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Analysis of the effect of feedback feeding on the farm-level occurrence of porcine epidemic diarrhea in Kagoshima and Miyazaki Prefectures, Japan

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ABSTRACT. When a large-scale epidemic of porcine epidemic diarrhea (PED) occurred in 2013 in Japan, feedback feeding (feeding feces and gut tissues of infected piglets) was attempted to impart immunity to sows and immunize nursing piglets via breastfeeding. This study evaluated the effect of feedback feeding on PED control at 172 farms in Kagoshima and Miyazaki Prefectures. Univariable and multivariable generalized linear models were used to analyze the associations between conduct of feedback feeding and damage from the outbreak (outbreak period and the number of piglet deaths) at the farm level. The within-farm outbreak period shortened over time after the regional outbreak began on Kyushu Island (P=0.009) and was longer on large-scale farms (mean 66.0 days, P=0.003) than small-scale farms (29.4 days) and on farms that used feedback feeding (145.2 days, P=0.059) than those that did not (66.0 days). The number of dead piglets decreased over time since the first regional case (P<0.001) and was higher at farrow-to-finish farms (3.8 piglets/sow, P<0.001) than reproduction farms (0.7 piglets/sow). The effect of feedback feeding on the number of dead piglets was not significant, but its interaction term with farm style had a significant effect (5.0 more piglet deaths at reproduction farms than fallow-to-finish farms, P=0.001). These results suggest that feedback feeding made the damage from PED worse, though it was well established at a later stage of the regional PED epidemic.

KEY WORDS: feedback feeding, immunization, Japan, porcine epidemic diarrhea

Porcine epidemic diarrhea virus (PEDV) belongs to the family *Coronaviridae*, subfamily *Coronavirinae*, genus *Alphacoronavirusis*, and is an enveloped, single-stranded, positive-sense RNA virus. Other pig-infecting coronaviruses include porcine hemagglutinating encephalomyelitis virus and transmissible gastroenteritis virus (TGEV). Although PED does not show hemagglutination, it causes diarrhea in pigs similarly to TGEV [20, 27]. The primary clinical manifestations of PED are severe watery diarrhea and associated dehydration in all ages of swine. Neonatal piglets exhibit high mortality, sometimes reaching 100%, due to dehydration, whereas the mortality rate declines after weaning. Other clinical symptoms include vomiting, anorexia, and depression. Economic losses caused by the death of pigs and the decline in productivity are of major concern in swine production [1, 7, 18, 38].

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PEDV was discovered in Europe in the 1970s [20], and PED continues to occur in Europe and Asia [10, 27]. In late 2010, highly virulent variants emerged in China [13, 30, 37], which caused a global pandemic. PEDV invaded the US in 2013 for the first time and spread throughout the American continent [9]. The strain isolated in the US in 2013 was similar to that isolated in China [9], and the strains isolated in Korea and Taiwan in 2014 were more closely related to the American strain than the Chinese strain [2, 3, 14, 19], suggesting a global virus footprint. In Japan, PED was firstly reported in 1983 [32] and caused two major outbreaks in the 1990s, with sporadic cases reported until 2006 [33]. Although there had been no reported cases since 2006, a large-scale epidemic began on October 1, 2013 [23, 31], causing outbreaks on 1,365 farms and the death of 493,605 pigs as of May 26, 2019, and the epidemic still persists even though the number of cases has declined [15]. Three types of strains were genetically identified in this epidemic; two of the strains caused outbreaks in the US and South Korea in recent years [36], and the other affected Vietnam, Thailand, and China [29, 36]. Reported risk factors associated with the rapid spread of PEDV in Japan included the density and proximity of farms, use of a common compost station and a pig excrement disposal service, and contamination at slaughterhouses, including insufficient disinfection time [23, 24, 34].

During this PED epidemic in Japan, feedback feeding−feeding sows the gut tissues of infected piglets [8, 11]−was attempted on farms at which PED occurred in order to impart immunity to sows and immunize nursing piglets via the sows' milk. In feedback feeding, PEDV-infected piglets are euthanized, and their intestines are added to feed for the sows at least 2 weeks before delivery. Producers must repeat the process until all fed animals exhibit clinical signs. This process can also be performed in nursery, growing, and finishing pigs to eliminate the disease from the entire herd, but additional care, such as disinfection of farm buildings and all-in/all-out movement, is needed, as the virus can easily spread within these groups of pigs. At last for feedback feeding, sentinel pigs are used to assess whether PEDV is present in a herd [8, 11]. Although vaccination of sows can safely induce lactogenic immunity against PEDV [11], farmers and veterinarians tend to conduct feedback feeding in situations in which a vaccine is not available.

In Japan, there are reports of both success in which the damage of PED outbreaks was mitigated by feedback feeding and failure that aggravated or prolonged the situation when farmers conducted feedback feeding with/without veterinarian guidance [16, 22, 29, 35]. Feedback feeding poses a risk of exacerbating an outbreak, as it involves live PEDV, and therefore the Japanese government discourages feedback feeding among producers [16]. However, there are no quantitative data reported on the effectiveness or damage of feedback feeding in Japan, and such information is limited even in other countries. This study was thus carried out to evaluate the effect of feedback feeding on PED control using a dataset collected by Toyomaki *et al.* [34] in 2013 and 2014 in Japan.

