- 1 Title: The relative transmissibility of shigellosis among male and female individuals in Hubei
- 2 **Province, China: a modelling study.**
- **3** Running title: Transmissibility of shigellosis.
- 4 Author and affiliations:
- 5 Zeyu Zhao^{1*}, Qi Chen^{2*}, Bin Zhao^{3*}, Mikah Ngwanguong Hannah⁴, Ning Wang⁵, Yuxin Wang⁶,
- 6 Xianfa Xuan⁶, Jia Rui¹, Meijie Chu¹, Yao Wang¹, Xingchun Liu¹, An Ran¹, Lili Pan¹, Yi-Chen
- 7 Chiang¹, Yanhua Su^{1#}, Benhua Zhao^{1#}, Tianmu Chen^{1#}
- 8 1. State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, School of Public Health,
- 9 Xiamen University, Xiamen City, Fujian Province, People's Republic of China;
- 10 2. Hubei Provincial Center for Disease Control and Prevention, Wuhan City, Hubei Province, People's
- **11** Republic of China;
- 12 3. State Key Laboratory of Molecular Vaccinology and Molecular Diagnosis, Laboratory Department,
- 13 Xiang'an Hospital of Xiamen University, Xiamen, Fujian, China;
- 14 4. Medical College, Xiamen University, Xiamen City, Fujian Province, People's Republic of China;
- 15 5. Respiration Department, Shanghai General Hospital, Shanghai, China
- 16 6. Department of Nephrology, Xiang'an hospital of Xiamen University, Xiamen, Fujian, China
- 17 * These authors contributed equally to this study.
- 18

19 # Corresponding author

20 Tianmu Chen

21 State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, School of Public Health,

- 22 Xiamen University
- 23 4221-117 South Xiang'an Road, Xiang'an District, Xiamen, Fujian Province, People's Republic of China
- **24** Tel: +86-13661934715
- 25 Email: 13698665@qq.com
- 26 Yanhua Su
- 27 State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, School of Public Health,
- 28 Xiamen University
- 29 4221-117 South Xiang'an Road, Xiang'an District, Xiamen, Fujian Province, People's Republic of China

- **30** Tel: +86-18965144848
- 31 Email: suyanhua813@xmu.edu.cn
- 32 Benhua Zhao
- 33 State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, School of Public Health,
- 34 Xiamen University
- 35 4221-117 South Xiang'an Road, Xiang'an District, Xiamen, Fujian Province, People's Republic of China
- **36** Tel: +86-15359221955
- 37 Email: benhuazhao@163.com
- 38
- 39

40 Abstract

41 Objective: Shigellosis has been a heavy burden in China. However, its relative transmissibility in male
42 and female individuals remains unclear.

43 Method: A sex-based Susceptible–Exposed–Infectious/Asymptomatic–Recovered (SEIAR) model was
44 applied to explore the dataset of reported shigellosis cases built by Hubei Province from 2005 to 2017. Two
45 indicators, secondary attack rate (SAR) and relative ratio of SAR between males and females, were
46 developed to assess the relative transmissibility in males and females.

- 47 Results: The number of cases and reported incidences in males and females demonstrated a significant 48 decreasing trend (Male trend: $\chi^2 = 11.268$, P = 0.001, Female trend: $\chi^2 = 11.144$, P = 0.001). SEIAR model 49 had a great fitting effect with the data of shigellosis (P < 0.001). Our simulation revealed that, when 50 parameter $\beta_{fm} = 0$, the greatest decrease in cases were obtained for different genders. The median value for 51 SAR_{mm} was 2.3225×10^{-8} (Range: $1.7574 \times 10^{-8} - 3.8565 \times 10^{-8}$), SAR_{mf} was 2.5729×10^{-8} (Range: 1.3772 $\times 10^{-8} - 3.2773 \times 10^{-8}$), SAR_{fm} was 2.7630 $\times 10^{-8}$ (Range: $1.8387 \times 10^{-8} - 4.2638 \times 10^{-8}$) and SAR_{ff} was 52 53 2.1061×10^{-8} (Range: $1.0201 \times 10^{-8} - 3.2140 \times 10^{-8}$). The median value of relative ratio calculated by SAR 54 in mm versus (vs) mf was 0.93 (Range: 0.75 - 1.47), mm vs fm was 0.90 (Range: 0.41 - 1.81), mm vs ff was 55 1.07 (Range: 0.55 – 2.93), mf vs fm was 0.99 (Range: 0.32 – 1.25), mf vs ff was 1.17 (Range: 0.43 – 3.21) 56 and ff vs fm was 0.75 (Range: 0.35 – 1.06).
- 57 Conclusion: Transmissibility of shigellosis is different among male and female individuals. Shigellosis
 58 seems to be more transmissible in males than in females.
- 59 Key words: Transmissibility; Shigellosis; Mathematical model
- 60

61 Author summary

62 Shigellosis, also known as bacillary dysentery, is an infectious disease caused by the genus *Shigella spp*.
63 Developing countries have high disease burden of shigellosis. However, its relative transmissibility in
64 male and female individuals remains unclear. In this study, we employed a mathematical model to
65 explore the dataset of reported shigellosis cases built by Hubei Province, China from 2005 to 2017. Two
66 indicators, secondary attack rate (SAR) and relative ratio of SAR between males and females, were
67 developed to assess the relative transmissibility in males and females. We found that shigellosis has

68 medium transmissibility among male and female individuals. The disease seems to be more69 transmissible in males than in females.

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75 Introduction

Shigellosis, also known as bacillary dysentery, is an infectious disease caused by the genus *Shigella spp*, and often occurs in summer and autumn. *Shigella flexneri* is the main cause of endemic diarrhoea in
low and middle income countries, and lays a heavy burden on these countries, especially in children aged
1-4 years old [1]. According to the Chinese Center for Disease Control and Prevention, about
150,000~450,000 cases were reported annually within the period 2005 to 2014 [2]. Although there has been
an improvement in the quality of water and sanitaion, shigellosis remains a major public health problem in
some developing countries, including China [3, 4].

