tilde{i}\|_{L^1} \right). \quad (2.18)$$

For the third component, it follows that

$$F_3(u) - F_3(\tilde{u}) = \begin{pmatrix} p(SM - \tilde{S}\tilde{M}) + \int_0^\infty \varphi(a)(e(a) - \tilde{e}(a)) da + \delta(R - \tilde{R}) \\ 0 \end{pmatrix}.$$

Hence, by (2.14) and (2.16),

$$\|F_3(u) - F_3(\tilde{u})\|_{\hat{X}} \leq C\|\beta\|_{L^\infty} \left(|S - \tilde{S}| + \|i - \tilde{i}\|_{L^1} \right) + \|\varphi\|_{L^\infty} \|e - \tilde{e}\|_{L^1} + \delta|R - \tilde{R}|. \quad (2.19)$$

For the fourth component, by (2.15), it results that

$$|F_4(u) - F_4(\tilde{u})| \leq \|\psi\|_{L^\infty} \|i - \tilde{i}\|_{L^1}. \quad (2.20)$$

Combining (2.17)–(2.20), we can choose

$$K_C = \max \{3C\|\beta\|_{L^\infty}, \|\varphi\|_{L^\infty}, 3C\|\beta\|_{L^\infty} + \|\psi\|_{L^\infty}, \delta\} > 0$$

such that

$$\|F(u) - F(\tilde{u})\|_X \leq K_C \left(|S - \tilde{S}| + \|e - \tilde{e}\|_{L^1} + \|i - \tilde{i}\|_{L^1} + |R - \tilde{R}| \right).$$

Therefore,

$$\|F(u) - F(\tilde{u})\|_X \leq K_C \|u - \tilde{u}\|_X. \quad (2.21)$$

This implies that F is locally Lipschitz continuous on X_0 . Since A is a Hille–Yosida operator on X and F is locally Lipschitz continuous on X_0 , the abstract Cauchy problem (2.8) admits a unique maximal integrated solution

$$u \in C([0, t_{\max}), X_0).$$

- To establish this step, we first prove that A is resolvent positive, that is,

$$(\lambda I - A)^{-1} X_+ \subset X_+, \quad \forall \lambda > -\mu. \quad (2.22)$$

Let

$$Y = \left(Y_S, \begin{pmatrix} Y_{e,1} \\ Y_{e,2} \end{pmatrix}, \begin{pmatrix} Y_{i,1} \\ Y_{i,2} \end{pmatrix}, Y_R \right)^T \in X_+.$$

Since A is block diagonal, the resolvent acts componentwise. The scalar components satisfy

$$(\lambda + \mu)^{-1} Y_S \geq 0, \quad (\lambda + \mu + \delta)^{-1} Y_R \geq 0,$$

for all $\lambda > -\mu$. For the exposed age-structured component, using (2.4), we obtain

$$w(a) = Y_{e,1} e^{-(\lambda+\mu)a} e^{-\int_0^a \varphi(s) ds} + \int_0^a e^{-(\lambda+\mu)(a-s)} e^{-\int_s^a \varphi(\tau) d\tau} Y_{e,2}(s) ds.$$

Since $Y_{e,1} \geq 0$, $Y_{e,2}(s) \geq 0$,

and all exponential factors are nonnegative, we get $w(a) \geq 0$, $\forall a \geq 0$. An identical argument using (2.5) yields

$$v(b) \geq 0, \quad \forall b \geq 0.$$

Hence, $(\lambda I - A)^{-1} Y \in X_+$, which establishes (2.22). Next, we show that for every $r > 0$, there exists $c \geq 0$ such that

$$F(u) + cu \in X_+, \quad \forall u \in B_X(0, r) \cap X_{0+}. \quad (2.23)$$

Let

$$u = \left(S, \begin{pmatrix} 0 \\ e \end{pmatrix}, \begin{pmatrix} 0 \\ i \end{pmatrix}, R \right)^T \in B_X(0, r) \cap X_{0+}.$$

Then $S \geq 0$, $e \geq 0$, $i \geq 0$, $R \geq 0$.

Moreover,

$$M = \int_0^\infty \beta(b) i(b) db \leq \|\beta\|_{L^\infty} \|i\|_{L^1} \leq r \|\beta\|_{L^\infty}.$$

Choose $c = r\|\beta\|_{L^\infty}$.

Then $c - M \geq 0$. Now,

$$F(u) + cu = \begin{pmatrix} \Pi + S(c - M) \\ \binom{(1-p)SM}{ce} \\ \left(pSM + \int_0^\infty \varphi(a)e(a) da + \delta R \right) \\ \int_0^\infty \psi(b)i(b) db + cR \end{pmatrix}.$$

All components of this vector are non negative. Hence,

$$F(u) + cu \in X_+.$$

Since conditions (2.22) and (2.23) are satisfied, it follows that

$$u(t) \in X_{0+}, \quad \forall t \in [0, t_{\max}).$$

This completes the proof.

Proposition 2.2.2. *For every $u_0 \in X_{0+}$, the corresponding solution is global and bounded. More precisely, $t_{\max} = +\infty$.*

Proof. From the previous proposition, the solution is nonnegative on its interval of existence. Define

$$N(t) = S(t) + \int_0^\infty e(t, a) da + \int_0^\infty i(t, b) db + R(t).$$

Differentiating $N(t)$ with respect to time and using the equations of system (2.1)-(2.3), we can obtain

$$\begin{aligned} \frac{d}{dt}N(t) &= \Pi - \mu S(t) - S(t)M(t) \\ &\quad + \int_0^\infty \left[-\frac{\partial e(t, a)}{\partial a} - (\mu + \varphi(a))e(t, a) \right] da \\ &\quad + \int_0^\infty \left[-\frac{\partial i(t, b)}{\partial b} - (\mu + \psi(b))i(t, b) \right] db \\ &\quad + \int_0^\infty \psi(b)i(t, b) db - (\mu + \delta)R(t). \end{aligned}$$

Integrating by parts, we use

$$\int_0^\infty -\frac{\partial e(t, a)}{\partial a} da = e(t, 0), \quad \int_0^\infty -\frac{\partial i(t, b)}{\partial b} db = i(t, 0).$$

Thus,

$$\begin{aligned} \frac{d}{dt}N(t) = & \Pi - \mu S(t) - S(t)M(t) + e(t, 0) + i(t, 0) \\ & - \mu \int_0^\infty e(t, a) da - \int_0^\infty \varphi(a)e(t, a) da \\ & - \mu \int_0^\infty i(t, b) db - \int_0^\infty \psi(b)i(t, b) db \\ & + \int_0^\infty \psi(b)i(t, b) db - \mu R(t) - \delta R(t). \end{aligned}$$

After straightforward simplification, we get

$$\frac{d}{dt}N(t) = \Pi - \mu \left(S(t) + \int_0^\infty e(t, a) da + \int_0^\infty i(t, b) db + R(t) \right).$$