MATERIALS AND METHODS

Study site

This study was performed in Kagoshima and Miyazaki Prefectures, located on Kyushu Island, the southwestern part of Japan. Kagoshima and Miyazaki Prefectures have the largest and the second largest numbers of pig producers and swine populations in Japan, respectively [16]. In total, 250 PEDV-infected farms were reported in these prefectures between December 3, 2013 and July 24, 2014, the study period.

Data sources

Pig farm data: Anonymized datasets of all pig farms [34] were provided by both prefectures (709 farms in Kagoshima Prefecture and 506 farms in Miyazaki Prefecture). The datasets included the administrative units to which the farms belonged; the type of operation (reproduction, farrow-to-finish, or fattening); the number of animals raised as of June 2014 and February 2014 in Kagoshima and Miyazaki Prefectures, respectively; PEDV infection status as of July 24, 2014; the dates of onset and end of within-farm outbreaks; and the number of dead pigs on the affected farms. Herd size categorization according to the type of operation followed the criteria of previous studies [16, 34]: (1) reproduction farms: small-scale referred to farms with ≤100 sows, middle-scale, 101–300 sows, and large-scale, >300 sows; (2) farrow-to-finish and fattening farms: small-scale, ≤1,000 pigs total, middle-scale, 1,001–3,000 pigs, and large-scale, >3,000 pigs.

In this study, among the above-mentioned datasets provided, information regarding the PEDV-infected farms at which PED occurred between December 3, 2013, and July 24, 2014, was used. Diagnosis of PED was made based on the following procedure. In both prefectures, prefectural Livestock Hygiene Service Centers (LHSCs) received notice of the occurrence of a suspected case from either the farmer or a veterinarian, and veterinarians at the LHSC sampled the diseased animals or feces. A diagnosis was made based on the combination of clinical symptoms, reverse transcription-polymerase chain reaction (RT-PCR) test, and immunohistochemistry testing. For cases in which only feces were sampled, the diagnosis was made based on clinical symptoms and RT-PCR analysis. The day of the end of the farm outbreak was based on observational confirmation of the absence of PED symptoms among pigs on the farm by the veterinarians of the LHSC. The number of infected farms within the study period in Kagoshima and Miyazaki Prefectures was 36 and 7 reproduction farms, 84 and 58 farrow-to-finish farms, and 49 and 16 fattening farms, respectively. The total number of infected farms in the respective prefectures was 169 and 81.

Postal questionnaire survey: Toyomaki *et al.* [34] conducted a postal questionnaire survey of all farms with confirmed PED and the same number of randomly selected confirmed non-affected farms, with the help of the Kagoshima and Miyazaki Prefectural Governments in 2014. The questionnaire consisted of four sections: attribution of farms and owners; compliance with the Standard of Rearing Hygiene Management–the Japanese livestock farming bio-security standards; practices of a wide variety of other activities potentially associated with prevention of PEDV introduction, including the conduct of feedback feeding; and the costs associated with prevention of PEDV introduction. In the present study, information collected using the questionnaire included the following: conduct of feedback feeding or not, stage of pigs applied, date of conduct, presence and attribution of the instructor, farmer's perception of the effect, and use of PEDV vaccine.

The questionnaire response rate among infected farms in Kagoshima and Miyazaki Prefectures was 29.6% (50/169) and 34.6% (28/81), respectively, and 31.2% (78/250) overall. These 78 PED-affected farms consisted of 12 reproduction (9 large- and 3 small-scale), 49 farrow-to-finish (16 large-, 15 middle-, and 18 small-scale), and 17 fattening farms (4 large-, 9 middle-, and 4 small-scale). The information for all fattening farms was excluded from the analyses because feedback feeding was not conducted at any of the fattening farms.

Correlating questionnaire survey results and outbreak data: The questionnaires, with identification numbers, were posted by the Kagoshima and Miyazaki Prefectures, as they own farm address information. After ethical clearance and approval by the prefectures as described below, the anonymized and digitized questionnaire survey results and PED epidemic information were correlated and sent to Rakuno Gakuen University electronically by the prefectures, maintaining anonymity.

Ethical approval

The research proposal for this particular study on the effect of feedback feeding was reviewed by the Rakuno Gakuen University Epidemiological Research Ethical Committee and approved (approval number: 15-6).

Descriptive epidemiology

The characteristics of the PED-affected farms were summarized by type of operation, farm size, and use of vaccination. PED occurrence within farms was described by the outbreak period, number of dead piglets, and recurrence rate. Regarding feedback feeding, the conduct of feeding (i.e., whether they conduct feedback feeding or not, which is available for all study population), and for farms that conducted feedback feeding, the day feeding was started after the farm's first case, the period between starting feeding and the end of PED occurrence, the contents of the feed, types of pigs fed (pregnant sows, nursing sows, sows not pregnant, suckling piglets, fattening pigs, or boars), presence and affiliation of feedback feeding instructors, and perception of the effect of feedback feeding were summarized.