83 Bacillary dysentery is an intestinal infectious disease, which can be transmitted via the consumption of 84 contaminated food or water [5]. Humans are the only natural host for *shigella*. Shigellosis has low 85 infectious dose and transmission primarily occurs from person-to-person [1]. Previously, a study was done 86 [6] in China during which it was evaluated that, contaminated water and food hardly contributed to 87 shigellosis. According to these reports, the incidence rate of bacillary dysentery is higher in males than in 88 females [7]. So, was there a shift route in the transmission of shigellosis in developing countries? What is 89 the process of transmission among individuals? What caused the different incidence in males and females? 90 The distribution of time and space were focused more in the model studies of shigellosis, while 91 population-based research was less [8-12]. Studies have showed that the Susceptible-Exposed-92 Infectious/Asymptomatic-Recovered-Water (SEIARW) model has a great fitting effect [6]. However, it 93 does not estimate the transmissibility of bacillary dysentery between males and females. Therefore, a new 94 model-SEIAR, is formed by simplifying the SEIARW model. We adopted secondary attack rate (SAR) to 95 quantify the infectivity of shigellosis and relative ratio to assess the transmissibility of shigellosis between

96 males and females.

97	In this study, we collected Shigellosis cases reported in Hubei Province, China, adopted SEIAR model
98	to fit the data, calculated related index and figured out the transmissibility of shigellosis between males and
99	females.

100

101 Materials and Methods

102 Data sources

A dataset of shigellosis reported cases built by Hubei Province from January 2005 to December 2017,
were collected from China Information System for Disease Control and Prevention. We cleared up the date
and sex (male or female) of onset of illness for each case. The informations of the population such as, birth
rate, death rate and total population were obtained from Hubei Statistical Yearbook.

107 Shigellosis model between different genders

108 According to a new review [1], the transmission of shigellosis is mainly from person-to-person in

109 developed countries. Therefore, the SEIAR model was developed according to the natural history of

110 shigellosis between male and female individuals (Figure 1). The pattern followed by the model was from

111 person-to-person, which contained susceptible (S), exposed (E), symptomatic (I), asymptomatic (A), and

112 recovered (R) individuals (Table 1). We used the subscript *m* to represent male and *f* to represent female. In

the model, we assumed that:

a) Relative rate of transmission among male and female individuals was β_m and β_f , respectively;

b) Relative rate of transmission from male to female was β_{mf} and from female to male was β_{fm} .

116 We assumed that in both males and females:

a) The disease does not spread vertically, and the individuals born in various groups are all susceptible.

118 The natural birth rate is *br*, and the natural mortality rate is *dr*;

b) The proportion of latency patients (1-p)E $(0 \le p \le 1)$ will change to infected person *I* after one

120 incubation period, while another part of the latent *pE* will become a latent infected person *A* after an

121 incubation period. Therefore, at time t, the speed from E to I is proportional to the latency group, the

122 proportional coefficient is $(1-p)\omega$, and the speed from E to A is proportional to the latency population, and

123 the proportional coefficient is $p\omega$;

c) The speeds removed from *I* and *A* are proportional to the number of people in both groups, and the
proportional coefficients are *γ* and *γ'*, respectively.

126 The model was expressed as follows:

127
$$\frac{dS_m}{dt} = brNq - \beta_m S_m (I_m + kA_m) - \beta_{fm} S_m (I_f + kA_f) - drS_m$$

128
$$\frac{dE_m}{dt} = \beta_m S_m (I_m + kA_m) + \beta_{fm} S_m (I_f + kA_f) - \omega E_m - dr E_m$$

29
$$\frac{dI_m}{dt} = (1-p)\omega E_m - \gamma I_m - (drI_m + fI_m)$$

$$130 \qquad \frac{dA_m}{dt} = p\omega E_m - \gamma' A_m - dr A_m$$

$$131 \qquad \frac{dR_m}{dt} = \gamma I_m + \gamma A_m - dr R_m$$

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132
$$\frac{dS_f}{dt} = brNq - \beta_f S_f (I_f + kA_f) - \beta_{mf} S_f (I_m + kA_m) - drS_f$$

133
$$\frac{dE_f}{dt} = \beta_f S_f (I_f + kA_f) + \beta_{mf} S_f (I_m + kA_m) - \omega E_f - dr E_f$$

134
$$\frac{dI_f}{dt} = (1-p)\omega E_f - \gamma I_f - (drI_f + fI_f)$$

$$135 \qquad \frac{dA_f}{dt} = p\omega E_f - \gamma' A_f - dr A_f$$

136
$$\frac{dR_f}{dt} = \gamma I_f + \gamma A_f - dr R_f$$

137
$$N = S_m + E_m + I_m + A_m + R_m + S_f + E_f + I_f + A_f + R_f$$

138 The left side of the equation shows the instantaneous rate of change of S, E, I, A and R at time t. In the 139 equations, the parameters β_m , β_f , β_{mf} , β_{fm} , k, ω , p, f, γ and γ ' refer to relative rate of transmission in males, 140 relative rate of transmission in females, relative rate of transmission from male to female, relative rate of 141 transmission from female to male, relative transmissibility of asymptomatic to symptomatic individuals, 142 incubation period, proportion of asymptomatic individuals, fatality of shigellosis, recovery rate of 143 symptomatic individuals, recovery rate of asymptomatic individuals. 144 In the model, we quantify the transmissibility of shigellosis by secondary attack rate (SAR), which is

145 defined as the probability that infection occurs among susceptible persons within a reasonable incubation 146 period, following contact with an infectious person or an infectious source. Relative ratio of transmission

