



Original Article

OPTIMAL CONTROL, VACCINATION AND AWARENESS IN TUBERCULOSIS AND HEPATITIS B VIRUS INFECTION: A QUALITATIVE CLINICAL MODELLING STUDY

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ABSTRACT

Background: Tuberculosis (TB) and chronic hepatitis B virus (HBV) infection remain important causes of preventable morbidity and mortality worldwide. Mathematical models can help explore how best to combine vaccination and public awareness to reduce disease burden.

Objective: To use a transmission model to study how vaccination and public-awareness campaigns can optimally reduce the burden of TB or HBV infection, while accounting for limited resources.

Methods: In this multi-centric collaborative qualitative study, we extended a standard compartmental infectious-disease model, dividing the population into susceptible (unvaccinated), vaccinated, acutely infected, asymptomatic chronic carriers, symptomatic chronic carriers, individuals with complications and recovered. Two time-dependent control variables were introduced: intensity of vaccination and intensity of awareness activities that reduce effective contact rates. Using optimal control theory (Pontryagin's Maximum Principle), we identified the combination of interventions over a one-year horizon that minimises both the total number of infected people and the costs of vaccination and awareness programmes. Model parameters were taken from published TB/HBV literature. Results were summarised using the basic reproduction number (R_0) and numerical simulations.

Results: Without additional intervention, acute infection and chronic carrier populations increased, with a corresponding rise in severe complications. With optimal control, early aggressive use of vaccination and awareness in the first three months produced a marked increase in recovered patients and a reduction in acute and chronic infection. The model predicted that vaccination has a stronger effect than awareness campaigns on driving R_0 below 1, but the combination of both strategies is more effective than either alone, especially when transmission rates are high. For plausible parameter values, R_0 decreased from approximately 2.4 with no control to <1 with feasible levels of vaccination and awareness.

Conclusions: In this model, prioritising high-coverage vaccination, supported by intensive short-term awareness campaigns, is an efficient strategy to control TB or HBV transmission. These findings support existing clinical and public-health recommendations to scale up vaccination, particularly for newborns and high-risk groups, while sustaining community education on infection prevention and linkage to care.

Keywords: Tuberculosis; hepatitis B; mathematical model; optimal control; vaccination; health education; basic reproduction number.

INTRODUCTION

Tuberculosis (TB) and chronic hepatitis B virus (HBV) infection remain major causes of preventable morbidity and mortality worldwide. TB, caused by *Mycobacterium tuberculosis*, can affect the lungs as well as extrapulmonary sites such as bones, kidneys and the central nervous system. HBV is a blood-borne and sexually transmitted infection that targets the liver and may progress from an acute, often asymptomatic episode to chronic infection, cirrhosis and hepatocellular carcinoma.¹

Despite the availability of effective vaccines (for HBV) and preventive and curative treatment (for both TB and HBV), many countries continue to experience persistent or resurging epidemics. Reasons include incomplete vaccination coverage, delayed diagnosis, gaps in treatment completion and low awareness about modes of transmission and prevention. Programmes must therefore decide how to allocate limited resources between interventions such as vaccination, case-finding, treatment and health-education campaigns.

Mathematical models are increasingly used to support such decisions by allowing us to explore "what-if" scenarios that would be difficult or costly to test in real life.² Transmission models can estimate the impact of different strategies on infection incidence and prevalence and can incorporate the costs of interventions. Optimal control theory is a mathematical framework that seeks the time-dependent combination of interventions that yields the best outcome according to a specified objective function.³⁻⁶

This study was conducted with the collaborative efforts of the experts from the departments of Respiratory Medicine, Transfusion Medicine, Computer Science and Mathematics from GMC, Kota, GSH, Tonk and UoK. A detailed mathematical analysis of a TB/HBV model, including proofs about existence, uniqueness and stability of solutions was done. In present article, we focus on the clinically oriented key ideas and findings that are most relevant to medical practitioners. The model structure has been tried to describe in intuitive terms, to summarise the optimal control approach and to highlight the main clinical and public-health implications.