Statistical analysis

Assessment of the efficacy of feedback feeding on PED control: To assess the efficacy of feedback feeding on within-farm PED control, a univariable generalized linear model (GLM) with gamma errors, for which an inverse-link was used, was first performed, selecting outbreak period as the response variable and conduct of feedback feeding as the explanatory variable. In addition, a GLM with quasi-Poisson errors was performed, selecting the number of dead piglets as the response variable and conduct of feedback feeding as the explanatory variable, with the number of sows as an offset. It is known that the number of piglets in a litter differs by sow's reproductive performance that may be influenced by their genetic characteristics (e.g., lineage and breed), and the total number of piglets at a time in a farm may be preferable option as an offset. However, PED outbreak in a farm was expected to have affected the health of both sows and piglets. The number of piglets at a farm could vary largely depending on the timing of data collection due to death of piglets, possible reduction of reproduction, and other unknown control efforts in each farm. There were no detailed data of actual piglets born at different timing, and the number of sows was selected as an offset.

Second, as the efficacy of within-farm PED control might be improved over time due to the accumulation of experience and information, such changes could be a confounder in the analysis of the association between the conduct of feedback feeding and within-farm outbreak status. Therefore, a univariable GLM with gamma errors was performed, selecting within-farm outbreak period as the response variable and the period between the date that the epidemic started on Kyushu Island (December 3, 2013) and the first case at each farm as the explanatory variable. Additionally, a GLM with quasi-Poisson errors was performed, selecting the number of dead piglets as the response variable and the period between the first case on Kyushu Island and the first case within the farm as explanatory variables, with the number of sows as an offset. To assess whether this learning effect occurred only on feedback feeding or on overall disease control skills, these analyses were performed on three datasets separately: selecting (1) only the PED-affected farms that conducted feedback feeding, (2) the affected farms that did not conduct feedback feeding, and (3) all affected farms that responded to the questionnaire.

Finally, to assess the efficacy of feedback feeding on within-farm PED control taking the other potential confounders into account, multivariable GLMs were performed (Fig. 1A), selecting the outbreak period and the number of dead piglets as the response variables, with the same error structures and offset as the univariable analyses, and conduct of feedback feeding, type of farm, farm size, learning effect (i.e., days from the first case on Kyushu Island), and interaction terms as explanatory variables. These potential confounders, which affect the damage caused by an outbreak and which are potentially associated with feedback feeding, were selected based on a priori knowledge and/or the authors' perceptions. A backward model simplification was conducted based on the likelihood ratio test using the "anova ()" function in statistical software R, with the χ^2 test for GLMs with gamma errors and F test for GLMs with quasi-Poisson errors. If feedback feeding was removed from the model during the simplification, a separate model retaining feedback feeding was also prepared to assess the adjusted effect of feedback feeding.

Factors facilitating the decision to conduct feedback feeding: To understand the factors that facilitated the farmers' decision to conduct feedback feeding, univariable GLMs with gamma errors were performed, selecting the period between the first case at the farm and the start of feedback feeding as the response variable and the presence of an instructor, farm size, and the period between

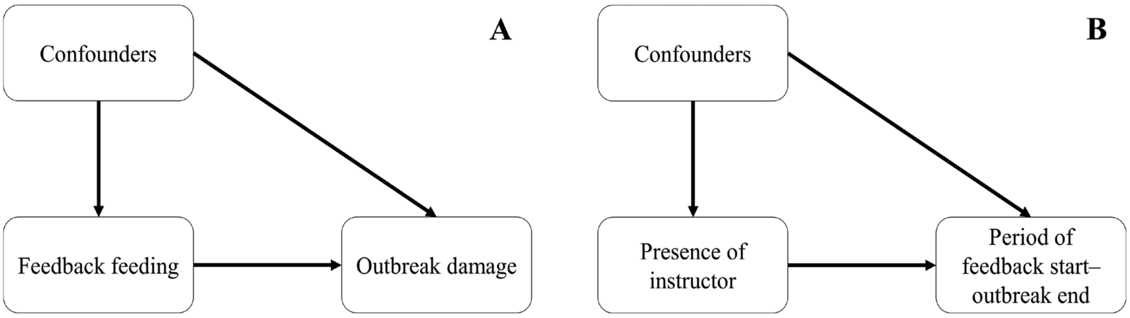

Fig. 1. Directed acyclic graphs showing **(A)** the assumed association between feedback feeding and damage caused by the outbreak, and **(B)** the association between the presence of an instructor and the feedback feeding start–outbreak end period. Outbreak damage shown in panel A is expressed as the outbreak period and the number of dead piglets. Confounders for panel A are type of farm, farm size, the learning effect, and vaccine-induced immunity category. Confounders for panel B are type of farm and farm size. It is assumed that the factors releasing arrows are the causes of the factors receiving the arrows (outcomes).

the day the epidemic started on Kyushu Island and the first case at each farm as the respective explanatory variables. Furthermore, Fisher's exact test was performed on the two-by-two table consisting of the conduct of feedback feeding and vaccination in order to examine whether a vaccine shortage triggered farmers to conduct feedback feeding.

Association between the presence of an instructor, type and size of farm, and the efficacy of feedback feeding: Even among farms that conducted feedback feeding, the trial could be successful at some farms and result in failure at other farms. To assess the effects of the presence of an instructor, the type of farm, and size of the farm in terms of enhancing the efficacy of feedback feeding, univariable GLMs with gamma errors were performed, selecting the period between the start of feedback feeding and the end of the PED outbreak at the farm as the response variables and the presence of an instructor, type of operation, and farm size as explanatory variables. In addition, a multivariable analysis was conducted to assess the effect of the presence of an instructor (Fig. 1B) by controlling for potential confounders (farm type and size) using a GLM with a gamma error. Model simplifications were performed using the same procedure as described in section 2.5.1.

