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ABSTRACT

In this work, we investigate how the seasonal variation in the number of individuals who are tested for an HIV antibody in outpatient clinics affects the HIV transmission patterns in China, which has not been well studied. Based on the characteristics of outpatient testing data and reported cases, we establish a periodic infectious disease model to study the impact of seasonal testing on HIV transmission. The results indicate that the seasonal testing is a driving factor for the seasonality of new cases. We demonstrate the feasibility of ending the HIV/AIDS epidemic. We find that the diagnostic rates related to testing play a crucial role in controlling the size of the epidemic. Specifically, when considering minimizing both infected individuals and diagnostic rates, the level of attention paid to undiagnosed infected individuals is always positively correlated with the optimal diagnostic rates, while the optimal diagnostic rates are negatively correlated with the size of the epidemic at the terminal time.

AIDS causes a large number of deaths in the world annually, including China. The impact of many interventions on HIV transmission has been extensively studied, such as antiretroviral therapy, screening, and pre-exposure prophylaxis. Understanding the effectiveness of these interventions is a prerequisite for controlling infectious diseases. We aim to explore the impact of seasonal testing on HIV transmission in China through an infectious disease model and real data. In addition, we also derive the threshold that determines whether the epidemic can be eliminated and how to reduce the size of the HIV/AIDS epidemic by regulating the diagnostic rates under limited resources. These results can provide mathematical insights for controlling the HIV/AIDS epidemic.

I. INTRODUCTION

In recent decades, the number of deaths caused by acquired immunodeficiency syndrome (AIDS) in China has been increasing. In 2003, AIDS was the fifth leading cause of death among all notifiable infectious diseases, and it became the first leading cause of deaths in 2008. By 2018, the number of deaths caused by AIDS was 4.3 times higher than that caused by all other notifiable infectious diseases.[1] In addition, there are various routes of human immunodeficiency virus (HIV) transmission.[2] In 2007, the number of new cases caused by sexual transmission exceeded the number of new cases caused by injecting drug use for the first time.[1] The proportion of new cases caused by the above two transmission routes among all new cases increased from 97.1% in 2012 to 98.5% in

2016.[3] Sexual transmission is currently the main route in China. During sex, the probability of male-to-female transmission is usually higher than that of female-to-male transmission.[4,5] The probability of female-to-female transmission is almost zero,[6] and the probability of male-to-male transmission is higher.[4] In addition, men who have sex with men (MSM) are more than ten times more likely to be infected with HIV than the general men.[4,7] MSM also play an important role in sexually transmitted diseases. Especially when some MSM are heterosexual, they are more likely to infect their female partners.[6] Thus, exploring the transmission patterns of HIV has always been the focus of studying how to control the HIV/AIDS epidemic.

Many diseases show seasonal characteristics, and the causes for seasonality are diverse.[8] Understanding the timing and causes of seasonality can provide important insights into mitigating the spread of disease.[9–11] In terms of respiratory diseases, pneumococcal infections increase each winter. Studies have shown that the photoperiod-dependent variation in host susceptibility may underlie pneumococcal seasonality.[12] There is obvious seasonality in tuberculosis cases, but the cause remains uncertain, which may be related to climate, air pollution, sunshine, or other factors.[13] The influenza virus spreads rapidly and poses great threat to high-risk populations, such as pregnant women, the elderly, and infants.[14] Several factors are thought to be associated with the seasonality of influenza, including temperature, humidity, rainfall, pondus hydrogenii, salinity, indoor crowding, and sunlight.[15] Mumps is known as a common childhood viral disease, and its seasonal patterns may be caused by climate and population aggregation.[16] The seasonality of COVID-19 cases is correlated with temperature, humidity, and social isolation rate.[17] Seasonal oscillations in diphtheria cases may be related to the resumption of school.[18] The correlation between various meteorological parameters, including low air humidity, wind speed, and dust load, and the seasonality of the incidence rate of meningitis has been studied.[19] In addition, many other diseases, such as tick-borne diseases,[20] scarlet fever,[21] measles,[22] chickenpox,[22] cholera,[23] hemorrhagic fever with renal syndrome,[24] and malaria[25] in humans, and bluetongue in cattle and sheep,[8] are thought to have seasonal characteristics. In China, the number of individuals who are tested for an HIV antibody in outpatient clinics related to the HIV/AIDS epidemic shows seasonal characteristics, and its impact on the dynamics of HIV transmission has not been well explored.

As one of the means to explore effective intervention strategies, optimal control theory has been applied to the prevention and control of the HIV/AIDS epidemic. Since no drugs can completely cure HIV infection currently, antiretroviral therapy (ART) is widely used as a drug intervention strategy that can significantly reduce the infectivity of infected individuals, and optimal control theory has been applied to study how to best distribute antiretroviral drugs to maximize the benefits of treatment.[26,27] Taking pre-exposure prophylaxis for high-risk susceptible individuals can prevent HIV infection.[28] By selecting the parameters related to treatment and pre-exposure prophylaxis as control variables of optimal control problems, costs and disease mortality can be minimized to the greatest possible extent. Screening has also been used in combination with optimal control theory to control the HIV/AIDS epidemic as one of the non-pharmaceutical interventions.[29,30] In addition, other non-pharmaceutical interventions, such as behavior change,[31] have also been optimized under limited resources.

In this work, we propose a periodic function related to diagnostic rates based on outpatient testing data. Then, the mathematical model is established in combination with the periodic diagnostic rates. We discuss the dynamic behavior of the mathematical model, including the existence and stability of disease-free and positive periodic solutions, as well as the uniform persistence of the model. The basic reproduction number of the model is derived. In addition, we use the model to fit the number of new cases to verify whether the periodic diagnostic rates contribute to the seasonality of the HIV/AIDS epidemics. Furthermore, we solve the optimal diagnostic strategy problem with constraints and provide the correlation between the optimal diagnostic rates and the size of the HIV/AIDS epidemic in different scenarios. This work ends with a summary and discussion of the above analysis.

II. METHODS

In this section, we develop an epidemic model with periodic diagnostic rates and study the transmission patterns of HIV.

A. Outpatient testing data and periodic diagnostic rates

The National Center for AIDS/STD Control and Prevention, Chinese Centers for Disease Control and Prevention (China CDC) provides the monthly number of individuals who are tested for an HIV antibody in the Voluntary Counseling and Testing (VCT) clinics from February 2012 to January 2016.[3] For convenience, the data are normalized as follows:

$$\text{Normalized data}_t = \frac{\text{Actual data}_t - \min\left(\text{Actual data}\right)}{\max\left(\text{Actual data}\right) - \min\left(\text{Actual data}\right)},$$

where t represents time. Figures 1(a) and 1(b) show the data before and after normalization, respectively.

Let $\kappa(t) = \frac{a_0}{2} + \sum_{n=1}^{2}\left[a_n \cos(n\omega t) + b_n \sin(n\omega t)\right]$, where ω, $a_0, a_i, b_i \in \mathbb{R}, i = 1, 2$. The China CDC provides data on diagnosed HIV-positive individuals (people with HIV infection and without AIDS) and diagnosed AIDS patients.[3] Infected and infectious individuals are divided into two groups: undiagnosed group and diagnosed group. The diagnostic rate controls the flow rate from the undiagnosed group to the diagnosed group, and the infectivity of these two groups is different because it is illegal for diagnosed infected individuals to spread the virus to susceptible individuals.[32] Thus, diagnosis has a key influence on the dynamics of HIV transmission. Based on seasonal variation in the number of individuals who are tested for an HIV antibody and the number of new cases, we define the periodic diagnostic rates related to HIV-positive cases and AIDS cases within one period as follows:

$$\kappa_H(t) = h \times \kappa(t), \quad 1 \le t \le 12, \tag{2.1}$$

$$\kappa_A(t) = a \times \kappa(t), \quad 1 \le t \le 12, \tag{2.2}$$

where h, a are positive constants.

In addition, we use the function $\kappa(t)$ related to the diagnostic rates to fit the normalized test data.[33] We obtain the values of

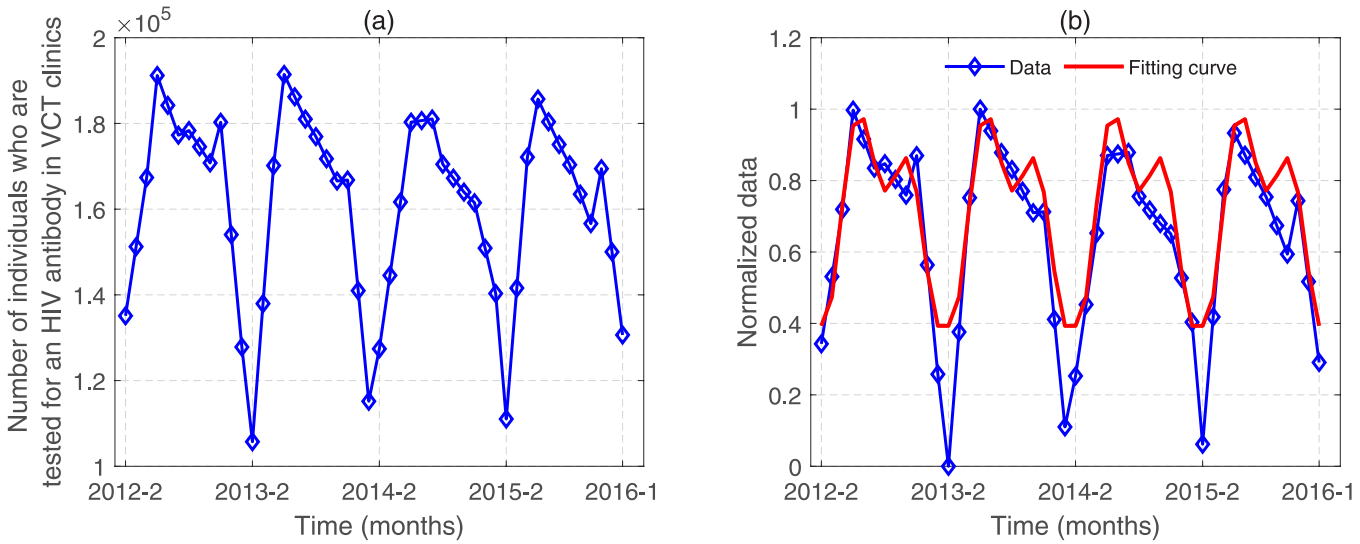

FIG. 1. Outpatient data and fitting curve. Subfigure (a) shows the monthly number of individuals who are tested for an HIV antibody in VCT clinics. In subfigure (b), the blue diamonds represent the normalization results of the data in subfigure (a), and the red curve represents the fitting result.

unknown parameters ω, a_0, a_i, and $b_i, i = 1, 2$ in $\kappa(t)$ as follows:

$$\omega = 0.5712,\ a_0 = 1.4803,\ a_1 = -0.1855,\ a_2 = -0.0083,$$
$$b_1 = -0.0840,\ b_2 = -0.1562, \tag{2.3}$$

and the fitting results are shown in Fig. 1(b). Note that the complete fitting curve is obtained by extending the fitting curve from February 2012 to January 2013 to the next three years.