- 147 is developed to assess the relative transmissibility of male versus female. We calculated the SAR and
- relative ratio by the equation as follows:
- 149 $SAR_{mm} = \beta_{mm}S_m \times 1/(\gamma * N_m)$
- 150 $SAR_{mf} = \beta_{mf}S_f \times 1/(\gamma * N_f)$
- 151 $SAR_{fm} = \beta_{fm}S_m \times 1/(\gamma * N_m)$
- 152 $SAR_{ff} = \beta_{ff}S_f \times 1/(\gamma * N_f)$
- 153 $mm vs mf = SAR_{mm}/SAR_{mf}$
- 154 $mm vs fm = SAR_{mm}/SAR_{fm}$
- 155 $mm vs ff = SAR_{mm}/SAR_{ff}$
- 156 $mf vs fm = SAR_{mf}/SAR_{fm}$
- 157 $mf vs ff = SAR_{mf}/SAR_{ff}$
- 158 $ff vs fm = SAR_{ff}/SAR_{fm}$

In the equation, we defined the subscripts; *mm*, *ff*, *mf* and *fm* as among males, among females, from
female to male, and from male to female, respectively. *mm* vs *mf*, *mm* vs *fm*, *mm* vs *ff*, *mf* vs *fm*, *mf* vs *ff*

161 and ff vs fm refer to mm, ff, mf and fm, which have similar definitions as with the subscript of SAR.

162 Estimation of Parameters

163 According to epidemiological characteristics of shigellosis and previous study [6], we set k, ω , γ and γ'

as 0.3125, 1.0000, 0.0741 and 0.0286, respectively. The proportions of asymptomatic individuals were

165 reported to range from 0.0037 to 0.2700 [13-15]. We set p = 0.1 in SEIAR model. The fatality rate of the

disease reported in a study decreased from 0.00031 to 0.00088 from 1991 to 2000 [16]. Considering

167 the fatality rate of shigellosis is extremely low, we set f = 0. The values of β_m , β_f , β_{mf} and β_{fm} were

168 generated by curve fitting using SEIAR model and reported shigellosis data. In order to simulate the

169 contribution of β_m , β_f , β_{mf} and β_{fm} during the transmission, we performed a "knock-out" simulation in five

170 scenarios: A) $\beta_m = 0$; B) $\beta_{mf} = 0$; C) $\beta_f = 0$; D) $\beta_{fm} = 0$; E) control (no intervention).

171 Simulation method and statistical analysis

172 Berkeley Madonna 8.3.18 (developed by Robert Macey and George Oster of the University of

173 California at Berkeley. Copyright ©1993-2001 Robert I. Macey & George F. Oster) was employed for

174 model simulation. Simulation methods were as previously described [6, 17-20]. Microsoft Office Excel

175	2007 (Microsoft, Redmond, WA, USA) and GraphPad Prism 7.00 (GraphPad Software, La Jolla California,
176	USA) were employed for figure development and data analysis. SPSS 21.0 (IBM Corp, Armonk, NY, USA)
177	was used to calculate coefficient of determination (R^2) by curve fitting, which was adopted to judge the
178	goodness of fit of the model.
179	Ethics
180	This effort of disease control was part of CDC's routine responsibility in Hubei Province; therefore,
181	institutional review and informed consent were not required for this study.
182	
183	Results
184	Epidemiological characteristics of shigellosis reported cases
185	From 2005 to 2017, 130770 shigellosis cases (including 73981male cases and 56789 female cases)
186	were reported in Hubei province (Figure 2). The median of incidences reported annually was 21.68 per
187	100000 persons (range: 6.10 – 32.63 per 100000 persons) in males and 17.91 per 100000 persons (range:
188	5.87 - 26.51 per 100000 persons) in females. It demonstrated that, the number of cases and reported
189	incidences in males and females had significantly decreased. (Male trend: $\chi^2 = 11.268$, $P = 0.001$, Female
190	trend: $\chi^2 = 11.144$, $P = 0.001$).
191	Curve fitting results

192 The results of curve fitting showed that the SEIAR model fitted the data well (Figure 3). The R² of
193 SEIAR model of different genders each year were shown in Table 1. The model had a great fitting effect
194 with the data of shigellosis (Supplementary Table 1).

195 The transmissibility of shigellosis

196 From Figure 4, the results of the "knock-out" simulation showed that the number of cases in different 197 genders using parameters $\beta_m = 0$, $\beta_f = 0$, $\beta_{mf} = 0$ and $\beta_{fm} = 0$ were lower than in the control group. When β_{fm}

198 = 0, the number of cases decreased most in different genders.

199 Figure 5 showed the difference between the mean and 95% confidence interval (*CI*) from 2005 to

200 2017 using β_m , β_f , β_{mf} and β_{fm} . The mean value when using β_m was 1.9240×10^{-9} (95% CI: 1.6621×10^{-9} –

201 6.6121 × 10⁻⁹), using β_f was 1.5645 × 10⁻⁹ (95% CI: 1.3521 × 10⁻⁹ – 1.7769 × 10⁻⁹), using β_{fm} was 2.1572 ×

202 $10^{-9} (95\% CI: 1.9159 \times 10^{-9} - 2.3986 \times 10^{-9})$ and using β_{mf} was $1.8750 \times 10^{-9} (95\% CI: 1.6846 \times 10^{-9} - 2.3986 \times 10^{-9})$

203 2.0654×10^{-9}).