Association between farmers' perceptions of the efficacy of feedback feeding and the magnitude of loss: Perception may be generally dependent on individual characteristics, and the perception of farmers regarding the efficacy of feedback feeding may not represent the actual magnitude of loss avoided by its implementation. Therefore, univariable GLMs with gamma and quasi-Poisson errors were performed, selecting within-farm outbreak period and the number of deaths in piglets as respective response variables and the level of efficacy of feedback feeding perceived (i.e., farmers' perceptions) as the explanatory variable. For the model of the number of deaths in piglets, the number of sows was included as an offset.

Farms that had missing data were excluded from all analyses. For an explanatory variable with ≥3 categories (i.e., farm size) in a GLM, its' overall significance was tested using a likelihood ratio test (i.e., the likelihood ratio of a model with the variable and the null model were tested). Also, the contrasts between the reference category (large size farm) and the others (middle and small) were tested. Statistical software R, version 3.5.2 [21], was used for all statistical analyses.

RESULTS

Descriptive epidemiology

The mean PED outbreak period was 51.0 days, and mean number of deaths in piglets was 546.4 among the 61 affected farms studied. The recurrence rate during the study period was 31.0% (18/58). Over a half of the farms (54.4%, 31/57) conducted feedback feeding, and the proportion of farms that conducted feedback feeding was not significantly different between reproduction farms (36.4%, 4/11) and farrow-to-finish farms (58.7%, 27/46, χ^2=1.0, df=1, P=0.3).

The mean number of sows at reproduction and farrow-to-finish farms was 801 (median: 788, range: 11–2,200) and 385 (median: 200, range: 18–2,000), respectively.

The mean, median, and range of the time at the farms before feedback feeding was initiated after PED occurred were 10.7, 7, and 1–60 days among the farms that conducted feedback feeding. The mean, median, and range of the time after starting feedback feeding until the end of PED occurrence at the farms were 58.6, 39, and 3–204 days, respectively. Table 1 shows a summary of the damages caused by PED stratified by farm type and conduct of feedback feeding.

Table 2 shows the mode of administration of feedback feeding. The most common method of feedback feeding was the administration of feces from infected pigs (68.0%, 17/25). Half of the farmers who used this method fed undiluted feces (32.0%, 8/25). Feeding intestine mince of dead piglets was the second most common method (24.0%, 6/25). Other than these, a variety of methods were used.

Table 3 shows the target animals of feedback feeding. All of the farms that conducted feedback feeding targeted pregnant sows (29/29), which is a general procedure to immunize piglets lactogenically. However, some farms used methods in which the most vulnerable susceptible piglets were directly exposed to PEDV: feeding nursing sows (34.5%, 10/29) and suckling piglets (3.4%,

Table 1. Descriptive epidemiology results

Variable	Feedback feeding conducted		Not conducted	
	Median (1st–3rd quartiles)	Range	Median (1st–3rd quartiles)	Range
Within-farm epidemic period (days)				
Reproduction	(n=4)		(n=7)	
	107 (73–144)	23–204	28 (21–43)	16–50
Farrow-to-finish	(n=27)		(n=18)	
	41 (24–64)	1–178	28 (15–40)	7–134
Number of piglets that died				
Reproduction	(n=4)		(n=7)	
	1,609 (1,006–1,908)	0–2,002	30 (6–435)	0–1,200
Farrow-to-finish	(n=27)		(n=19)	
	196 (100–967)	20–3,471	120 (53–461)	3–2,725
Days between the farm's first case and start of feedback feeding				
Reproduction	(n=4)		Not applicable	
	2 (1–12)	1–40		
Farrow-to-finish	(n=27)		Not applicable	
	7 (3–10)	1–60		
Days between the start of feedback feeding and end of the outbreak within a farm				
Reproduction	(n=4)		Not applicable	
	88 (44–144)	22–204		
Farrow-to-finish	(n=25)		Not applicable	
	38 (22–68)	3–159		

Table 2. Mode of administration of feedback feeding (n=25)

Method	Response (%)
Administration of feces*	17 (68.0)
Undiluted feces	8 (32.0)
Diluted feces	8 (32.0)
Diluted feces with antibiotics	1 (4.0)
Administration of intestinal mince**	6 (24.0)
Administration of feed leftover by diseased sows	1 (4.0)
Administration of vomit and excreta from diseased sows	1 (4.0)
Nose-to-nose contact between sows and piglets with symptoms	1 (4.0)
Placement of sows before parturition in the same room with piglets exhibiting symptoms	1 (4.0)

*Pig stage from which the feces were obtained: unknown (11 farms), piglets (4, before/after weaning is unknown), suckling piglets (1), weaned piglets (1), and sows (1). **Pig stage from which intestines were obtained: suckling piglets (3 farms), unknown (1), piglets (1, before/after weaning is unknown), dead piglets (1).