B. Model formulation

Based on the characteristics of new cases reported in China,[1,34] we only focus on high-risk behaviors (high-risk sex or needle sharing) in the model. According to the concept of the compartment model,[35] we divide the high-risk population into the following four groups (compartments), namely, susceptible individuals S, undiagnosed infected individuals E, diagnosed HIV-positive individuals H, and diagnosed AIDS patients A. Let $N = S + E + H + A$, where N represents the size of high-risk population.

For high-risk population, U is a constant recruitment of susceptible individuals, which means that U susceptible individuals merge to the high-risk population per unit time. We assume that the natural death rate of individuals is constant, denoted by d. The disease-induced mortality rates of infected individuals without AIDS and with AIDS are μ_h and μ_a, respectively.

Let c_1 be the average number of contacts between an undiagnosed infected individual and susceptible individuals per unit time, β_1 is the probability of being infected per contact between the susceptible individual and the undiagnosed infected individual, then $\beta_1 c_1$ represents the adequate contact rate. Note that the infection does not occur when infected individuals come into contact with non-susceptible individuals, and the proportion of high-risk susceptible individuals in the total population N is S/N. Therefore, the adequate contact rate between an infected individual and susceptible individuals is

$$\beta_1 c_1 \frac{S}{N},$$

then the number of susceptible individuals infected by all infected individuals (including undiagnosed infected individuals and diagnosed infected individuals[32]) per unit time is

$$\beta_1 c_1 \frac{S}{N} E + \beta_2 c_2 \frac{S}{N} (H + \theta A),$$

where c_2 is the average number of contacts between a diagnosed HIV-positive individual and susceptible individuals per unit time, β_2 represents the probability of being infected per contact between the susceptible individual and the diagnosed HIV-positive individual, and θ is the coefficient that represents the infectivity of diagnosed AIDS patients relative to diagnosed HIV-positive individuals. Additionally, an undiagnosed infected individual becomes an HIV-positive individual or an AIDS patient after being diagnosed,[3,34] and the diagnostic rates are in Eqs. (2.1) and (2.2). Diagnosed HIV-positive individuals transfer to diagnosed AIDS patients at the rate σ. All the parameters are assumed to be positive.

Let $\beta_E = \beta_1 c_1$, $\beta_D = \beta_2 c_2$. We use the following model of differential equations to capture the transmission dynamics of HIV:

$$\frac{dS}{dt} = U - \beta_E \frac{S}{N} E - \beta_D \frac{S}{N} (H + \theta A) - dS,$$
$$\frac{dE}{dt} = \beta_E \frac{S}{N} E + \beta_D \frac{S}{N} (H + \theta A) - \kappa_H(t) E - \kappa_A(t) E - dE, \tag{2.4}$$

$$\frac{dH}{dt} = \kappa_H(t)E - \sigma H - dH - \mu_h H,$$
$$\frac{dA}{dt} = \kappa_A(t)E + \sigma H - dA - \mu_a A.$$

It is shown that the state variables of (2.4) remain non-negative with non-negative initial conditions. Considering the biologically feasible region

$$\Omega = \left\{(S,E,H,A) \in \mathbb{R}^4_+ : N = S + E + H + A \le \frac{U}{d}\right\},$$

we have the following conclusion.

Theorem 2.1: *The set Ω is positively invariant for Model (2.4).*

The proof is given in Appendix A.

In mathematical epidemiology, the basic reproduction number, denoted as R_0, is the expected number of infected individuals produced by an infected individual during the infectious period.[36,37] We derive R_0 of Model (2.4) (see Appendix B) and prove that the disease-free periodic solution is globally asymptotically stable if $R_0 < 1$ (see Appendix C), which means that if the interventions are taken to reduce R_0 to be below 1, the disease will become extinct. Model (2.4) has at least one positive periodic solution and the disease is uniformly persistent if $R_0 > 1$ (see Appendix D), meaning that the infectious disease will become endemic if R_0 is greater than 1. Figure 7 shows the numerical results corresponding to the above theoretical results (see Appendix E).

C. Statistical analysis

In China, the average life expectancy of people in 2010 and 2015 was 74.83 years and 76.34 years, respectively.[38] Therefore, we assume $d = 1/(75.59 \times 12)$. The median survival time of HIV-positive individuals and AIDS patients is 5.81 and 3.14 years, respectively,[34] then $\mu_h = 1/(5.81 \times 12)$, $\mu_a = 1/(3.14 \times 12)$. The average time from reported HIV infection to AIDS is 8.62 years,[34] then $\sigma = 1/(8.62 \times 12)$. We assume that AIDS patients have no ability to infect others,[34] that is, $\theta = 0$. The number of diagnosed HIV-positive individuals and AIDS patients in February 2012 was 235 924 and 123 420, respectively.[3] Hence, $H(0) = 235924$ and $A(0) = 123420$. In addition, we assume that $S(0) \in [1, 2 \times 10^8]$ and $E(0) \in [1, 2 \times 10^6]$.

Next, we will describe the method to simulate the dynamics of HIV transmission using Model (2.4). Let $C_H(t)$ and $C_A(t)$ represent the monthly number of new diagnosed HIV-positive individuals and AIDS patients, respectively. We use the values of $\kappa_H(t)E(t)$ and $\kappa_A(t)E(t)$ in Model (2.4) as the approximations of the monthly number of new diagnosed HIV-positive individuals and AIDS patients, respectively, that is,

$$C_H(t) = \kappa_H(t)E(t), \quad 0 \le t \le 48,$$
$$C_A(t) = \kappa_A(t)E(t), \quad 0 \le t \le 48,$$

where the values of $\kappa_A(t)$ and $\kappa_H(t)$ are obtained by extending their values from February 2012 to January 2013 in Eqs. (2.1) and (2.2) to the following three years.

III. FITTING AND PREDICTION RESULTS

Accuracy is an important criterion for evaluating the effectiveness of fitting and prediction. The mean absolute percentage error (MAPE) and the root mean square percentage error (RMSPE) are commonly used to estimate the performance and reliability of fitting and prediction.[39] MAPE and RMSPE that are related to actual and fitted values are defined as

$$\text{MAPE} = \frac{1}{n}\sum \left|\frac{\text{Actual value}_t - \text{Fitted value}_t}{\text{Actual value}_t}\right| \times 100\%, \quad (3.1)$$

$$\text{RMSPE} = \sqrt{\frac{1}{n}\sum \left[\frac{\text{Actual value}_t - \text{Fitted value}_t}{\text{Actual value}_t}\right]^2} \times 100\%, \quad (3.2)$$

where t represents time and n represents the number of actual and fitted values.

We use the Markov Chain Monte Carlo (MCMC) method[40,41] to fit Model (2.4) with the monthly number of new diagnosed HIV-positive cases and AIDS cases. Figures 2(a) and 2(b) show the fitting results of the monthly number of new HIV-positive cases and new AIDS cases, respectively. In addition, we can obtain the values of unknown parameters a and h in Eqs. (2.1) and (2.2) are 0.0250 [95%CI : (0.0222, 0.0278)] and 0.0376 [95%CI : (0.0332, 0.0420)], respectively. According to Eqs. (2.1)–(2.3), we plot Figs. 2(c) and 2(d), which show the values of periodic diagnostic rate $\kappa_H(t)$ related to HIV-positive individuals and periodic diagnostic rate $\kappa_A(t)$ related to AIDS patients, respectively. Other unknown parameters and initial conditions in Model (2.4) are shown in Table I.

In addition, we use the parameter values estimated by the data from February 2012 to January 2015 to predict the epidemic trend for the following year, which is presented in Figs. 2(a) and 2(b). The fitting and prediction results indicate that the periodic diagnostic rates contribute to the seasonal patterns in new cases. By calculating Eqs. (3.1) and (3.2), we obtain the values of MAPE and RMSPE that are related to fitting and prediction (see Table II), which means that our fitting results have a certain degree of confidence, and the model performs well in short-term forecasting.

Furthermore, the basic reproduction number R_0 can be calculated by Lemma B.2 in Appendix B. We randomly select 20% of the 10 000 samples from the fitting results as the final distribution of unknown parameters to calculate R_0, and R_0 is estimated to be 1.1571 [95%CI : (1.0403, 1.3059)] [see Fig. 3(a)], which means that the HIV/AIDS epidemic will persist in China without other interventions. Figure 3(b) shows the correlation between h in Eq. (2.1) and R_0, which represents the correlation between diagnostic rate κ_H and R_0. Figure 3(c) shows the correlation between a in Eq. (2.2) and R_0, representing the correlation between diagnostic rate κ_A and R_0. The Pearson correlation coefficient (PCC) reflects the correlation between two variables. The PCC between the diagnostic rates and R_0 is -0.3409 ($p < 0.01$) and -0.7743 ($p < 0.01$), respectively, indicating a negative correlation between the diagnostic rates and R_0.

