Original Article

Basic Reproduction Number as a Measure of the Rapidity of the Inter-farm Spread of Porcine Epidemic Diarrhea during the Initial Phase of the Epidemic in Japan in 2013–2014

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(Received 26 Nov, 2018/Accepted 16 Apr, 2019)

Summary

The Japanese swine industry was heavily affected by the global porcine epidemic diarrhea (PED) outbreaks, started in the country in 2013. This study was conducted to quantify the infectivity of PED at the farm level in the initial phase of an epidemic in Kagoshima Prefecture, the largest swine producing area in Japan.

A compartmental model was developed with the following five components of farm status according to the situation of within-farm PED infection : susceptible with no infected pig (S) ; exposed with at least one infected pig but no pig showing clinical symptoms (E) ; infectious with at least one pig showing symptoms, but the farmer has not yet reported it to the veterinary authorities, whether intentionally or unintentionally (In) ; infectious with pigs showing symptoms, and recognized by the veterinary authorities as an infected farm (Id) ; and recovered with all pigs having recovered from PED (R). Parameters were solved to maximize the likelihood of daily new cases and cumulative number of recovered farms modelled given the actual numbers during the first 40 days of the epidemic using data provided by the Kagoshima Prefectural government. The incubation period was set at two days, and the first case of each farm was assumed to be reported on the next day to the authority. The basic reproduction number R_0 was calculated using the next generation matrix.

As results, the infectious period and R_0 were estimated to be 54.4 days and 5.39, respectively. In conclusion, inter-farm infectiousness was very high during the initial phase, and the long infectious period at the farm level, in addition to the common source infections already reported, contributed to the rapid spread of the disease.

Keywords : Porcine epidemic diarrhea, basic reproduction number, compartment model, Japan

Introduction

Porcine epidemic diarrhea (PED) is caused by PED virus (PEDv), which is an enveloped, single-stranded, positive-sense RNA virus within the family *Coronaviridae*, genus *Alphacoronavirus*. A global PED pandemic that occurred in 2013 involved then PEDv-free countries such as the United States, Canada, Mexico, Korea, Taiwan, and Japan[1,3,8,16,19,21,24,25]. Seven years after the end of the previous PED epidemic, the first case of PED in Japan was reported in Okinawa, the southernmost prefecture, in October 2013. On December 3, 2013, a PED outbreak occurred in Kagoshima Prefecture, which is isolated from Okinawa Prefecture by the East China Sea. Kagoshima Prefecture has the largest swine population in Japan (1.37 million pigs[14]), and PED rapidly spread not only within the prefecture but throughout Japan. Epidemiologic studies demonstrated that the factors most associated with PED spread were cross-contamination at slaughterhouses and along roads, and an insufficient level of bio-security at farms[15,22,23]. However, little is known regarding how rapidly the disease spread between farms.

Infectious disease modeling is a powerful tool for assessing the rapidity with which an epidemic spreads and for *a priori* predic-

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tions of disease spread in various scenarios. The basic reproduction number, denoted as R_0, is defined as the average number of secondary cases caused by a primary case in a totally susceptible population[28], and determining this variable is a key objective in infectious disease modeling. In addition, R_0 is a useful indicator of the infectiousness of a disease agent and can be used to estimate the immunity threshold. Although commonly applied at the individual level, R_0 is also useful for examining animal health at the farm level. Only one study on the farm level R_0 for PED has been reported from Canada[7], which used the incidence decay and exponential adjustment (IDEA) model. At the animal level, a study in Japan[17] used a compartment model for understanding within-farm PED dynamics, without focusing on the estimation of R_0.

The aims of this study were to quantify the infectiousness of PEDv during the initial phase of the 2013–2014 epidemic on Kyushu Island, Japan, and assess how rapidly farmers reported the outbreak to the veterinary authorities, using an infectious disease modeling approach.

Materials and Methods

Study population

This study was conducted using data regarding the infection status of the 229 pig farms, including 57 farms affected by PED during below mentioned 40 days, and the dates of occurrence and end of the PED outbreak at the affected farms in Higashi-Kushira town, Kanoya city, Kimotsuki town, Osaki town, and Tarumizu city (Figure 1), where the initial phase of the epidemic produced a spatio-temporal disease cluster[23]. These areas included 105 farrow-to-finisher, 34 reproduction, and 90 fattening farms. The period used for the analysis encompassed 40 days between December 3, 2013, the day the PED epidemic in Kagoshima Prefecture began, and January 11, 2014.