Table 3. Stage of pigs administered feedback feeding (n=29)

Category	Response (%)
Pregnant sows	29 (100.0)
Nursing sows	10 (34.5)
Sows not pregnant	18 (62.1)
Suckling piglets	1 (3.4)
Fattening pigs	1 (3.4)
Boars	13 (44.8)

1/29); or that can spread PEDV entire herd: feeding fattening pigs (3.4%, 1/29) and boars (44.8%, 13/29). Among the farms where there was a feedback feeding instructor, 90.0% (18/20) received advice from veterinarians, whereas 10.0% (2/20) received advice from other farmers. One of the two farms in the latter category sought advice from other farmers that conducted feedback feeding using undiluted feces (a procedure was not available for the other farm).

Regarding the perception of farmers of the efficacy of feedback feeding, the proportion of farmers who felt it was effective was 71.0% (22/31).

The proportion of affected farms that used a PEDV vaccine during the study period was 94.9% (56/59).

Statistical analysis

Assessment of the efficacy of feedback feeding on PED control: From the univariable analyses, the mean outbreak period at farms that conducted feedback feeding (estimated mean: 62.6 days) was significantly longer than at farms that did not conduct feedback feeding (32.9 days, difference in reciprocal=-1.4×10^{-2}, standard error (SE)=5.6×10^{-3}, P=0.012). The average number of deaths in piglets per sow at farms that conducted feedback feeding (estimated mean: 1.4 piglets/sow) tended to be larger than at farms that did not conduct feedback feeding (estimated mean: 0.9 piglets/sow), though the difference was not statistically significant (difference in log=4.8×10^{-1}, SE=2.5×10^{-1}, P=0.063, Supplementary Table 1). The outbreak period among all the affected farms studied was significantly shortened over time after the first case on Kyushu Island (slope of reciprocal=1.4×10^{-4}, SE=4.5×10^{-5}, P=0.004). When this change was compared between farms that conducted feedback feeding and those that did not, a reduction in the within-farm outbreak period over time was observed among the farms that conducted feedback feeding (difference in reciprocal=1.1×10^{-4}, SE=5.5×10^{-5}, P=0.061), though the difference was not significant. A reduction in the within-farm outbreak period over time was not observed among the farms that did not conduct feedback feeding (difference in reciprocal=8.8×10^{-5}, SE=8.5×10^{-5}, P=0.310, Fig. 2). Similarly, the number of deaths in piglets significantly declined over time among all affected farms (slope in log=-8.0×10^{-3}, SE=2.3×10^{-3}, P<0.001) and among the farms that conducted feedback feeding (slope in log=-1.0×10^{-2}, SE=2.7×10^{-3}, P<0.001) but not among the farms that did not conduct feedback feeding (slope in log=-1.6×10^{-3}, SE=4.7×10^{-3}, P=0.734, Fig. 3).

Also, from the univariable analyses, although the outbreak period did not differ between reproduction farms and farrow-to-finish farms (difference in reciprocal=-3.3×10^{-3}, SE=5.5×10^{-3}, P=0.551), the number of deaths in piglets was lower at reproduction farms than farrow-to-finish farms (difference in log=-5.8×10^{-1}, SE=2.9×10^{-1}, P=0.045). There was no difference in the outbreak period based on farm size category (likelihood ratio test P=0.192 compared with null model). The number of dead piglets tended to vary with farm size (overall P=0.082), and it was significantly higher at middle-scale farms than large-scale farms (difference in log=6.0×10^{-1}, SE=3.0×10^{-1}, P=0.020), but there was no difference between large- and small-scale farms (difference in log=-1.0×10^{-1}, SE=6.0×10^{-1}, P=0.903, Supplementary Table 1).

Table 4 shows the results of the multivariable analysis of the within-farm outbreak period (n=56). The final model found that the outbreak period significantly declined over time (slope in reciprocal=1.0×10^{-4}, SE=3.8×10^{-5}, P=0.009) and was significantly longer at large-scale farms (66.0 days) as compared with small-scale farms (29.4 days, difference in reciprocal=1.9×10^{-2}, SE=6.0×10^{-3}, P=0.003). Conduct of feedback feeding was not statistically significant (P=0.059); however, it remained in the final model by the backward model simplification and exhibited a trend in which the outbreak period for farms that conducted feedback feeding was longer (145.2 days) than for farms that did not (66.0 days, difference in reciprocal=-8.3×10^{-3}, SE=4.3×10^{-3}, P=0.059).

Table 5 shows the results of the multivariable analysis of the number of deaths in piglets (n=57). The number of deaths in piglets significantly declined over time (slope in log=-9.5×10^{-3}, SE=2.1×10^{-3}, P<0.001) and was significantly greater at farrow-to-finish farms (3.8 piglets/sow) compared with reproduction farms (0.7 piglets/sow, difference in log=-1.7, SE=3.9×10^{-1}, P<0.001).