204	The results of SAR from 2005 to 2017 were showed in Figure 6 and Figure 7. The median value of
205	SAR_{mm} was 2.3225×10^{-8} (Range: $1.7574 \times 10^{-8} - 3.8565 \times 10^{-8}$). The median value of SAR_{mf} was 2.5729×10^{-8}
206	10^{-8} (Range: $1.3772 \times 10^{-8} - 3.2773 \times 10^{-8}$). The median value of SAR_{fm} was 2.7630×10^{-8} (Range: 1.8387
207	$\times 10^{-8} - 4.2638 \times 10^{-8}$). The median value of SAR_{ff} was 2.1061×10^{-8} (Range: $1.0201 \times 10^{-8} - 3.2140 \times 10^{-8}$).
208	⁸).
209	The results of relative ratio of the dataset were depicted in Figure 8. The median value of relative ratio
210	calculated by SAR in mm vs mf was 0.93 (Range: $0.75 - 1.47$). The median value of relative ratio in mm vs
211	<i>fm</i> was 0.90 (Range: 0.41 – 1.81), <i>mm</i> vs <i>ff</i> was 1.07 (Range: 0.55 – 2.93), <i>mf</i> vs <i>fm</i> was 0.99 (Range: 0.32
212	- 1.25), <i>mf</i> vs <i>ff</i> was 1.17 (Range: 0.43 – 3.21) and <i>ff</i> vs <i>fm</i> was 0.75 (Range: 0.35 – 1.06) (Figure 9).
213	
214	Discussion
215	In this study, we were the first ones to make the transmission of shigellosis between different genders
216	clear. We applied SEIAR model to explore the differences of the water-borne infectious disease in males
217	and females for the first time. It has guiding significance for controlling the prevalence of shigellosis.
218	Validity of the model
219	According to R^2 of linear regression, the model of SEIAR has a high good-of-fitness with the reported
220	data in different genders. It is consistent with the results of a research [6], suggesting the model is suitable
221	for this study.
222	Epidemiological characteristics
223	In recent years, although the incidence of shigellosis has a decreasing trend in China [16, 21, 22], it is
224	still relatively high level in Hubei province from 2005 to 2017. The difference incidence of shigellosis
225	cases in male and female is observed by the descriptive epidemiology [23, 24]. However, all of them do not
226	clarify the reasons for the difference. A study indicates that there were more male than female cases (the
227	ratio of male to female is 1.3:1), which is consistent with our results in descriptive epidemiology [25].
228	According to a new review[1], the transmission pattern of shigellosis has shifted from water/food-to-
229	person to from person-to-person, with high risk groups being particularly men who have sex with other
230	men in developed country. Does this mean that the transmissibility of shigellosis among males is stronger
231	than among females? We developed SEIAR model to verify this hypothesis. However, we obtained the
232	number of cases in five hypotheses using "knock-out" simulation. When $\beta_{fm} = 0$, the number of cases 9

dropped most in different genders, which means that the female-to-male had a large contribution during the

transmission. It is important to isolate and treat female cases, and to strengthen the personal health.

235 Transmissibility of Shigellosis in different genders

236 Compared with HIV which has different transmissibility in different genders, shigellosis is not 237 particularly highly contagious in different genders [26]. Our results showed that the mean values of the 238 transmission parameters among males and females, from male to female, and from female to male are 239 different, and they have the following order: $\beta_{fm} > \beta_m > \beta_{mf} > \beta_f$. The median values of *SAR* have the 240 following order: $SAR_{fm} > SAR_{mf} > SAR_{mm} > SAR_{ff}$. The median values of relative ratio of SAR have the 241 following order: mf vs ff > mm vs ff > mf vs fm > mm vs mf > mm vs fm > ff vs mf. All the results have a 242 common feature, that the transmission is mainly female-to-male. These findings showed that male 243 individuals are more transmissible than female individuals. Therefore, the different transmissibility 244 between males and females is the reason for the difference in distribution between genders. 245 There are a large number of studies focused on the distribution of incidence in different age groups [1, 246 7, 16, 22]. And the high-risk group is under 5 years old and over 60 years old. Combining with our results 247 and the actual situation of China, whether it can be considered related to the tradition of the elderly 248 bringing children at home. Elderly people, especially grandmothers, have more daily contact with their 249 children, which lead to such high transmission rates. Meanwhile, the transmissibility of shigellosis in 250 different age groups further needs to be studied.

251 Limitation

According to a recent study, although it is mainly transmitted from person to person [1], the shigellosis is still a water/food-borne disease. For this reason, there has been an impact on our result given that we simplified the SIEARW model and ignored environmental factors (water and food). At the same time, the parameters of SIEAR model come from relevant references and Hubei Statistical Yearbook, not from collection, this has an impact on the accuracy of our model.

257 Conclusions

In Hubei Province, The incidence of shigellosis in males is higher than that in female, causing the
disease to be a burden. The transmissibility of shigellosis is different in male and female individuals. Males
seem to be more transmissible than females and the transmission is mainly female-to-male.

261

262 Data Availability Statement:

All relevant data are within the paper and its Supporting Information files.

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- valuable assistance in coordinating data collection.
- 267
- 268
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- 270 Reference

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385 Male; B: Female; $\beta_m = 0$, control transmission among male; $\beta_{fm} = 0$, control transmission among

- female; $\beta_f = 0$, control transmission from female to male; $\beta_{mf} = 0$, control transmission from male to
- 387 female; and control defined as "None").
- Figure 5. The parameter of β_m , β_f , β_{mf} and β_{fm} during the transmission from 2005 to 2017 in Hubei (A:
- 389 β_m , transmission relative rate among male; B: β_f , transmission relative rate among female; C: β_{mf} ,
- 390 transmission relative rate from male to female; D: β_{fm} , transmission relative rate from male to
- 391 female).
- 392 Figure 6. The SAR_{mn}, SAR_m, SAR_{fm} and SAR_{ff} estimated by Model from 2005 to 2017 in Hubei (A:
- 393 *mm*, among male; B: *mf*, from male to female; C: *fm*, from female to male; D: *ff*, among female).
- Figure 7. Box-plot of SAR from 2005 to 2017 in Hubei (*mm*: among male; *ff*: among female; *fm*: from
- 395 female to male; *mf*: from male to female).
- 396 Figure 8. The five kinds of relative ratio from 2005 to 2017 in Hubei (A: *mm* vs *mf*, among male
- 397 versus from male to female; B: mm vs fm, among male versus from female to male; C: mm vs ff,
- among male versus among female; D: *mf* vs *fm*, from male to female versus from female to male; E:
- 399 *mf* vs *ff*, from male to female versus among female; F: *ff* vs *fm*, among female versus from female to
- 400 male).
- 401 Figure 9. Box-plot of relative ratio from 2005 to 2017 in Hubei (*mm*: among male; *ff*: among female;
- 402 *fm*: from female to male; *mf*: from male to female).
- 403