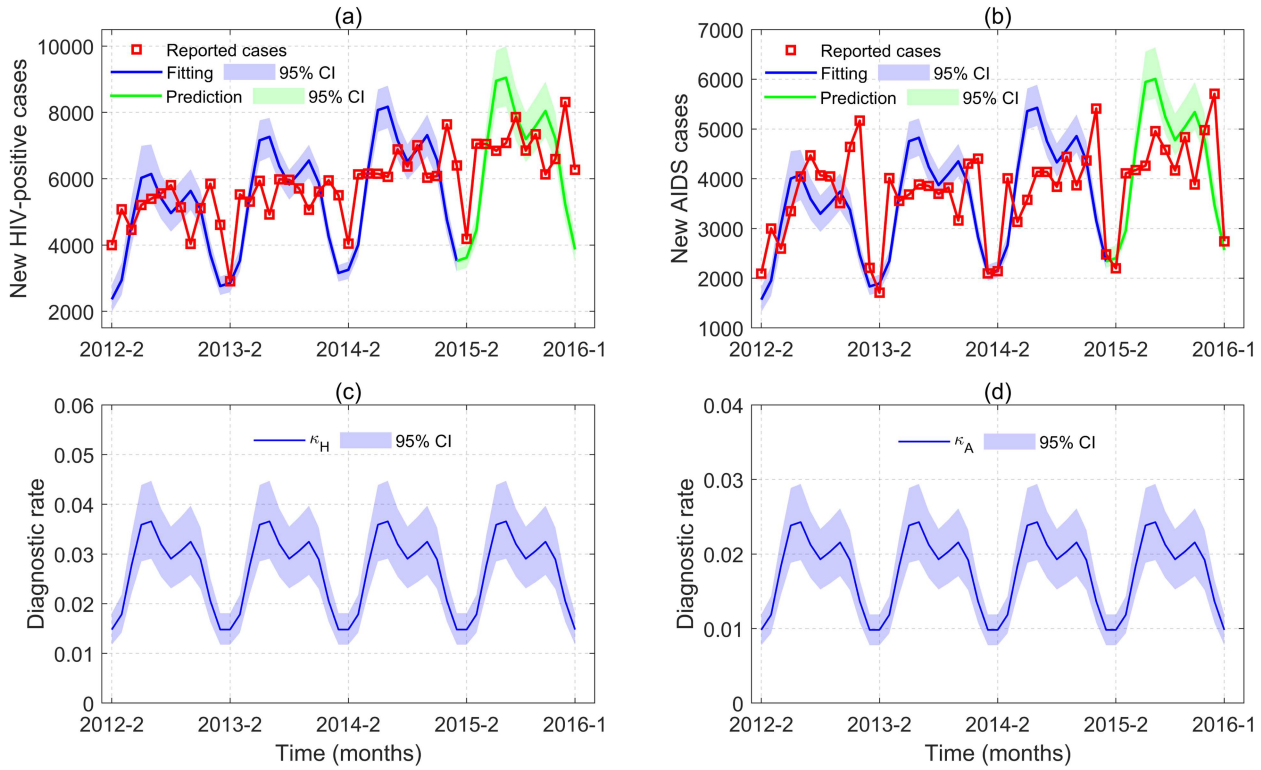

FIG. 2. Reported cases and fitting results. Subfigures (a) and (b) show the fitting and prediction curves of the monthly number of new HIV-positive cases and new AIDS cases. Red squares represent the reported cases. Subfigures (c) and (d) show the periodic diagnostic rates related to HIV-positive individuals and AIDS patients, respectively. The solid line represents the mean value, and the shaded region is the 95% confidence interval.

TABLE I. Parameters for the Model (2.4).

Parameter	Description	Mean value	Std	Source
U	Constant recruitment rate (person month^{-1})	4.5956×10^6	3.0058×10^6	MCMC
β_E	Transmission rate from undiagnosed infected individuals to susceptible individuals (month^{-1})	0.0309	0.0007	MCMC
β_D	Transmission rate from HIV-positive individuals to susceptible individuals (month^{-1})	0.0215	0.0015	MCMC
κ_H	Diagnostic rate of undiagnosed HIV-positive individuals (month^{-1})	See Fig. 2(c)	…	MCMC
κ_A	Diagnostic rate of undiagnosed AIDS patients (month^{-1})	See Fig. 2(d)	…	MCMC
σ	Progression rate from reported HIV-positive individuals to AIDS patients (month^{-1})	0.0097	…	Ref. 34
θ	Coefficient for the infectivity of AIDS patients relative to HIV-positive individuals (dimensionless)	0	…	Ref. 34
d	Natural death rate (month^{-1})	$1/(75.59 \times 12)$	…	Ref. 38
μ_a	Disease-induced mortality rate of AIDS patients (month^{-1})	0.0265	…	Ref. 34
μ_h	Disease-induced mortality rate of HIV-positive individuals (month^{-1})	0.0143	…	Ref. 34
$S(0)$	Initial number of susceptible individuals (person)	1.3350×10^8	4.1909×10^7	MCMC
$E(0)$	Initial number of undiagnosed infected individuals (person)	1.6051×10^5	9.9603×10^3	MCMC
$H(0)$	Initial number of diagnosed HIV-positive individuals (person)	235 924	…	Ref. 3
$A(0)$	Initial number of diagnosed AIDS patients (person)	123 420	…	Ref. 3

TABLE II. The fitting and predicting accuracy of Model (2.4).

	Fitting(%)		Prediction(%)	
Data	MAPE	RMSPE	MAPE	RMSPE
New HIV-positive cases	20.20	25.83	19.62	24.51
New AIDS cases	19.99	24.72	19.06	23.13

IV. CONTROL STRATEGY

The infectivity of diagnosed infected individuals as a source of infection is lower than that of undiagnosed infected individuals.[42] Therefore, diagnosis is one of the most effective strategies to control the HIV/AIDS epidemic. In this section, we investigate the optimal diagnostic strategy within the framework of optimal control problems.

A. Formulation of the optimal diagnostic problem

We denote the control variable related to diagnostic rates as $u(t)$. Let $\phi = (S, E, H, A)^T$, the optimal diagnostic model by extending Model (2.4) is as follows:

$$\phi_t = \begin{bmatrix} \dot{S} \\ \dot{E} \\ \dot{H} \\ \dot{A} \end{bmatrix} = \begin{bmatrix} U - \beta_E \frac{S}{N} E - \beta_D \frac{S}{N} (H + \theta A) - dS \\ \beta_E \frac{S}{N} E + \beta_D \frac{S}{N} (H + \theta A) - dE \\ -\sigma H - dH - \mu_h H \\ \sigma H - dA - \mu_a A \end{bmatrix} + u \begin{bmatrix} 0 \\ -hE - aE \\ hE \\ aE \end{bmatrix}, \tag{4.1}$$

with the initial conditions

$$S(t_0) = S_0, E(t_0) = E_0, H(t_0) = H_0, A(t_0) = A_0. \tag{4.2}$$

The control function $u(t)$ is bounded $[0 \le au(t) \le u_{\max}, 0 \le hu(t) \le u_{\max}]$ in Ω_u, where

$$\Omega_u = \left\{ u(t) \in L^1[t_0, t_f] \middle| 0 \le u(t) \le \min\left\{ \frac{u_{\max}}{a}, \frac{u_{\max}}{h} \right\} \right\}. \tag{4.3}$$

Here, $u_{\max}$ is a fixed positive constant. t_0 and t_f are the initial time and terminal time, respectively.

Our goal is to minimize the infected populations $L(t, \phi, u)$, including diagnosed infected individuals (excluding AIDS patients because they are not infectious), undiagnosed infected individuals, and newly infected individuals.[43] For convenience, $L(t, \phi, u)$ is defined as

$$L(t, \phi, u) = \left(A_1 E(t) + A_2 H(t) + A_3 (a + h) u(t) E(t)\right)^2,$$

where the quantities A_1, A_2, and A_3 represent the level of attention paid to undiagnosed infected individuals, diagnosed HIV-positive individuals, and newly infected individuals, respectively. We consider the following objective functional associated with Model (4.1):

$$J(u) = \int_{t_0}^{t_f} \left(A_1 E(t) + A_2 H(t) + A_3 (a + h) u(t) E(t)\right)^2 \mathrm{d}t. \tag{4.4}$$

Combining Eqs. (4.1)–(4.4), the optimal diagnostic strategy can be formulated as the following optimal control problem with

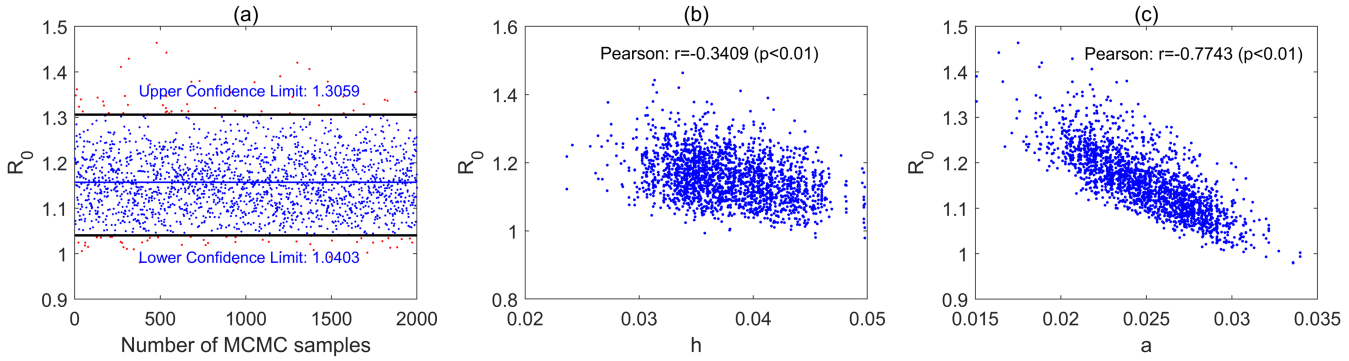

FIG. 3. Basic reproduction numbers R_0 calculated by the MCMC fitting results and the impact of diagnostic rates on R_0. Subfigure (a) shows the value of R_0 for each sample. The blue dots indicate the value of R_0 within the 95% confidence interval, the red dots indicate the value of R_0 outside the 95% confidence intervals, and the black lines indicate the upper and lower confidence limits. Subfigure (b) shows the correlation between h in Eq. (2.1) and R_0. Subfigure (c) shows the correlation between a in Eq. (2.2) and R_0.

inequality constraints and free terminal states:[44]

$$\begin{cases} \min J(u) = \int_{t_0}^{t_f} \left(A_1 E(t) + A_2 H(t) + A_3 (a+h) u(t) E(t)\right)^2 \mathrm{d}t \\ \text{s.t.} \\ \frac{\mathrm{d}S}{\mathrm{d}t} = U - \beta_E \frac{S}{N} E - \beta_D \frac{S}{N} (H + \theta A) - dS, \\ \frac{\mathrm{d}E}{\mathrm{d}t} = \beta_E \frac{S}{N} E + \beta_D \frac{S}{N} (H + \theta A) - hu(t) E - au(t) E - dE, \\ \frac{\mathrm{d}H}{\mathrm{d}t} = hu(t) E - \sigma H - dH - \mu_h H, \\ \frac{\mathrm{d}A}{\mathrm{d}t} = au(t) E + \sigma H - dA - \mu_a A, \\ S(t_0) = S_0, E(t_0) = E_0, H(t_0) = H_0, A(t_0) = A_0, \\ 0 \le u(t) \le \min\left\{\frac{u_{\max}}{a}, \frac{u_{\max}}{h}\right\}. \end{cases} \tag{4.5}$$