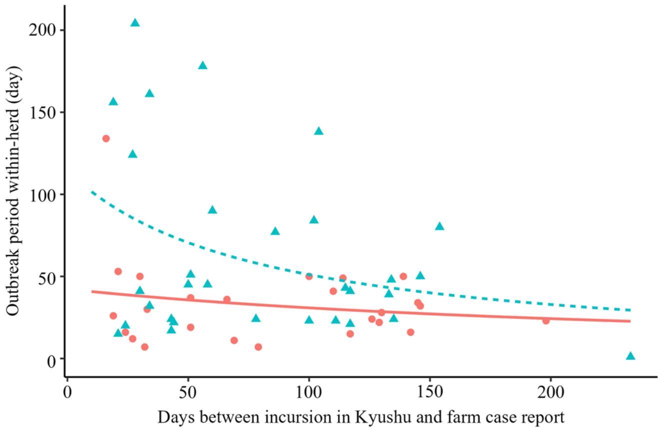

Fig. 2. Relationship between the outbreak period within-herd and days between incursion in Kyushu and farm case reports. Triangles show the observations of feedback feeding farms, and a dashed line shows the model prediction; circles show the observations of non–feedback feeding farms, and a solid line shows the model prediction.

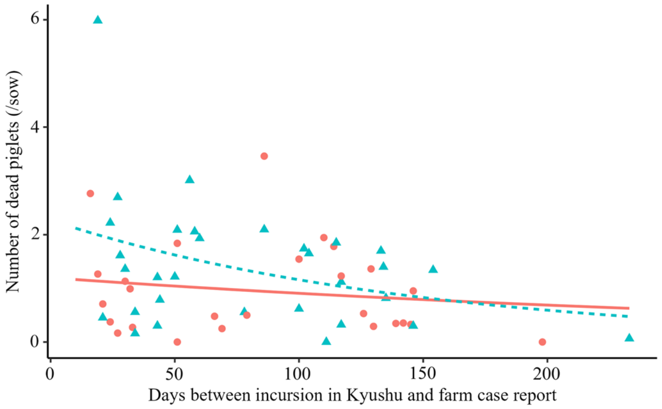

Fig. 3. Relationship between the number of dead piglets (/sow) and days between incursion on Kyusyu Island and farm case reports. Triangles show the observations of feedback feeding farms, and a dashed line shows the model prediction; circles show the observations of non–feedback feeding farms, and a solid line shows the model prediction.

Table 4. Multivariable analysis results: effect of feedback feeding on the within-farm outbreak period (n=56)

Variable	Estimate in reciprocal	Standard error	P-value
(Intercept)	1.5×10^{-2}	5.1×10^{-3}	-
Conduct of feedback feeding	-8.3×10^{-3}	4.3×10^{-3}	0.059
Time since the first case on Kyushu Island	1.0×10^{-4}	3.8×10^{-5}	0.009
Farm size (large-scale as reference)			
Middle-scale farm	8.8×10^{-4}	3.3×10^{-3}	0.791
Small-scale farm	1.9×10^{-2}	6.0×10^{-3}	0.003

Table 5. Multivariable analysis results: effect of feedback feeding on the number of deaths in piglets (*n*=57)

Variable	Estimate in logarithm	Standard error	*P*-value
(Intercept)	1.3	2.6×10^{-1}	-
Feedback feeding	-2.4×10^{-1}	2.2×10^{-1}	0.262
Time since the first case on Kyushu Island	-9.5×10^{-3}	2.1×10^{-3}	<0.001
Type of operation (farrow-to-finish as reference)			
Reproduction farm	−1.7	3.9×10^{-1}	<0.001
Interaction between feedback feeding and type of operation (farrow-to-finisher as reference)			
Feedback feeding: Reproduction	1.6	4.6×10^{-1}	0.001

Table 6. Multivariable analysis results: effect of the presence of an instructor on the period between the start of feedback feeding and the end of the outbreak within a farm (*n*=29)

Variable	Estimate in reciprocal	Standard error	*P*-value
(Intercept)	2.7×10^{-2}	7.1×10^{-3}	-
Presence of instructor	-1.5×10^{-2}	7.0×10^{-3}	0.039
Farm size (large-scale as reference)			
Middle-scale farm	4.8×10^{-4}	4.4×10^{-3}	0.913
Small-scale farm	2.4×10^{-2}	9.9×10^{-3}	0.021

This model included a significant interaction term between the conduct of feedback feeding and type of operation, and the effect of feedback feeding on the number of dead piglets was poorer at reproduction farms (5.0 more piglets' deaths/sow; difference in log=1.6, SE=4.6×10^{-1}, *P*=0.001) than farrow-to-finish farms. The adjusted effect of feedback feeding per se on the number of deaths in piglets was not significant (difference in log=-2.4×10^{-1}, SE=2.2×10^{-1}, *P*=0.262).

Factors that facilitated the decision to conduct feedback feeding: The time taken until the start of feedback feeding after the within-farm outbreak was significantly shorter at farms where a feedback feeding instructor was present (7.4 days, *n*=21) than at farms without an instructor (17.6 days, *n*=10, difference in reciprocal=7.9×10^{-2}, SE=3.8×10^{-2}, *P*=0.049). The time taken until the start of feedback feeding did not differ by farm size category (large-scale: 13.0 days, *n*=15, reference; middle-scale: 10.4 days, *n*=9, difference in reciprocal=1.9×10^{-2}, SE=4.4×10^{-2}, *P*=0.675; small-scale: 6,0 days, *n*=7, difference in reciprocal=9.0×10^{-2}, SE=7.8×10^{-2}, *P*=0.260) and did not change over time from the day the epidemic started on Kyushu Island to the first case at each farm (*n*=32, slope in reciprocal=1.3×10^{-4}, SE=4.5×10^{-4}, *P*=0.770). The proportion of farms that used a PEDV vaccine was not significantly different between farms that conducted feedback feeding (96.7%, 29/30) and those that did not (92.3%, 24/26, Fisher's exact test, *P*=0.592, Supplementary Table 2).

