Journal of Biomedical and Translational Research
pISSN 2508-1357 eISSN 2508-139X

Original Article
J Biomed Transl Res 2021;22(4):179-188
https://doi.org/10.12729/jbtr.2021.22.4.179

The diagnostic analysis of the presumptive cases of foot and mouth disease (FMD) vaccine-associated adverse reaction in Korea

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Received: Dec 9, 2021
Revised: Dec 14, 2021
Accepted: Dec 14, 2021

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Abstract

We conducted diagnostic investigations to analyze the causes of abortions (46 cases, 65.7%), deaths (22 cases, 31.4%) and muscular lesions (2 cases, 2.9%) occurred after foot and mouth disease (FMD) vaccination in livestock farms in Korea. Bacterial culture, enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) were performed to detect the causative agents of abortion in bovine and caprine. The diagnostic results showed that 36 (51.4%) cases, referring as “Identified”, were occurred by influence of underlying disease including bovine viral diarrhea (12 cases, 17.1%), neosporosis (7 cases, 10.0%), septicemic colibacillosis (5 cases, 7.1%), Q fever (4 cases, 5.7%) and other abnormal conditions (8 cases, 11.4%) not by vaccination. Other 2 (3.0%) cases were suspected to be vaccine-associated adverse reaction on the basis of pathological findings (shock lung, oil-component-induced granuloma) and clinical symptoms (dyspnea with pulmonary edema). The other 32 (45.7%) cases were determined “Unknown” because any pathogens and pathological changes were not identified. However, many of the “Unknown” cases were presumptive to be the vaccine-related adverse reaction based on epidemiological investigation, especially, the cases which showed the clinical signs within 2 days after the vaccination. It is important to conduct pathological, microbiological and epidemiological investigation to diagnose whether the cases are from vaccine-associated adverse reaction or not.

Keywords: adverse reactions; foot-and-mouth disease; FMD vaccine

INTRODUCTION

Foot and mouth disease (FMD), one of the most contagious diseases, has a great potential for serious economic losses in animal industry. That is why most countries are strongly conducting the sanitary prophylaxis (quarantine in immigration, animal movement restriction, preventive slaughter of animals, etc.) and the medical prophylaxis (vaccination) in order to control the dis-

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Acknowledgements
This study was conducted with the budget, a head of experiment and research (20703), of Chungbuk Veterinary Service and Laboratory.

Ethics Approval
Not applicable.

ease. In endemic countries, vaccination is estimated to be quite effective. Countries concerned about sporadic outbreaks, such as Argentina, Bolivia, Botswana, Brazil, Colombia, Kazakhstan, and Malaysia, maintain its FMD-free status through vaccination.

In Korea, a nationwide vaccination was first implemented in response to the massive outbreak in 2010. Afterward, the outbreaks have dramatically decreased. Although FMD has occurred sporadically since 2014, the intensive nationwide vaccinations have been strongly implemented every year, especially at the time of special prevention season (October to May) or when FMD is likely to occur or develop [1]. However, irrespective of the effectiveness, there have been frequent complaints that the vaccine might be a cause of abortions or deaths. In response to such complaints, Korea government conducted official survey to examine the causal relationship between the vaccination and those events in 2011. That survey failed to find any confirmed cases of adverse reactions, including abortion or death, due to FMD vaccination. Some vaccinated animals, however, experienced stress, fever, pain, loss of appetite, lethargy, a temporary decrease in milk production or a retarded growth rate.

Despite the report, the number of submitted cases due to abortion or death has been significantly increased after annual intensive inoculation practice. It has been serious problems in the livestock farms for many years. Some farmers tend to distrust or avoid the vaccination and even require to stop vaccination. It is now an obstacle to the FMD control policy. However, there were few actual informations to solve the distrust against the FMD vaccine. Therefore, it is necessary and important to identify the causes of those coincident events, and inform the actual field situations to resolve the disputes between the government and the farmers through the laboratory diagnosis.

MATERIALS AND METHODS

Preparation of samples

From January, 2017 to June, 2018, 70 cases (46 abortions, 22 deaths, 2 muscular lesions from 63 cattles, 6 goats and 1 pig) considered to have shown adverse reactions against the vaccination were submitted to Chungbuk Veterinary Service and Laboratory. We conducted diagnostic procedures including bacteriologic, virologic and histopathologic examinations according to the standard guidelines for animal disease diagnosis [2]. According to the guidelines, samples within 2 weeks and in good condition were utilized for the diagnosis.

