Interaction analysis on transmissibility of main pathogens of hand, foot, and mouth disease in Xi'an: a modelling study

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Abstract

Objectives: Hand, foot, and mouth disease (HFMD) has spread widely and led to high disease burden in many countries, but the interaction among the pathogens of the disease remains unclear. In this study, we aimed to analyze the interaction of the main pathogens of HFMD using a mathematical model.

Method: A dataset on reported HFMD cases was collected in Xi'an City. A long-term etiological surveillance was conducted focusing on the pathogens of the disease including Enterovirus A71 (EV71), Coxsachievirus A16 (CoxA16), and other enteroviruses. A susceptible–infectious–recovered model was adopted to calculate the reproduction number during the ascending period of reported cases (defined as Rasc) and the descending period (defined as Rdes).

Results: In Xi'an, Rasc and Rdes of HFMD was 1.39 (95% CI: 1.31 – 1.48) and 0.70 (95% CI: 0.65 – 0.74), respectively. CoxA16 and other enteroviruses interacted with each other and decreased the value of Rasc. However, Rdes of CoxA16 was increased by other enteroviruses directionally. However, during the reported cases decreasing period, interactions only occurred between EV71 and other enteroviruses and between CoxA16 and other enteroviruses. These interactions all decreased Rasc but increased Rdes of affected pathogens.

Conclusions: The interaction of the pathogens exists in Xi'an City. The reproduction number of the affected pathogen is adjusted and verges to 1 by the interaction.

Introduction

Hand, foot, and mouth disease (HFMD) is a common infectious disease and has spread widely in China and in many other countries [1–7]. Traditionally, epidemiological studies are focusing on describing incidence and the demographic characteristics (age, sex, and so on) of the disease. However, those epidemiological characteristics are based on the transmission force or the transmissibility of the disease. Reproduction number, which is defined as the expected number of secondary infections that result from introducing a single infected individual into an otherwise susceptible population [8, 9], is commonly employed to quantify the transmissibility.

Many mathematical models, including susceptible – infectious – recovered (SIR), time series SIR, susceptible – exposed – infectious – recovered (SEIR), susceptible – exposed – infectious – quarantined – recovered (SEIQR), and susceptible – exposed – infectious – asymptomatic – recovered – environment (SEIARW), have been employed to calculate the reproduction number of HFMD [10–15]. The reproduction number of EV71 and CoxA16 was also estimated [16]. However, the interaction on the transmissibility of the main pathogens of HFMD remains unclear.

In this study, data on reported HFMD cases were collected in Xi'an City. A long-term etiological surveillance was conducted in Xi'an City to calculate the incidence of EV71, CoxA16, and other

enteroviruses. A SIR model was adopted to calculate the transmissibility and its interaction of the three pathogens.

Methods

Study sites and data collection

In this study, Xi'an City in Shaanxi Province were selected as study sites. Xi'an City, the capital city of Shaanxi Province, has a population of more than 9.6 million and includes 11 districts and 2 counties.

An etiological surveillance was conducted from 2009 in the two cities. A dataset was built based on the weekly number of reported cases and death cases from January 2009 to December 2016 in Xi'an City. Each month, 5 stool or anus swab samples were collected from clinically diagnosed cases in each district or county. The samples were sent to the laboratory of municipal Center for Disease Control and Prevention to test the pathogens (EV71, CoxA16, and other enteroviruses denoted as "Other") of the disease by polymerase chain reaction. The proportion of the three pathogens was therefore calculated to estimate the numbers of HFMD cases infected with EV71, CoxA16, or other enteroviruses.

In addition, population of the cities, birth rate and death rate of the population were collected from statistical yearbooks announced by the statistical bureau of the two cities.

Patient and public involvement

The patients and the public were not involved in this study.

Simulation model and transmissibility estimation

A susceptible-infectious-recovered (SIR) model was adopted considering the natural birth rate and death rate of the population. The equations of the model were shown as follows:

[Due to technical limitations, the formulas could not be displayed here. Please see the supplementary files section to access the formulas.]