Hence, $N'(t) = \Pi - \mu N(t)$, Therefore, by solving this differential equation it yields

$$N(t) = \frac{\Pi}{\mu} + \left(N(0) - \frac{\Pi}{\mu} \right) e^{-\mu t}.$$

Consequently,

$$N(t) \leq \max \left\{ N(0), \frac{\Pi}{\mu} \right\}, \quad t \geq 0.$$

Therefore, it yields

$$N(t) \leq \mathcal{D}, \quad \text{with } \max \left\{ N(0), \frac{\Pi}{\mu} \right\} = \mathcal{D}, \quad t \geq 0.$$

Since all components are nonnegative, it follows that

$$0 \leq S(t), \int_0^\infty e(t, a) da, \int_0^\infty i(t, b) db, R(t) \leq \mathcal{D}.$$

Therefore, the solution remains bounded on its interval of existence. If $t_{\max} < +\infty$, then the blow-up alternative implies

$$\|u(t)\|_X \rightarrow +\infty \quad \text{as } t \rightarrow t_{\max}.$$

However, since the solution is non negative,

$$\|u(t)\|_X = S(t) + \int_0^\infty e(t, a) da + \int_0^\infty i(t, b) db + R(t) = N(t),$$

and $N(t)$ is bounded. This contradiction shows that $t_{\max} = +\infty$. Thus, the solution exists globally and remains bounded for all $t \geq 0$.

2.3 Disease-Free Equilibrium and Basic Reproduction Number

In this section, we derive the disease-free equilibrium E^0 and the basic reproduction number $\mathcal{R}_0$, which characterizes the threshold dynamics of the disease.

The disease-free equilibrium corresponds to the absence of infection in the population, i.e.,

$$e = i = R = 0.$$

Setting the susceptible equation at equilibrium gives

$$0 = \Pi - \mu S^0,$$

and therefore

$$S^0 = \frac{\Pi}{\mu}.$$

Hence, the disease-free equilibrium E^0 of system (2.1)-(2.3) is given by

$$E^0 = \left(\frac{\Pi}{\mu}, 0, 0, 0 \right). \quad (2.24)$$

Now, before introducing the basic reproduction number $\mathcal{R}_0$, we define the survival probabilities in the latency and infectious classes as follows

$$\Psi_1(a) = e^{-\int_0^a (\mu + \varphi(\tau)) d\tau}, \quad \Psi_2(b) = e^{-\int_0^b (\mu + \psi(\tau)) d\tau}. \quad (2.25)$$

Moreover, by using these quantities, we define

$$\Omega_1 = \int_0^\infty \varphi(a) \Psi_1(a) da, \quad (2.26)$$

$$\Omega_2 = \int_0^\infty \psi(b) \Psi_2(b) db, \quad (2.27)$$

$$\Omega_3 = \int_0^\infty \beta(b) \Psi_2(b) db. \quad (2.28)$$

Here, Ω_1 denotes the probability that a latent individual becomes infectious, Ω_2 the probability of recovery, and Ω_3 the cumulative infectivity generated during the infectious period.

Furthermore, at the disease-free equilibrium E^0 , a newly infected individual becomes infectious either directly with probability p or after passing through the latent stage with probability $(1 - p)\Omega_1$. Hence, the effective probability of reaching the infectious class is $p + (1 - p)\Omega_1$. Therefore, the expected number of secondary infections generated by one infectious individual is then

$$\mathcal{R}_{01} = S^0 [p + (1 - p)\Omega_1] \Omega_3.$$

The model also accounts for relapse from the recovered class, yielding the additional contribution

$$\mathcal{R}_{02} = \frac{\delta}{\mu + \delta} \Omega_2.$$

Thus, the specific expression of the basic reproduction number $\mathcal{R}_0$ of system (2.1)-(2.3) is

$$\mathcal{R}_0 = \frac{\Pi}{\mu} [p + (1 - p)\Omega_1] \Omega_3 + \frac{\delta}{\mu + \delta} \Omega_2. \quad (2.29)$$

2.4 Local Stability of the Disease-Free Equilibrium

In this section, we investigate the local asymptotic stability of the disease-free equilibrium associated with system (2.1)-(2.3). The disease-free equilibrium is given by $E^0 = (S^0, 0, 0, 0)$.

The local behavior of the system around E^0 is determined through the spectral analysis of the linearized system.

Let $S(t) = S^0 + \tilde{S}(t)$, where $S^0 = \frac{\Pi}{\mu}$, and $e(t, a) = \tilde{e}(t, a)$, $i(t, b) = \tilde{i}(t, b)$, $R(t) = \tilde{R}(t)$.

Substituting into system (2.1)-(2.3), we obtain the linearized system:

$$\left\{ \begin{array}{l} \frac{d\tilde{S}(t)}{dt} = -\mu\tilde{S}(t) - S^0\tilde{M}(t), \quad \tilde{M}(t) = \int_0^\infty \beta(b)\tilde{i}(t, b) db, \\ \frac{\partial\tilde{e}(t, a)}{\partial t} + \frac{\partial\tilde{e}(t, a)}{\partial a} = -(\mu + \varphi(a))\tilde{e}(t, a), \\ \frac{\partial\tilde{i}(t, b)}{\partial t} + \frac{\partial\tilde{i}(t, b)}{\partial b} = -(\mu + \psi(b))\tilde{i}(t, b), \\ \frac{d\tilde{R}(t)}{dt} = \int_0^\infty \psi(b)\tilde{i}(t, b) db - (\mu + \delta)\tilde{R}(t). \end{array} \right. \quad (2.30)$$

The corresponding boundary conditions are

$$\left\{ \begin{array}{l} \tilde{e}(t, 0) = (1 - p)S^0\tilde{M}(t), \\ \tilde{i}(t, 0) = pS^0\tilde{M}(t) + \int_0^\infty \varphi(a)\tilde{e}(t, a) da + \delta\tilde{R}(t). \end{array} \right. \quad (2.31)$$

We now seek exponential solutions of the form

$$\tilde{S}(t) = x_1 e^{\lambda t}, \quad \tilde{e}(t, a) = x_2(a) e^{\lambda t}, \quad \tilde{i}(t, b) = x_3(b) e^{\lambda t}, \quad \tilde{R}(t) = x_4 e^{\lambda t}.$$

Substituting into the system (2.30)-(2.31) and ignoring the first equation for x_1 , we

get

$$\begin{cases} x_2'(a) = -(\lambda + \mu + \varphi(a))x_2(a), \\ x_3'(b) = -(\lambda + \mu + \psi(b))x_3(b), \\ \lambda x_4 = \int_0^\infty \psi(b)x_3(b) db - (\mu + \delta)x_4, \\ x_2(0) = (1-p)S^0 \int_0^\infty \beta(b)x_3(b) db, \\ x_3(0) = pS^0 \int_0^\infty \beta(b)x_3(b) db + \int_0^\infty \varphi(a)x_2(a) da + \delta x_4. \end{cases} \quad (2.32)$$