Collection of epidemic data

A list of anonymized all pig farms and the beginning and ending dates of the within-farm PED outbreaks in the above-mentioned cities and towns were provided by Kagoshima Prefecture.

According to the Act on Domestic Animal Infectious Disease Control, swine producers are required to immediately report suspected cases of PED to the local Prefectural Livestock Hygiene Service Center (LHSC). Soon after receiving a report from a farm, official veterinarians of the LHSC visit the farm to collect biological samples and information and confirm the diagnosis of PED infection using RT-PCR. In the Kagoshima Prefecture database, the date of the report, which in most cases is the same as the date of diagnosis, is recorded, and this date was used to prepare the daily number of new case reports data. To prepare the accumulated number of recovered farms data, we used the date following the day when the last case was reported for each farm.

Fig. 1 Map showing the locations of selected areas involved in the study : Higashi Kushira town, Kanoya city, Kimotsuki town, Osaki town, and Tarumizu city of Kagoshima Prefecture.

The infectious disease model

A compartmental model was applied in this study. As the epidemic data were available at the farm level, the unit of interest was set at the farm level for the modelling. The total number of pig farms in the study areas was allocated into five compartments according to infection status of farms : susceptible with no infected pig (S) ; exposed with at least one infected pig but no pig showing clinical symptoms (E) ; infectious with at least one pig showing symptoms, but the farmer has not yet reported it to the veterinary authorities, whether intentionally or unintentionally (In) ; infectious with pigs showing symptoms, and recognized by the veterinary authorities as an infected farm (Id) ; and recovered with all pigs at the farm having recovered from PED (R). The number of farms in each of these five compartments changed daily according to changes in infection status.

The dynamics of the changes in the number of farms in the five compartments were expressed using the following ordinary differential equations (ODEs) :

$dS = -\beta S(In+Id)/(S+E+In+Id+R)$ Equation 1,
$dE = \beta S(In+Id)/(S+E+In+Id+R) - \kappa E$ Equation 2,
$dIn = \kappa E + \eta In$ Equation 3,
$dId = \eta In - \gamma Id$ Equation 4, and
$dR = \gamma Id$ Equation 5

where β represents the force of infection, κ represents the rate at which one or more pigs at the infected farm began showing clinical symptoms, η represents the rate at which owners reported the occurrence of PED to the veterinary authorities, and γ repre-

Table 1 Fixed and initial values used in the model

Parameters	Value	Source
Fixed values		
Total number of susceptible pig farms before PED epidemic	229	Kagoshima Prefecture
Incubation period: $1/\kappa$ (days)	2	Day 2: Madson et al. (2014).
Days between first case at the farm and reporting: $1/\eta$	1	A scenario taking into account a delay during off-farm time.
Initial values for parameter estimation		
Force of infection: β	0.1	The value suggested in a preparatory search of ε maximizing the likelihood of the model
Days between report and recovery at farm level: $1/\gamma$	27	The mean duration between report and recovery at farms calculated from actual data was 26.6 days.
A period between the start of ODE and the first PED case in Kagoshima: ε	27	Preparatory search of ε maximizing the likelihood of the model

sents the rate at which all pigs at the infected farm recovered after the occurrence of PED.

The ODEs expressed in Equations 1 through 5 were modelled using the ode() function of the deSolve package, version 1.21[24], with statistic software R version 3.5.1[21]. For the incubation period, $1/\kappa$, a point estimate, was set at 2 days based on the literature[12]. The time taken between the first case at the farm and reporting : $1/\eta$ was assumed to be one day, taking the possibility of starting symptoms during off-farm hours into account (Table 1). The total number of susceptible pig farms in the study area before the PED epidemic began was 229. In addition, to ensure a good fit for the line predicting the number of daily cases and cumulative number of recovered farms, the period between the starting date used in the ODEs and the first report to Kagoshima Prefecture was modeled separately as ε.

The likelihood function was written using the case count at the farm level and accumulated number of recovered farms as Equations 6 to 8.

$$L(C,CR|\theta)=\Pi_{t=1}^{40}\left(\frac{Cprd_t^{\,C_t}}{C_t!}\cdot e^{-Cprd_t}\times\frac{CRprd_t^{\,CR_t}}{CR_t!}\cdot e^{-CRest_t}\right) \quad \text{Equation 6}$$

$$CR_t=\Sigma_{t=1}^{40} R_t \quad \text{Equation 7}$$

$$CRprd_t=\Sigma_{t=1}^{40} Rprd_t \quad \text{Equation 8}$$

where C_t is the observed number of cases, $Cprd_t$ is the predicted number of cases by the ODE, CR_t is the cumulated number of recovered farms R_t (Equation 7) and $CRprd_t$ is the predicted cumulated number of recovered farms $Rprd_t$ (Equation 8) at the day t. The likelihood function $L(C, CR|\theta)$ is a conditional to the parameter set θ which consists of the parameters other than κ and η in Equations 1 through 5 (i.e., β ; $1/\gamma$ as the farm-level infectious period ; and ε, as parameter set θ).