B. Analysis of optimal controls

Before solving the optimal control problem, we first apply the following assumptions to prove the existence of the optimal solution (see Theorem 5.1 in Ref. 45)

- **(A1)** The set of controls and corresponding state variables is non-empty.
- **(A2)** The admissible control set, Ω_u, is convex and closed.
- **(A3)** Each right hand side of the equations in (4.1) is continuous and is bounded by a sum of the bounded control and state, and can be written as a linear function of u with coefficients depending on time and state.
- **(A4)** The integrand of the objective functional, $L(t, \phi, u)$, is convex.
- **(A5)** There exist constants q, $p > 0$, and $b > 1$ such that the integrand of the objective functional satisfies

$$L(t, \phi, u) \ge q|u|^b - p.$$

It is obvious that the set of controls and corresponding state variables is non-empty and the admissible control set is convex and closed. The Lipschitz property and boundedness of the state system imply that assumption (A3) is satisfied. Since the second derivative of $L(t, \phi, u)$ is non-negative, convexity can be obtained. By the Lipschitz property of differential equation, when $E(t_0) > \varepsilon$, there exists a sufficiently small $\delta > 0$ such that $E(t_0 + \delta) \ge \varepsilon$, and

$$\begin{aligned} &\left(E(t) + H(t) + au(t) E(t) + hu(t) E(t)\right)^2 \\ &\quad \ge \left(a^2 + h^2\right)\varepsilon^2 u^2(t) \ge q|u|^b - p, \quad t \in [t_0, t_0 + \delta], \end{aligned}$$

where $q = \left(a^2 + h^2\right)\varepsilon^2$, $b = 2$, and $p, \varepsilon > 0$. Hence, assumption (A5) is satisfied. We have the following conclusion.

Theorem 4.1: *For the objective functional $J(u)$ associated with Model (4.1) defined in Ω_u, there exists an optimal diagnostic strategy u^* that minimizes $J(u)$.*

Let $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4)^T$. To find the optimal solution, we define the Hamiltonian function $\mathcal{H}$ for the control problem as

$$\mathcal{H} = L(t, \phi, u) + \lambda_1 \frac{\mathrm{d}S}{\mathrm{d}t} + \lambda_2 \frac{\mathrm{d}E}{\mathrm{d}t} + \lambda_3 \frac{\mathrm{d}H}{\mathrm{d}t} + \lambda_4 \frac{\mathrm{d}A}{\mathrm{d}t},$$

where λ_1, λ_2, λ_3, and λ_4 are the adjoint variables. By applying Pontryagin's maximum principle,[46] the state equation, the adjoint equation, and the optimality condition as follows:

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = \frac{\partial \mathcal{H}(t, \phi, u, \lambda)}{\partial \lambda}, \tag{4.6}$$

$$\frac{\mathrm{d}\lambda}{\mathrm{d}t} = -\frac{\partial \mathcal{H}(t, \phi, u, \lambda)}{\partial \phi}, \tag{4.7}$$

$$0 = \frac{\partial \mathcal{H}(t, \phi, u, \lambda)}{\partial u}. \tag{4.8}$$

Next, we apply the necessary conditions combined with Hamiltonian function $\mathcal{H}$ to determine the adjoint system and transversality conditions. Let $G = (\beta_D S(H + \theta A) + \beta_E S E)/N^2$. From Eq. (4.7), the adjoint system can be derived as follows:

$$\begin{aligned} \frac{\mathrm{d}\lambda_1}{\mathrm{d}t} &= \lambda_1 \left(d + \frac{\beta_D (H + \theta A) + \beta_E E}{N} - G\right) - \lambda_2 \left(\frac{\beta_D (H + \theta A) + \beta_E E}{N} - G\right), \\ \frac{\mathrm{d}\lambda_2}{\mathrm{d}t} &= -\lambda_1 \left(G - \frac{\beta_E S}{N}\right) + \lambda_2 \left(d + au + hu - \frac{\beta_E S}{N} + G\right) - \lambda_3 hu - \lambda_4 au - 2\left(A_1 + A_3 (a+h) u\right)\left(A_1 E + A_2 H + A_3 (a+h) uE\right), \\ \frac{\mathrm{d}\lambda_3}{\mathrm{d}t} &= -\lambda_1 \left(G - \frac{\beta_D S}{N}\right) + \lambda_2 \left(G - \frac{\beta_D S}{N}\right) + \lambda_3 \left(d + \mu_h + \sigma\right) - \lambda_4 \sigma - 2A_2 \left(A_1 E + A_2 H + A_3 (a+h) uE\right), \\ \frac{\mathrm{d}\lambda_4}{\mathrm{d}t} &= -\lambda_1 \left(G - \frac{\beta_D \theta S}{N}\right) + \lambda_2 \left(G - \frac{\beta_D \theta S}{N}\right) + \lambda_4 \left(d + \mu_a\right), \end{aligned} \tag{4.9}$$

with the transversality conditions

$$\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = 0.$$

By solving Eq. (4.8) and using the property of the control space, the optimal control can be expressed as

$$u^*(t) = \max\left\{\min\left\{\frac{\lambda_2(a+h)E - \lambda_3 hE - \lambda_4 aE - 2A_3(a+h)E(A_1E + A_2H)}{2\left[A_3(a+h)E\right]^2}, \min\left\{\frac{u_{\max}}{a}, \frac{u_{\max}}{h}\right\}\right\}, 0\right\}. \tag{4.10}$$

According to Eqs. (2.1), (2.2), and (4.10), the optimal diagnostic rates related to HIV-positive cases and AIDS cases are as follows:

$$\kappa_H^*(t) = h \times u^*(t), \tag{4.11}$$

$$\kappa_A^*(t) = a \times u^*(t). \tag{4.12}$$

C. Numerical simulations

In this subsection, we numerically demonstrate the correlation between the optimal diagnostic rates, the level of attention paid to infected individuals, and the size of the HIV/AIDS epidemic using a forward–backward sweep method.[47]

In the following simulations, we investigate two scenarios to show the effectiveness of the optimal diagnostic strategy. In Scenario 1, we fix the level of attention paid to diagnosed infected individuals and study the impact of different levels of attention paid to undiagnosed infected individuals on the optimal diagnostic rates and the size of the HIV/AIDS epidemic. Let $A_2 = A_3 = 1$ and consider the following four cases: In Case 1, Case 2, and Case 3, the level of attention paid to undiagnosed infected individuals decreases successively, meaning that the values of A_1 are 10, 1, and 0.1, respectively. Furthermore, we provide uncontrolled solutions (Case 4) for comparison in simulations to demonstrate the effectiveness of the optimal strategy. In Scenario 2, we set $A_1 = 1$ and consider the following four cases: In Case 5, Case 6, and Case 7, the values of A_2 are 10, 1, and 0.1, respectively, and $A_3 = A_2$. In addition, we provide uncontrolled solutions (Case 8) for comparison. The simulation results for Scenario 1 and Scenario 2 are displayed in Figs. 4 and 5, respectively. Unless otherwise stated, parameters and initial conditions used in each case are listed in Table I.

Figures 4(e) and 4(f) show that the level of attention paid to undiagnosed infected individuals is always positively correlated with the optimal diagnostic rates. Figures 4(a)–4(c) show that if the same level of attention (i.e., Case 2: $A_1 = A_2 = A_3 = 1$) is paid to undiagnosed infected individuals, diagnosed HIV-positive individuals, and newly infected individuals, the number of undiagnosed infected individuals can be effectively reduced, and the size of the HIV/AIDS epidemic at the terminal time is smaller than that in an uncontrolled case [see Fig. 6(a)]. Furthermore, we assume that the level of attention paid to undiagnosed infected individuals is ten times higher than that of other infected individuals (i.e., Case 1: $A_1 = 10$, $A_2 = A_3 = 1$), and the size of infected population at the terminal time is even smaller compared with that in Case 2. However, if the level of attention paid to diagnosed HIV-positive individuals and

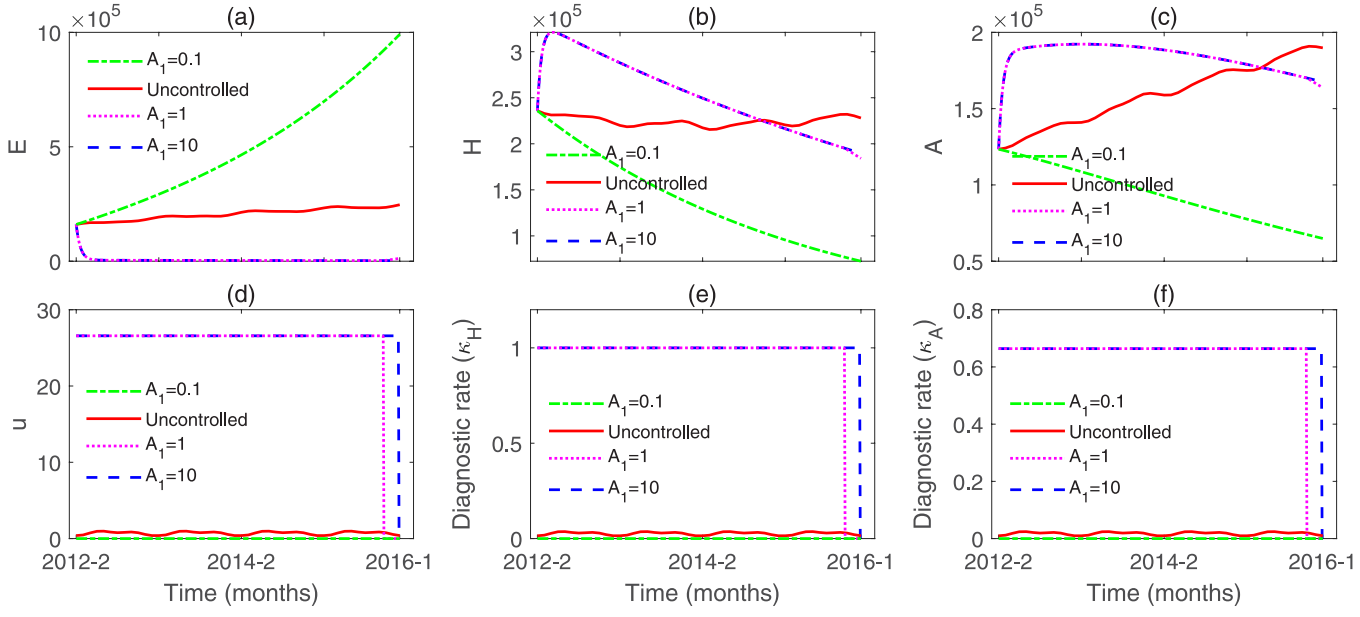

FIG. 4. Numerical simulation of Scenario 1. Subfigures (a)–(c) show the number of undiagnosed infected individuals, diagnosed HIV-positive individuals, and diagnosed AIDS patients, respectively. Subfigures (d)–(f) show the optimal solution of the control variable and diagnostic rates, respectively, where $A_2 = A_3 = 1$, $u_{\max} = 1$. The blue dashed line, the pink dotted line, the green dashed–dotted line, and the red solid line represent Case 1, Case 2, Case 3, and Case 4, respectively.