Pathological examinations

Necropsies on 70 cases were carried out precisely in accordance with standard pathological procedure. On the lesion checked during necropsy, specific procedures including bacterial isolation, viral gene amplification and pathological examination were applied. In order to observe histopathologic findings of the lesions, the main organs including brain, liver, heart, kidney, spleen, intestine and placenta were fixed in 10% neutral formalin for 24 hours, followed by routine tissue processing and paraffin embedment. The paraffin sections (2 μm thickness) were stained with hematoxylin-eosin for microscopy. The different stains including immunohisto-

https://doi.org/10.12729/jbtr.2021.22.4.179

chemistry were also done if necessary.

Bacterial examinations

In order to isolate bacteria from the lesions, both Sheep Blood agar and MacConkey agar were used for general aerobic and anaerobic culture. When single colonies observed after incubation, MALDI-TOF (Microflex™ Bruker, Billericay, MA, USA) was utilyzed for identification of the bacterial colonies.

Polymerase chain reaction (PCR) in aborted cases

Gene amplifications were performed for the agents causing abortion in bovine or caprine such as *Brucella abortus*, *Coxiella burnetii*, *Campylobacter fetus*, *Listeria monocytogenes*, *Leptospira spp*., *Chlamydophila abortus*, *Neospora caninum*, *Toxoplasma gondii*, bovine viral diarrhea virus (BVDV), infectious bovine rhinotrachitis virus (IBRV), Ainovirus (AINOV), Chuzan virus (CHUV), Akabane virus (AKAV), Ibaraki virus (IBAV), bovine ephemeral fever virus (BEFV). DNA/RNA were extracted from various tissue samples using a Viral Gene-spin™ Viral DNA/RNA Extraction kit (Intron, Seongnam, Korea) according to the manufacturer's instructions. The primer sequences used for the PCR are shown in Table 1. For amplification of the viral genes, commercial viral detection kits were used for AINOV, CHUV, AKAV, IBAV, and BEFV (MEDIAN diagnostics™, Chuncheon, Korea) and for BVDV (PowerCheck™, Kogenebiotech, Seoul, Korea). Briefly, 20 μL of PCR mixture contained 0.5 μL of 10 pmol of each primer, 3 μL of template and 16 μL of free water in the PCR mastermix (i-StartTaq, INTRON™). The each PCR conditions were applied as described in references indicated in Table 1.

Table 1. Nucleotide sequences of primers used for PCR amplification

Target organisms		Target gene	Sequence (5'→3')	Product size (bp)	Reference
Bacteria	*Brucella abortus*	16s RNA	TCGAGCGCCCGCAAGGGG	905	[3]
			AACCATAGTGTCTCCACTAA		
	Coxiella burnetii	IS1111	TATGTATCCACCGTAGCCAGTC	687	[4]
			CCCAACAACACCTCCTTATTC		
	Listeria monocytogenes	hly	CGGAGGTTCCGCAAAAGATG	234	[5]
			CCTCCAGAGTGATCGATGTT		
	Leptospira spp.	secY	CTGAATCGCTGTATAAAAGT	285	[6]
			GGAAAACAAATGGTCGGAAG		
	Chlamydophila abortus	pmp	ATGAAACATCCAGTCTACTGG	300	[7]
			TTGTGTAGTAATATTATCAAA		
Protozoa	*Neospora caninum*	Nc-5	CTCGCCAGTCAACCTACGTCTTCT	350	[8]
			CCCAGTGCGTCCAATCCTGTAAC		
	Toxoplasma gondii	B1	GGAACTGCATCCGTTCATGA	501	[9]
			CAGACGAATCACGGAACTG		
Virus	IBRV	gC	TACGACTCGTTCGCGCTCTC	476	[10]
			GGTACGTCTCCAAGCTGCCC		

PCR, polymerase chain reaction; IBRV, infectious bovine rhinotrachitis virus.

Antibody detection

Enzyme-linked immunosorbent assay (ELISA) for the antibody detection was performed for *Coxiella burnetii* and *Neospora canis* using commercial ELISA kits (Idexx, Tampa, FL, USA), and plate agglutination test for *Brucella abortus* using Rose bengal agent provided from Animal and Plant Quarantine Agency.

Statistical analysis

The distributions of categorical variables (the number of occurrence of cases from the day of vaccination to 14th day) were compared by a chi-square test between "Identified" and "Unknown" with SPSS 25.0. P values of <0.05 were considered to be significant.