Solving the ODE part of system (2.32) gives

$$x_2(a) = x_2(0)e^{-\int_0^a (\lambda + \mu + \varphi(\tau)) d\tau},$$

and

$$x_3(b) = x_3(0)e^{-\int_0^b (\lambda + \mu + \psi(\tau)) d\tau}.$$

After a straightforward computation, the characteristic equation at the disease-free equilibrium E^0 of the linearized system (2.30)–(2.31) is obtained as follows:

$$1 = S^0 [p + (1-p)\Omega_1(\lambda)] \Omega_3(\lambda) + \frac{\delta}{\lambda + \mu + \delta} \Omega_2(\lambda), \quad (2.33)$$

where

$$\Omega_1(\lambda) = \int_0^\infty \varphi(a)e^{-\int_0^a (\lambda + \mu + \varphi(\tau)) d\tau} da, \quad (2.34)$$

$$\Omega_2(\lambda) = \int_0^\infty \psi(b)e^{-\int_0^b (\lambda + \mu + \psi(\tau)) d\tau} db, \quad (2.35)$$

$$\Omega_3(\lambda) = \int_0^\infty \beta(b)e^{-\int_0^b (\lambda + \mu + \psi(\tau)) d\tau} db. \quad (2.36)$$

Theorem 2.4.1. *The disease-free equilibrium E^0 is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

Proof. Let λ be an eigenvalue of the linearized system (2.30)–(2.31) and assume $\text{Re}(\lambda) \geq 0$. Then, we have

$$|\Omega_1(\lambda)| \leq \Omega_1, \quad |\Omega_2(\lambda)| \leq \Omega_2, \quad |\Omega_3(\lambda)| \leq \Omega_3, \quad \left| \frac{\delta}{\lambda + \mu + \delta} \right| \leq \frac{\delta}{\mu + \delta}.$$

Now, by taking the modulus in the characteristic equation (2.33) yields

$$1 \leq S^0 [p + (1-p)\Omega_1] \Omega_3 + \frac{\delta}{\mu + \delta} \Omega_2 = \mathcal{R}_0.$$

Thus, if $\mathcal{R}_0 < 1$, no eigenvalue can satisfy $\operatorname{Re}(\lambda) \geq 0$, and hence all eigenvalues lie in the left half-plane, proving local asymptotic stability of E^0 whenever $\mathcal{R}_0 < 1$.

Next assume $\mathcal{R}_0 > 1$. Define

$$\vartheta(\lambda) = S^0[p + (1-p)\Omega_1(\lambda)]\Omega_3(\lambda) + \frac{\delta}{\lambda + \mu + \delta}\Omega_2(\lambda).$$

The characteristic equation (2.33) reads $\vartheta(\lambda) = 1$. Since

$$\vartheta(0) = \mathcal{R}_0 > 1, \quad \vartheta(\lambda) \rightarrow 0 \text{ as } \lambda \rightarrow +\infty,$$

by continuity there exists $\lambda^* > 0$ such that $\vartheta(\lambda^*) = 1$. Hence the system (2.30)-(2.31) admits a positive real eigenvalue, implying instability of E^0 if $\mathcal{R}_0 > 1$.

2.5 Global Stability of the Disease-Free Equilibrium

We establish the global asymptotic stability of the disease-free equilibrium E^0 under the condition $\mathcal{R}_0 < 1$, using a Lyapunov functional and LaSalle's invariance principle.

Before proceeding, we introduce the function

$$g(x) = x - 1 - \ln x, \quad x > 0,$$

which satisfies $g(x) \geq 0$, with equality if and only if $x = 1$. We define the constants

$$\xi_1 = p + (1-p)\Omega_1, \quad \xi_2 = \frac{\delta}{\mu + \delta}, \quad \xi_3 = \frac{\xi_2}{\xi_1}.$$

We also introduce the age-dependent functions

$$\gamma_1(a) = \int_a^\infty \varphi(\tau) e^{-\int_a^\tau (\mu + \varphi(s)) ds} d\tau, \quad \gamma_2(b) = \int_b^\infty [\beta(\tau) + \xi_3 \psi(\tau)] e^{-\int_b^\tau (\mu + \psi(s)) ds} d\tau.$$

It follows that $\gamma_1(0) = \Omega_1$ and $\gamma_2(0) = \Omega_3 + \xi_3 \Omega_2$. Moreover, we have

$$\gamma_1'(a) = (\mu + \varphi(a))\gamma_1(a) - \varphi(a), \quad \gamma_2'(b) = (\mu + \psi(b))\gamma_2(b) - [\beta(b) + \xi_3 \psi(b)].$$

We now introduce the Lyapunov functional $V(t)$ as follows:

$$V(t) = V_1(t) + V_2(t) + V_3(t) + V_4(t),$$

where

$$\begin{aligned} V_1(t) &= S^0 g\left(\frac{S(t)}{S^0}\right), \\ V_2(t) &= \int_0^\infty \gamma_1(a) e(t, a) da, \\ V_3(t) &= \xi_1 S^0 \int_0^\infty \gamma_2(b) i(t, b) db, \\ V_4(t) &= \xi_2 S^0 R(t). \end{aligned}$$

Since $g(x) \geq 0$ and all state variables are non-negative, we have $V(t) \geq 0$.

Differentiating V_i along solutions of system (2.1)-(2.3) gives:

$$\begin{aligned}\frac{dV_1}{dt} &= -\mu \frac{(S - S^0)^2}{S} - S(t)M(t) + S^0 M(t), \\ \frac{dV_2}{dt} &= \Omega_1 e(t, 0) - \int_0^\infty \varphi(a) e(t, a) da, \\ \frac{dV_3}{dt} &= \xi_1 S^0 (\Omega_3 + \xi_3 \Omega_2) i(t, 0) - \xi_1 S^0 M(t) - \xi_1 \xi_3 S^0 \int_0^\infty \psi(b) i(t, b) db, \\ \frac{dV_4}{dt} &= \xi_2 S^0 \int_0^\infty \psi(b) i(t, b) db - \xi_2 S^0 (\mu + \delta) R(t).\end{aligned}$$

Using the definition of $M(t) = \int_0^\infty \beta(b) i(t, b) db$ together with the relations between the constants, all non-local terms cancel after straightforward algebraic simplification, leading to

$$\frac{dV}{dt} = -\mu \frac{(S - S^0)^2}{S} - (1 - \mathcal{R}_0) i(t, 0). \quad (2.37)$$

If $\mathcal{R}_0 < 1$, then $\frac{dV}{dt} \leq 0$. Moreover, $\frac{dV}{dt} = 0$ implies

$$S(t) = S^0, \quad i(t, 0) = 0,$$

which leads to

$$i(t, b) = 0, \quad e(t, a) = 0, \quad R(t) = 0.$$

Thus the largest invariant set contained in $\{\frac{dV}{dt} = 0\}$ is $\{E^0\}$. Therefore, by LaSalle's invariance principle, every solution converges to E^0 as $t \rightarrow \infty$. Hence, the disease-free equilibrium is globally asymptotically stable whenever $\mathcal{R}_0 < 1$.