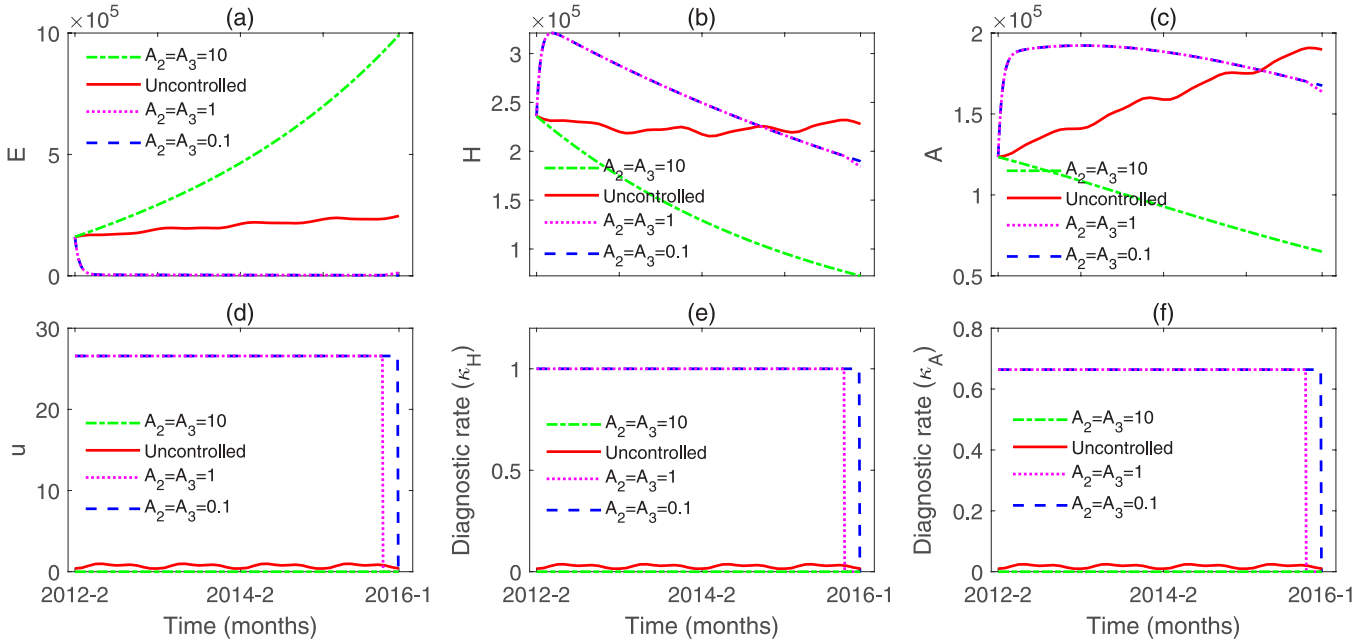

FIG. 5. Numerical simulation of Scenario 2. Subfigures (a)–(c) show the number of undiagnosed infected individuals, diagnosed HIV-positive individuals, and diagnosed AIDS patients, respectively. Subfigures (d)–(f) show the optimal solution of the control variable and diagnostic rates, respectively, where $A_1 = 1$, $u_{max} = 1$. The green dashed–dotted line, the pink dotted line, the blue dashed line, and the red solid line represent Case 5, Case 6, Case 7, and Case 8, respectively.

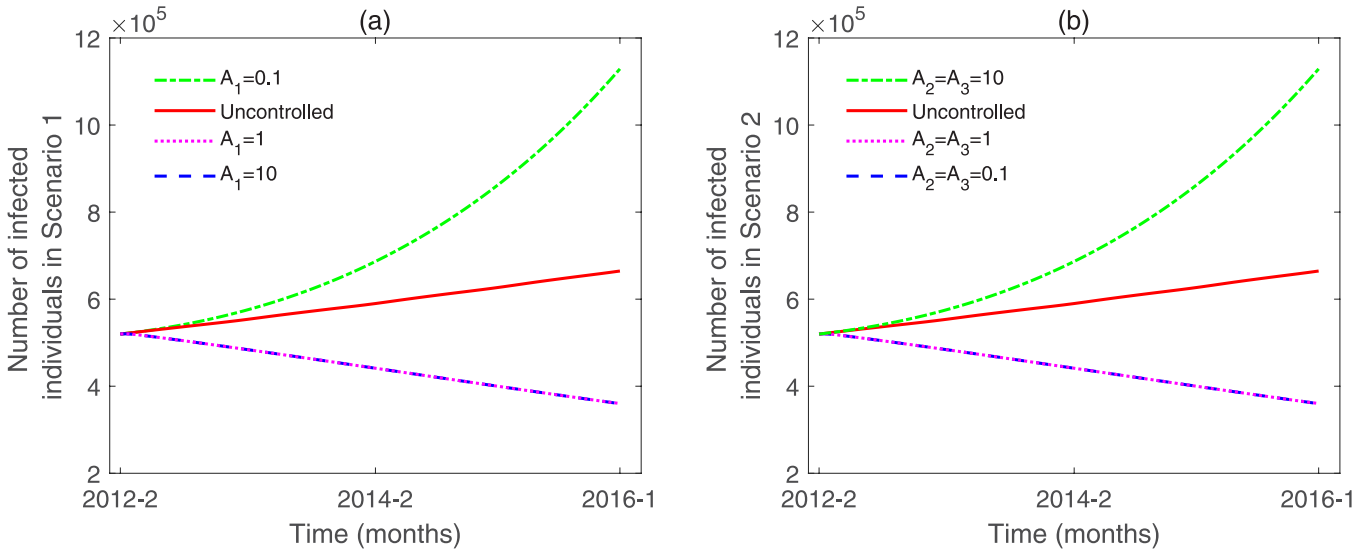

FIG. 6. The number of infected individuals in Scenario 1 and Scenario 2. Subfigures (a) and (b) show the number of infected individuals in Scenarios 1 and 2, respectively, including undiagnosed infected individuals, diagnosed HIV-positive individuals, and newly infected individuals. The meanings represented by the lines in subfigures (a) and (b) are the same as those in Figs. 4 and 5, respectively.

newly infected individuals is ten times higher than that paid to undiagnosed infected individuals (i.e., Case 3: $A_1 = 0.1$, $A_2 = A_3 = 1$), the size of infected population at the terminal time is larger than that in an uncontrolled case.

In addition, when the level of attention paid to undiagnosed infected individuals is higher or lower (Case 1 or Case 3), an increase or decrease in the number of diagnosed infected individuals at the early stage will always be accompanied by a decrease or increase in the number of undiagnosed infected individuals. Over time, the number of undiagnosed cases remains low in Case 1, and the number of diagnosed cases first increases and then decreases. However, in Case 3, the number of undiagnosed cases has been increasing, while the number of diagnosed cases has been decreasing, and increasing faster than decreasing. Thus, reducing the level of attention paid to undiagnosed infected cases may reduce the number of diagnosed infected cases in the short term, but the size of the epidemic has been increasing. If undiagnosed infected population in HIV transmission is taken seriously, the epidemic will be effectively controlled. The numerical results of Scenario 2 shown in Figs. 5 and 6(b) are the same as those of Scenario 1 shown in Figs. 4 and 6(a), which also indicates that paying more attention to undiagnosed infected individuals who are more infectious is key to controlling the HIV/AIDS epidemic.

V. SUMMARY AND DISCUSSION

In this work, we use the periodic epidemic model to analyze the impact of seasonal testing on HIV transmission patterns in China and how to effectively control the HIV/AIDS epidemic. The model is established based on the reported data. The reported outpatient data show that the monthly number of individuals who are tested for an HIV antibody in VCT clinics shows seasonal characteristics. We infer that the seasonal testing is a driving factor for the seasonality of new cases. If the changes in the new cases lead to the changes in the number of individuals who are tested for an HIV antibody, then there will be a time lag between the two changes due to delayed reporting, which is two months.[3] As is shown in Figs. 1(a), 2(a), and 2(b), the time lag does not exist. Therefore, we assume that the diagnostic rates associated with HIV-positive individuals and AIDS patients have periodic characteristics and construct a periodic function about the diagnostic rates. The new case data provided by the China CDC indicate that the undiagnosed infected individuals will be reported as HIV-positive cases or AIDS cases after they are diagnosed. Thus, we consider the compartment representing HIV-positive cases and the compartment representing AIDS cases in the model, and the inputs of both compartments are related to the periodic diagnostic rates. In summary, the model with periodic diagnostic rates is developed based on real data. Therefore, the results obtained from the model are reliable.

Several conclusions of this work are as follows. First, we conduct theoretical analysis of the periodic model. The basic reproduction number, R_0, of the model is obtained. When $R_0 < 1$, the disease-free periodic solution is globally stable. When $R_0 > 1$, the model is uniformly persistent, and there is at least one positive periodic solution. Therefore, the value of the epidemic threshold, R_0, determines whether the HIV/AIDS epidemic can be controlled. Correlation analysis shows that increasing the diagnostic rates can reduce R_0, thereby eliminating the epidemic. In addition, we use the periodic epidemic model to fit both the number of new HIV-positive cases and new AIDS cases, and the results suggest that the seasonality of the number of individuals who are tested for an HIV antibody in VCT clinics contributes to the seasonal patterns in new cases. The causes of seasonal patterns can be divided into four categories, namely, survival of pathogen outside hosts, host behavior, host immune function, and abundance of vectors and non-human hosts.[22] Our analysis suggests that the emergence of seasonal characteristics of the HIV/AIDS epidemic in China can be attributed to host behavior.