In the equations, S, I, R, and N refer to susceptible individuals, infectious individuals, recovered individuals, and number of the whole population, respectively. Parameters a , b , f , β , and γ refer to natural birth rate of the population, death rate of the population, fatality of HFMD, transmission relative rate, and recovered relative rate, respectively.

The reproduction number was utilized to quantify the transmissibility of HFMD. We assumed that the reproduction number of the disease during the ascending period of reported cases (defined as R_{asc}) was different to the one during the descending period (defined as R_{des}). They were calculated by the following equations:

[See supp. files]

In the equations, β_{asc} and β_{des} refer to transmission relative rate during the ascending and descending period, respectively.

Parameter estimation and statistical analysis

Parameters a, b, and f were calculated from the collected data. According to the published study [10, 14], the infectious period of HFMD was about two weeks, therefore $\gamma = 0.5$. From the collected data of reported HFMD cases, an epidemic peak were divided into ascending and descending parts which were employed to fit the SIR model to calculate β_{asc} and β_{des} in each year.

Berkeley Madonna 8.3.18 (developed by Robert Macey and George Oster of the University of California at Berkeley. Copyright ©1993–2001 Robert I. Macey & George F. Oster) was employed to run the model and least root mean square was adopted to assess goodness of fit. SPSS 13.0 (IBM Corp., Armonk, NY, USA) was employed to analyze the difference and the interaction of β_{asc} and β_{des} among the three main pathogens of the disease. Eleven models (Linear, Logarithmic, Inverse, Quadratic, Cubic, Power, Compound, S, Logistic, Growth, Exponential, and Logistic) in SPSS 13.0 were employed to fit the yearly trends of reported HFMD cases and fatality.

Results

Epidemiological features of the disease in Xi'an City

From January 2009 to December 2016, 170,567 HFMD cases (including clinically diagnosed cases and confirmed cases) were reported in Xi'an City, among which 30 were death cases with a fatality of 0.02%. The number of reported HFMD cases increased yearly with a Linear model of “ $Y = 14661.57 + 1479.845X$ ” where Y and X refer to number of reported cases and sequence of year from 1 to 8, although no statistical significance was observed ($R^2 = 0.326$, $F = 2.896$, $P = 0.140$) (Fig. 1-A). However, the fatality of the disease decreased yearly. An Inverse model best fitted the decreasing trend with the equation of “ $Y = 0.007 + 0.034/X$ ” where Y and X refer to the fatality and sequence of year from 1 to 8, and a statistical significance was observed ($R^2 = 0.727$, $F = 15.958$, $P = 0.007$) (Fig. 2-A). From 2009 to 2016, 7,710 stool or anal swab specimens were collected from the reported cases, among which, 2,496 were tested EV71 positive, 1,434 were Cox A16 positive, and 1,434 were other enteroviruses positive.

Transmissibility of the three pathogens

The results of model fitting showed that 18 epidemic peaks of HFMD cases were reported from 2009 to 2016 in Xi'an City, with R_{asc} and R_{des} of 1.39 (95% CI: 1.31–1.48) and 0.70 (95% CI: 0.65–0.74), respectively (Fig. 3-A). The number of epidemic peaks of EV71, CoxA16, and other enterovirus was 16, 18, and 17, respectively. The R_{asc} of EV71, CoxA16, and other enterovirus was 1.47 (95% CI: 1.37–1.57), 1.61 (95% CI: 1.34–1.88), and 1.50 (95% CI: 1.38–1.61), with no statistical significance among the three pathogens ($F = 0.626$, $P = 0.539$). The R_{des} of EV71, CoxA16, and other enterovirus was 0.64 (95% CI:

0.58–0.70), 0.57 (95% CI: 0.48–0.67), and 0.66 (95% CI: 0.60–0.71), with no statistical significance among the three pathogens ($F = 1.506$, $P = 0.232$).