Optimal Control System

Optimal control theory is a mathematical approach based on the calculus of variations that seeks to determine time-dependent intervention strategies capable of optimizing a prescribed objective. In epidemiological modelling, it provides a powerful tool for designing control policies that reduce disease burden while accounting for implementation costs. In this chapter, we apply optimal control techniques to identify effective intervention strategies for reducing the susceptible, latent, and infectious populations.

To formulate the control problem, we introduce two time-dependent control functions $u_1(t)$ and $u_2(t)$, with $t \in [0, T]$, into the age-structured model (2.1)-(2.3).

- The control $u_1(t)$ represents the vaccination effort applied to susceptible individuals. Vaccination moves susceptible individuals into the recovered class; consequently, the term $u_1(t)S(t)$ appears as a removal term in the susceptible equation and as a recruitment term in the recovered equation.

- The control $u_2(t)$ represents relapse-prevention effort. This intervention reduces the rate at which recovered individuals return to the infectious class. Since relapse occurs at rate δ , the factor $1 - u_2(t)$ scales this transition. Thus, $u_2(t) = 0$ corresponds to the absence of relapse control, while $u_2(t) = 1$ represents maximal suppression of relapse.

Therefore, the controlled system takes the following form:

$$\left\{ \begin{array}{l} \frac{dS(t)}{dt} = \Pi - \mu S(t) - S(t) \int_0^\infty \beta(b)i(t, b) db - u_1(t)S(t), \\ \frac{\partial e(t, a)}{\partial t} + \frac{\partial e(t, a)}{\partial a} = -(\mu + \varphi(a))e(t, a), \\ \frac{\partial i(t, b)}{\partial t} + \frac{\partial i(t, b)}{\partial b} = -(\mu + \psi(b))i(t, b), \\ \frac{dR(t)}{dt} = \int_0^\infty \psi(b)i(t, b) db - (\mu + \delta(1 - u_2(t)))R(t) + u_1(t)S(t). \end{array} \right. \quad (3.1)$$

$$\begin{cases} e(t, 0) = (1 - p)S(t) \int_0^\infty \beta(b)i(t, b) db, \\ i(t, 0) = pS(t) \int_0^\infty \beta(b)i(t, b) db + \int_0^\infty \varphi(a)e(t, a) da + \delta(1 - u_2(t))R(t). \end{cases}$$

The initial conditions are

$$S(0) = S_0, \quad e(0, a) = e_0(a), \quad i(0, b) = i_0(b), \quad R(0) = R_0. \quad (3.2)$$

For convenience, we define

$$E(t) = \int_0^\infty e(t, a) da, \quad I(t) = \int_0^\infty i(t, b) db. \quad (3.3)$$

The admissible control set is defined by

$$U = \left\{ (u_1, u_2) \in (L^\infty(0, T))^2 : 0 \leq u_1(t) \leq u_{1,\max}, \ 0 \leq u_2(t) \leq u_{2,\max}, \ t \in [0, T] \right\}. \quad (3.4)$$

Here, $u_{1,\max}$ and $u_{2,\max}$ denote the maximal admissible levels of vaccination and relapse-prevention effort, respectively, with

$$0 < u_{1,\max} \leq 1, \quad 0 < u_{2,\max} \leq 1.$$

The objective is to reduce the susceptible, latent, and infectious populations over the intervention period $[0, T]$, while minimizing the implementation costs of vaccination and relapse-prevention strategies. Accordingly, we define the objective functional by

$$J(u_1, u_2) = \int_0^T \left[S(t) + E(t) + I(t) + \frac{B_1}{2} u_1^2(t) + \frac{B_2}{2} u_2^2(t) \right] dt, \quad (3.5)$$

where $B_1 > 0$ and $B_2 > 0$ are weight constants associated with the costs of the two control strategies. Thus, the optimal control problem consists of finding a pair of admissible controls $(u_1^*, u_2^*) \in U$ such that

$$J(u_1^*, u_2^*) = \inf_{(u_1, u_2) \in U} J(u_1, u_2), \quad (3.6)$$

subject to the controlled state system (3.1)-(3.2).

We establish the existence of an optimal control pair associated with the control problem defined in Sections (3.1)-(3.2).

3.1 Existence and uniqueness of an optimal control

Throughout, the admissible control set is

$$\mathcal{U}_a = \left\{ (u_1, u_2) \in L^\infty(0, T)^2 : 0 \leq u_i(t) \leq u_{i,\max} \text{ a.e. on } [0, T], i = 1, 2 \right\},$$

and the objective functional is split as

$$J(u_1, u_2) = J_s + J_c, \quad J_s = \int_0^T (S + E + I) dt, \quad J_c = \int_0^T \left(\frac{B_1}{2} u_1^2 + \frac{B_2}{2} u_2^2 \right) dt.$$

We write $\|\beta\|_\infty, \|\varphi\|_\infty, \|\psi\|_\infty$ for the L^∞ norms of the (nonnegative) kernels and $M(t) = \int_0^\infty \beta(b)i(t, b) db$ for the force of infection.

Lemma 3.1.1 (Convexity and weak lower semicontinuity of J_c). *The control cost J_c is convex on $\mathcal{U}_a$ and weakly lower semicontinuous on $L^2(0, T)^2$.*

Proof. The map $x \mapsto x^2$ is convex, so for $\lambda \in [0, 1]$ and a.e. t , $(\lambda u_i + (1 - \lambda)v_i)^2 \leq \lambda u_i^2 + (1 - \lambda)v_i^2$. Multiplying by $B_i/2 > 0$ and integrating gives $J_c(\lambda u + (1 - \lambda)v) \leq \lambda J_c(u) + (1 - \lambda)J_c(v)$, i.e. convexity. Since J_c is also strongly continuous on the Hilbert space $L^2(0, T)^2$, and a convex strongly continuous functional on a Hilbert space is weakly lower semicontinuous, the claim follows.

Theorem 3.1.2 (Existence of an optimal control). *There exists an optimal control pair $(u_1^*, u_2^*) \in \mathcal{U}$ such that*

$$J(u_1^*, u_2^*) = \min_{(u_1, u_2) \in \mathcal{U}_a} J(u_1, u_2).$$

Proof. The admissible control set $\mathcal{U}_a$ is nonempty, convex, and bounded in $L^2(0, T)^2$. Since it is also strongly closed, it is weakly closed.

