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Mathematical modeling of Breastfeeding's protective effects against HFMD in northern Thailand

Sherif Eneye Shuaib, Isanee Chesu, Arthit Intarasit, Pakwan Riyapan*

Department of Mathematics and Computer Science, Faculty of Science and Technology, Prince of Songkla University, Pattani, 94000, Thailand.

Abstract

According to the World Health Organization's guidelines, a two-year breastfeeding period is strongly recommended, with research demonstrating its significant benefits in reducing childhood illnesses and mortality rates. Acknowledging this evidence, this study aims to explore this recommendation by focusing on a specific infection, namely Hand, Foot, and Mouth Disease (HFMD). We do so by extending and analyzing an SEIR epidemic model uniquely designed for HFMD transmission and how it affects regional residency in Thailand. The proposed model examines two equilibria: disease-free and endemic, revealing local and global stability conditions determined by the basic reproduction number (R_{bfeed}). Our analysis includes global stability for both disease-free and endemic equilibrium points, using a quadratic Lyapunov function for the global stability assessment of the endemic point. Additionally, we conducted a sensitivity analysis of different parameters for the basic reproduction number to enhance our understanding of model dynamics. Finally, numerical simulations, which include the simulation of general dynamics, examining the impact of breastfeeding, data fitting, model validation, and predicting future HFMD forecasts, were conducted using RStudio and Python software. These simulations help us explore the effects of breastfeeding on HFMD transmission, offering insights into the potential implications for controlling hand, foot, and mouth disease among children in Thailand.

Keywords: Breastfeeding, hand foot, and mouth disease, mathematical model, rural and urban provinces.

2020 MSC: 92D30, 34D20, 92B05, 92D25.

1. Introduction

Enteroviruses are a genus of viruses that cause various types of illnesses in humans and are widely prevalent globally. They belong to the *Picornaviridae* family and include *polioviruses*, *coxsackieviruses*, *rhinoviruses*, and *echoviruses*. They are further divided into 12 species with over 200 distinct serotypes [42]. Diseases caused by enteroviruses include *Poliomyelitis*, *Pleurodynia*, *Hemorrhagic conjunctivitis*, *Pneumonia*, *Meningitis*, *Hand foot and Mouth Disease* (HFMD), and *Sinusitis*. Apart from the *poliovirus* vaccine, no other vaccine or effective treatment exists to curb the spread of the diseases caused by the different viruses. Though infections are typically self-limiting, they can result in significant morbidity and have an economic impact ([14, 28, 39]).

*Corresponding author
Email addresses: sherifeneyeshuaib@gmail.com (Sherif Eneye Shuaib), isanee062206@gmail.com (Isanee Chesu), arthit.i@psu.ac.th (Arthit Intarasit), pakwan.r@psu.ac.th (Pakwan Riyapan)

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HFMD is a prevalent viral infection caused by *enteroviruses*, typically the *Coxsackievirus A16* serotype, which is mainly transmitted through the fecal-oral route via direct or indirect contact with excretions from infected persons. The incubation period of HFMD ranges from 3 to 6 days, with preschool children under 5 years of age being the most commonly affected group. However, sporadic cases have been reported in adults [41]. The contagiousness of HFMD is most prominent during the acute phase of the illness, but the virus may persist in stools for up to 8 to 12 weeks following the infection [3]. There is currently no vaccine or treatment for HFMD, and preventive measures include avoiding direct contact with infective persons, disinfecting contaminated surfaces, and maintaining proper personal hygiene habits [6].

Since 2001, the Bureau of Epidemiology, Ministry of Public Health, Thailand (MOPH) mandated hospital-based surveillance of HFMD [3]. From 2007 to 2011, the reported HFMD cases in Thailand ranged from 2,000 to 18,000 and the annual mortality rate during this period ranged from 2 to 6 [4]. The first large-scale HFMD outbreak in Thailand occurred in 2012 ([36, 37]) followed by a second outbreak in 2016 [4]. Between 2012–2016, the prevalence of HFMD in Thailand was associated with the *CV-A6* or *CV-A16* virus. In 2017, a nationwide HFMD outbreak predominantly caused by *EV-A71*, along with *CV-A6* and *CV-A16*, affected many provinces of Thailand with Chanthaburi and Phayao provinces having the highest incidences ([5, 35]). The Thai Department of Disease Control reported 67,912 HFMD cases with six deaths in 2018 with the highest incidences observed in children aged 1, 2, and 3 years accounting for 26.04%, 23.57%, and 18.87%, respectively. With the frequent outbreaks, HFMD has been a critical health issue in Thailand, affecting children's health, their social life, and education as they require isolation from healthy children [18].

In 2001, the World Health Organization (WHO) issued a guideline recommending exclusive breastfeeding of infants for six months [31]. Empirical studies have established the numerous benefits of breastfeeding, including enhanced child development ([17, 30, 38]), academic performance ([29, 49]) and decreased risks of both infectious and noninfectious diseases such as otitis media, gastroenteritis, necrotizing enterocolitis, respiratory illness, sudden infant death syndrome, obesity, and hypertension [11]. Additionally, breastfeeding has been demonstrated to protect against enterovirus infections during infancy ([12, 40, 50]). The promotion of breastfeeding is an effective intervention in preventing infant deaths, with estimates suggesting that its implementation could potentially save the lives of 820,000 children under five years of age globally, particularly those below six months [13].

Exclusive breastfeeding for the first 6 months of an infant's life has been reported to protect against gastrointestinal tract infections ([10, 18, 40]). Maternal antibodies found in breast milk are believed to play a vital role in this protection, while lactoferrin is another factor that is useful in this aspect ([27, 32]). Zhu et al. [52] investigated whether breastfeeding and other factors influence the fever and disease course in children with hand, foot, and mouth disease (HFMD). The study involved 372 preschool children with HFMD, and the results revealed that prolonged exclusive breastfeeding, autumn birth, and high gestational age were protective factors against the incidence of fever in HFMD. Lin et al. [22] examined the protective effect of exclusive breastfeeding against HFMD in Guangdong Province, China, which involved 316 cases and 566 controls. Their results showed that exclusive breastfeeding during the first 6 months had a significantly beneficial effect. They concluded that exclusive breastfeeding may protect children within 28 months of age from HFMD infection. Li et al. [21] retrospectively analyzed demographic, environmental, and breastfeeding data on 603 children with severe HFMD and 1036 children with mild HFMD to assess whether breastfeeding duration affects the risk of severe HFMD later in childhood. Multivariate analysis revealed that breastfeeding for 6–12 months significantly reduced the risk of severe HFMD, as well as breastfeeding for more than 12 months.

Although breastfeeding has several benefits, the exclusive breastfeeding rate in Thailand has never met national and global targets and remains low. Breastfeeding rates are lower among higher educated and wealthier women in urban areas, compared to less educated and poor women living in rural areas [15]. A national survey conducted in 1981 confirmed a decline in breastfeeding duration, with significant differences observed among rural-urban women, their educational levels, and their geographical locations. The same survey also revealed that Thai mothers introduce supplementary food, such as rice mixed

with fruit and eggs, within the first few months of a child's life [16]. Starting in 2002, Thailand has been monitoring the rate of exclusive breastfeeding using a 24-hour recall period. Multiple Indicator Cluster Surveys (MICS) conducted in 2005-2006 [24], 2012 [46], and 2015-2016 [25] showed a gradual improvement in the six-month exclusive breastfeeding rate over the last decade [45]. However, the 2019 MICS survey recorded a sharp decline, indicating that Thailand is unlikely to achieve the 2025 target without significant efforts [26]. Despite improvements, substantial disparities in breastfeeding practices persist between urban and rural women.