Parameter estimation

The parameter set θ was estimated by maximum-likelihood estimation (MLE) using the optim() function of the optimx package[18]. Data regarding the daily number of new case reports, and cumulative number of recovered farms were prepared for the first 40 days after the start of the epidemic in the study area and used to maximize the likelihood. Initial values given to the parameters to be solved are shown in Table 1.

Calculation of inter-farm spread R_0

A next-generation matrix (NGM)[4] was used to calculate the inter-farm spread R_0. Solving the NGM, R_0 was calculated as Equation 9. The detail of matrix calculation is provided in the Supplementary document.

$$R_0=\beta\left(\frac{1}{\eta}+\frac{1}{\gamma}\right) \quad \text{Equation 9}$$

Results

Model checking

The dynamics of the actual PED epidemic are plotted in Figure 2, with curves showing the daily number of cases and cumulative number of recovered farms predicted using the ODEs. The actual number of cases increased sharply over the first 7 days and the predicted curves obtained using the ODEs fit the actual epidemic and recovery curves well over the study period.

Parameter estimation

Table 2 shows the parameters estimated. The mean period of the PED epidemic, which is infectious period, at the farm level was estimated at 54.4 days (1 day until reported, $1/\eta$, and 53.4

Table 2 Estimates of various parameters using MLE

Parameter	Value
Force of infection, β	0.099
Days between report and recovery at the farm level, $1/\gamma$	53.4
Days between start of ODE and the first case, ε	27.0

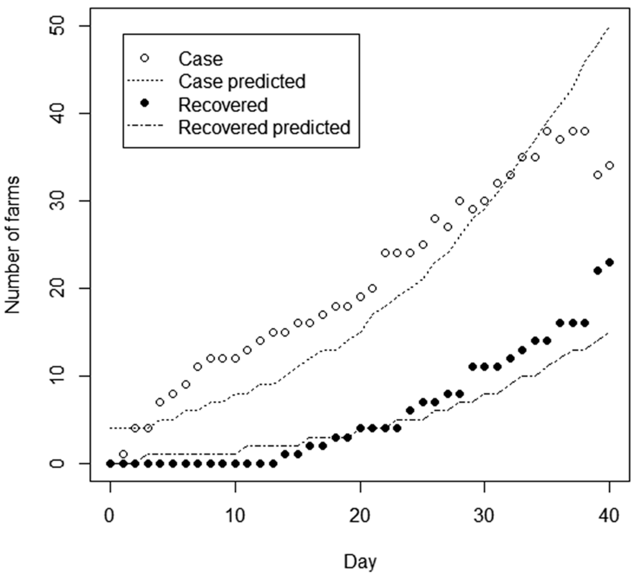

Fig. 2 Comparison of the actual daily number of new PED cases and cumulative number of recovered farms with predicted curves.

days until recovery after that, $1/\gamma$). The days between start of ODE and the first case, ε was estimated to be 27 days.

Estimation of inter-farm spread R_0

Using the estimated parameter values, the local inter-farm spread R_0 was calculated at 5.39.

Discussion

This study quantified the speed of inter-farm spread of PED during the initial phase of an epidemic in Kagoshima Prefecture in 2013 and 2014 that resulted in a nationwide epidemic. Although R_0 has generally been used at the individual level in infectious disease modeling particularly in human populations, farm animals have characteristics that do not apply to people. For example, farm animals cannot move freely between farms, while people move and have contacts randomly among populations. In this study, as the information on the days of within-farm first case and recovery were available for each farm, we used a farm as a unit of interest. The advantages of the farm-level modeling is that the available data can be utilized and the speed of between-farm spread can be quantified. But at the same time, it has a disadvantage that it cannot consider the variability in the dynamics of within-herd epidemics among different farms. Another challenge emerged in dealing a farm as a unit of modeling was that a farm per se does not have known biological characteristics in terms of infection dynamics, and parameters such as infectious period and recovery rate cannot be obtained through experiments. We therefore estimated these parameters using the empirical data of farm infection during the actual epidemic, and calculated R_0 using NGM[4]. Another study on estimating inter-farm R_0 for PED in Canada used IDEA model, which has been used for projecting epidemic process of ebola[5, 6] and Middle East respiratory syndrome coronavirus (MERS)[13] infections in human populations. The structure of IDEA model for PED is simple and has only two parameters : fixed generation interval and control effect[7]. It successfully showed the change of control effect over time, but did not describe mechanic transmission process. Our study employed a compartment model, and is the first study using mechanic transmission model for PED inter-farm spread.