METHODS

Model structure

We used a deterministic compartmental model that divides the total population into the following mutually exclusive groups:

- S(t): Unvaccinated susceptible individuals – people who do not yet have TB or HBV and have not received a protective vaccine dose.
- V(t): Vaccinated individuals – people who have received the vaccine; they have partial protection but can still be infected if exposed.
- A(t): Acutely infected individuals – patients in the early phase of infection.
- Cn(t): Asymptomatic chronic carriers – individuals with chronic infection but no symptoms; they can transmit the pathogen.
- Cs(t): Symptomatic chronic carriers – individuals with chronic infection who have clinical symptoms.
- Dc(t): Individuals with disease complications – patients with advanced disease (e.g. cirrhosis or liver cancer for HBV).
- R(t): Recovered individuals – people who have cleared the infection and are assumed to have long-lasting immunity.

At any time t , the total population $N(t)$ is the sum of all compartments:

$$N(t) = S(t) + V(t) + A(t) + Cn(t) + Cs(t) + Dc(t) + R(t).$$

The model assumes that new individuals enter the population through birth at rate Π . A proportion p of newborns are vaccinated at birth, and the remaining $(1-p)$ are unvaccinated. All individuals may die from background causes at a constant natural mortality rate μ , and those with complications or advanced chronic disease may have an additional disease-related mortality rate δ .

Infection process

Susceptible and vaccinated individuals can be infected when they have effective contact with acutely infected patients or chronic carriers. The force of infection (rate at which susceptibles become infected) is written as:

$$\lambda = \beta [A + \eta_n Cn + \eta_s Cs + \eta_c Dc],$$

where β is the baseline transmission rate and η_n , η_s and η_c are modification factors capturing that asymptomatic carriers, symptomatic carriers and patients with complications may differ in infectiousness.

We assume that symptomatic chronic carriers are more infectious than asymptomatic carriers, and that patients with complications have at least as high infectiousness as symptomatic carriers.

Vaccinated individuals have partial protection: their risk of infection is multiplied by a factor r ($0 < r < 1$), which reflects vaccine efficacy. Vaccine-induced protection may wane over time at rate ω , moving people from vaccinated back to susceptible.

Disease progression

Among newly infected individuals, a fraction f enter an asymptomatic route and later become chronic carriers without initial symptoms. The remaining fraction $(1-f)$ develop symptomatic acute infection.

From the acute compartment, individuals may progress to asymptomatic chronic carriage, progress to symptomatic chronic carriage, or recover or die according to model parameters.

Asymptomatic chronic carriers can later develop symptoms at rate ξ or recover at rate γ . Symptomatic chronic carriers may recover (effective treatment at rate $\theta\gamma$, where $\theta > 1$ reflects intensified treatment), progress to complications at rate ν , die from the disease at rate δ , or experience natural mortality μ . Patients with complications can die either from natural causes μ or from disease-related causes δ .

Recovered individuals are assumed to have long-lasting infection-acquired immunity and do not become susceptible again within the model time frame.

Control variables: vaccination intensity and awareness

We considered two time-dependent control variables:

- $u_1(t)$: intensity of vaccination efforts, representing how strongly vaccination is scaled up beyond the baseline rate ψ (for example outreach, catch-up campaigns, or improving coverage among high-risk groups).

- $u_2(t)$: intensity of awareness and health-education efforts, representing community activities that reduce effective contact rates (for example knowledge about cough etiquette, safer injection practices, screening and linkage to care).

Both u_1 and u_2 are constrained between 0 and 1, where 0 means no additional effort beyond routine practice and 1 means maximum feasible effort.

In the model, $u_1(t)$ increases the flow of people from S to V (more vaccination of susceptibles). The control $u_2(t)$ reduces the effective contact rate (by lowering β in practice) and increases the rate at which susceptibles move to the recovered compartment R through behaviour change and earlier healthcare seeking.

Objective function and optimal control

The goal of the optimal control problem is to find time profiles $u_1^*(t)$ and $u_2^*(t)$ on a finite time horizon $[0, T]$ that minimise a combined measure of disease burden and intervention cost.