Several studies using different mathematical models have been proposed to study the transmission dynamics HFMD in Thailand. Chadsuthi and Wichapeng [7] simulated the transmission of HFMD in contaminated environments in Bangkok using a customized model with seven compartments representing different stages of disease progression. Their findings emphasized the importance of early intervention and prevention measures such as improving hygiene practices, reducing contact between individuals, and increasing environmental sanitation to control the spread of the disease. Pongsumpun and Wongvanich [33] developed an age-structured model of HFMD transmission in Thailand which utilized two SEIR models to study the disease's transmission in two age groups: below and above ten years old. The study found a high transmission rate of HFMD in children below ten years of age compared to those above ten years old. Their study concluded that an age-structured model of HFMD transmission could provide a useful tool for policymakers to make informed decisions about control and prevention strategies. Wongvanich et al. [51] developed a dynamic model to study the transmission of HFMD in Thailand and assess the impact of control measures such as vaccination and quarantine. The model also accounted for regional residency and identified the most effective intervention strategies, including increasing vaccination coverage and implementing quarantine measures to control the spread of the disease. Lamwong et al. [19] investigated the dynamics of HFMD transmission using a mathematical model that incorporated the age structure of the population. The results revealed that the age structure of the population has a significant impact on the transmission dynamics of HFMD, with the disease spreading more rapidly among young children. Verma et al. [48] studied the transmission dynamics of HFMD in Thailand using an SEIRS epidemiological model with dynamic vitals and incorporating reinfections. They introduced periodic seasonality to reproduce the seasonal effect of the disease and applied a K-means clustering algorithm to cluster the provinces into different groups based on the uneven spread pattern of HFMD across the provinces in Thailand.

Currently, very little emphasis is placed on communicable diseases as most healthcare systems and governments are still focused on mitigating the spread of COVID-19. Furthermore, an analysis of HFMD data from all regions of Thailand in 2020 revealed that the Northern, Central, Western, Eastern, NorthEastern, and Southern regions had 13,111, 6,662, 4,503, 7,650, 19,318, 6,647 cases, respectively, while Bangkok had 9,312 cases. These findings indicate that the North and Northeastern regions of Thailand continue to experience a significant number of HFMD cases even before the emergence of SARS-CoV-2. Based on a nationwide epidemiological model developed in Thailand, the basic reproduction number for HFMD exceeds 1, indicating that the disease is likely to persist in the foreseeable future under similar environmental and cultural conditions [36]. Hence, it is crucial to identify and implement effective preventive measures to minimize the risks associated with HFMD.

1.1. Research gap and novelty

A thorough exploration of various research databases revealed no studies on the mathematical association between breastfeeding and the occurrence of HFMD. This study aims to fill this significant research gap by building upon the SEIR model proposed by Wongvanich et al. [51]. The novel contribution of this research lies in extending the model to incorporate more realistic considerations, explicitly focusing on hand, foot, and mouth disease (HFMD) in children in both rural and urban areas of Northern Thailand.

This study aims to utilize mathematical modeling techniques to examine the impact of breastfeeding on the transmission and severity of HFMD among children in these regions. This investigation is particularly relevant given previous findings by Wongvanich et al. [51], which suggest that the transmission of

HFMD may differ between urban and rural areas due to varying socio-economic conditions and health behaviors.

The objective of this study is to extend the existing SEIR model by introducing a breastfeeding compartment to better understand the dynamics of HFMD transmission and severity among children in urban and rural areas of Northern Thailand, considering the breastfeeding rates in these two areas. Additionally, this study seeks to provide insights for policymakers to inform decision-making and policy development based on the model's findings.

1.2. Research methodology

This study systematically investigates the impact of breastfeeding on hand, foot, and mouth disease in children in both rural and urban areas. The investigation begins with a comprehensive literature review to understand the transmission dynamics of the virus. Following this, a dynamic mathematical model is formulated using ordinary differential equations theory. Due to the complexity of the nonlinear equations involved, finding a general solution is difficult. As a result, equilibrium points, the basic reproduction number, and stability analysis are used to elucidate disease patterns and determine the conditions for disease eradication. The model's robustness is further validated through global stability analysis using a common quadratic Lyapunov function and LaSalle's invariance principle.

To support these findings, extensive numerical simulations are performed with the deSolve package [43], employing the fourth-order Runge-Kutta method in RStudio version 1.1.442, with additional analyses conducted using Python software.

The paper is organized as follows. Section 2 describes the development of the mathematical model. Section 3 presents the model analysis, including the proof of positivity, the basic reproduction number, and stability analysis. Section 4 provides a sensitivity analysis for different parameters relating to R_{bfeed}. Section 5 includes numerical simulations to support our analytical results. The paper concludes with Section 6, summarizing our findings.

2. Model development

The model formulated here is an extension of the model proposed by Wongvanich et al. [51], where they formulated an extension of the SEIR model. The model is deterministic and accounts for important characteristics to understand the HFMD disease dynamics. These characteristics include (i) transmission rate in both rural and urban areas, (ii) incubation period, (iii) quarantine rate, and (iv) recovery rate. The model comprises nine compartments with the entire human population originally subdivided into susceptible, exposed, infectious, quarantined, and recovered compartments. The susceptible, exposed, and infectious compartments are further subdivided into urban and rural provinces, respectively. The entire compartments considered in the model formulation are presented in Table 1 while the epidemiological parameters used in the model formulation are presented in Table 2.

Table 1: The compartments considered in the model formulation.

Compartments	Meaning
S_u	Susceptible humans in the urban region
S_r	Susceptible humans in the rural region
B	Breastfeeding compartment
E_u	Exposed humans in the urban region
E_r	Exposed humans in the rural region
I_u	Infectious humans in the urban region
I_r	Infectious humans in the rural region
Q	Quarantined human population
R	Recovered human population
N_T	Total number of the human population

Table 2: The description of the parameters used in the model formulation.

Parameters	Description
β_r	Transmission rate of HFMD in rural provinces
β_u	Transmission rate of HFMD in urban provinces
δ	Constant death rate
λ	Intrinsic incubation rate
η	Quarantine rate
γ_r	Breastfeeding rate in rural provinces
γ_u	Breastfeeding rate in urban provinces
ϖ_r	Waning rate of maternal antibodies in rural provinces
ϖ_u	Waning rate of maternal antibodies in urban provinces
ε_r	Expected decrease of HFMD infection in rural provinces
ϵ_u	Expected decrease of HFMD infection in urban provinces
r	Recovery rate.

By consolidating the variables and parameters elucidated in the preceding section, the sub-populations under consideration in the model are described using a system of ordinary differential equations (ODEs) given as:

$$\begin{aligned}
\frac{dS_u}{dt} &= \delta N_T + \varpi_u B - \beta_u S_u(I_u + I_r) - (\gamma_u + \delta)S_u,\\
\frac{dS_r}{dt} &= \delta N_T + \varpi_r B - \beta_r S_r(I_u + I_r) - (\gamma_r + \delta)S_r,\\
\frac{dB}{dt} &= (\gamma_u - \epsilon_u\beta_u I_u)S_u + (\gamma_r - \varepsilon_r\beta_r I_r)S_r - (\varpi_u + \varpi_r + \delta)B,\\
\frac{dE_u}{dt} &= \beta_u S_u(I_u + I_r) - (\lambda + \delta)E_u,\\
\frac{dE_r}{dt} &= \beta_r S_r(I_u + I_r) - (\lambda + \delta)E_r,\\
\frac{dI_u}{dt} &= \lambda E_u + \epsilon_u\beta_u S_u I_u - (\eta + \delta)I_u,\\
\frac{dI_r}{dt} &= \lambda E_r + \varepsilon_r\beta_r S_r I_r - (\eta + \delta)I_r,\\
\frac{dQ}{dt} &= \eta(I_u + I_r) - (r + \delta)Q,\\
\frac{dR}{dt} &= rQ - \delta R,
\end{aligned} \tag{2.1}$$