404 Tables

Variable	Description	Unit
S _m	Male susceptible individuals	Individuals
S_f	Female susceptible individuals	Individuals
E_m	Male exposed individuals	Individuals
E_f	Female exposed individuals	Individuals
I_m	Male infectious individuals	Individuals
I_f	Female infectious individuals	Individuals
A_m	Male asymptomatic individuals	Individuals
A_f	Female asymptomatic individuals	Individuals
R_m	Male recovered individuals	Individuals
R_f	Female recovered individuals	Individuals
Ν	Total number of population	Individuals

405 Table 1. Variables with the intersex transmission SEIAR model

406

407

Parameter	Description	Unit	Value	Range	Method
β_m	Relative rate of trasmission	Individuals ⁻¹ ·days ⁻¹	_	$\geqslant 0$	Curve fitting
ρ_m	among male individuals	individuals days		~ 0	
0	Relative rate of transmission	Individualar! davar!		$\geqslant 0$	Curve fitting
β_f	among female individuals	Individuals ⁻¹ ·days ⁻¹		<i>>></i> 0	
0	Relative rate of transmission	T. dissides 11 dassed	_	$\geqslant 0$	Curve fitting
β_{fm}	from female to male	Individuals ⁻¹ ·days ⁻¹		≥ 0	
0	Relative rate of transmission	T. dissides 11 dassed	_	$\geqslant 0$	Curve fitting
β_{mf}	from male to female	Individuals ⁻¹ ·days ⁻¹		≥ 0	
	Relative transmissibility rate				
k	of asymptomatic to	1	0.3125	0-1	References[6]
	symptomatic individuals				
	Proportion of the		0.1		
р	asymptomatic	1		0.0037-0.2700	References[13-15]
ω	Incubation relative rate	days-1	1	$\geqslant 0$	References[6]

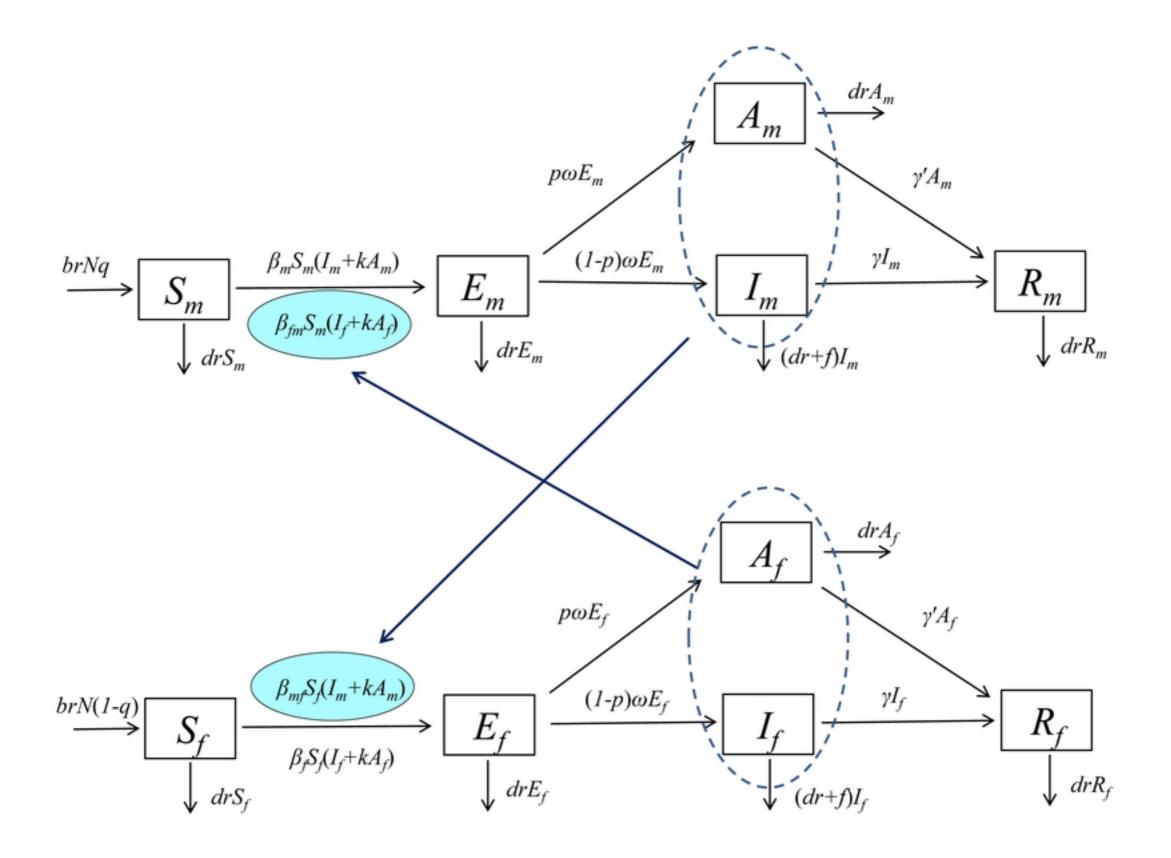
Table 2. Parameter description and values of SEIAR model