The transmissibility of the three pathogens kept in a stable level during the study period except some fluctuation of the transmissibility of CoxA16 from 2010 to 2011 in Xi'an City (Fig. 4). The trends of the transmissibility in Changsha City were similar to which in Xi'an City, but the fluctuation was more common. The R_{asc} of EV71 increased in 2017. The R_{asc} of CoxA16 increased obviously from late 2014 to 2015. The R_{asc} of the other enteroviruses increased obviously in 2009 (Fig. 4).

Interaction of the three pathogens

To analyze the interaction of the three pathogens, we compared the transmissibility for each other among the three pathogens (Table 1). We found that difference of R_{asc} between CoxA16 (mean = 1.61) and CoxA16 + Other (mean = 1.25) and the difference between Other (mean = 1.50) and CoxA16 + Other (mean = 1.25) were statistically significant in Xi'an City. There was no statistical significance of R_{asc} between any other two groups in the city. There was also no statistical significance of R_{des} between any two groups in the city except between CoxA16 (mean = 0.57) and CoxA16 + Other (mean = 0.70) (Table 1). These differences revealed that, during the reported cases increasing period, CoxA16 and other enteroviruses interacted with each other and their transmissibility (R_{asc}) was weakened by the interaction (Fig. 5-A). However, during the reported cases decreasing period, the interaction of the two viruses was directional, and the transmissibility (R_{des}) of CoxA16 increased when other enteroviruses spread in the same period (Fig. 5-B).

Table 1
Interaction of transmissibility of HFMD's three pathogens in Xi'an and
Changsha City

Transmissibility	Compared groups	Xi'an City	
		t	P
R_{asc}	EV71 v.s. EV71 + CA16	0.831	0.413
	EV71 v.s. EV71 + Other	0.300	0.766
	EV71 v.s. EV71 + CA16 + Other	1.110	0.275
	CA16 v.s. CA16 + EV71	1.306	0.201
	CA16 v.s. CA16 + Other	2.206	0.034
	CA16 v.s. CA16 + EV71 + Other	1.489	0.146
	Other v.s. Other + EV71	0.615	0.543
	Other v.s. Other + CA16	2.151	0.038
	Other v.s. Other + EV71 + CA16	1.388	0.174
R_{des}	EV71 v.s. EV71 + CA16	-0.982	0.334
	EV71 v.s. EV71 + Other	-0.953	0.348
	EV71 v.s. EV71 + CA16 + Other	-1.625	0.114
	CA16 v.s. CA16 + EV71	-1.857	0.073
	CA16 v.s. CA16 + Other	-0.614	0.543
	CA16 v.s. CA16 + EV71 + Other	-2.375	0.023
	Other v.s. Other + EV71	-0.483	0.632
	Other v.s. Other + CA16	0.656	0.516
	Other v.s. Other + EV71 + CA16	-1.193	0.241

These differences revealed that, the interaction of the three pathogens was more complex in Changsha City than in Xi'an City. During the reported cases increasing period, EV71 and CoxA16 interacted with each other, but the interaction between EV71 and other enteroviruses and between CoxA16 and other enteroviruses were both directional. These interactions all decreased the transmissibility (R_{asc}) of affected pathogens (Fig. 5-C).

However, during the reported cases decreasing period, interactions only occurred between EV71 and other enteroviruses and between CoxA16 and other enteroviruses. The transmissibility (R_{des}) of EV71 and CoxA16 was both increased when other enteroviruses spread in the same period (Fig. 5-D).

Discussion

After analyzing the reported data of HFMD cases, we found that the number of reported cases increased but fatality decreased yearly in the two cities. The decreased fatality might due to the enhanced surveillance system and improved diagnosis and treatment ability of health departments (clinics and hospitals). The increased incidence reveals that the pathogens of HFMD are still spreading in the cities.