Define

$$m = \inf_{(u_1, u_2) \in \mathcal{U}_a} J(u_1, u_2) \geq 0.$$

Let $\{(u_1^n, u_2^n)\}_{n \geq 1} \subset \mathcal{U}_a$ be a minimizing sequence satisfying

$$J(u_1^n, u_2^n) \longrightarrow m \quad \text{as } n \rightarrow \infty.$$

Because $\mathcal{U}_a$ is bounded in the reflexive Banach space $L^2(0, T)^2$, the Banach–Alaoglu theorem ensures the existence of a subsequence, still denoted by $\{(u_1^n, u_2^n)\}$, and controls $(u_1^*, u_2^*) \in L^2(0, T)^2$ such that

$$u_i^n \rightharpoonup u_i^* \quad \text{weakly in } L^2(0, T), \quad i = 1, 2.$$

Since $\mathcal{U}_a$ is weakly closed, it follows that $(u_1^*, u_2^*) \in \mathcal{U}_a$.

Let (S_n, E_n, I_n, R_n) denote the state variables associated with (u_1^n, u_2^n) . By Proposition 2.2.2, the sequences $\{S_n\}$, $\{E_n\}$, $\{I_n\}$, and $\{R_n\}$ are uniformly bounded and uniformly equicontinuous on $[0, T]$. Therefore, by the Arzelà–Ascoli theorem, there exists a further subsequence such that

$$S_n \rightarrow S^*, \quad E_n \rightarrow E^*, \quad I_n \rightarrow I^*, \quad R_n \rightarrow R^*$$

uniformly on $[0, T]$.

Passing to the limit in the integral formulation of the state system, and using the uniform convergence of the state variables together with the weak convergence of the controls, we conclude that (S^*, E^*, I^*, R^*) is precisely the state associated with the control pair (u_1^*, u_2^*) .

Finally, the uniform convergence of the state variables yields

$$J_s(u_1^n, u_2^n) \rightarrow J_s(u_1^*, u_2^*).$$

Moreover, by Lemma 3.1.1, the control cost functional is weakly lower semicontinuous, so that

$$J_c(u_1^*, u_2^*) \leq \liminf_{n \rightarrow \infty} J_c(u_1^n, u_2^n).$$

Consequently,

$$J(u_1^*, u_2^*) \leq \liminf_{n \rightarrow \infty} J(u_1^n, u_2^n) = m.$$

Since $(u_1^*, u_2^*) \in \mathcal{U}_a$, by definition of m we also have

$$m \leq J(u_1^*, u_2^*).$$

Therefore,

$$J(u_1^*, u_2^*) = m,$$

which proves that (u_1^*, u_2^*) is an optimal control pair.

To derive the necessary optimality conditions, we use the Gâteaux derivative. Let $u_1^\varepsilon(t) = u_1(t) + \varepsilon v_1(t)$, and $u_2^\varepsilon(t) = u_2(t) + \varepsilon v_2(t)$, where v_1 and v_2 are admissible variation functions and $0 < \varepsilon < 1$ and let $(S^\varepsilon, e^\varepsilon, i^\varepsilon, R^\varepsilon)$ be the solution of (3.1)–(3.2) corresponding to $(u_1^\varepsilon, u_2^\varepsilon)$. Define the variations

$$\bar{S}(t) = \lim_{\varepsilon \rightarrow 0} \frac{S^\varepsilon(t) - S(t)}{\varepsilon}, \quad \bar{e}(t, a) = \lim_{\varepsilon \rightarrow 0} \frac{e^\varepsilon(t, a) - e(t, a)}{\varepsilon},$$

$$\bar{i}(t, b) = \lim_{\varepsilon \rightarrow 0} \frac{i^\varepsilon(t, b) - i(t, b)}{\varepsilon}, \quad \bar{R}(t) = \lim_{\varepsilon \rightarrow 0} \frac{R^\varepsilon(t) - R(t)}{\varepsilon}.$$

Then the linearized system of (3.1)–(3.2) is given by

$$\left\{ \begin{array}{l} \frac{d\bar{S}(t)}{dt} = -(\mu + u_1(t))\bar{S}(t) - S(t)v_1(t) - \bar{S}(t)M(t) - S(t)\bar{M}(t), \\ \frac{\partial \bar{e}(t, a)}{\partial t} + \frac{\partial \bar{e}(t, a)}{\partial a} = -(\mu + \varphi(a))\bar{e}(t, a), \\ \frac{\partial \bar{i}(t, b)}{\partial t} + \frac{\partial \bar{i}(t, b)}{\partial b} = -(\mu + \psi(b))\bar{i}(t, b), \\ \frac{d\bar{R}(t)}{dt} = \int_0^\infty \psi(b)\bar{i}(t, b) db - (\mu + \delta(1 - u_2(t)))\bar{R}(t) \\ \quad + \delta R(t)v_2(t) + u_1(t)\bar{S}(t) + S(t)v_1(t), \end{array} \right. \quad (3.7)$$

with boundary conditions

$$\left\{ \begin{array}{l} \bar{e}(t, 0) = (1 - p) [\bar{S}(t)M(t) + S(t)\bar{M}(t)], \\ \bar{i}(t, 0) = p [\bar{S}(t)M(t) + S(t)\bar{M}(t)] + \int_0^\infty \varphi(a)\bar{e}(t, a) da \\ \quad + \delta(1 - u_2(t))\bar{R}(t) - \delta R(t)v_2(t), \end{array} \right. \quad (3.8)$$

where

$$\bar{M}(t) = \int_0^\infty \beta(b)\bar{i}(t, b)db.$$

The Gâteaux derivative of the objective functional $J(u_1, u_2)$ in the direction (v_1, v_2) is given by the following expression:

$$J'_{(v_1, v_2)}(u_1, u_2) = \int_0^T [\bar{S}(t) + \bar{E}(t) + \bar{I}(t) + B_1 u_1(t)v_1(t) + B_2 u_2(t)v_2(t)] dt, \quad (3.9)$$

where

$$\bar{E}(t) = \int_0^\infty \bar{e}(t, a) da, \quad \bar{I}(t) = \int_0^\infty \bar{i}(t, b) db.$$

Furthermore, let us introduce the adjoint variables $\lambda_1(t)$, $\lambda_2(t, a)$, $\lambda_3(t, b)$, $\lambda_4(t)$ associated respectively with $S(t)$, $e(t, a)$, $i(t, b)$, and $R(t)$, respectively. Then, by using integration by parts and the transversality conditions, the adjoint system of (3.1)–(3.2) is obtained as

$$\left\{ \begin{array}{l} \frac{d\lambda_1(t)}{dt} = (\mu + u_1(t))\lambda_1(t) + [\lambda_1(t) - (1-p)\lambda_2(t,0) - p\lambda_3(t,0)]M(t) \\ \quad - u_1(t)\lambda_4(t) - 1, \\ \frac{\partial\lambda_2(t,a)}{\partial t} + \frac{\partial\lambda_2(t,a)}{\partial a} = (\mu + \varphi(a))\lambda_2(t,a) - \varphi(a)\lambda_3(t,0) - 1, \\ \frac{\partial\lambda_3(t,b)}{\partial t} + \frac{\partial\lambda_3(t,b)}{\partial b} = (\mu + \psi(b))\lambda_3(t,b) \\ \quad + [\lambda_1(t) - (1-p)\lambda_2(t,0) - p\lambda_3(t,0)]\beta(b)S(t) \\ \quad - \psi(b)\lambda_4(t) - 1, \\ \frac{d\lambda_4(t)}{dt} = (\mu + \delta(1 - u_2(t)))\lambda_4(t) - \delta(1 - u_2(t))\lambda_3(t,0). \end{array} \right. \quad (3.10)$$