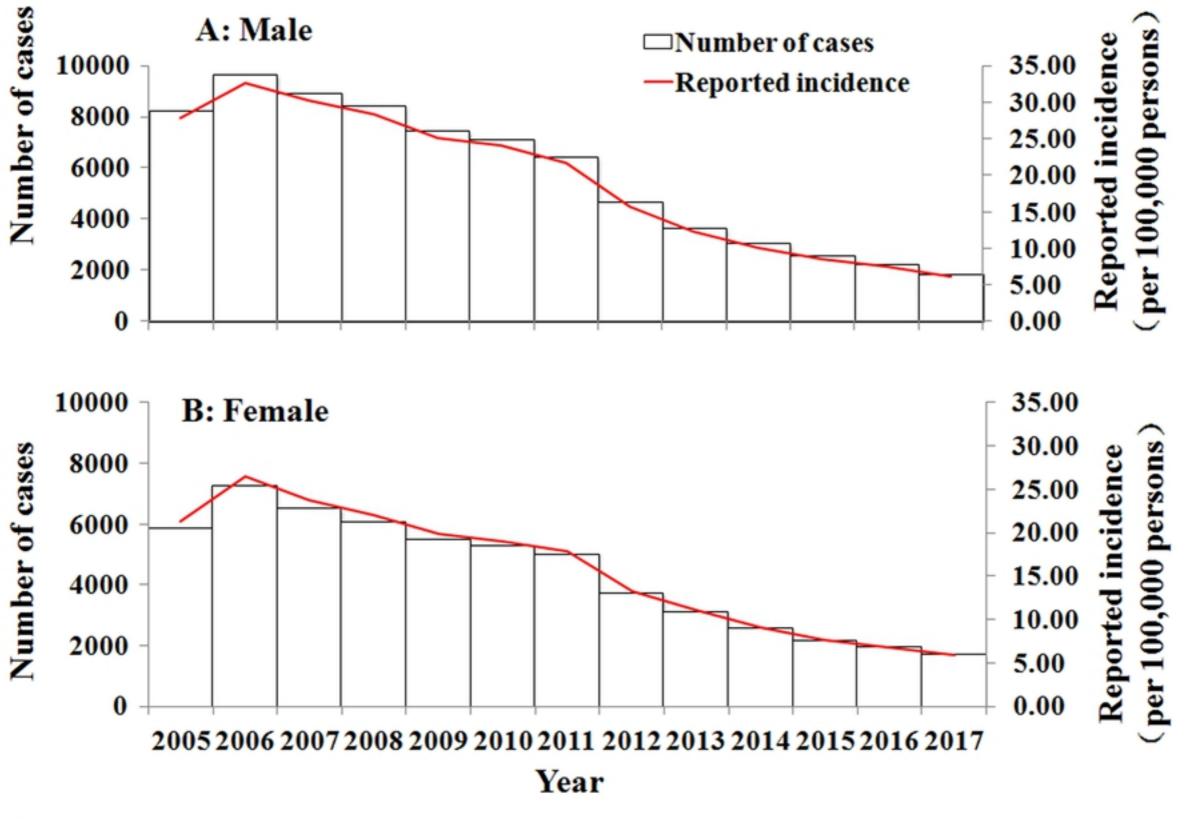
γ	Recovery rate of the symptomatic individuals	days-1	0.0741	$\geqslant 0$	References[6]
γ'	Recovery rate of the	days-1	0.0286	$\geqslant 0$	References[6]
f	asymptomatic individuals Fatality of the disease	1	0	0-1	References[16]
br	Birth rate of the population	1	_	0.0087-0.0126	Hubei Statistical Yearbook
dr	Death rate of the population	1	_	0.0057-0.0070	Hubei Statistical Yearbook

Table 3. R^2 of model and reported cases in different genders from 2005 to 2017 in Hubei

Province, China

Year	Male		Female	
real	R^2	р	R^2	р
2005	0.989	< 0.001	0.991	< 0.001
2006	0.995	< 0.001	0.992	< 0.001
2007	0.992	< 0.001	0.987	< 0.001
2008	0.984	< 0.001	0.986	< 0.001
2009	0.982	< 0.001	0.984	< 0.001
2010	0.989	< 0.001	0.982	< 0.001
2011	0.985	< 0.001	0.982	< 0.001
2012	0.989	< 0.001	0.979	< 0.001
2013	0.977	< 0.001	0.983	< 0.001
2014	0.986	< 0.001	0.983	< 0.001
2015	0.977	< 0.001	0.965	< 0.001
2016	0.985	< 0.001	0.988	< 0.001
2017	0.986	< 0.001	0.978	< 0.001