RESULTS

Clinical conditions of presumptive vaccine-associated adverse reaction cases were summarized at Table 2. The occurrence of the reactions according to age are shown at Table 3 and 4. The diagnostic results were summarized at Table 5. Briefly, from the total 70 cases, 39 (55.7%) cases, referred to "Identified", were identified to have the reasonable causes of abortions, death or muscular lesions. On the other hand, 31 (44.3%) cases, referred to "Unknown", were animals that any lesions or causative agents have not been identified through the diagnostic procedures. From the 39 "Identified" cases, the causes of 22 abortion cases were composed of BVD (11), neosporosis (7), mummification (2), Q fever (1) and Akabane disease (1) in bovine

Table 2. Summary of clinical conditions showed in animals inoculated with FMD vaccine

Conditions	No. of cases (%)			
	Total	Bovine	Caprine	Porcine
	70 (100)	63 (100)	6 (100)	1 (100)
Abortions	46 (65.7)	41 (65.0)	5 (83.3)	-
Deaths	22 (31.4)	21 (33.4)	1 (16.7)	-
Muscular lesions	2 (2.8)	1 (1.6)	-	1 (100)

FMD, foot and mouth disease.

Table 3. Classification of 46 aborted fetuses from the vaccinated animals by age (month)

Causes	Total (%)	No. of fetuses (%)						
		3	4	5	6	7	8	9
Unknown	20 (100)	-	-	-	3 (15)	4 (20)	5 (25)	8 (40)
Identified	26 (100)	2	-	6	3	3	7	5

Table 4. Classification of 22 death cases from the vaccinated animals by age

Causes	Total	No. of cases (%)								
		1–4 d	5–8 d	1 m	5 m	7 m	8 m	2 yr	3yr	4 yr
Unknown	11	3 (27.3)	4 (36.4)	3 (27.3)	1 (9.1)	-	-	-	-	-
Identified	11	-	4 (36.4)	1 (9.1)	-	1 (9.1)	1 (9.1)	2 (18.2)	1 (9.1)	1 (9.1)

d, days; m, months; yr, years.

https://doi.org/10.12729/jbtr.2021.22.4.179

Table 5. The diagnostic results on 70 presumptive cases of FMD vaccine-associated adverse reaction

Clinical condition (No.)	Animal (No.)		Diagnostic results		
			Causes of condition	No. of cases (%)	
Abortion (46)	Bovine (41)	Unknown (19)	Unknown	19	(27.1)
			Bovine viral diarrhea	11	(15.7)
		Identified (22)	Neosporosis	7	(10.0)
			Mummification without any pathogen	2	(2.9)
			Q fever	1	(1.4)
			Akabane disease with hydrocephalus	1	(1.4)
	Caprine (5)	Unknown (1)	Unknown	1	(1.4)
		Identified (4)	Q fever	3	(4.3)
			Listeriosis	1	(1.4)
Death (22)	Bovine (21)	Unknown (11)	Unknown	11	(15.7)
			Colibacillosis with severe fibrinous serositis	4	(5.7)
			Colibacillosis with meningoencephalitis	1	(1.4)
			Dyspnea with pulmonary edema	1	(1.4)
		Identified (10)	Bovine viral diarrhea	1	(1.4)
			Mannheimiosis with severe fibrinopurulent pneumonia	1	(1.4)
			Septicemia due to bone fracture	1	(1.4)
			Tympany	1	(1.4)
	Caprine (1)	Identified (1)	Luminal acidosis	1	(1.4)
Muscular lesion (2)	Bovine (1)	Identified (1)	Sarcocystis infection with eosinophilic granulomatous myositis	1	(1.4)
	Porcine (1)	Identified (1)	Pyogranulomatous myositis without pathogenic agent	1	(1.4)

FMD, foot and mouth disease.

and Q fever (3) and listeriosis (1) in caprine. The causes of 10 deaths in bovine were colibacillosis (5), dyspnea with pulmonary edema (1), BVD (1), mannheimiosis with severe fibrinopurulent pneumonia (1), septicemia by bone fracture (1) and tympany (1). In caprine, luminal acidosis (1) and muscular lesions (2) pyogranulomous myositis by oil component in FMD vaccine and eosinophilic granulomatous myositis by sarcocystis infection were diagnosed.