The calculated R_0 value was very high, at 5.39, and this number can be interpreted as indicating that every single farm had the potential to infect more than five farms with PED during the initial phase of the epidemic in Kagoshima Prefecture. This farm level R_0 was equivalent to highly contagious human infectious diseases such as rubella (R_0 6–7) and mumps (R_0 4–7)[28] at the individual level. As R_0 over 1.0 indicates possibility of major epidemic, the PED outbreak in this region could be catastrophic. Theoretically, the final epidemic size can be calculated as 97.7%[4] of the farms (224 out of 229 farms) using the R_0 value 5.39. However, the actual epidemic was contained to 94 farms as of 2014 July 24th in this locality, when the local epidemic almost ceased by then. This can be reasoned by the strengthened control measures after the detection of the first case. For instance, in farms, vaccination against PED was encouraged and disinfection of personnel and vehicle was also strengthened after the announcement of the first case in Kyushu Island. In addition, in slaughterhouses, separation of receiving hours and strengthening of disinfection started (personal communication to veterinary officers). Further study may be needed to assess the control effects of such measures using the other modelling approaches such as IDEA model[5]. The inter-farm R_0 in Canada was estimated to be 1.87[7], and the R_0 in Kagoshima Prefecture was much higher than that. The R_0 estimation in Canada excluded the initial epidemic period caused by a point source exposure related to PEDv contaminated swine feed[7, 20], and care should be taken in comparing between their and our results.

Previous reports identified several reasons for the rapid spread in Japan over the first few months of the epidemic : common source infections in slaughterhouses, pig excrement transportation services, common composting, and roads[23, 27]. As Equation 9 shows, in addition to the high force of infection β, this high R_0 was also due to the long infectious period at each farm. According to personal communications with swine veterinarians, generally within-farm epidemic persisted, even with a short period of absence of additional cases before their final recovery from PED infection (which contributed to the long infectious period) in the study area, and this persistence of the disease at the farm level facilitated the rapid spread of PED.

The time between the onset of the first case at the farm and reporting was fixed at 1.0 day, considering a scenario that PED symptoms started during off-farm hours for several farms. According to two field swine veterinarians from the study area, the symptoms were obvious in susceptible piglets[1] and generally farmers called a veterinarian and LHSC immediately after they confirmed symptoms. Therefore the assumption of 1.0 day as the average time to report was thought to be reasonable (personal communications). In our model, all farms were assumed to report on the next day of disease onset of the first case. This is simply because the observed data dealt with only reported case farms as cases. There is, therefore, a limitation that the model ignored the force of infection from non-reported but infected farms.

There is another limitation in this study that our model assumed that all of the pig farms were homogenous ; however, there are different types of pig farms, and farrow-to-finisher and reproduction farms were reported to have significantly higher hazard ratios for PED compared with fattening farms[27]. Susceptibility to PED differs according to age ; piglets are highly susceptible, whereas older pigs, including weaners and finishers, exhibit self-limiting clinical signs[10]. The data provided did not include much detailed information to have these farms further categorized, and all the farms were dealt equally.

In terms of incubation period, this study employed a setting of 2 days. Shorter incubation periods have been reported in a study inoculating US strain PC21A to 10- to 35-day-old pigs[9] (24–48 hours), and in another study an S-INDEL-variant isolate to 5-day-old pigs (1 day)[2]. However, based on the experiments involving 3–4 days piglets[11] and 3-week-old pigs[12], the most common incubation period in piglets was considered to be 2 days. Considering the farm situation, the starting time of infectivity refers to the start of a scenario in which PEDv shed by infected pigs is carried to another farm. Our study dealt with inter-farm spread, and the employment of 2 days for farm-level incubation time was thus appropriate.

In conclusion, this study quantified the between-farm infectiousness during the initial phase of a PEDv epidemic on Kyushu Island, Japan. The approach used in this study could be applied to compare the infectiousness of PEDv during epidemics in other areas or at other times. The R_0 was very high, and we found that one reason for this was the long infectious period. Therefore, during PED epidemics, in addition to strengthening bio-security to prevent infection at susceptible farms, PED control at affected farms is critically important.