Furthermore, we solve the optimal diagnostic strategy under limited resources. We propose a more feasible objective functional to minimize the size of infected population. The infected population in the objective functional is consisted of newly infected population and existing infected population. The size of newly infected population is estimated by the product of the control variable and the number of undiagnosed infected individuals. The results show that the higher the level of attention paid to undiagnosed infected individuals, the greater the values of the optimal diagnostic rates and the smaller the size of the HIV/AIDS epidemic in the terminal time. In addition, higher diagnostic rates will inevitably lead to an increase in the number of new diagnosed cases and a decrease in the number of undiagnosed infected individuals at the early stage. Over time, the number of undiagnosed individuals is minimized, and as a result, the number of diagnosed infected individuals is also minimized. Therefore, while other interventions remain unchanged, focusing on undiagnosed infected individuals will promote the transfer of individuals from the compartment representing undiagnosed infected individuals to the compartment representing diagnosed infected individuals, thereby reducing the number and infectivity of infectious sources.

We discussed the impact of the seasonality in tests on the HIV transmission patterns. We plan to investigate the mechanism behind the seasonality of the tests in the following study, but it is natural to hypothesize that the seasonality in the mass public movement (from rural to urban) and the health access availability could be potential factors. Our study has several limitations. In the model, we only focus on high-risk behaviors (high-risk sex or needle sharing). However, new cases caused by mother-to-child transmission, etc., are not separated from the data used for model fitting, which may lead to an overestimation of the infectivity of infected individuals. Using average life expectancy to approximate natural death rate without considering age heterogeneity may underestimate the risk of HIV transmission.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Kai Zhang and Ling Xue conceptualized the problem, investigated the model, and wrote the manuscript. Xuezhi Li, Daihai He, and Zhihang Peng validated the model, analysis, and numerical simulations. All authors reviewed the manuscript.

Kai Zhang: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Validation (equal); Writing – original draft (equal). **Ling Xue:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Validation (equal); Writing – original draft (equal). **Xuezhi Li:** Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Software (equal); Validation (equal); Writing – original draft (equal). **Daihai He:** Data curation (equal); Formal analysis (equal); Software (equal); Validation (equal); Writing – original draft (equal). **Zhihang Peng:** Data curation (equal); Formal analysis (equal); Validation (equal); Writing – original draft (equal).

DATA AVAILABILITY

The data that support the findings of this study are available within the article.

APPENDIX A: PROOF OF THEOREM 2.1

First, we prove that $S(t) \geq 0, E(t) \geq 0, H(t) \geq 0$, and $A(t) \geq 0$ with the initial value $S(0) \geq 0, E(0) \geq 0, H(0) \geq 0$, and $A(0) \geq 0$ for all $t \geq 0$.

From the first equation of Model (2.4), we have

$$S(t) = S(0)\, e^{-\int_0^t (\psi(\tau)+d)\mathrm{d}\tau} + e^{-\int_0^t (\psi(\tau)+d)\mathrm{d}\tau} \int_0^t U e^{\int_0^{\tau_1} (\psi(\tau)+d)\mathrm{d}\tau} \mathrm{d}\tau_1,$$

$$\forall t \geq 0,$$

where $\psi(t) = \beta_E E / N + \beta_D (H + \theta A) / N$. Hence, $S(t) \geq 0$ when $S(0) \geq 0$ for all $t \geq 0$.

Let

$$W(t) = \min\{E(t), H(t), A(t)\}, \quad \forall t \geq 0.$$

Assuming that $W(t_1) = 0$, $t_1 \geq 0$. If $W(t) = E(t)$, then $E(t_1) = 0$, $H(t_1) \geq 0$, and $A(t_1) \geq 0$. From the second equation of Model (2.4), we have

$$\left.\frac{\mathrm{d}E}{\mathrm{d}t}\right|_{t=t_1} = \beta_D \frac{S}{N}(H + \theta A) \geq 0.$$

Similarly, if $W(t) = H(t)$ or $W(t) = A(t)$, we have

$$\left.\frac{\mathrm{d}H}{\mathrm{d}t}\right|_{t=t_1} = \kappa_H(t) E \geq 0$$

and

$$\left.\frac{\mathrm{d}A}{\mathrm{d}t}\right|_{t=t_1} = \kappa_A(t) E + \sigma H \geq 0,$$

respectively. Hence, when the initial values $S(0) \geq 0$, $E(0) \geq 0$, $H(0) \geq 0$, and $A(0) \geq 0$, the solution of Model (2.4) $[S(t), E(t), H(t), A(t)] \in \mathbb{R}^4_+$.

Next, we show that the solution is bounded. From Model (2.4), we have

$$\frac{\mathrm{d}N}{\mathrm{d}t} = U - dN - \mu_h H - \mu_a A \leq U - dN.$$

Thus,

$$N(t) \leq \frac{U}{d} + \left(N(0) - \frac{U}{d}\right) e^{-dt},$$

which yields that

$$\lim_{t\to\infty} N(t) \leq \frac{U}{d}.$$

Therefore, the region Ω is a positively invariant set of Model (2.4). This completes the proof.

APPENDIX B: BASIC REPRODUCTION NUMBER

Before defining the basic reproduction number of Model (2.4), we first verify whether the conditions (A1)–(A7) proposed by Wang and Zhao[48] are satisfied. Let $x_i = (E, H, A, S)^T$, $i = 1, \ldots, 4$, then the compartments can be divided into two types: infected compartments, labeled by $i = 1, 2, 3$, and an uninfected compartment, labeled by $i = 4$. Using the notation used in Ref. 48, Model (2.4) can be written as

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = \mathcal{F}_i(t,x) - \mathcal{V}_i(t,x) \triangleq f_i(t,x), \quad i = 1, \ldots, 4,$$

where $\mathcal{V}_i(t,x) = \mathcal{V}_i^-(t,x) - \mathcal{V}_i^+(t,x)$, and

$$\mathcal{F}(t,x) = \begin{bmatrix} \beta_E \frac{S}{N} E + \beta_D \frac{S}{N}(H + \theta A) \\ 0 \\ 0 \\ 0 \end{bmatrix},$$

$$\mathcal{V}^-(t,x) = \begin{bmatrix} \kappa_H(t) E + \kappa_A(t) E + dE \\ \sigma H + dH + \mu_h H \\ dA + \mu_a A \\ \beta_E \frac{S}{N} E + \beta_D \frac{S}{N}(H + \theta A) + dS \end{bmatrix},$$

$$\mathcal{V}^+(t,x) = \begin{bmatrix} 0 \\ \kappa_H(t) E \\ \kappa_A(t) E + \sigma H \\ U \end{bmatrix}.$$

It is clear that conditions (A1)–(A5) are satisfied, where

(A1) For each $1 \leq i \leq 4$, the functions $\mathcal{F}_i(t,x)$, $\mathcal{V}_i^-(t,x)$, and $\mathcal{V}_i^+(t,x)$ are nonnegative and continuous on $\mathbb{R} \times \mathbb{R}^4_+$ and continuously differential with respect to x.

(A2) There is a positive real number ω such that for each $1 \leq i \leq 4$, the functions $\mathcal{F}_i(t,x)$, $\mathcal{V}_i^-(t,x)$, and $\mathcal{V}_i^+(t,x)$ are ω-periodic in t.

(A3) If $x_i = 0$, then $\mathcal{V}_i^- = 0$. In particular, if $x \in X_s$, then $\mathcal{V}_i^- = 0$ for $i = 1, 2, 3$, where X_s is the set of all disease-free states:

$$X_s := \{x \geq 0 : x_i = 0, \forall i = 1, 2, 3\}.$$

(A4) $\mathcal{F}_i = 0$ for $i = 4$.
(A5) If $x \in X_s$, then $F_i(x) = V_i^+(x) = 0$ for $i = 1, 2, 3$.

We define

$$M(t) := \left(\frac{\partial f_4\left(t, x^0(t)\right)}{\partial x_4}\right)_{1\times 1},$$

where $x^0(t) = \left(0, 0, 0, \frac{U}{d}\right)$ is the disease-free periodic solution. Let $\Phi_M(t)$ be the monodromy matrix of the linear ω-periodic model $\frac{dz}{dt} = M(t)z$. Furthermore, we obtain $\Phi_M(t) = e^{-dt}$, that is, $\rho(\Phi_M(\omega)) < 1$, where $\rho(\Phi_M(\omega))$ is the spectral radius of $\Phi_M(\omega)$. Thus, condition

(A6) $\rho(\Phi_M(\omega)) < 1$

is satisfied.

Following Ref. 48, we have

$$D_x\mathcal{F}\left(t, x^0(t)\right) = \begin{pmatrix} F(t) & 0 \\ 0 & 0 \end{pmatrix}, \; D_x\mathcal{V}\left(t, x^0(t)\right) = \begin{pmatrix} V(t) & 0 \\ J(t) & -M(t) \end{pmatrix},$$

where $F(t)$ and $V(t)$ are two 3×3 matrices defined by

$$F(t) = \left(\frac{\partial \mathcal{F}_i\left(t, x^0(t)\right)}{\partial x_j}\right)_{1\leq i,j\leq 3}, \; V(t) = \left(\frac{\partial \mathcal{V}_i\left(t, x^0(t)\right)}{\partial x_j}\right)_{1\leq i,j\leq 3},$$

respectively, and $J(t)$ is a 1×3 matrix. Then,

$$F(t) = \begin{bmatrix} \beta_E & \beta_D & \theta\beta_D \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

$$V(t) = \begin{bmatrix} \kappa_H(t) + \kappa_A(t) + d & 0 & 0 \\ -\kappa_H(t) & \sigma + d + \mu_h & 0 \\ -\kappa_A(t) & -\sigma & d + \mu_a \end{bmatrix}.$$

It is obvious that $F(t)$ is non-negative, and $-V(t)$ is cooperative in the sense that the off-diagonal elements of $-V(t)$ are non-negative.

Let $Y(t, s)$, $t \geq s$, be the evolution operator of the linear ω-periodic model,

$$\frac{dy}{dt} = -V(t)y, \tag{B1}$$

that is, for each $s \in \mathbb{R}$, the 3×3 matrix $Y(t, s)$ satisfies

$$\frac{d}{dt}Y(t, s) = -V(t)Y(t, s), \; \forall t \geq s, \; Y(s, s) = \boldsymbol{I},$$

where $\boldsymbol{I}$ is the 3×3 identity matrix. Let $\Phi_{-V}(t)$ be the monodromy matrix of model (B1), and it is clear that $\rho(\Phi_{-V}(\omega)) < 1$. Therefore, condition

(A7) $\rho(\Phi_{-V}(\omega)) < 1$

is also satisfied.