The transversality conditions are

$$\lambda_1(T) = 0, \quad \lambda_2(T, a) = 0, \quad \lambda_2(t, \infty) = 0, \quad (3.11)$$

and

$$\lambda_3(T, b) = 0, \quad \lambda_3(t, \infty) = 0, \quad \lambda_4(T) = 0. \quad (3.12)$$

Using the adjoint system (3.10)-(3.12), the Gâteaux derivative (3.9) reduces to

$$\begin{aligned} J'_{(v_1, v_2)}(u_1, u_2) &= \int_0^T v_1(t) \left[B_1 u_1(t) + (\lambda_4(t) - \lambda_1(t))S(t) \right] dt \\ &\quad + \int_0^T v_2(t) \left[B_2 u_2(t) + \delta(\lambda_4(t) - \lambda_3(t, 0))R(t) \right] dt. \end{aligned} \quad (3.13)$$

Theorem 3.1.3. *Let $(u_1^*, u_2^*) \in U$ be an optimal control pair minimizing (3.5), and let (S^*, e^*, i^*, R^*) and $(\lambda_1, \lambda_2, \lambda_3, \lambda_4)$ be the corresponding state and adjoint variables. Then the optimal controls are characterized by*

$$u_1^*(t) = \min \left\{ u_{1,\max}, \max \left\{ 0, \frac{(\lambda_1(t) - \lambda_4(t))S^*(t)}{B_1} \right\} \right\}, \quad (3.14)$$

and

$$u_2^*(t) = \min \left\{ u_{2,\max}, \max \left\{ 0, \frac{\delta(\lambda_3(t, 0) - \lambda_4(t))R^*(t)}{B_2} \right\} \right\}. \quad (3.15)$$

Proof. Using the adjoint system (3.10), the Gâteaux derivative reduces to (3.13). Since (u_1^*, u_2^*) is optimal, the variational inequality

$$J'(u_1^*, u_2^*)(u_1 - u_1^*, u_2 - u_2^*) \geq 0$$

holds for all $(u_1, u_2) \in U$.

Hence, the pointwise optimality conditions yield

$$B_1 u_1^*(t) + (\lambda_4(t) - \lambda_1(t))S^*(t) = 0,$$

and

$$B_2 u_2^*(t) + \delta(\lambda_4(t) - \lambda_3(t, 0))R^*(t) = 0.$$

Therefore, the unconstrained controls are

$$u_1(t) = \frac{(\lambda_1(t) - \lambda_4(t))S^*(t)}{B_1},$$

and

$$u_2(t) = \frac{\delta(\lambda_3(t, 0) - \lambda_4(t))R^*(t)}{B_2}.$$

Projecting these expressions onto the admissible intervals

$$0 \leq u_1(t) \leq u_{1,\max}, \quad 0 \leq u_2(t) \leq u_{2,\max},$$

we obtain (3.14) and (3.15). This completes the proof.

3.2 Numerical simulations and discussion

In this section we illustrate the theoretical results obtained above by solving the optimality system numerically and discussing the epidemiological meaning of the optimal strategies. All state variables are expressed as fractions of a reference population, so that multiplying any value by the population size gives an absolute head count; for a reference population of 100,000 individuals the quantities below translate directly into numbers of people (for instance $I(0) = 0.0038$ corresponds to 381 infectious individuals). The baseline parameter values are listed in Table 3.1 and the initial conditions in Table 3.2.

$$\beta(b) = \beta_1 e^{-\frac{1}{2}(b-2)^2} \left(1 + 0.35 \sin \frac{\pi b}{2} \right), \quad \varphi(a) = \varphi_1 e^{-\varphi_2 a}, \quad \psi(b) = \psi_1 (1 - e^{-\psi_2 b})$$

In the following We compare four scenarios: (i) *no control* ($u_1 \equiv u_2 \equiv 0$); (ii) *relapse prevention only* ($u_1 \equiv 0$, u_2 optimal); (iii) *vaccination only* (u_1 optimal, $u_2 \equiv 0$); and (iv) the *combined* strategy (both controls optimal).

Table 3.1: Baseline parameter values (rates in yr^{-1} ; population variables as fractions of the reference population).

Symbol	Meaning	Value	Equivalent / note
μ	natural mortality rate	0.0131	mean lifespan 76.34 yr
Π	recruitment rate of susceptibles	0.0124	$\approx 1,240$ per $10^5/\text{yr}$
p	fast-progression fraction	0.1227	$1 - p = 0.8773$ enter latency
δ	relapse rate	0.1000	mean time to relapse 10 yr
β_1	transmission scale in $\beta(b)$	3.5	peak contact transmission
φ_1	amplitude of $\phi(a) = a_1 e^{-a_2 a}$	0.0213	latent $\rightarrow$ infectious progression
φ_2	decay of $\phi(a)$	0.0602	with latent age a
ψ_1	saturation recovery rate	0.3000	$\psi(b)$
ψ_2	rise rate of $\psi(b)$	0.5000	with infectious age b

Table 3.2: Initial conditions (fractions of the reference population; counts per 100,000 in parentheses).

Variable	Fraction	Per 100,000
$S(0)$ susceptible	0.7500	75,000
$E(0)$ latent	0.2405	24,049
$I(0)$ infectious	0.0038	381
$R(0)$ recovered	0.0057	570
$V(0)$ vaccinated/immune	0.0000	0

3.2.1 Effect of the controls on the SEIR dynamics

Figure 3.1 shows the four state variables $S(t)$, $E(t)$, $I(t)$ and $R(t)$ under the four scenarios. The two controls act on the epidemic through two very different mechanisms, and the figure makes this contrast clear.