Associations between the presence of an instructor, type and size of the farm, and the efficacy of feedback feeding: The time taken until the end of the within-farm PED occurrence after starting feedback feeding was not significantly different between farms with a feedback feeding instructor (70.2 days) and those without an instructor (32.7 days, difference in reciprocal=-1.6×10^{-2}, SE=8.3×10^{-3}, *P*=0.060), between farrow-to-finish farms (50.9 days) and reproduction farms (100.3 days, difference in reciprocal=-9.3×10^{-3}, SE=5.5×10^{-3}, *P*=0.103), or between middle-scale farms (56.6 days) and large-scale farms (77.8 days, difference in reciprocal=5.0×10^{-3}, SE=5.0×10^{-3}, *P*=0.371). However, time taken until the end of the within-farm PED occurrence after starting feedback feeding was significantly shorter at small-scale farms (25.3 days) than at large-scale farms (difference in reciprocal=2.7×10^{-2}, SE=1.2×10^{-2}, *P*=0.033). In the multivariable analysis (Table 6, n=29), farms having an instructor had a longer period between the start of feedback feeding and the end of the within-farm PED occurrence (difference in reciprocal=-1.5×10^{-2}, SE=7.0×10^{-3}, *P*=0.039), and small-scale farms had a shorter period than large-scale farms (difference in reciprocal=2.4×10^{-2}, SE=9.9×10^{-3}, *P*=0.021). The period did not differ between middle- and large-scale farms (difference in reciprocal=4.8×10^{-4}, SE=4.4×10^{-3}, *P*=0.913).

Association between the perception of farmers regarding the efficacy of feedback feeding and the magnitude of loss: There were no statistically significant associations between the farmers' perceptions of the efficacy of feedback feeding and the outbreak (*n*=31, difference in reciprocal=-3.4×10^{-3}, SE=5.0×10^{-3}, *P*=0.510) or the number of dead piglets (*n*=31, difference in log=3.8×10^{-1}, SE=2.9×10^{-1}, *P*=0.204).

The results of all univariable analyses are shown in Supplementary Tables 1 and 2.

DISCUSSION

Sporadic cases of PED have continued to occur in Japan in 2021, although the large-scale outbreak that took place in 2013 has abated. A long within-farm infectious period, even over half a year, has been observed at some farms, and the high recurrence rate shown in our study suggests a persistent nature of PED once it occurs on a farm. Approximately half of the PED-affected farms conducted feedback feeding, which suggests farmers were alarmed and made the decision to mitigate the damage, even at the risk of losing piglets from PEDV infection, as they must have known that the materials used for the feeding contained live PEDV.

The literature on the methods of feedback feeding recommends macerating and washing the intestines of symptomatic piglets with cold water and then adding the material to the feed of sows, as feces of piglets contain a much higher virus load than those of sows or piglets that died of the disease [6, 8, 26]. However, the literature also recommends a variety of methods, including the use of feces, nose-to-nose contact, and mixing infected and unaffected pigs, even at various stages of growth. The key ideas of feedback feeding are to force the entire herd, particularly sows, to become infected with PEDV at once, strict all in/all out movement of animals for farrowing accompanied with disinfection of rooms, and ensuring the elimination of PEDV using sentinel animals [6]. In this study, all of the farms targeted pregnant sows, with some variation in the stages at which feeding was applied. As the methods described in the literature varied [8, 11], it is understandable that the procedures adopted by the Japanese veterinarians and farmers also varied. While this study did not prove a positive effect of feedback feeding on mitigating within-farm PED occurrence, there is a report of success in stopping within-farm PED occurrence in 1 month by quick and complete administration of feedback feeding to all sows on the farm [35]. Another study reported that delaying the start of feedback feeding after the first infection within a farm increases the resulting damage from PEDV infection (in terms of both the number of dead piglets and within-farm outbreak period) [5]. In our study, not all of the affected farms administered feedback feeding to nursing sows and sows not pregnant, and it is not known whether rapid and complete infection of all sows was achieved. The outbreak-associated damage at farms that conducted feedback feeding declined over time since the date of PED occurrence on Kyushu Island, as shown in this study, suggesting that inconsistent feedback feeding procedures and/or difficulties in controlling the viral load, especially in the early stage of the outbreak when the procedures were not well-known to farmers, might have exacerbated the damage caused by PED. As the knowledge on PED is accumulated, the delay in the detection of PED can be shortened. This early detection might contribute to less outbreak damage as well.

It should be noted that the effect of feedback feeding in this study may be affected by the selection bias due to the low response rate (about 30%) of the questionnaire survey. Assuming dedicated farmers tend to respond to the questionnaire, the efficacy of the feedback feeding may be overestimated (i.e., a positive effect is more likely to be detected). In the study population, the feedback feeding still had a negative impact on the outbreak. The farms with a positive impact of feedback feeding observed in other studies [35] could be more intensive and well-managed. The situation might be worse in the general pig farm population.