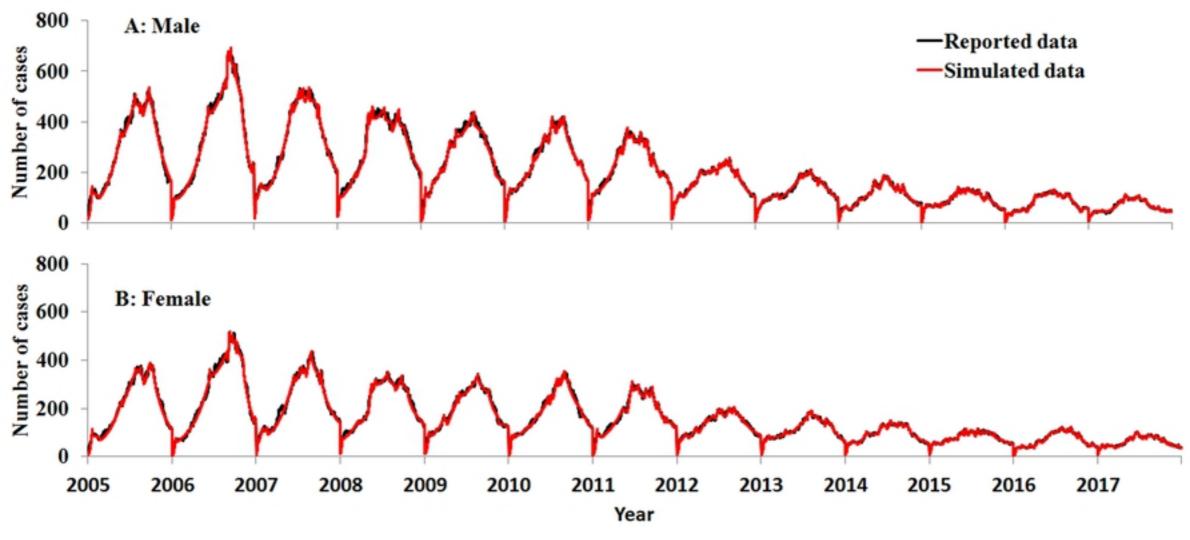
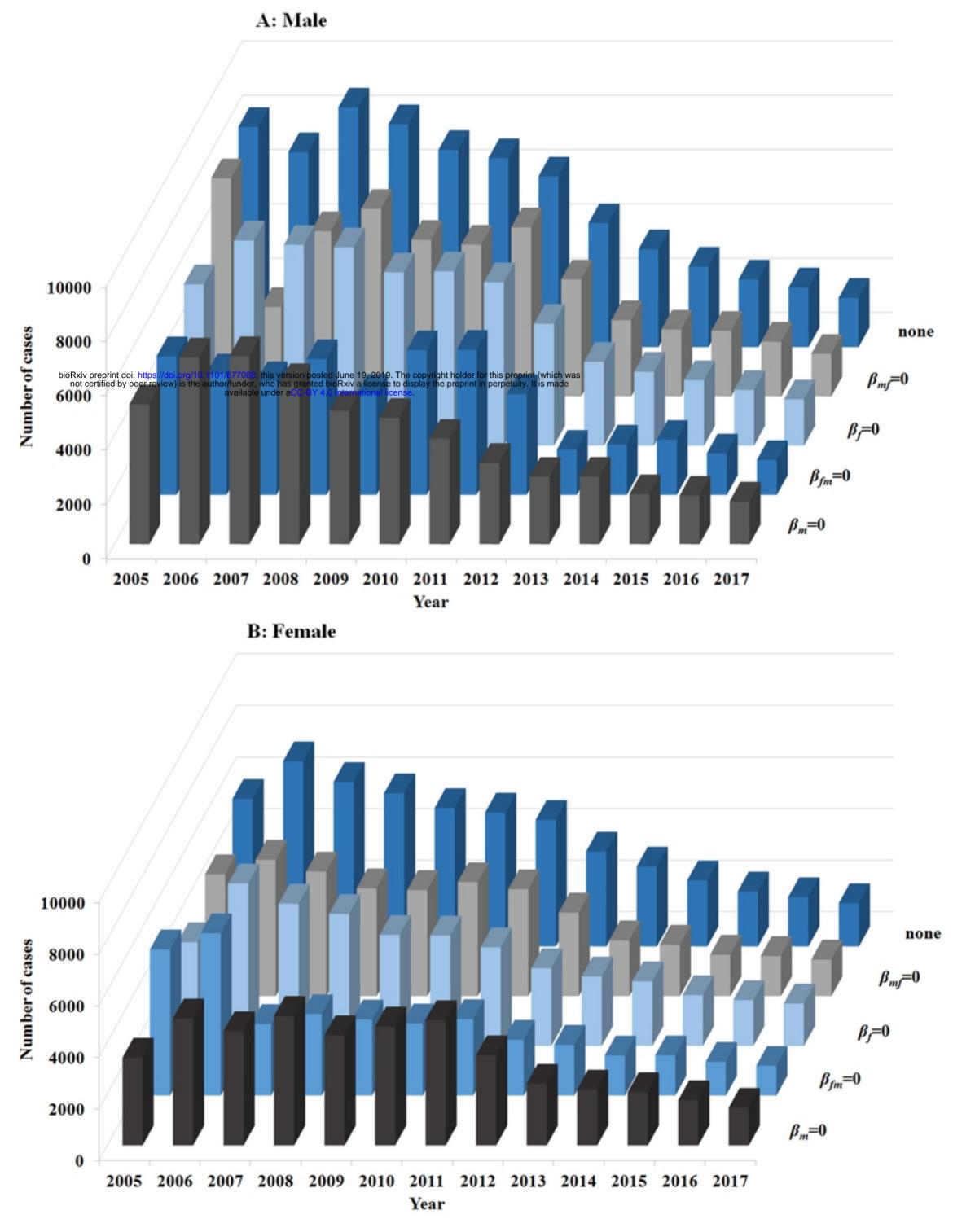
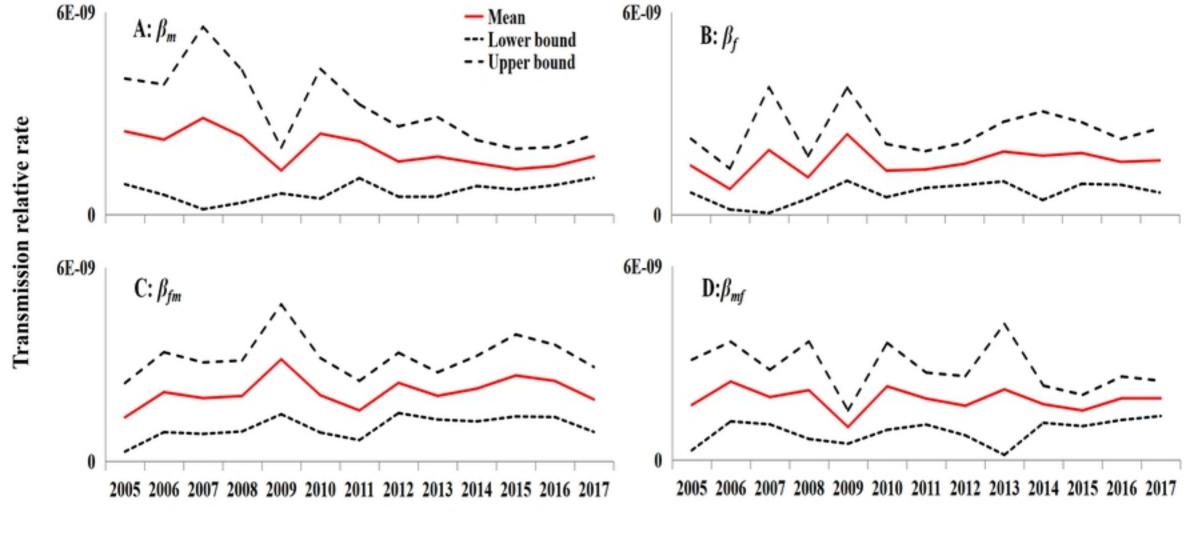
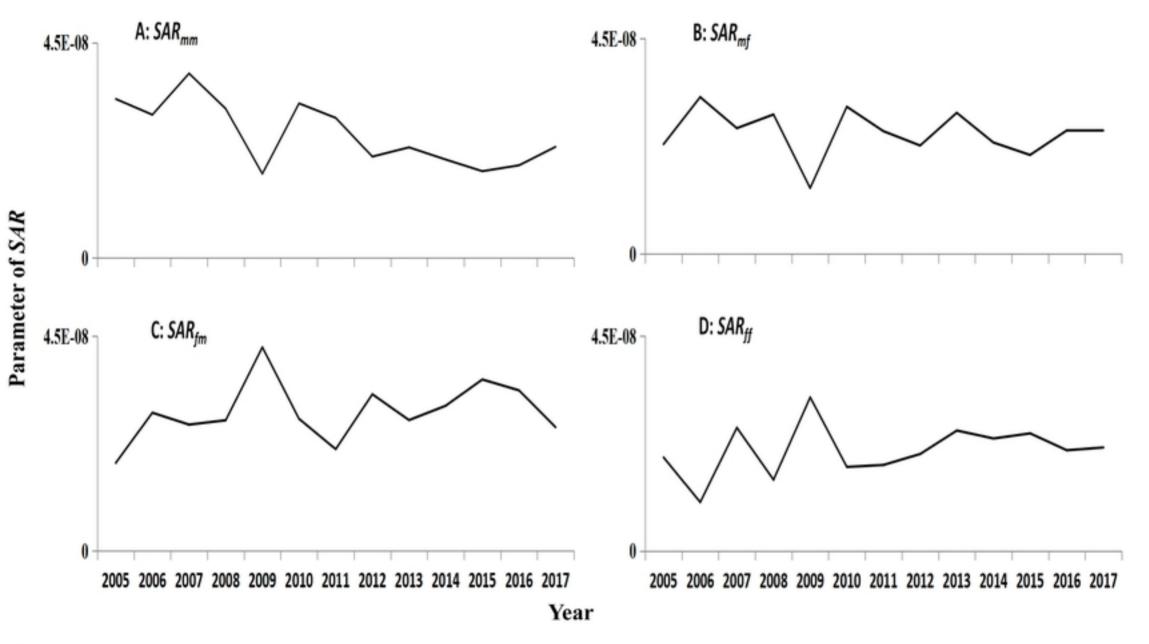