where $N_T = S_u + S_r + B + E_u + E_r + I_u + I_r + Q + R$. Model (2.1) can be normalized into

$$\begin{aligned}
\frac{dS_{uN}}{dt} &= \delta + \varpi_u B_N - \beta_u S_{uN}(I_{uN} + I_{rN}) - (\gamma_u + \delta)S_{uN},\\
\frac{dS_{rN}}{dt} &= \delta + \varpi_r B_N - \beta_r S_{rN}(I_{uN} + I_{rN}) - (\gamma_r + \delta)S_{rN},\\
\frac{dB_N}{dt} &= (\gamma_u - \epsilon_u\beta_u I_{uN})S_{uN} + (\gamma_r - \varepsilon_r\beta_r I_{rN})S_{rN} - (\varpi_u + \varpi_r + \delta)B_N,\\
\frac{dE_{uN}}{dt} &= \beta_u S_{uN}(I_{uN} + I_{rN}) - (\lambda + \delta)E_{uN},\\
\frac{dE_{rN}}{dt} &= \beta_r S_{rN}(I_{uN} + I_{rN}) - (\lambda + \delta)E_{rN},\\
\frac{dI_{uN}}{dt} &= \lambda E_{uN} + \epsilon_u\beta_u S_{uN} I_{uN} - (\eta + \delta)I_{uN},\\
\frac{dI_{rN}}{dt} &= \lambda E_{rN} + \varepsilon_r\beta_r S_{rN} I_{rN} - (\eta + \delta)I_{rN},\\
\frac{dQ_N}{dt} &= \eta(I_{uN} + I_{rN}) - (r + \delta)Q_N,\\
\frac{dR_N}{dt} &= rQ_N - \delta R_N,
\end{aligned} \tag{2.2}$$

where

$$S_{uN} = \frac{S_u}{N_T}, S_{rN} = \frac{S_r}{N_T}, B_N = \frac{B}{N_T}, E_{uN} = \frac{E_u}{N_T}, E_{rN} = \frac{E_r}{N_T}, I_{uN} = \frac{I_u}{N_T}, I_{rN} = \frac{I_r}{N_T}, Q_N = \frac{Q}{N_T}, R_N = \frac{R}{N_T}.$$

3. Analysis of the model

3.1. Positivity of solutions

Theorem 3.1. *The solutions of the system of equations given in (2.2) with non-negative initial conditions $S_{uN}(0)$, $S_{rN}(0)$, $B_N(0)$, $E_{uN}(0)$, $E_{rN}(0)$, $I_{uN}(0)$, $I_{rN}(0)$, $Q_N(0)$, and $R_N(0)$, will remain non-negative for all $t > 0$.*

Proof. Consider the first equation in the system:

$$\frac{dS_{uN}}{dt} = \delta + \varpi_u B_N - \beta_u S_{uN}(I_{uN} + I_{rN}) - (\gamma_u + \delta)S_{uN}.$$

Rearranging terms, we have

$$\frac{dS_{uN}}{dt} + (\gamma_u + \delta + \beta_u(I_{uN} + I_{rN}))S_{uN} \geqslant \delta + \varpi_u B_N.$$

Let $\xi = \gamma_u + \delta + \beta_u(I_{uN} + I_{rN})$. Integrating both sides, we get

$$S_{uN}(t) \geqslant S_{uN}(0)e^{-\xi t} + \int_0^t e^{-\xi(t-s)}(\delta + \varpi_u B_N)ds.$$

Since $e^{-\xi(t-s)}$ is positive for all $t > s$, the integral is non-negative. Therefore, $S_{uN}(t) \geqslant S_{uN}(0)e^{-\xi t} \geqslant 0$ for all $t > 0$. By applying a similar procedure to the remaining equations in the system, we can show that S_{rN}, B_N, E_{uN}, E_{rN}, I_{uN}, I_{rN}, Q_N, and R_N remain non-negative for all $t > 0$. Thus, the solutions of the system with non-negative initial conditions will remain non-negative for all time $t > 0$. □

3.2. Equilibrium points and basic reproduction number

The equilibrium points of Eq. (2.2) are obtained by setting the right-hand side of all sub-equations to zero and solving for the respective variables. The resulting equilibrium points obtained from the calculation of the disease-free E^*_{dfe} and endemic fixed points E^{**}_{ee} are provided below:

$$E^*_{dfe} = (S^*_{uN}, S^*_{rN}, B^*_N, 0, 0, 0, 0, 0, 0),$$

where

- $S^*_{uN} = \frac{\delta^2+(\gamma_r+\varpi_r+\varpi_u)\delta+2\gamma_r\varpi_u}{\delta^2+(\gamma_r+\gamma_u+\varpi_r+\varpi_u)\delta+(\gamma_u+\varpi_u)\gamma_r+\varpi_r\gamma_u}$;
- $S^*_{rN} = \frac{\delta^2+(\gamma_u+\varpi_r+\varpi_u)\delta+2\varpi_r\gamma_u}{\delta^2+(\gamma_r+\gamma_u+\varpi_r+\varpi_u)\delta+(\gamma_r+\varpi_r)\gamma_u+\gamma_r\varpi_u}$;
- $B^*_N = \frac{(\gamma_r+\gamma_u)\delta+2\gamma_r\gamma_u}{\varpi_u+\varpi_r+\delta}$,

and

$$E^{**}_{ee} = (S^{**}_{uN}, S^{**}_{rN}, B^{**}_N, E^{**}_{uN}, E^{**}_{rN}, I^{**}_{uN}, I^{**}_{rN}, Q^{**}_N, R^{**}_N),$$

where

$$S^{**}_{uN} = \frac{\delta + \varpi_u B^{**}_N}{\beta_u(I^{**}_{uN} + I^{**}_{rN}) + \gamma_u + \delta}, \qquad S^{**}_{rN} = \frac{\delta + \varpi_r B^{**}_N}{\beta_r(I^{**}_{uN} + I^{**}_{rN}) + \gamma_r + \delta},$$

$$B^{**}_N = \frac{(\gamma_u - \epsilon\beta_u I^{**}_{uN})S^{**}_{uN} + (\gamma_r - \varepsilon_r\beta_r I^{**}_{rN})S^{**}_{rN}}{\varpi_u + \varpi_r + \delta}, \qquad E^{**}_{uN} = \frac{\beta^{**}_u S^{**}_{uN}(I^{**}_{uN} + I^{**}_{rN})}{\lambda + \delta},$$

$$E^{**}_{rN} = \frac{\beta_r S^{**}_{rN}(I^{**}_{uN} + I^{**}_{rN})}{\lambda + \delta}, \qquad I^{**}_{uN} = \frac{\lambda E^{**}_{uN}}{(\eta + \delta) - \epsilon_u \beta_u S^{**}_{uN}},$$
$$I^{**}_{rN} = \frac{\lambda E^{**}_{rN}}{(\eta + \delta) - \varepsilon_r \beta_r S^{**}_{rN}}, \qquad Q^{**}_{N} = \frac{\eta(I^{**}_{uN} + I^{**}_{rN})}{(r + \delta)}, \quad R^{**}_{N} = \frac{rQ^{**}_{N}}{\delta}.$$

The basic reproduction number (R_0) is a fundamental epidemiological measure defined as the expected number of secondary infections generated by a single infectious individual in a completely susceptible population [9]. The value of R_0 determines the behavior of the disease, where the disease is expected to die out if $R_0 < 1$, while it will cause a short-term outbreak or persist in the population if $R_0 > 1$.