The significantly higher number of deaths in piglets per sow at farrow-to-finisher farms than reproduction farms suggests that farrow-to-finisher farms had a higher virus load due to the entrance of transportation vehicles that visited slaughterhouses. A higher risk of infection at farrow-to-finisher farms than reproduction farms during this epidemic has been reported [23, 34], and these reports also suggested that there was a risk of cross-contamination at slaughterhouses. However, since the interaction between the farm operation type and practice of feedback feeding on the number of deaths in piglets was significant, the damage associated with feedback feeding was greater at reproduction farms than farrow-to-finisher farms. A possible reason for this difference might be that feedback feeding has a greater negative impact on reproduction farms due to their larger number of sows and piglets compared with farrow-to-finisher farms. It was reported that the effect of feedback immunization varies considerably depending on the procedures used, even if they comply with recommended methods [4]. Therefore, more detailed evaluations of feedback feeding will be necessary for the future. The number of deaths in piglets was analyzed by the GLM setting the number of sows as an offset in this study. This could cause bias if the number of piglets per sow differs among farms (i.e., the number of piglets per sow could be a potential confounder for the number of dead piglets). We could not account for this issue in this study, as the numbers of live piglets in studied farms at the time of data collection were heavily influenced by the outbreaks, and there were no detailed data including dynamics of actual number of piglets in the studied farm.

Two primary factors affected swine producers’ decision to start feedback feeding: the limited efficacy of PEDV vaccines, and the recommendation of instructors. A clinical report clearly described apparent symptoms, such as vomiting and diarrhea, in vaccinated sows in the outbreak in Japan [35]. The PEDV strains that caused the epidemic in Japan were of genogroup 2, whereas the vaccines available were based on genogroup 1 [25]. In laboratory and field experiments, the vaccine for sows based on genogroup 1 exhibited a mitigating effect against PED caused by a genogroup 2 field strain [25]. Although such experiments showed that the vaccine had efficacy, the majority of the affected farms studied used the PEDV vaccine, and half of them practiced feedback feeding. Therefore, it can be said that the PEDV vaccine could not sufficiently prevent or mitigate the damage clinically. In the field situation, PEDV viral load might have been too high to protect the intestinal villi of piglets with lactogenic immunity induced by the vaccine. Although enough vaccine was not circulated at the beginning of the outbreak [29], a shortage of PEDV vaccine was not the motivation for starting feedback feeding, as the majority of farms that conducted feedback feeding used the vaccine, and the proportion that used the vaccine was not different compared with farms that did not practice feedback feeding. The farms with feedback feeding instructors present started feedback feeding at an earlier stage of the within-farm outbreak period than farms without an instructor, suggesting that instructors facilitated the start of feedback feeding even though a vaccine was available for most of the farms. The severe damage caused by the PEDV infection could be one of the reasons for this phenomenon.

The period from the beginning of feedback feeding to the end of PED occurrence was longer at farms with a feedback feeding instructor than at farms without an instructor. The procedures the instructors recommended might have been inconsistent, which in turn affected the outbreak duration. Adequate knowledge and preparation are required when administering feedback feeding.

The farmers’ perceptions were not associated with the effect of feedback feeding on the outbreak period or the number of dead piglets. Feedback feeding might have had a negative impact on the PED outbreak, especially at reproduction farms. However, approximately 70% of farmers responded that feedback feeding had a positive effect. The importance of evidence-based (not perception-based) practices was thus reconfirmed by this study.

It should be noted that neither vaccine use nor immune status at farms were controlled in this study due to limited information when the vaccines were used. A detailed evaluation of vaccine use/immune status and outbreak damage/conduct of feedback feeding should be performed in further research. A manual regarding the distribution of vaccines in an emergency was prepared in Japan as a result of the instability of vaccine demand due to this PED epidemic [15]. A manual describing measures to combat PED was also prepared, but feedback feeding is not recommended in this manual [17]. The effectiveness of feedback feeding depends on the quality of lactogenic immunity. The quality of immunity varies with factors such as viral load in feed, parity, the health status of sows, the timing of immunization, stress caused by vaccination, and type of virus strain [12, 28]. Therefore, in order to determine the best means of effectively immunizing piglets by feedback feeding, further research will be needed. However, it should also be noted that although the viral load in feed was not assessed in this study, the evidence obtained in this study that the interaction effects between feedback feeding and farm-types/time since PED occurrence in Kyushu are valuable to look back and assess the countermeasures to PED outbreak in Japan.

In conclusions, this study revealed that in the early stage of the recent PED outbreak on Kyushu Island, Japan, feedback feeding had a negative impact on the within-farm outbreak period and number of deaths in piglets, especially at reproduction farms. The negative impact of feedback feeding was mitigated during the study period, suggesting that the procedures used gradually improved. Feedback feeding was conducted despite the availability of a PEDV vaccine during the outbreak period, being facilitated by instructors such as veterinarians. However, since feedback feeding had a negative impact on the outbreak, the procedures must have been sub-optimal, especially during the early stage of the outbreak. These procedures should be re-evaluated to obtain a better understanding of feedback feeding for potential future use in case effective vaccines are not available.

POTENTIAL CONFLICTS OF INTEREST. The authors declare no conflict of interest.

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