According to the theory proposed by Wang and Zhao,[48] we assume that $\phi(s)$, ω-periodic in s, is the initial distribution of infected individuals. Therefore, $F(s)\phi(s)$ is the distribution of newly infected individuals produced by the infected individuals who were introduced at time s, and $Y(t, s)F(s)\phi(s)$ represents the distribution of infected individuals who were newly infected at time s and remain in the infected compartments at time t, $t \geq s$. We define

$$\begin{aligned}\psi(t) &:= \int_{-\infty}^{t} Y(t, s)F(s)\phi(s)\,ds \\ &= \int_0^{\infty} Y(t, t-a)F(t-a)\phi(t-a)\,da, \; a \in [0, \infty),\end{aligned}$$

where $\psi(t)$ denotes the distribution of accumulated newly infected individuals at time t produced by all infected individuals $\phi(s)$ introduced up to t.

Let C_ω be the ordered Banach space of all ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^3$, which has the corresponding maximum norm $\|\cdot\|$ and the positive cone $C_\omega^+ := \{\phi \in C_\omega : \phi(t) \geq 0, \forall t \in \mathbb{R}\}$. Then, we define the next infection operator $L : C_\omega \to C_\omega$ as follows,

$$(L\phi)(t) = \int_0^{\infty} Y(t, t-a)F(t-a)\phi(t-a)\,da, \; \forall t \in \mathbb{R}, \; \phi \in C_\omega, \tag{B2}$$

and define the basic reproduction number of periodic epidemic model (2.4) by

$$R_0 := \rho(L),$$

where $\rho(L)$ is the spectral radius of L.

Lemma B.1: *[See Theorem 2.2 in Wang and Zhao[48]] Assume that (A1)–(A7) hold. The following statements are valid:*

(i) $R_0 = 1$ *if and only if* $\rho(\Phi_{F-V}(\omega)) = 1$.
(ii) $R_0 > 1$ *if and only if* $\rho(\Phi_{F-V}(\omega)) > 1$.
(iii) $R_0 < 1$ *if and only if* $\rho(\Phi_{F-V}(\omega)) < 1$.

Therefore, the disease-free periodic solution $x^0(t)$ is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Following Ref. 48, we introduce the linear ω-periodic model,

$$\frac{d\omega}{dt} = \left[-V(t) + \frac{F(t)}{\lambda}\right]\omega, \; t \in \mathbb{R}, \tag{B3}$$

where parameter $\lambda \in (0, \infty)$, and

$$-V(t) + \frac{F(t)}{\lambda} = \begin{bmatrix} \frac{\beta_E}{\lambda} - \kappa_H(t) - \kappa_A(t) - d & \frac{\beta_D}{\lambda} & \frac{\theta\beta_D}{\lambda} \\ \kappa_H(t) & -(\sigma + d + \mu_h) & 0 \\ \kappa_A(t) & \sigma & -(d + \mu_a) \end{bmatrix}.$$

Let $W(t, s, \lambda)$, $t \geq s$, $s \in \mathbb{R}$, be the evolution operator of Model (B3) on $\mathbb{R}^3$. We use the numerical algorithm to calculate the basic reproduction number according to the following Lemma.

Lemma B.2: *[See Theorem 2.1 in Wang and Zhao[48]] Let (A1)–(A7) hold. Then, the following statements are valid:*

(i) *If* $\rho(W(\omega,0,\lambda))=1$ *has a positive solution* λ_0, *then* λ_0 *is an eigenvalue of L. Hence,* $R_0>0$.
(ii) *If* $R_0>0$, *then* $\lambda=R_0$ *is the unique solution of* $\rho(W(\omega,0,\lambda))=1$.
(iii) $R_0=0$ *if and only if* $\rho(W(\omega,0,\lambda))<1$ *for all* $\lambda>0$.

APPENDIX C: GLOBAL STABILITY OF A DISEASE-FREE PERIODIC SOLUTION

Theorem C.1: *Disease-free periodic solution* $x^0=\left(\frac{U}{d},0,0,0\right)$ *is globally asymptotically stable if* $R_0<1$ *in* Ω.

Proof. From Lemma B.1, we obtain that the disease-free periodic solution $x^0=\left(\frac{U}{d},0,0,0\right)$ is locally asymptotically stable when $R_0<1$. Therefore, we only need to prove that x^0 is globally attractive when $R_0<1$.

Obviously, $S(t)\le N(t)$. Hence, $S(t)/N(t)\le 1+\eta$ for $\forall\eta>0$. We consider the following linear model:

$$\begin{aligned}\frac{d\hat{E}}{dt}&=\beta_E(1+\eta)\hat{E}+\beta_D(1+\eta)\left(\hat{H}+\theta\hat{A}\right)-\kappa_H(t)\hat{E}\\&\quad-\kappa_A(t)\hat{E}-d\hat{E},\\\frac{d\hat{H}}{dt}&=\kappa_H(t)\hat{E}-\sigma\hat{H}-d\hat{H}-\mu_h\hat{H},\\\frac{d\hat{A}}{dt}&=\kappa_A(t)\hat{E}+\sigma\hat{H}-d\hat{A}-\mu_a\hat{A}.\end{aligned}\tag{C1}$$

Let $x=\left(\hat{E},\hat{H},\hat{A}\right)^T$, Model (C1) can be rewritten as the following equation:

$$\frac{dx}{dt}=(F(t)-V(t)+\eta m(t))x,$$

where

$$m(t)=\begin{bmatrix}\beta_E & \beta_D & \beta_D\theta\\0&0&0\\0&0&0\end{bmatrix}.$$

By Lemma 2.1 in Zhang and Zhao,[49] there exists a positive, ω-periodic function $\bar{v}(t)$ such that $v(t)=e^{pt}\bar{v}(t)$ is a solution of Model (C1), where $p=\frac{1}{\omega}\ln\rho\left(\Phi_{F-V+\eta m}(\omega)\right)$. Since $\rho\left(\Phi_{F-V+\eta m}(\omega)\right)$ is continuous for all small η, we can choose η small enough such that $\rho\left(\Phi_{F-V+\eta m}(\omega)\right)<1$. Therefore, $v(t)\to 0$ as $t\to\infty$.

For any nonnegative initial value $\left(\hat{S}(0),\hat{E}(0),\hat{H}(0),\hat{A}(0)\right)$ of Model (C1), there is a sufficiently large $M>0$ such that

$$\left(\hat{E}(0),\hat{H}(0),\hat{A}(0)\right)^T\le M\bar{v}(0).$$

Then,

$$\left(\hat{E}(t),\hat{H}(t),\hat{A}(t)\right)^T\le Mv(t),\quad\forall t\ge 0,$$

where $Mv(t)$ is also a solution of Model (C1).[50] By the comparison principle,[51] it follows that

$$(E(t),H(t),A(t))^T\le\left(\hat{E}(t),\hat{H}(t),\hat{A}(t)\right)^T\le Mv(t),\quad\forall t\ge 0.$$

Hence,

$$\lim_{t\to\infty}E(t)=0,\lim_{t\to\infty}H(t)=0,\lim_{t\to\infty}A(t)=0.$$

By the theory of asymptotically autonomous semiflows,[52] we have $S(t)\to\frac{U}{d}$ as $t\to\infty$. Therefore, the disease-free periodic solution $x^0=\left(\frac{U}{d},0,0,0\right)$ is globally attractive. This completes the proof. □

APPENDIX D: UNIFORM PERSISTENCE OF THE DISEASE

Theorem D.1: *If* $R_0>1$, *there exists a positive constant* ε *such that the solution* $(S(t),E(t),H(t),A(t))$ *with the initial value condition* $x_0=(S_0,E_0,H_0,A_0)$ *of Model (2.4) satisfies*

$$\liminf_{t\to\infty}(E(t),H(t),A(t))>(\varepsilon,\varepsilon,\varepsilon),$$

and Model (2.4) admits at least one positive periodic solution.

Proof. We define

$$\begin{aligned}X&:=\mathbb{R}^4_+,\\X_0&:=\{(S,E,H,A)\in X:E>0,H>0,A>0\},\\\partial X_0&:=X\backslash X_0=\{(S,E,H,A)\in X:E=0\text{ or }H=0\text{ or }A=0\}.\end{aligned}$$

Let $P:X\to X$ be the Poincaré map associated with Model (2.4), that is,

$$P(x_0)=\varphi(\omega,x_0),\quad\forall x_0\in X,$$

where $\varphi(\omega,x_0)$ is the unique solution of Model (2.4) with $\varphi(0,x_0)=x_0$, ω represents the period. Obviously,

$$P^m(x_0)=\varphi(m\omega,x_0),\quad\forall m\ge 0.$$

Theorem 2.1 implies that the solutions of Model (2.4) are uniformly bounded, which means that P is point dissipative on X. By Definition 1.1.2 and Theorem 1.1.3 in Zhao,[53] P is compact and has a global attractor.

Set

$$\begin{aligned}M_\partial&=\{x_0\in\partial X_0:P^m(x_0)\in\partial X_0,\forall m\ge 0\},\\\Gamma&=\{(S,E,H,A)\in X:E=0,H=0,A=0\}.\end{aligned}$$

We first prove that $M_\partial=\Gamma$. Clearly, $\Gamma\subseteq M_\partial\subseteq\partial X_0$. Hence, we only need to prove that $M_\partial\subseteq\Gamma$. For any $x_0\in\partial X_0\backslash\Gamma$, the following inequality is established based on Model (2.4):

$$E(t) \geq e^{-(\Delta_1+\Delta_2+d)t}\left(E(0)+\int_0^t\left(\beta_E\frac{S(\tau)}{N(\tau)}E(\tau)+\beta_D\frac{S(\tau)}{N(\tau)}(H(\tau)+\theta A(\tau))\right)e^{(\Delta_1+\Delta_2+d)\tau}\mathrm{d}\tau\right)>0,$$

$$H(t) \geq e^{-(\sigma+d+\mu_h)t}\left(H(0)+\int_0^t\Delta_1 E(\tau)\,e^{(\sigma+d+\mu_h)\tau}\mathrm{d}\tau\right)>0,$$

$$A(t) \geq e^{-(d+\mu_a)t}\left(A(0)+\int_0^t(\Delta_2 E(\tau)+\sigma H(\tau))\,e^{(\sigma+d+\mu_h)\tau}\mathrm{d}\tau\right)>0,$$

where $\Delta_1=\min\{\kappa_H(t),\forall t\geq 0\}$, $\Delta_2=\min\{\kappa_A(t),\forall t\geq 0\}$, this implies that for $t>0$ sufficiently small, $(S,E,H,A)\in X_0$, then $x_0\notin M_\partial$. It is easy to see that for all $x_0\in M_\partial$, we have $x_0\in\Gamma$. Hence, $M_\partial\subseteq\Gamma$.