One of the "Identified", there was a fatal bovine case which died of dyspnea with pulmonary edema, suspected to be vaccine-associated adverse reaction. The case was first in Korea that suddenly collapsed and died of severe pulmonary lesions after FMD vaccination. In history, on May 20 in 2017, the cow (Korean indigenous cattle, female, 24 months old, 400 kg, apparently healthy) was inoculated with FMD bivalent (O manisa + O 3039) vaccine (Green-Cross Veterinary Product, Yongin, Korea) in the jugular region intramuscularly and suddenly died after vaccination. The farmers injected the vaccine to 10 cattles around 7 o'clock in the morning. Approximately 1 hour later, one of the 10 cattles suddenly became depressed, took a sitting position with labored breathing and then fell down to death (Fig. 1A). Just before the death it showed dyspnea with reddish foamy nasal and oral discharge. On gross examinations, the cow showed severe pulmonary swelling and diffuse reddness in both lobes of the lungs, which failed to collapse when the thoracic cavity was opened. On cut surface, the lung parenchyma was like a wet sponges oozing fluids. The interlobular septae were markedly distended with fluid (Fig. 1B). However, no changes were observed in other internal organs.

Histopathologically, the lungs showed severe congestion with the thickening of alveolar walls. The terminal bronchioles and alveoli were diffusely filled with abundant proteinaceous fluid, fibrin, large numbers of erythrocytes, neutrophils, and macrophages. Interlobular septae were markedly thickened by the accumulation of fluid (Fig. 1C). In the liver, severe congestion was observed in various size of vessels (Fig. 1D). In laboratory examinations, no bacteria were isolated from the lungs, kidneys, liver and spleen. The viruses which can cause respiratory diseases including BRSV, IBRV, PI-3 virus, BVDV, and adenovirus were not detected by PCR.

DISCUSSION

Even though vaccination policy for preventing FMD outbreak has been implemented in many countries, there are only few reports on vaccine-induced adverse reaction, making it difficult to estimate the situation related FMD vaccine problem in other countries. In this study, we diagnosed and analyzed various causes of the potential adverse reaction cases related to FMD vaccination in Korea.

Generally, some vaccine used for veterinary purposes often have the potential for adverse