In the context of disease control, a related measure, the control reproduction number (R_c), can be defined to assess the effectiveness of control measures such as testing and isolation, treatment, or vaccination in limiting the spread of the disease. In this study, the BRN denoted as R_{bfeed} will be used to assess the effectiveness of breastfeeding in limiting the spread of HFMD.

To compute R_{bfeed}, the next-generation matrix method is employed. The next generation matrix is a matrix that represents the expected number of new infections caused by each infected individual in the population. The R_{bfeed} is the spectral radius of the next generation matrix, which is the largest eigenvalue of $\rho(FV^{-1})$, where F and V are the jacobian matrices obtained from the inflow and outflow of infection in the model.

In this study, the R_{bfeed} is the addition of the BRN in both rural and urban provinces denoted as R_{rural} and R_{urban}, respectively. This is defined below:

$$R_{bfeed} = R_{urban} + R_{rural} = \frac{\epsilon_u \beta_u S^{*}_{uN}}{\eta + \delta} + \frac{\varepsilon_r \beta_r S^{*}_{rN}}{\eta + \delta} = \frac{\epsilon_u \beta_u S^{*}_{uN} + \varepsilon_r \beta_r S^{*}_{rN}}{\eta + \delta}, \tag{3.1}$$

where

$$S^{*}_{rN} = \frac{\delta^2 + (\gamma_u + \varpi_r + \varpi_u)\,\delta + 2\varpi_r\gamma_u}{\delta^2 + (\gamma_r + \gamma_u + \varpi_r + \varpi_u)\,\delta + (\gamma_r + \varpi_r)\,\gamma_u + \gamma_r\varpi_u}$$

and

$$S^{*}_{uN} = \frac{\delta^2 + (\gamma_r + \varpi_r + \varpi_u)\,\delta + 2\gamma_r\varpi_u}{\delta^2 + (\gamma_r + \gamma_u + \varpi_r + \varpi_u)\,\delta + (\gamma_u + \varpi_u)\,\gamma_r + \varpi_r\gamma_u}.$$

From Eq. (3.1) we can obtain the BRN in the absence of breastfeeding, R_0, by setting the parameters relating to breastfeeding in Eq. (3.1) to be zero. Thus, by setting $\gamma_r = \gamma_u = \varpi_u = \varpi_r = 0$, we obtain

$$R_0 = \frac{\epsilon_u \beta_u + \varepsilon_r \beta_r}{\eta + \delta}.$$

3.3. Global stability analysis of DFE

The global stability of DFE for the model (2.2) is proved by using a common quadratic Lyapunov function and LaSalle's invariance principle.

Theorem 3.2. *If* $R_{bfeed} < 1$, *then the DFE of model Model* (2.2) *is globally asymptotically stable in* N_T.

Proof. We choose the Lyapunov function of the form below:

$$V = aS^2_{uN} + bS^2_{rN} + cB^2_N + dE^2_{uN} + eE^2_{rN} + fI^2_{uN} + gI^2_{rN} + hQ^2_N + iR^2_N;$$

where a, b, c, d, e, f, g, h, and i are positive constants. Computing the time derivative of V along the solutions of the system yields:

$$\begin{aligned}\frac{dV}{dt} &= 2aS_{uN}\frac{dS_{uN}}{dt} + 2bS_{rN}\frac{dS_{rN}}{dt} + 2cB_N\frac{dB_N}{dt} + 2dE_{uN}\frac{dE_{uN}}{dt} \\ &\quad + 2fE_{rN}\frac{dE_{rN}}{dt} + 2gI_{uN}\frac{dI_{uN}}{dt} + 2hQ_{uN}\frac{dQ_N}{dt} + 2iR_N\frac{dR_N}{dt}.\end{aligned} \tag{3.2}$$

Simplifying Eq. (3.2) by substituting in the derivatives from the system of equations, we obtain

$$V' = -2(\gamma_u+\gamma_r)B_N^2 - (\delta+\varpi_u+\varpi_r)(\delta B_N + S_{uN}^2 + S_{rN}^2) - 2\lambda(E_{uN}+E_{rN})^2 - 2\eta(I_{uN}+I_{rN})^2. \quad (3.3)$$

For the DFE to be globally asymptotically stable, we need to show that Eq. (3.3) is negative definite. From the expression of V' in Eq. (3.3), the term $-2(\gamma_u+\gamma_r)$ is always negative because B_N is non-negative. The term $-(\delta+\varpi_u+\varpi_r)(\delta B_N + S_{uN}^2 + S_{rN}^2)$ is also always negative because all the terms in the expression are non-negative except for the negative δB_N term, which can be made arbitrarily large by choosing a sufficiently large B_N. The third and fourth terms are also always negative because they are squares of non-negative terms that can only be zero when their corresponding variables are zero. Hence based on the above analysis, Eq. (3.3) is negative definite and the DFE of model (2.2) is globally asymptotically stable. □

3.4. Global stability analysis of EE

The global asymptotic stability of the model is proved using a common quadratic Lyapunov function. This study will take a similar approach to the idea presented in De Leon [47].

Theorem 3.3. *If* $R_{bfeed} > 1$, *then the endemic equilibrium point of the model* (2.2) *is globally asymptotically stable in the region* Ω_{Hfmd}.

Proof. Suppose that we define

$$V : \{(S_{uN}, S_{rN}, B_N, E_{uN}, E_{rN}, I_{uN}, I_{rN}, Q) \in \Omega_{Hfmd} : S_{uN}, S_{rN}, B_N, E_{uN}, E_{rN}, I_{uN}, I_{rN}, Q_N > 0\} \to \mathcal{R}.$$

A common quadratic function using the model can be constructed as follows:

$$\begin{aligned} &V(S_{uN}, S_{rN}, B_N, E_{uN}, E_{rN}, I_{uN}, I_{rN}, Q_N) \\ &= \frac{1}{2}\Big[(S_{uN}-S_{uN}^{**}) + (S_{rN}-S_{rN}^{**}) + (B_N-B_N^{**}) + (E_{uN}-E_{uN}^{**}) \\ &\quad + (I_{uN}-I_{uN}^{**}) + (I_{rN}-I_{rN}^{**}) + (Q_N-Q_N^{**}) + (R_N-R_N^{**})\Big]^2. \end{aligned} \quad (3.4)$$

This implies that V is C^1 in the interiror of Ω_{Hfmd}, where E_{ee}^{**} represents the global minimum of V on Ω_{Hfmd}, and

$$V(S_{uN}^{**}, S_{rN}^{**}, B_N^{**}, E_{uN}^{**}, E_{rN}^{**}, I_{uN}^{**}, I_{rN}^{**}, Q_N^{**}, R_N^{**}) = 0.$$

Differentiating V along the solutions of model (3.4), we obtain

$$\begin{aligned} V' &= (S_{uN}-S_{uN}^{**}) + (S_{rN}-S_{rN}^{**}) + (B_N-B_N^{**}) + (E_{uN}-E_{uN}^{**}) + (I_{uN}-I_{uN}^{**}) + (I_{rN}-I_{rN}^{**}) \\ &\quad + (Q_N-Q_N^{**}) + (R_N-R_N^{**}) \times \frac{d}{dt}(S_{uN}+S_{rN}+B_N+E_{uN}+E_{rN}+I_{uN}+I_{rN}+Q_N+R_N), \end{aligned} \quad (3.5)$$

where

$$\begin{aligned} &\frac{d}{dt}(S_{uN}+S_{rN}+B_N+E_{uN}+E_{rN}+I_{uN}+I_{rN}+Q_N+R_N) \\ &\quad = 2\delta - \delta(S_{uN}+S_{rN}+B_N+E_{uN}+E_{rN}+I_{uN}+I_{rN}+Q_N+R_N). \end{aligned}$$