Formally, the objective function is:

$$J(u_1, u_2) = \int_0^T [a_0 A(t) + a_1 C_n(t) + a_2 C_s(t) + a_3 D_c(t) + \frac{1}{2} (b_1 u_1(t)^2 + b_2 u_2(t)^2)] dt.$$

Here, a_0 – a_3 are positive weights assigned to each infected or diseased group, reflecting their clinical importance (for example complications may be weighted more heavily than acute infection). The coefficients b_1 and b_2 are positive cost parameters for vaccination and awareness, respectively. The quadratic terms penalise very aggressive control strategies, representing increasing marginal cost or logistical difficulty.

Mathematically, we applied Pontryagin's Maximum Principle to derive necessary conditions for optimality.⁴ In intuitive terms, this principle introduces shadow prices for each compartment and leads to a set of differential equations that, when solved together with the original model, identify the optimal interventions over time.

We also calculated the basic reproduction number (R_0), which summarises the average number of secondary infections caused by a typical infectious individual in a fully susceptible population. When $R_0 < 1$, each generation of infection is smaller than the previous one and the disease eventually dies out; when $R_0 > 1$, the disease can persist or grow.

Parameter values and simulation settings

Parameter values (birth rate, mortality, progression rates, recovery rates, vaccine waning, etc.) were taken from published TB and HBV modelling studies and clinical literature. Transmission rates β were varied over a plausible range (0.8–1.98), and different levels of the controls u_1 and u_2 were explored.

Because acute HBV infection typically resolves or stabilises within six months in immunocompetent adults, the main simulations were run over a one-year period. This time frame allows us to capture the short-term impact of intensified interventions while still observing longer-term trends in chronic infection and complications.

RESULTS (QUALITATIVE SUMMARY)

Baseline scenario without intensified control

In the absence of any additional vaccination or awareness efforts ($u_1 = 0$, $u_2 = 0$), the model predicts that the number of acutely infected individuals $A(t)$ increases from low baseline levels. A proportion of these individuals transition into chronic asymptomatic or symptomatic carrier states (C_n , C_s). Over time, there is a gradual accumulation of patients with disease complications $D_c(t)$. The recovered compartment $R(t)$ increases steadily, but not enough to prevent ongoing transmission.

These behaviours correspond to an R_0 greater than 1, indicating that the infection can persist and potentially become endemic.

Impact of optimal vaccination and awareness

When both controls are allowed to vary over time and are optimised using the objective function, the model suggests an early, high-intensity phase of both vaccination and awareness during roughly the first three months. During this period, the number of susceptibles falls as more people are vaccinated, and behavioural changes reduce effective transmission.

As a result, the number of acutely infected individuals drops, and fewer people enter chronic carrier states or develop complications. The recovered compartment grows more rapidly, reflecting both immunologically recovered patients and those who benefit from vaccination.

After the initial period, the optimal strategy gradually reduces the intensity of both controls, as the pool of susceptibles shrinks and the effective reproduction number moves below 1. At this stage, maintaining maximal effort provides diminishing returns relative to cost.

Effect on the basic reproduction number (R_0)

By examining R_0 as a function of u_1 and u_2 , the model shows that with no additional control ($u_1 = 0$, $u_2 = 0$), R_0 is approximately 2.39 under the chosen parameter values. As either u_1 or u_2 increases, R_0 decreases, but the slope of reduction is steeper for u_1 (vaccination) than for u_2 (awareness).

When both controls are used together at moderate to high levels, R_0 can be driven below 1, implying that the infection can be brought under control and eventually eliminated in the model population. In other words, vaccination has a stronger direct impact on transmission, while awareness campaigns act as a valuable complement by reducing risky contacts and encouraging early diagnosis and treatment.

Sensitivity to transmission rate

For higher transmission rates ($\beta = 1.49$ – 1.98), the model indicates that without intensified control, infection quickly becomes more widespread and the burden of chronic carriage and complications increases. Even at these higher β values, appropriate combinations of vaccination and awareness can still reduce total infection over time, although sustained efforts are required.