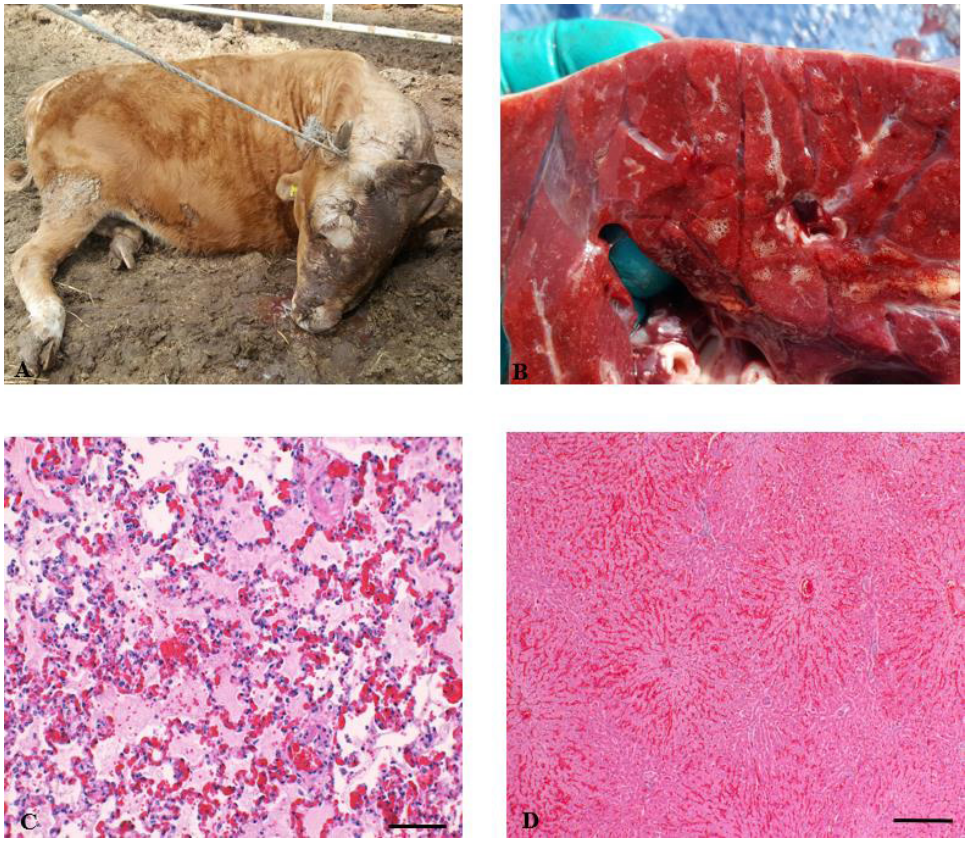

Fig. 1. Morphologic features of a dead case after FMD vaccination. (A) A cow died shortly after the vaccination. Note the discharge of sanguineous-foamy fluid from the mouth and the nose. (B) The cut surface of the cow's lungs. Note the red foamy fluid in the bronchi, and the interlobular septae markedly distended with clear fluid. (C) A microphotograph of the pulmonary lesion. The alveoli are filled with abundant eosinophilic fibrinous inflammatory exudates and RBCs. (D) A micrograph of hepatic lesion. The sinosoids and central veins are severely congested. H&E stain. Scale bars = 200 μm (C), 400 μm (D). FMD, foot and mouth disease.

https://doi.org/10.12729/jbtr.2021.22.4.179

reaction in vaccinated animals [11]. Several adverse reaction cases after administration of routine animal vaccine similar to coincidence after FMD vaccination in Korea have been reported in other countries. The calves following administration of a combination vaccine showed fever and depression and died of pulmonary edema in 8 hours, suggesting that synergistical actions among endotoxins or other bacterial components and some adjuvants enhance fatal inflammatory responses [12]. In swine, vaccinated pigs with oil-in-water type adjuvant vaccine against porcine pleuropneumonia showed fever, malaise and anorexia [13]. It was also reported that the components such as safonin and oil emulsion in vaccines might cause chemical stimulation [14]. In the case of FMD vaccine adverse reaction, urticarial, exudative and necrotic dermatitis were observed in dairy cows 8 days later after vaccination, due to anaphylaxis caused by vaccine components [15]. And Ferreira et al. reported that FMD vaccines could elicit inflammatory and acute phase reactions, known to impair cow pregnancy maintenance [16]. Unfortunately, most reports of adverse reactions following vaccination have been anecdotal, and relatively few have been documented in the scientific literature, making it difficult to assess mechanisms by which certain vaccine components, or combinations thereof, may cause adverse reactions [12].

There were various comments about the causes of adverse reaction happening after annual FMD vaccination in Korea. Livestock farmers argued that currently using FMD vaccine with thick oil based feature was severely stressful to the animals and it could be causes of inappetence, death or abortion during or after inoculation. Oil-based adjuvant containing most veterinary vaccine have contributed to the enhancement of veterinary vaccine efficacy and have greatly contributed to the prevention of many epidemics. At the same time, it often caused some side effects such as inflammation, granulomatous lesions and aseptic abscesses at the injection site, fever and anorexia [14]. Most FMD vaccines contain inactivated FMD virus serotypes and an oil-based adjuvant [17]. Some reports documented adjuvant-containing FMD vaccine led to innate immune responses related to antigen presentation to T cell lymphocytes, including inflammation and acute phase reactions [14, 17] known to cause pregnancy loss in cattle [18]. It has been known that adverse reactions such as fever, pain, anorexia, lethargy and decrease in milk production and growth rate occur after the vaccination in domestic livestock farms [13]. It is also reported that excessive emulsifier containing in oil based FMD vaccine temporarily induced clinical signs [13]. Especially, in swine, body temperature could rise to 41°C–42°C after 6–12 hours of inoculation and malaise with anorexia last for several days. Weak animals may consequently show a decrease of daily gain in weight, or worst case may occasionally die. Also, pregnant females may more frequently be provoked to abortion [19]. For these reasons, FMD vaccine manufacturers may acknowledge the potential adverse reaction by notifying them through the user manual for the safe usage of vaccine.

On the other hand, the opinion of Korean government on the livestock farmers' comments were contrary. According to the official survey conducted by Korea government on whether the cases of animal death or abortion after vaccination were related to FMD vaccine in 2011, the stress induced during fastening the animals for inoculation could cause fever, pain, loss of appetite and lethargy. This could lead to temporary decrease of milk production and/or the

growth rate, and there has not yet been confirmed the cases of adverse reactions such as animal death or abortion caused by FMD vaccination [1, 20]. In accordance with the literature, especially Novak W [21], or the veterinary biologic guidelines [22, 23] on the definition of vaccine adverse reaction, even these not-vaccine-related signs were also asserted or considered as the adverse reaction. However, Korean government does not tend to regard the signs such as fever, pain, loss of appetite and lethargy occurring after vaccination as a category of adverse reaction. This was probably because the vaccine adverse reactions were not clearly defined in the relevant regulations, and there was not enough scientific verification procedure on whether adverse reaction were caused directly by vaccine components or during vaccination.