Thus, Eq. (3.5) becomes:

$$\begin{aligned} V' &= (S_{uN}-S_{uN}^{**}) + (S_{rN}-S_{rN}^{**}) + (B_N-B_N^{**}) + (E_{uN}-E_{uN}^{**}) + (I_{uN}-I_{uN}^{**}) + (I_{rN}-I_{rN}^{**}) \\ &\quad + (Q_N-Q_N^{**}) + (R_N-R_N^{**}) \times (2\delta - \delta(S_{uN}+S_{rN}+B_N+E_{uN}+E_{rN}+I_{uN}+I_{rN}+Q_{rN}+R_N). \end{aligned} \quad (3.6)$$

Using $2\delta = \delta\left(S_{uN}^{**} + S_{rN}^{**} + B_N^{**} + E_{uN}^{**} + E_{rN}^{**} + I_{uN}^{**} + I_{rN}^{**} + Q_N^{**} + R_N^{**}\right)$, Eq. (3.6) becomes

$$\begin{aligned} V' = &\left(S_{uN} - S_{uN}^{**}\right) + \left(S_{rN} - S_{rN}^{**}\right) + \left(B_N - B_N^{**}\right) + \left(E_{uN} - E_{uN}^{**}\right) + \left(I_{uN} - I_{uN}^{**}\right) + \left(I_{rN} - I_{rN}^{**}\right) \\ &+ \left(Q_N - Q_N^{**}\right) + \left(R_N - R_N^{**}\right) \times \left[\delta\left(S_{uN}^{**} + S_{rN}^{**} + B_N^{**} + E_{uN}^{**} + E_{rN}^{**}\right.\right. \\ &\left.\left. + I_{uN}^{**} + I_{rN}^{**} + Q_N^{**} + D_N^{**}\right) - \delta\left(S_{uN} + S_{rN} + B_N + E_{uN} + E_{rN} + I_{uN} + I_{rN} + Q_N + R_N\right)\right]. \end{aligned} \tag{3.7}$$

Suppose we denote

$$\begin{aligned} A = &\left(S_{uN} - S_{uN}^{**}\right) + \left(S_{rN} - S_{rN}^{**}\right) + \left(B_N - B_N^{**}\right) + \left(E_{uN} - E_{uN}^{**}\right) \\ &+ \left(I_{uN} - I_{uN}^{**}\right) + \left(I_{rN} - I_{rN}^{**}\right) + \left(Q_N - Q_N^{**}\right) + \left(R_N - R_N^{**}\right), \end{aligned}$$

We can then rewrite (3.7) as

$$V' = [A] - \delta\,[A]\,. \tag{3.8}$$

To simplify, let

$$\begin{aligned} G_1 &= S_{uN} - S_{uN}^{**}, & G_2 &= S_{rN} - S_{rN}^{**}, & G_3 &= B_N - B_N^{**}, \\ G_4 &= E_{uN} - E_{uN}^{**}, & G_5 &= E_{rN} - E_{rN}^{**}, & G_6 &= I_{uN} - I_{uN}^{**}, \\ G_7 &= I_{rN} - I_{rN}^{**}, & G_8 &= Q_N - Q_N^{**}, & G_9 &= R_N - R_N^{**}, \end{aligned}$$

Substituting G_1, G_2, G_3, G_4, G_5, G_6, G_7, G_8, and G_9, respectively, into Eq. (3.8), we obtain:

$$\begin{aligned} V' = &\left[G_1 + G_2 + G_3 + G_4 + G_5 + G_6 + G_7 + G_8\right] \\ &\times \left(-\delta\left[G_1 + G_2 + G_3 + G_4 + G_5 + G_6 + G_7 + G_8\right]\right) \leqslant 0. \end{aligned} \tag{3.9}$$

Hence V' is negative. In Eq. (3.9), $V' = 0$ if and only if the following conditions hold: $S_{uN} = S_{uN}^{**}$, $S_{rN} = S_{rN}^{**}$, $B_N = B_N^{**}$, $E_{uN} = E_{uN}^{**}$, $E_{rN} = E_{rN}^{**}$, $I_{uN} = I_{uN}^{**}$, $I_{rN} = I_{rN}^{**}$, $Q_N = Q_N^{**}$, $R_N = R_N^{**}$. Thus the largest compact invariant set in

$$\left\{\left(S_{uN}^{**}, S_{rN}^{**}, B_N^{**}, E_{uN}^{**}, E_{rN}^{**}, I_{uN}^{**}, I_{rN}^{**}, Q_N^{**}, R_N^{**}\right) \in N_T : \frac{dV}{dt} = 0\right\},$$

is the singleton E_{ee}^{**}, where E_{ee}^{**} is the EEP. Hence by Lasalle's invariance principle [20], E_{ee}^{**} is globally asymptotically stable in the interior of Ω_{Hfmd}. □

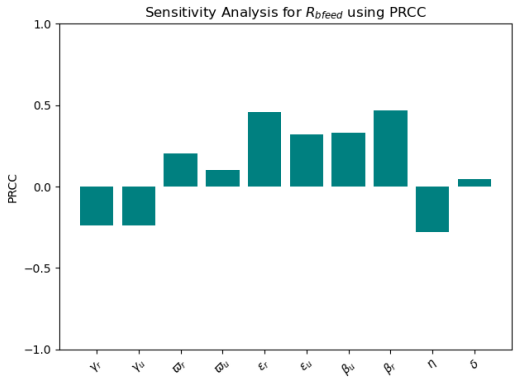
4. Sensitivity analysis

The objective of this section is to discuss the sensitivity of R_{bfeed}, R_{urban}, and R_{rural} to model parameters in (3.1). To this end, we employ the Latin Hypercube Sampling/Partial Rank Correlation Coefficient (LHS/PRCC) method [1]. The selected parameters are those that can be used to inform policies such as the rate of breastfeeding in both rural and urban provinces (γ_r and γ_u), waning rate of maternal antibodies (ϖ_r and ϖ_u), the expected decrease of HFMD infection in both rural and urban provinces (ε_r and ϵ_u), constant death rate δ, and quarantine rate η. We generate 3000 samples of the model parameters, using LHS and used uniform distributions [7], which are listed in Table 3 for all ten parameter values in R_{bfeed} and eight parameters in both R_{urban} and R_{rural}.

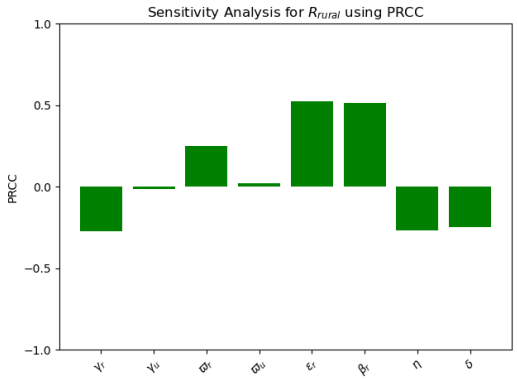
Next, we examine the monotonic relationships between the parameters and the model outcomes using the Partial Rank Correlation Coefficient (PRCC). The sign of the PRCC indicates the direction of the linear association, while its magnitude signifies the strength of this association. The PRCC values range from -1 to 1, with values above 0.5 considered to indicate a significant relationship between the model output and a specific parameter value.

Table 3: PRCC values on the outcome of R_{bfeed}, R_{urban}, R_{rural}.