Figure 3









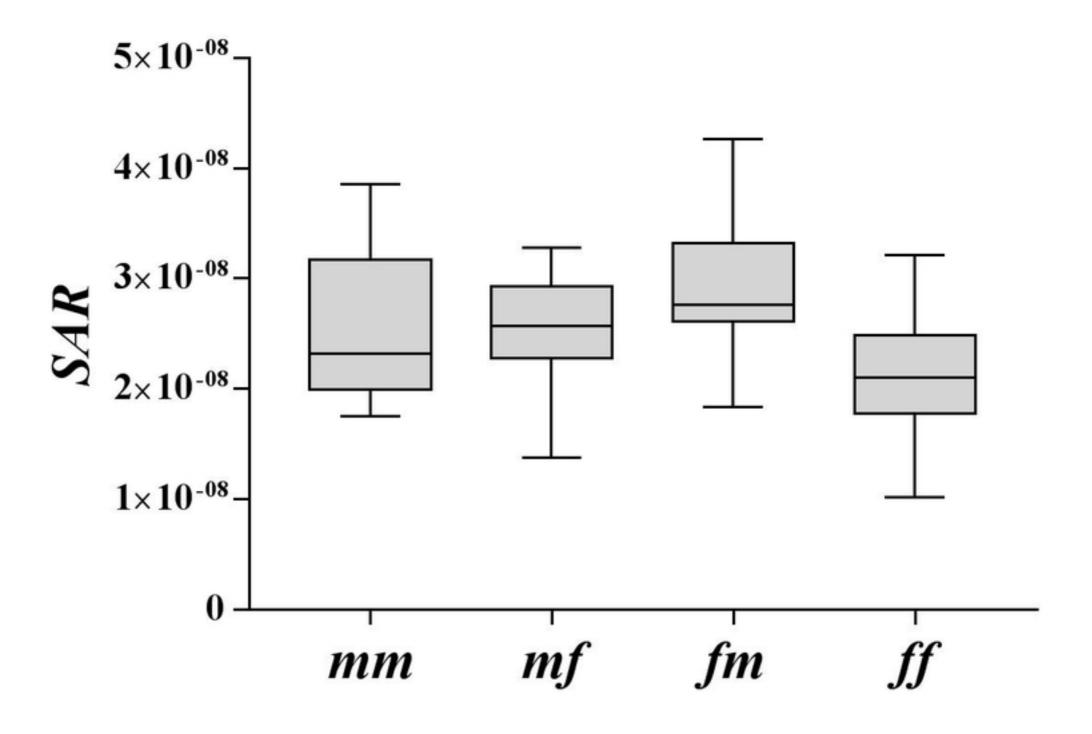


Figure 7