Considering that the effectiveness of interventions exists during the reported cases descending period, we experientially recommend that the transmissibility of HFMD could be estimated by using R_{asc} . Calculated by the SIR model, we found that the transmissibility (R_{asc}) of EV71, CoxA16, and the other enteroviruses in Xi'an City was 1.47, 1.61, and 1.50, respectively. These results indicated that the transmissibility of HFMD is lower than influenza. Commonly, the reproduction number of influenza was 1.4–2.0 [17], and was 1.81 in Changsha City [18]. Therefore, the results of our study are reliable. According to the stable trends of the transmissibility of the three pathogens of HFMD, the transmission force would keep in a stable level, thus we could make an evidence-based prediction that HFMD would still spread in Xi'an cities. Countermeasures, including surveillance, case diagnosis, case isolation, vaccination of EV71 vaccine, hand hygiene, social distance, and health promotion, should be strengthened to control and prevent the disease.

The results of interaction analysis showed that CoxA16 and other enteroviruses interacted with each other in Xi'an City during the reported cases increasing period. The transmissibility of CoxA16 or other enteroviruses might be decreased if the two viruses co-transmit in the same population. However, during the reported cases decreasing period, the interaction was directional.

The reason of the difference in Xi'an City remains unclear. It might result from the geographic difference. Xi'an City locates in the central west of China, which has warm and semi-humid continental monsoon climate (temperature, rainfall, and relative humidity), as well as developed socioeconomic factors [19–22]. These factors might affect the activity of the pathogens and the mode of contact among individuals. Furthermore, it is unknown whether the pathogens have the special genomic features in Xi'an City.

There is another phenomenon that the results of the interactions among the pathogens are similar between R_{asc} and R_{des} . After interacting, the transmissibility (R_{asc} or R_{des}) of the affected pathogen was adjusted and verged to 1, in Xi'an City. The reason of the phenomenon is also unknown. Therefore, it is essential to explore the mechanism and the risk factors of the interaction clearly, and we strongly recommend that more research should be focused on these issues to provide more evidence to control and prevent HFMD.

Declarations

Contributors: YB and KL designed the study. YB, SC, KL, ZS, FY, JW and DY collected data. TC, YB and SC and performed the analysis. YB wrote the first draft of this paper. All authors contributed to the writing of the manuscript.

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Competing interests: None declared.

Data sharing statement: Extra data is available by emailing to the first authors (Yao Bai, 402359346@qq.com) on reasonable request.

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Figures

A: Xi'an City

EV71

$R_{asc} = 1.47$ (95% CI : 1.37 - 1.57)
 $R_{des} = 0.64$ (95% CI : 0.58 - 0.70)

CA16

$R_{asc} = 1.61$ (95% CI : 1.34 - 1.88)
 $R_{des} = 0.57$ (95% CI : 0.48 - 0.67)

Other

$R_{asc} = 1.50$ (95% CI : 1.38 - 1.61)
 $R_{des} = 0.66$ (95% CI : 0.60 - 0.71)

EV71 + CA16

$R_{asc} = 1.41$ (95% CI : 1.30 - 1.51)
 $R_{des} = 0.68$ (95% CI : 0.63 - 0.73)

EV71 + Other

$R_{asc} = 1.45$ (95% CI : 1.34 - 1.56)
 $R_{des} = 0.67$ (95% CI : 0.63 - 0.72)

CA16 + Other

$R_{asc} = 1.25$ (95% CI : 1.07 - 1.43)
 $R_{des} = 0.62$ (95% CI : 0.51 - 0.72)

EV71 + CA16 + Other

$R_{asc} = 1.39$ (95% CI : 1.31 - 1.48)
 $R_{des} = 0.70$ (95% CI : 0.65 - 0.74)

Figure 1

Yearly number of reported HFMD cases and its trend in Xi'an City (A)

Figure 2

Fatality of HFMD and its trend in Xi'an City (A)

Figure 3

Results of model fitting and the transmissibility of HFMD's three pathogens in Xi'an(A) .

Figure 4

The trends of the transmissibility of HFMD. A, Xi'an City, EV71; B, Xi'an City, CA16; C, Xi'an City, Other.

Figure 5

The interaction modes of the transmissibility of HFMD in Xi'an City A, Xi'an City, R_{asc} ; B, Xi'an City, R_{des} ; Arrow indicates the direction of interaction from one pathogen to another one; no arrow refers to no interaction.

Supplementary Files

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- [Methodsformulas.docx](#)