In this study, we confirmed that 51.4% of total 70 cases were not related to vaccine-associated adverse reaction but to underlying diseases. Among these, there were some cases which could be easily distinguishable from the causes through the external appearance of the dead bodies. Especially, some calves with excessive frontal head protrusion related to hydrocephalus, some cattle showing emaciation condition resulting from severe respiratory problem, calves with leg bone fracture or tympany, or mummified fetus could be sufficiently judged that the causes were not related to FMD vaccination, even if farmers were not a specialist. Moreover, BVD or neosporosis were identified as major causes of abortion in this study, which were consistent with the previous study on the situation of bovine abortion in Korea [24]. On the other hand, we could not clearly identify the causative agents or associated lesions which can directly be related to abortion or death in 31 (44.2%) cases. For these cases, we could not judge whether the results were from the adverse reactions or not.

There were differences when compare the occurrence according to animal age and time laps between “Unknown” and “Identified”. Occurrence of “Unknown” was mainly in late stage (7–9 months) of gestation period in abortion cases and within one week after birthday in death cases. On the other hand, in cases of “Identified”, there was no tendency occurred at certain period of time but it tended to depend on the time of onset of underlying disease. This means that vaccination for the pregnant animal at late gestation period or newborn animal ($\leqq$ 8th days) may rise the possibility of vaccine-associated adverse reaction.

And when comparing time laps from at vaccination to occurrence (Fig. 2), the occurrence at early periods (from the 0 day to 2nd days) of “Unknown” were 2.7 times higher than that of “Identified” ($p < 0.05$). This epidemiological investigation means that there were no other factors to be considered except the direct influence of vaccine or vaccine-related stress.

As the intensive vaccination policy is enhanced, controversies between the government and the farmhouse over the adverse reactions would be continuously repeated. To resolve this problems, it is necessary to clarify the cause of the occurrence through diagnosis and epidemiological examinations, then to offer the results to make the livestock farmers understand the facts. And it is also necessary for the farmers to establish the history database about their usual abortions or deaths so that they can be used for comparative analysis of the unidentified abortions or deaths occurring after the vaccination.

https://doi.org/10.12729/jbtr.2021.22.4.179

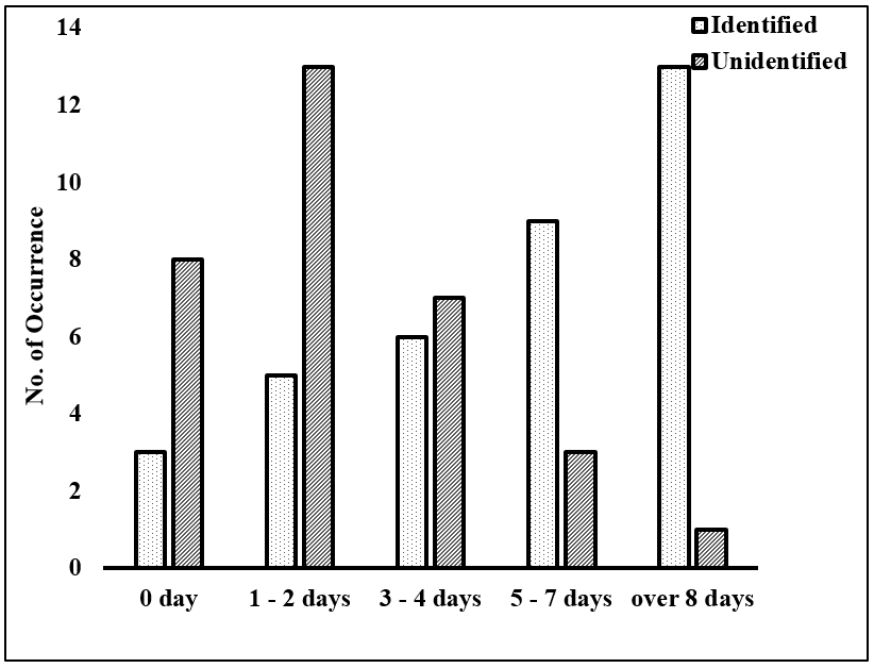

Fig. 2. Comparison of the numbers of occurrence of the event according to time laps between "Identified" and "Unknown".

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