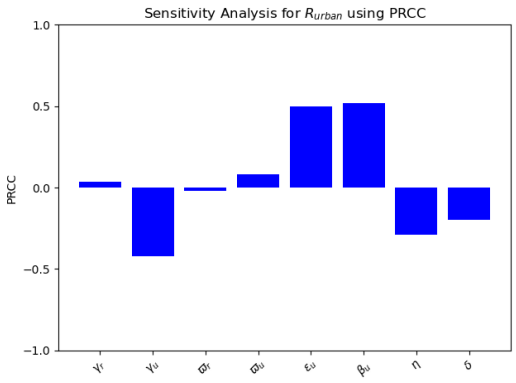
Parameters	**Distribution**	**PRCC values** R_{bfeed}	**PRCC values** R_{urban}	**PRCC values** R_{rural}
γ_r	$U(0.2, 0.4)$	-0.2377	0.0356	-0.2715
γ_u	$U(0.1, 0.3)$	-0.2364	-0.4196	-0.0135
ϖ_r	$U(0.0015, 0.0030)$	0.2049	-0.0224	0.2499
ϖ_u	$U(0.00075, 0.00095)$	0.1000	0.0837	0.0200
ε_r	$U(0.001, 0.005)$	0.4563	—	0.5223
ϵ_u	$U(0.001, 0.005)$	0.3182	0.4965	—
β_u	$U(0.001, 0.005)$	0.3313	0.5171	—
β_r	$U(0.001, 0.005)$	0.4686	—	0.5121
η	$U(0.0001, 0.0005)$	-0.2810	-0.2882	-0.2654
δ	$U(0.0001, 0.0005)$	0.0464	-0.1983	-0.2468



(a) Sensitivity plot of R_{bfeed}.



(b) Sensitivity plot of R_{urban}.



(c) Sensitivity plot of R_{rural}.

Figure 1: Sensitivity plots for R_{bfeed}, R_{urban}, and R_{rural}.

Figures 1a, 1b, and 1c revealed intriguing insights into the impact of various parameters on the basic reproduction numbers (R_{bfeed}, R_{urban}, and R_{rural}) of the HFMD transmission model. Among the parameters studied, γ_u and η consistently exhibit negative effects across all scenarios, indicating that an increase in the breastfeeding rate in urban provinces (γ_u) and the quarantine rate (η) leads to a decrease in the basic reproduction numbers in both urban and rural areas.

Conversely, γ_r shows a mixed impact, with a negative effect on R_{bfeed} and R_{rural} but a positive effect on R_{urban}, suggesting a complex relationship between the breastfeeding rate in rural provinces and the urban basic reproduction number. Similarly, ϖ_r has a positive effect on R_{bfeed} and R_{rural} but a negative effect on R_{urban}, indicating a contrasting impact of the waning rate of maternal antibodies in rural provinces across different settings.

The expected decrease of HFMD infection in urban provinces (ϵ_u) consistently shows a positive effect, suggesting that an increase in the expected decrease of HFMD infection leads to an increase in the urban basic reproduction number. This result is intriguing and warrants further investigation into the specific mechanisms underlying this relationship.

The transmission rates of HFMD in urban and rural provinces (β_u and β_r) exhibit a positive effect, indicating that an increase in these rates leads to an increase in the basic reproduction numbers in both settings. This highlights the importance of controlling the transmission rates to mitigate the spread of HFMD.

Overall, the sensitivity analysis provides valuable insights into the factors influencing the basic reproduction numbers of HFMD in urban and rural areas. These findings can inform public health policies and interventions aimed at reducing the transmission and impact of HFMD in different population settings.

5. Numerical investigations

Numerical investigations were carried out using the model to answer the research questions posed in Section 1, which include following. (i) Are there differences in the protective effects of breastfeeding against HFMD between urban and rural provinces of Thailand? (ii) Based on available data, what can we expect in terms of the occurrence of hand, foot, and mouth disease (HFMD) in Thailand in 2025? (iii) What are the implications of this result for policymakers in terms of their decision-making and policy development? The simulations were carried out using the deSolvepackage [43] with the fourth-order Runge-Kutta method in RStudio programming software version 1.1.442 and Matlab version R2022b version 9.13 [44].

5.1. Simulation of the general dynamics

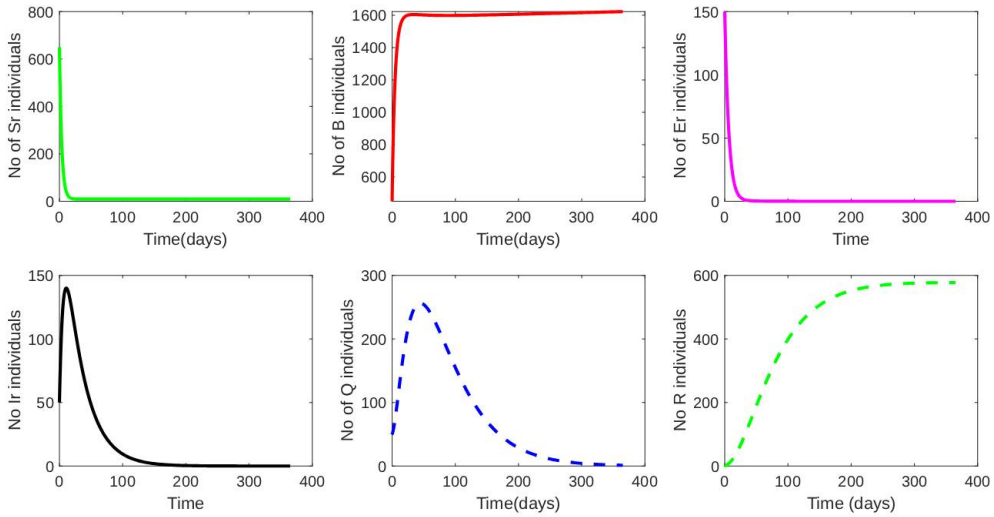
The general dynamics of all compartments in rural and urban provinces are simulated in this section. The simulations were generated using the parameter values in Table 4 and the initial conditions below:

$$\begin{aligned}\text{InitialCond} &= \big[S_u(0), S_r(0), B(0), E_u(0), E_r(0), I_u(0), I_r(0), Q(0), R(0)\big],\\ &= \big[650, 650, 450, 150, 150, 50, 50, 50, 0\big].\end{aligned}$$

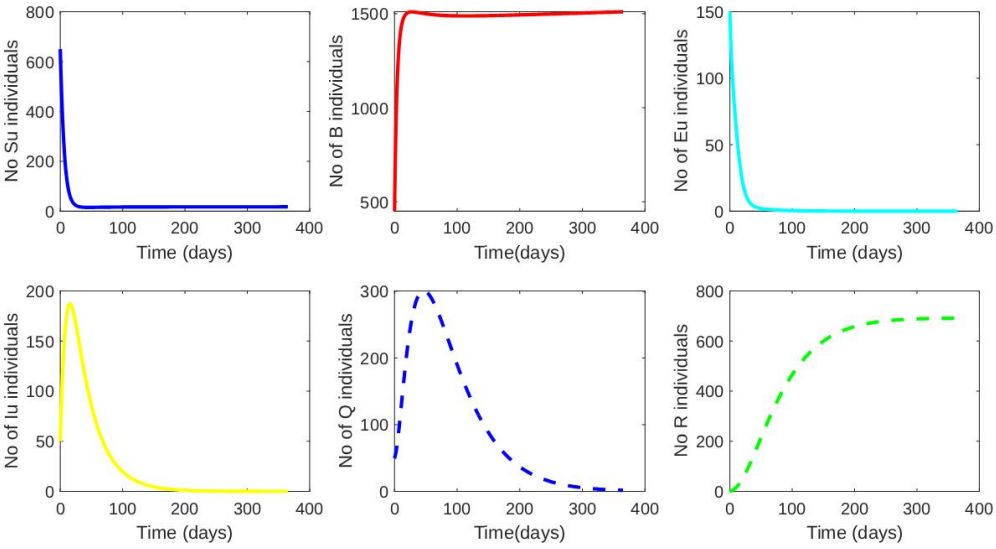
Table 4: The parameter values used in the numerical simulation.