Acknowledgement

We thank Kagoshima Prefecture for approval to access relevant data. This research was supported by Japan Agency for Medical Research and Development (grant number : JP18fk0108050).

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Supplementary document 2

Matrix calculation to obtain PED inter-farm spread R_0.

$NGM = -T\Sigma^{-1}$ Equation S1

where the matrix T represents transmission, and the matrix Σ represents transitions[4]. The term T is expressed as Equation S2, where the horizontal order from left to right shows the status causing transmission, E, In, and Id, and the vertical order from top to bottom shows the status being transmitted to (In and Id, the second and third columns can transmit to E, the first row).

$$T = \begin{pmatrix} 0 & \beta & \beta \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad \text{Equation S2}$$

The term Σ is expressed as Equation S3, where the relationship of transition in the status of a farm in the order of E, In, and Id, from rows to columns, as same as that for T.

$$\Sigma = \begin{pmatrix} -\kappa & 0 & 0 \\ \kappa & -\eta & 0 \\ 0 & \eta & -\gamma \end{pmatrix} \quad \text{Equation S3}$$

The inverse of Σ, Σ^{-1}, is calculated as Equation S4:

$$\Sigma^{-1} = -\frac{1}{\kappa\eta\gamma}\begin{pmatrix} \eta\gamma & 0 & 0 \\ \kappa\gamma & \kappa\gamma & 0 \\ \kappa\eta & \kappa\eta & \kappa\eta \end{pmatrix} \quad \text{Equation S4}$$

Using Equation S1, the NGM is obtained as Equation S5:

$$NGM = -T\Sigma^{-1} = -\frac{1}{\kappa\eta\gamma}\begin{pmatrix} \beta\kappa(\gamma+\eta) & \beta\kappa(\gamma+\eta) & \beta\kappa\eta \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad \text{Equation S5}$$

R_0 is the largest eigenvalue λ of the NGM and is solved by taking the determinant of the following equation (Equations S6):

$$NGM - \lambda I = \begin{pmatrix} \beta\left(\frac{1}{\eta}+\frac{1}{\gamma}\right)-\lambda & \beta\left(\frac{1}{\eta}+\frac{1}{\gamma}\right) & \frac{\beta}{\gamma} \\ 0 & -\lambda & 0 \\ 0 & 0 & -\lambda \end{pmatrix} = 0 \quad \text{Equation S6}$$

when I represents the unit matrix; and

$$\lambda^2\left\{\beta\left(\frac{1}{\eta}+\frac{1}{\gamma}\right)-\lambda\right\} = 0 \quad \text{Equation S7}$$

Thus, the eigenvalue λ and R_0 are solved as follows:

$$\lambda = \left\{0, \beta\left(\frac{1}{\eta}+\frac{1}{\gamma}\right)\right\} \quad \text{Equation S8, and}$$

$$R_0 = \beta\left(\frac{1}{\eta}+\frac{1}{\gamma}\right) \quad \text{Equation 9}$$

原　著

2013-2014 年の日本の豚流行性下痢流行初期における農場間伝播速度の指標としての基本再生産数

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要旨

日本の養豚業は 2013 年に国内に侵入した世界的な豚流行性下痢（PED）の流行により甚大な被害を被った。本研究は，国内最大の養豚地帯である鹿児島県にて発生した PED 流行初期における農場レベルでの感染力を定量化するために実施された。

農場内感染状況により農場を以下の 5 つのコンパートメントに分けたコンパートメントモデルを作成した：感染豚がいない感受性期（*S*）; 少なくとも一頭の感染豚がいるが一頭も症状を呈していない暴露期（*E*）; 少なくとも一頭の豚が症状を呈しているが，意図的にあるいは意図せずにまだ獣医当局に報告されていない感染性期（*In*）; 症状を呈している豚がおり，獣医当局に感染農場として認識されている感染性期（*Id*）; 全ての豚が PED から回復した回復期（*R*）。

パラメーターは，鹿児島県から提供された流行開始から 40 日間の実際のデータを基に，日ごとの新発生数と累積清浄化農場数の最尤推定により導出した。潜伏期間は 2 日間，獣医当局へは発生翌日に通報されるものと仮定した。基本再生産数 R_0 は次世代行列を用いて計算した。

結果として，感染性期間および R_0 はそれぞれ 54.4 日と 5.39 と推定された。まとめとして，流行初期の農場間感染力は非常に高く，これまですでに報告されている共通感染源感染に加えて農場の感染性期間の長期化が本病の迅速な拡大の原因となっていたことが明らかとなった。

キーワード : 豚流行性下痢，基本再生産数，コンパートメントモデル，日本

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