- **Vaccination u_1 acts upstream.** The vaccination control transfers susceptible individuals into the immune class, $S \xrightarrow{u_1} R$. Consequently, the susceptible population declines much faster than in the no-control and relapse-only scenarios. By reducing the pool of susceptibles, vaccination lowers the force of infection $M(t) = \int_0^\infty \beta(b)i(t, b) db$ and limits the number of new infections. This leads to a substantial reduction in both the exposed and infectious classes, while the recovered/immune population increases steadily through the accumulation of vaccinated individuals. Overall, vaccination acts directly on trans-

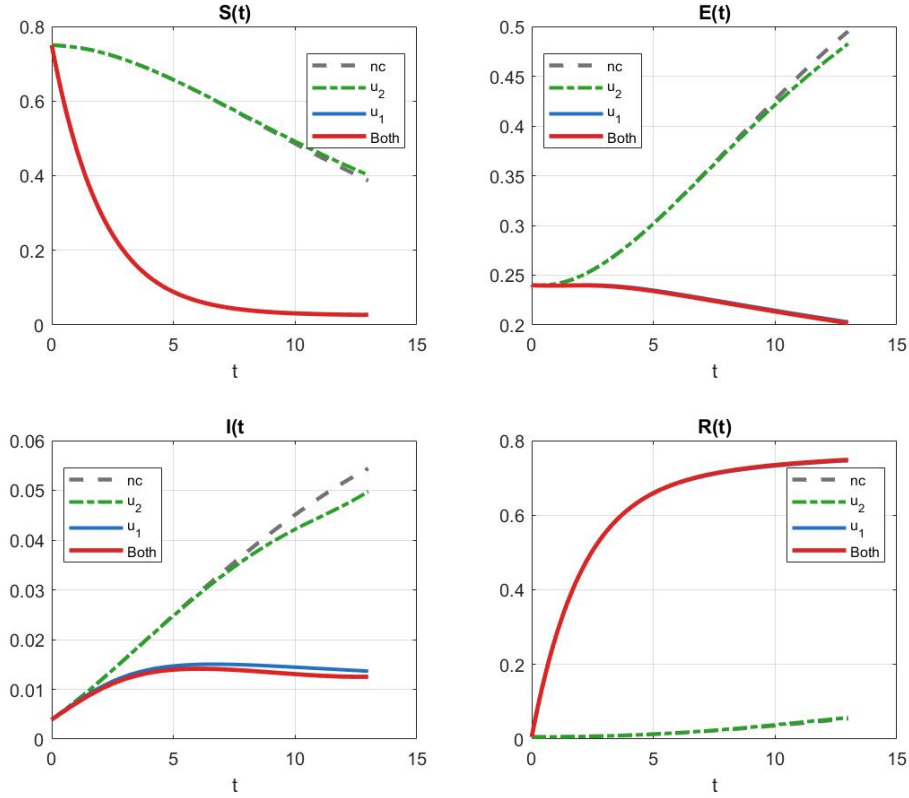


Figure 3.1: Time evolution of S , E , I and R under the four scenarios: no control, u_2 only, u_1 only, and both.

mission and produces the largest improvement across all epidemiological compartments.

- **Relapse prevention u_2 acts downstream.** The control u_2 reduces the relapse flow through the factor $(1 - u_2)$, acting only on the transition $\delta(1 - u_2)R \rightarrow I$. Its impact is therefore more targeted than that of vaccination. Since it neither reduces susceptibility nor alters the primary transmission pathway, the trajectories of $S(t)$ and $E(t)$ remain close to those of the uncontrolled case. Its main effect appears in the infectious class, where limiting reactivation reduces the number of active TB cases. Although relapse prevention alone cannot suppress transmission, it removes an important source of recurrent infection.

- **The combined strategy is optimal.** The combined strategy benefits from both mechanisms: vaccination reduces new infections, while relapse prevention limits the return of recovered individuals to the infectious class. As a result, the infectious population remains lower than under either single-control intervention, while the exposed population is also minimized and the protected class is enhanced. This ranking—from no control, to

relapse prevention only, to vaccination only, and finally to the combined strategy—is consistent with the objective functional, which seeks to minimize the overall disease burden while balancing intervention costs.

3.2.2 Influence of the latent age a and the infectious age b

Because the model is age-structured, the progression rate $\varphi(a)$ and the recovery rate $\psi(b)$ depend on the time elapsed in the latent and infectious compartments. To quantify their role we vary the mean latent period (through $a_1 = 12/a$, with a in months) and the mean infectious period (through $\psi_0 = 12/b$, with b in months): a *longer* latent period corresponds to a *slower* progression ϕ , and a longer infectious period to a slower recovery ψ .

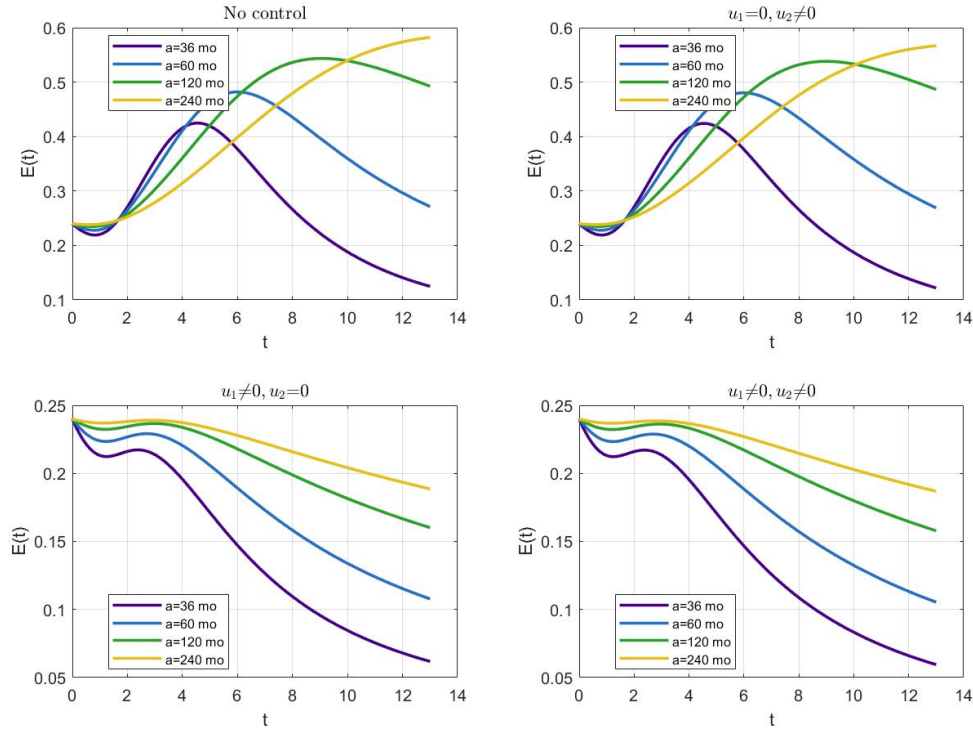


Figure 3.2: Sensitivity of the latent class $E(t)$ to the latent period a .

Latent period a and the behaviour of $E(t)$ (Figure 3.2). Under no control (and similarly under the u_2 -only strategy), the latent period strongly influences the evolution of the latency population. A shorter latent period corresponds to a faster progression from latency to infection, causing the latent class to reach an early maximum before declining as individuals leave the compartment. In contrast, a longer latent period slows

this progression, allowing exposed individuals to remain latent for longer and leading to a sustained accumulation of $E(t)$ over time. The intermediate values of a produce trajectories between these two extremes. When vaccination is introduced ($u_1 \neq 0$), the inflow of new exposed individuals is substantially reduced, and the latency population decreases for all latent periods. Although the decline remains faster for shorter latent periods than for longer ones, the same ordering of the curves is maintained. These results indicate that increasing the latent period enlarges the latent reservoir and reduces the speed at which control measures can eliminate it.