Parameter	Value	Source
β_r	$1.0\times10^{-4} - 5.0\times10^{-4}$	Estimated
β_u	$1.0\times10^{-4} - 5.0\times10^{-4}$	Estimated
δ	3.605×10^{-4}	[51]
λ	1.667×10^{-1}	[53]
η	3.333×10^{-2}	[8]
γ_r	2.7×10^{-1}	[34]
γ_u	1.35×10^{-1}	[34]
ϖ_u	$\gamma_u/180$	Estimated
ϖ_r	$\gamma_r/180$	Estimated
ϵ_u	1.0×10^{-3}	Estimated
ε_r	ϵ_u	

Figures 2a and 2b illustrate the dynamics observed in rural and urban provinces of Thailand, respectively. In Figure 2a, it can be observed that the rate of breastfeeding is higher in the rural province compared to the urban province. Furthermore, the rural province exhibited fewer infections compared to the urban province Figure 2b. These trends were also reflected in the quarantined and recovered compartments.



(a) Dynamics in rural provinces of Northern Thailand.



(b) Dynamics in the urban province of Northern Thailand.

Figure 2: General dynamics of HFMD in rural and urban province of Northern Thailand.

5.2. *Examining the impact of breastfeeding*

To examine the impact of an exclusive breastfeeding intervention on HFMD in rural and urban provinces of Northern and Northeastern Thailand, we considered two groups: the control group and the intervention group. We assume that in the control group, breastfeeding was not practiced, while in the intervention group, exclusive breastfeeding was practiced for six months. To capture both groups in simulation, we set γ_r, γ_u, ϖ_r, and ϖ_u to be zero in the breastfeeding compartment for the control group and retained their original values for the intervention group. The simulation results are presented in Figures 3 and 4. Additionally, the associated R_{bfeed} values are provided in Table 5.

Table 5: The BRN value obtained from the simulation of Figures 3 and 4.

Control Group	R_{bfeed}	Intervention Group	R_{bfeed}
Infected rural	$0.978 < 1$	Infected rural	$0.7572 < 1$
Infected urban	$1.292 > 1$	Infected urban	$0.6632 < 1$

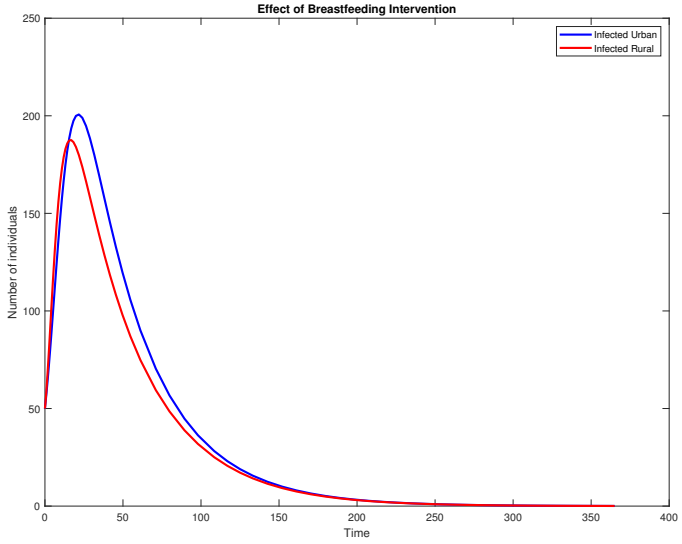


Figure 3: Results obtained from comparison of breastfeeding practices in both the control and intervention groups.

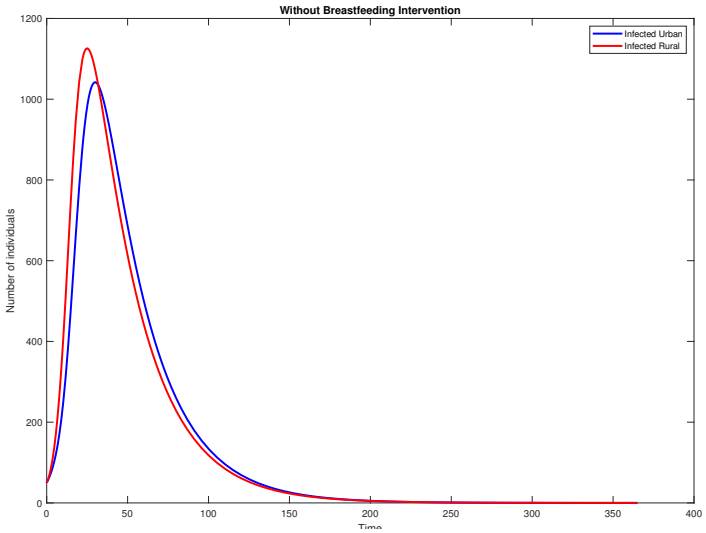


Figure 4: Results obtained from comparison of breastfeeding practices in both the control and intervention groups.

The simulation results revealed a striking difference in the infection curves and counts between the control and intervention groups, respectively. These findings align with previous studies ([21, 22, 52]) that have consistently reported similar results, indicating that breastfeeding does offer a protective effect against HFMD.

5.3. Data fitting and model validation

This section provides an overview of the available data concerning HFMD in Thailand. The data on confirmed infection cases were obtained from the study conducted by Verma et al. [48]. To validate our model, we utilized data from four distinct provinces in Northern Thailand, namely Chiang Mai, Chiang Rai, Lampang, and Nan. The four provinces were classified as either urban or rural. Chiang Mai and Chiang Rai were categorized as urban provinces, whereas Lampang and Nan were considered rural provinces. This classification adheres to the criteria established by Thailand's National Statistical Office (NSO) [23]. According to the NSO, an urban province refers to a locality with a population of 10,000 or more or a locality with a population of less than 10,000 but with a population density of $1,000$ persons

per square kilometer or more. The data in Table 6 represents the number of infected children in each of these provinces for the year 2020.

Table 6: Number of infected children in the four different provinces of Thailand for the Year 2020 from January to July.

Month	ChangMai	ChangRai	Nan	Lampang
January	179	156	89	86
February	100	120	60	38
March	77	59	26	12
April	20	16	1	3
May	33	21	2	4
June	22	21	7	3
July	14	12	3	4