The higher the underlying β , the longer and more intense the control measures need to be to maintain $R_0 < 1$.

DISCUSSION

This modelling study illustrates, in a simplified and clinically interpretable way, how combining vaccination and public-awareness interventions can efficiently reduce the burden of TB or HBV infection in a population.⁷⁻¹⁰

Several points are particularly relevant to clinicians and programme managers:

1. Vaccination is the cornerstone of control. In the model, increasing vaccination coverage (u_1) has the largest effect on reducing R_0 and the number of newly infected individuals. This supports current recommendations for widespread HBV vaccination, especially at birth and in early childhood, and emphasises the importance of preventive therapy and treatment completion in TB control.¹¹⁻¹³
2. Health-education and awareness campaigns are valuable adjuncts. Although awareness initiatives alone are less potent than vaccination in the model, they significantly enhance the overall impact when combined with vaccination. Such programmes can promote early testing, improve adherence to treatment, and reduce risky behaviours that facilitate transmission.¹⁴
3. Early, intensive control is more efficient than delayed or uniformly low-level control. The optimal strategy concentrates resources in the early phase of the intervention, when there are still many susceptibles and the potential to prevent new infections is greatest. For clinicians and planners, this argues for strong initial scale-up phases when new programmes are introduced.^{15,17}
4. Chronic carriers require attention even when they are asymptomatic. Asymptomatic chronic carriers (C_n) contribute substantially to transmission in the model, because they often remain undiagnosed and untreated. This underscores the value of screening programmes (for example antenatal HBV testing and contact tracing for TB) and linkage to care.¹⁸⁻²⁰

5. Preventing complications is both clinically and economically important. Individuals with disease complications (Dc) are weighted heavily in the objective function, reflecting the high clinical burden and cost of cirrhosis, liver cancer or advanced TB. By preventing progression to these states through earlier vaccination, diagnosis and effective treatment, the model suggests substantial long-term benefits.²¹⁻²³

CLINICAL AND PUBLIC-HEALTH IMPLICATIONS

Translating the mathematical results into practice, the study supports the following broad recommendations:

- Scale up vaccination programmes as a priority, aiming for high coverage in newborns, children and high-risk adults (for example household contacts, healthcare workers, people living with HIV).
- Combine vaccination with structured awareness campaigns, especially during the initial years of programme expansion, to accelerate behaviour change and uptake of testing and treatment.
- Use short, intensive intervention periods (for example the first 3–6 months of a campaign) to rapidly reduce transmission, followed by maintenance-level efforts rather than constant maximal intensity.
- Target chronic carriers and high-risk groups for screening and early treatment, recognising their role in sustaining transmission.
- Monitor programme performance using epidemiological indicators, including estimates of R_0 where feasible, to assess whether interventions are sufficient to push the epidemic below the threshold for sustained transmission.

LIMITATIONS (FROM A CLINICAL PERSPECTIVE)

As with any mathematical model, several simplifications should be kept in mind:

- The model assumes a homogeneously mixing population and does not explicitly represent age structure, co-morbidities (such as HIV) or social networks, all of which can influence TB and HBV transmission.
- Treatment adherence, drug resistance and reinfection are not modelled in detail.
- Parameter values were drawn from published literature and may not perfectly represent specific local contexts.
- Costs are represented in abstract terms (weights b_1 and b_2) rather than actual financial units.

Therefore, the results should be interpreted as qualitative guidance on the relative value and timing of interventions, not as exact quantitative predictions.

CONCLUSION

Using a clinically oriented transmission model with optimal control, we show that vaccination is the most powerful single lever for reducing TB or HBV transmission. Awareness and health-education campaigns complement vaccination and improve outcomes, particularly when implemented early and at high intensity.

The combination of these strategies can reduce the basic reproduction number below 1 and substantially lower the number of acute infections, chronic carriers and patients with complications, even in settings with relatively high baseline transmission.

For clinicians and public-health professionals, the key message is that investing in robust vaccination programmes, supported by targeted awareness activities, is both medically and economically justified as part of comprehensive strategies to control and eventually eliminate TB and HBV.

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