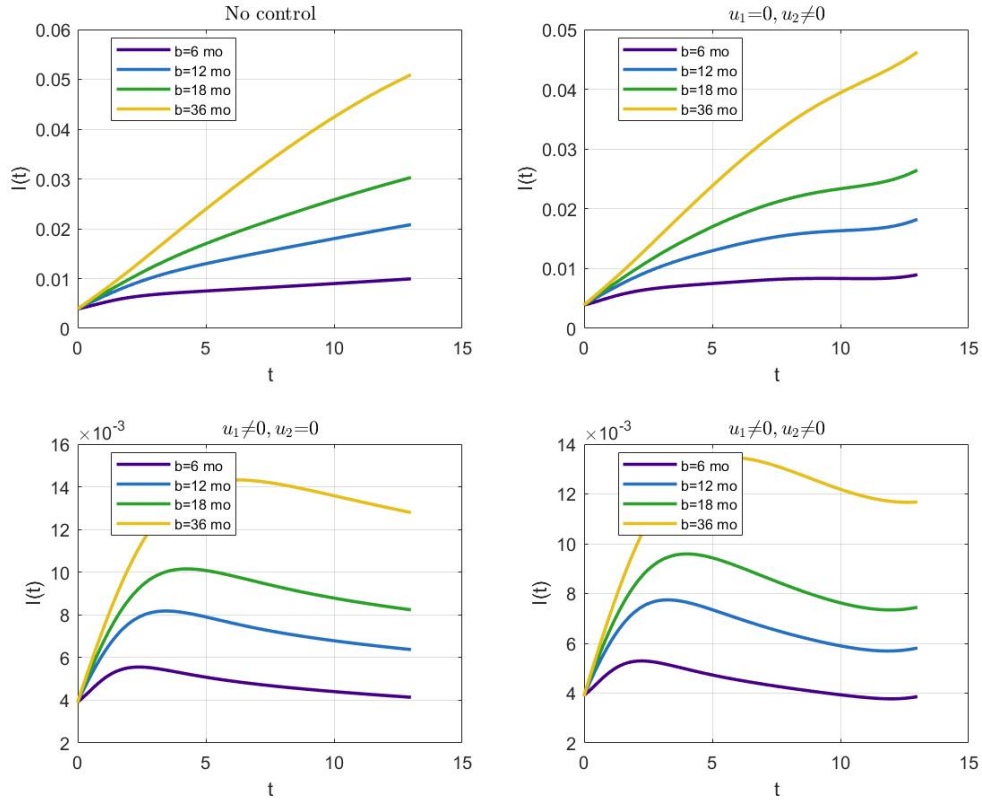


Figure 3.3: Sensitivity of the infectious class $I(t)$ to the infectious period b .

Infectious period b and the behaviour of $I(t)$ (Figure 3.3). The infectious period is a key determinant of the size of the infectious population. In the absence of control, longer infectious periods allow infected individuals to remain infectious for extended durations, leading to a greater accumulation of $I(t)$, whereas shorter infectious periods promote faster recovery and lower infectious levels. The relapse-prevention strategy (u_2 only) reduces the infectious burden by limiting reactivation from the recovered class, with a more noticeable effect when the infectious period is long. A much stronger reduction is

obtained when vaccination is introduced. By decreasing transmission at its source, u_1 lowers the number of new infectious cases for all values of b and changes the trajectory of $I(t)$ from sustained growth to a rise followed by decline. Although the relative ordering of the curves remains unchanged, the combined strategy consistently produces the lowest infectious levels, particularly when longer infectious periods increase the contribution of relapse to disease persistence.

3.3 Discussion and Conclusion

The numerical simulations demonstrate the importance of combining epidemiological control measures with an age-structured description of tuberculosis progression. The optimal-control analysis reveals that vaccination is the most effective intervention for reducing disease transmission. By acting directly on the susceptible population, vaccination decreases the force of infection and consequently reduces both the latent and infectious burdens. In contrast, relapse prevention acts only on individuals who have already recovered and therefore has a more limited, although still beneficial, impact on disease dynamics. While relapse control alone cannot substantially alter the course of the epidemic, it reduces the reactivation of tuberculosis and contributes to lowering the number of active infectious cases.

The results further show that the combined strategy consistently outperforms either intervention applied separately. Vaccination limits the generation of new infections, whereas relapse prevention suppresses an additional pathway through which infectious individuals can re-enter the transmission process. The simultaneous implementation of both controls therefore produces the smallest infectious burden and the largest protected population, illustrating the value of integrated intervention strategies in tuberculosis management.

The sensitivity analysis highlights the significant role played by the age-dependent progression and recovery mechanisms. Increasing the latent period leads to a larger accumulation of latent individuals, creating a substantial reservoir of infection that can sustain disease persistence over long time horizons. Similarly, increasing the infectious period prolongs the time during which infected individuals contribute to transmission, resulting in higher levels of active disease. These findings emphasize that the temporal characteristics of disease progression are as important as the control measures themselves in determining the overall epidemic outcome.

Overall, the study shows that effective tuberculosis control requires both the reduction of transmission and the limitation of disease reactivation. Moreover, the age-structured

framework provides valuable insight into how latent and infectious durations influence epidemic behaviour and the effectiveness of interventions. The results suggest that vaccination should remain the cornerstone of tuberculosis control programmes, while relapse prevention serves as an important complementary strategy, particularly in populations where long infectious periods and recurrent infections contribute significantly to disease persistence.

Conclusion

In this dissertation, we studied an age-structured SEIR epidemic model describing the transmission dynamics of tuberculosis, while taking into account the latency stage, the infection stage, and the possibility of relapse after recovery. The introduction of the latency age a and the infection age b allowed us to represent more accurately the evolution of individuals within the different epidemiological classes. After formulating the model, we studied the existence and uniqueness of solutions, and we established their positivity and boundedness in order to ensure the biological meaning of the model. We also determined the disease-free equilibrium E_0 and derived the basic reproduction number R_0 , then investigated the stability of this equilibrium by using suitable mathematical tools such as the linearization method, Lyapunov functionals, and LaSalle's invariance principle. In the last part, optimal control theory was applied by introducing two time-dependent controls, where $u_1(t)$ represents vaccination and $u_2(t)$ represents relapse prevention. The aim was to reduce the number of susceptible, latent, and infectious individuals while taking into account the cost of the interventions. In general, this study shows that age-structured models combined with optimal control provide an appropriate mathematical framework for understanding the spread of tuberculosis and for suggesting strategies that may help reduce its transmission and limit the effect of relapse.

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