By Theorem C.1, we know that $x^0=\left(\frac{U}{d},0,0,0\right)$ is globally asymptotically stable in set M_∂. Therefore, $A_\partial=\left\{\left(\frac{U}{d},0,0,0\right)\right\}$ is the maximal compact invariant set of P in ∂X_0. Note that every orbit in M_∂ approaches to A_∂, and A_∂ is acyclic and isolated in M_∂.[54]

Next, we prove that $W^s(A_\partial)\cap X_0=\emptyset$ and A_∂ is isolated in set X. By the continuity of the solutions with respect to the initial values, there exists a $\varrho>0$ such that for all $x_0\in X_0$ with $\left\|x_0-x^0\right\|\leq\varrho$,

$$\left\|\varphi(t,x_0)-\varphi\left(t,x^0\right)\right\|\leq\varepsilon,\quad\forall\varepsilon>0,\quad\forall t\in[0,\omega].$$

We further claim that

$$\limsup_{m\to\infty}\mathbf{d}\left(P^m(x_0),x^0\right)\geq\varrho,\tag{D1}$$

where $\mathbf{d}(x,y)$ represents the distance between x and y. Using the counter-evidence method, we assume that (D1) does not hold, that is,

$$\limsup_{m\to\infty}\mathbf{d}\left(P^m(x_0),x^0\right)<\varrho$$

for some $x_0\in X_0$. Without loss of generality, we assume that $\mathbf{d}\left(P^m(x_0),x^0\right)<\varrho,\forall m\geq 0$. It follows that

$$\left\|\varphi(t,P^m(x_0))-\varphi\left(t,x^0\right)\right\|<\varepsilon,\quad\forall m\geq 0,\quad\forall t\in[0,\omega].$$

For any $t\geq 0$, let $t=m\omega+t'$, where $t'\in[0,\omega)$, and m is the largest integer less than or equal to $\frac{t}{\omega}$, we have

$$\left\|\varphi(t,x_0)-\varphi\left(t,x^0\right)\right\|=\left\|\varphi\left(t',P^m(x_0)\right)-\varphi\left(t',x^0\right)\right\|<\varepsilon,\quad\forall t\geq 0.$$

It follows that there exists $\omega'>0$ such that $\frac{U}{d}-\varepsilon\leq S(t)\leq\frac{U}{d}+\varepsilon$, $0\leq E(t)\leq\varepsilon$, $0\leq H(t)\leq\varepsilon$, $0\leq A(t)\leq\varepsilon$, $\frac{U}{d}-\varepsilon\leq N(t)\leq\frac{U}{d}+4\varepsilon$ for $t>\omega'$. From the second equation of Model (2.4), we obtain

$$\begin{aligned}\frac{\mathrm{d}E}{\mathrm{d}t}&\geq\beta_E\frac{U/d-\varepsilon}{U/d+4\varepsilon}E+\beta_D\frac{U/d-\varepsilon}{U/d+4\varepsilon}(H+\theta A)-\kappa_H(t)E\\&\quad-\kappa_A(t)E-dE\\&\geq\beta_E\left(1-\frac{5\varepsilon}{U/d+4\varepsilon}\right)E+\beta_D\left(1-\frac{5\varepsilon}{U/d+4\varepsilon}\right)(H+\theta A)\\&\quad-\kappa_H(t)E-\kappa_A(t)E-dE.\end{aligned}$$

The following comparison model is considered:

$$\begin{aligned}\frac{\mathrm{d}\tilde{E}}{\mathrm{d}t}&=\beta_E(1-\tilde{\eta})\tilde{E}+\beta_D(1-\tilde{\eta})\left(\tilde{H}+\theta\tilde{A}\right)-\kappa_H(t)\tilde{E}\\&\quad-\kappa_A(t)\tilde{E}-d\tilde{E},\\\frac{\mathrm{d}\tilde{H}}{\mathrm{d}t}&=\kappa_H(t)\tilde{E}-\sigma\tilde{H}-d\tilde{H}-\mu_h\tilde{H},\\\frac{\mathrm{d}\tilde{A}}{\mathrm{d}t}&=\kappa_A(t)\tilde{E}+\sigma\tilde{H}-d\tilde{A}-\mu_a\tilde{A},\end{aligned}\tag{D2}$$

where $\tilde{\eta}=\frac{5\varepsilon}{U/d+4\varepsilon}$. Let $x=\left(\tilde{E},\tilde{H},\tilde{A}\right)^T$, Model (D2) can be rewritten as the following equation:

$$\frac{\mathrm{d}x}{\mathrm{d}t}=\left(F(t)-V(t)-\tilde{\eta}\tilde{m}(t)\right)x,$$

where

$$\tilde{m}(t)=\begin{bmatrix}\beta_I&\beta_D&\beta_D\theta\\0&0&0\\0&0&0\end{bmatrix}.$$

By Lemma 2.1 in Zhang and Zhao,[49] there exists a positive ω-periodic function $\check{\nu}(t)$ such that $\tilde{\nu}(t)=e^{\tilde{p}t}\check{\nu}(t)$ is a solution of Model (D2), where $\tilde{p}=\frac{1}{\omega}\ln\rho\left(\Phi_{F-V-\tilde{\eta}\tilde{m}}(\omega)\right)$. Note that $\rho\left(\Phi_{F-V-\tilde{\eta}\tilde{m}}(\omega)\right)>1$, and $\tilde{p}$ is a positive constant. By the comparison principle, we obtain

$$\lim_{t\to\infty}(E(t),H(t),A(t))=(\infty,\infty,\infty),$$

which contradicts with $0\leq E(t)\leq\varepsilon$, $0\leq H(t)\leq\varepsilon$, $0\leq A(t)\leq\varepsilon$. Hence, $W^s(A_\partial)\cap X_0=\emptyset$ is proved and A_∂ is isolated in set X. By Theorem 1.3.1 in Zhao,[53] P is uniformly persistent with respect to $(X_0,\partial X_0)$. Thus, the solutions of Model (2.4) are uniformly persistent with respect to $(X_0,\partial X_0)$ by Theorem 3.1.1 in Zhao,[53] that is, there exists a positive constant ε such that the solution $(S(t),E(t),H(t),A(t))$ with the initial value condition $x_0=(S_0,E_0,H_0,A_0)$ of Model (2.4) satisfies

$$\liminf_{t\to\infty}(E(t),H(t),A(t))>(\varepsilon,\varepsilon,\varepsilon).$$

In addition, we prove the existence of a positive ω-period solution of Model (2.4), that is, P has a fixed point, denoted by $(S^*(0),E^*(0),H^*(0),A^*(0))\in X_0$. It is easy to see that $S^*(0)\geq 0$, $E^*(0)>0$, $H^*(0)>0$, and $A^*(0)>0$. We now prove that $S^*(0)>0$. Suppose that $S^*(0)=0$. From the first equation of Model (2.4),

we have

$$\frac{\mathrm{d}S^*(t)}{\mathrm{d}t} = U - \left(\beta_I \frac{1}{N^*} E + \beta_D \frac{1}{N^*}(H^* + \theta A^*) + d\right) S^*,$$

which yields that

$$S^*(t) = e^{\int_0^t -(\varpi(\tau_1)+d)\mathrm{d}\tau_1}\left[S^*(0) + \int_0^t U e^{\int_0^{\tau_2}(\varpi(\tau_1)+d)\mathrm{d}\tau_1}\mathrm{d}\tau_2\right]$$
$$= e^{\int_0^t -(\varpi(\tau_1)+d)\mathrm{d}\tau_1}\int_0^t U e^{\int_0^{\tau_2}(\varpi(\tau_1)+d)\mathrm{d}\tau_1}\mathrm{d}\tau_2,$$

where $\varpi(t) = \beta_E E^*/N^* + \beta_D(H^* + \theta A^*)/N^*$, and the following inequality can be obtained:

$$S^*(m\omega) = e^{\int_0^{m\omega} -(\varpi(\tau_1)+d)\mathrm{d}\tau_1}\int_0^{m\omega} U e^{\int_0^{\tau_2}(\varpi(\tau_1)+d)\mathrm{d}\tau_1}\mathrm{d}\tau_2 > 0.$$

From the periodicity of $S^*(t)$, we have $S^*(0) = S^*(m\omega) = 0$, $m = 1, 2, 3\ldots$, which is contradictory to $S^*(m\omega) > 0$. Thus, $S^*(0) > 0$.

From the above proof and the positive invariance of X_0, we obtain that

$$\varphi(t, (S^*(0), E^*(0), H^*(0), A^*(0))) \in \mathrm{Int}\left(\mathbb{R}^4_+\right), \quad \forall t > 0,$$

that is, $(S^*(0), E^*(0), H^*(0), A^*(0))$ is a positive fixed point of P, and $(S^*(t), E^*(t), H^*(t), A^*(t))$ is the positive ω-period solution of Model (2.4). This completes the proof. □

APPENDIX E: PLOT OF A PERIODIC SOLUTION

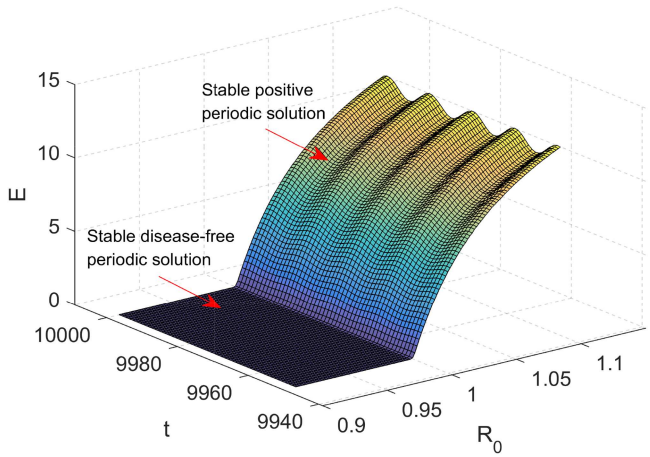

FIG. 7. The existence of a disease-free periodic solution and a positive periodic solution. When $R_0 < 1$, there exists a stable disease-free periodic solution. When $R_0 > 1$, there exists a stable positive periodic solution.

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