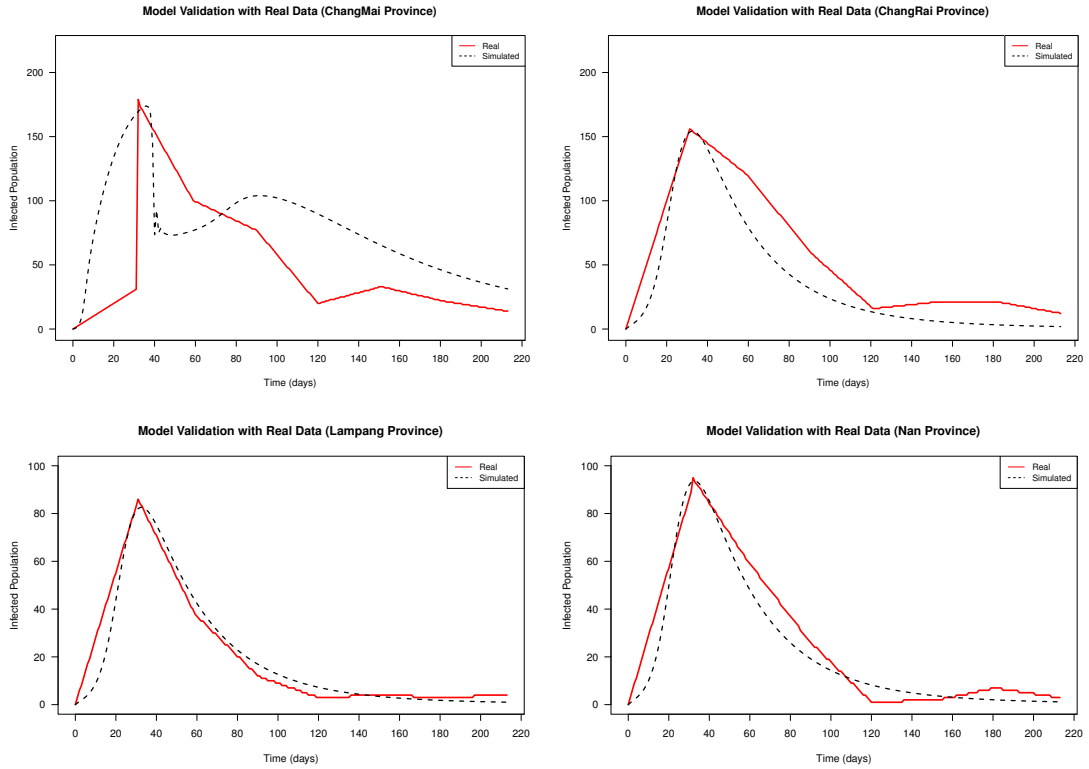


Figure 5: Result of the model fitted to ChangMai, ChangRai, Nan, and Lampang provinces of Northern Thailand.

The analysis of the fit revealed that model (2.2) predominantly aligns with the data from the rural provinces, specifically Lampang and Nan. Below are possible reasons why the model may have exhibited a better fit with Lampang and Nan compared to Chiang Mai and Chiang Rai.

- In this study, Lampang and Nan are originally classified as rural provinces. This suggests that both provinces have lower population densities compared to Chiang Mai and Chiang Rai. The lower population density might have contributed to a more controlled spread of HFMD, aligning with the assumptions of our model.

- Urban provinces are generally known to have better healthcare infrastructure and resources compared to rural provinces. This disparity in healthcare facilities might have influenced the reporting and detection of HFMD cases, potentially resulting in variations between urban and rural data.

- The difference in cultural and environmental factors, such as hygiene practices, population mobility, and socioeconomic conditions between urban and rural provinces, may have influenced the observed HFMD cases.
- The discrepancies in data accuracy and reporting between rural and urban provinces could have affected the quality and reliability of the data used in this study. Inconsistent or under-reporting reporting may have occurred in the reported regions.

5.4. Future HFMD forecast

To predict the future outbreak of HFMD in Thailand, we analyzed a 10-year dataset (2010-2019) of reported cases by conducting a forecast using the Autoregressive Integrated Moving Average (ARIMA) model. ARIMA allows us to consider the impact of past or lagged values and stochastic error terms in explaining time series patterns. The general form of an ARIMA model is as follows:

$$\Delta^d Y_t = \delta + \theta_1 \Delta^d Y_{t-1} + \cdots + \theta_p \Delta^d Y_{t-p} + \alpha_1 \epsilon_{t-1} + \cdots + \alpha_q \epsilon_{t-q} + \epsilon_t. \tag{5.1}$$

In Eq. (5.1), the parameters used are defined below.

- $\Delta^d Y_t$ represents the differenced time series data (of order d) at time t;
- δ is the drift term;
- $\theta_1, \ldots, \theta_p$ are the coefficients of the autoregressive (AR) terms;
- $\alpha_1, \ldots, \alpha_q$ are the coefficients of the moving average (MA) terms;
- ϵ_t represents the error term at time t.

The *auto.arima* function of the *R software forecast package* was used for identifying the corresponding ARIMA models and forecasting analysis. First, we performed a change point analysis on the dataset in Table 6 to detect various points where significant changes have occurred. These change points were observed in the years 2012 (150% growth), 2015 (-37% decline), and 2018 (-1.35% decline). Next, using the identified change points, we projected the number of HFMD cases for the period from 2020 to 2025. The forecasted outcomes are displayed in Table 7.

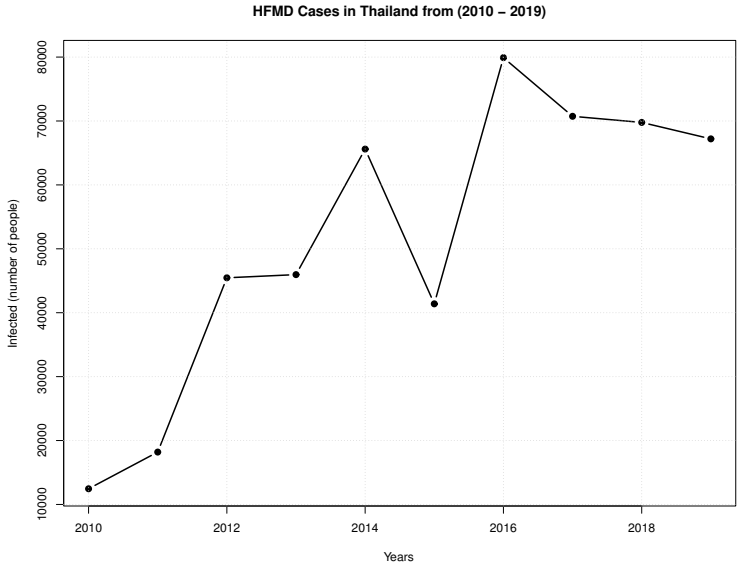


Figure 6: Number of children who are infected with HFMD in Thailand from January 2010 to 2019.

Table 7: Forecasted HFMD cases from 2020 to 2025, incorporating change points and utilizing existing data.

Forecasted year	Forecasted results
2020	65,579
2021	64,164
2022	70,733
2023	63,061
2024	63,328
2025	63,545

The following are important points to note from the forecast in Table 7.

- From 2010 to 2019, there was a general increasing trend in the number of HFMD cases, as evident from the increasing values over the years. However, there is a declining trend in the forecasted values, indicating a decline in the projected number of HFMD cases during the forecasted years.
- The forecasted values take into account the identified change points in the data (2012, 2015, and 2018). These change points suggest shifts or changes in the underlying pattern of HFMD cases, which can influence future trends.
- Overall, the forecasted values from 2020 to 2025 suggest a potential decrease in the number of HFMD cases compared to the period from 2010 to 2019.

6. Conclusion, limitations, and policy implications

This study contributes to the understanding of the relationship between breastfeeding and Hand, Foot, and Mouth Disease (HFMD) in Thailand, focusing on both rural and urban provinces of Northern Thailand. By developing and analyzing a mathematical model, we aimed to assess the protective effect of breastfeeding against HFMD and its potential for reducing disease transmission. One of our study's strengths is the use of a mathematical model to explore the dynamics of HFMD transmission. While our model simplifies the complex social and biological factors that influence breastfeeding practices and disease transmission, it provides valuable insights into the potential impact of breastfeeding on HFMD.

In addition to our findings, an age-structured model could significantly deepen our understanding of the relationship between breastfeeding and HFMD. This approach would enable a more nuanced analysis of how various age groups contribute to disease transmission and how breastfeeding practices influence these dynamics. Future research can be carried out to explore this research approach. This study also addresses a research gap by providing mathematical and computational evidence regarding the effects of breastfeeding on HFMD. This fills an important gap in the literature and provides valuable insights into the impact of breastfeeding on disease transmission. Additionally, the comprehensive analysis conducted in this study, including model fitting and validation, ensures that the results are robust and reliable. The simulation results provide forecasts of future HFMD outbreaks based on existing data, which is valuable for policymakers and public health officials in planning and implementing effective strategies to mitigate the impact of HFMD.

In conclusion, while this study represents a first step in assessing the impact of breastfeeding on HFMD using mathematical modeling, further research is needed to validate and expand upon these findings. We hope that this study will stimulate more research in this area and contribute to the growing body of evidence on the protective effects of breastfeeding against infectious diseases.

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