Human *Streptococcus suis* Infections in Thailand

Subjects: Infectious Diseases
Contributor: Anusak Kerdsin

Streptococcus suis is a zoonotic pathogen causing substantial economic losses to the pig industry, as well as being a human health burden due to infections worldwide, especially in Southeast Asia. In Thailand, there was high cumulative incidence in humans during 1987–2021, mostly in males. At least five large outbreaks have been documented after the largest outbreak in China in 2005, which was related to the consumption of raw pork or dishes containing pig's blood. The major clinical features are sepsis or meningitis, with hearing loss a major complication of *S. suis* disease. Thai human *S. suis* isolates have shown diversity in serotypes and sequence types (STs), with serotype 2 and STs 1 and 104 being major genotypes. *β*-Lactam antibiotics can be used in empirical treatment for human *S. suis* infections; however, intermediate resistance to penicillin has been reported. Reducing *S. suis* incidence in Thailand requires a multidimensional approach, with combined efforts from the government and public health sectors through policy, regulations, education, and active surveillance.

Streptococcus suis | serotype | sequence type | Thailand

1. Introduction

Streptococcus suis is a Gram-positive coccus bacterium responsible for major infections in pigs and significant economic losses in the pig industry worldwide. The most important clinical manifestations associated with *S. suis* infection in pigs are meningitis, arthritis, endocarditis, pneumonia, rhinitis, abortion, and vaginitis [1]. It is also an emerging zoonotic pathogen causing serious diseases in humans, including meningitis, sepsis, septic shock, infective endocarditis, and septic arthritis [1][2]. The number of reported human *S. suis* cases has substantially increased, with Southeast Asian countries leading the counts, especially Thailand and Vietnam [1][2][3]. Occupations related to pigs or pork, exposure to pig or pork products, or the consumption of raw pork products are the main risk factors of human infection [1][3].

S. suis is an encapsulated pathogen, with the capsular polysaccharide antigens being the basis for classification into serotypes [1]. Among 29 serotypes, serotype 2 is considered the most pathogenic and a frequent cause of human disease worldwide [1]. In Western countries, such as the United Kingdom, Spain, Germany, the Netherlands, Canada, and the United States, as well as in Japan, China, and Hong Kong, most human *S. suis* cases have occurred after occupational exposure involving pig handling among pig farmers, bleeders, abattoir workers, carcass cutting and processing workers, butchers, and cooks [3]. However, in Southeast Asian countries, such as Thailand, Vietnam, and Indonesia, a nontrivial number of human cases has occurred in individuals consuming meals containing raw pork meat, blood, and other related products [3]. Two studies in Thailand showed that *S. suis* human infections were responsible for an estimated loss in productivity-adjusted life years to the gross domestic product of USD11.3 million, which equates to USD36,033 lost per person and out-of-pocket expenses for individuals and their families that averaged USD140 (GBP104 or THB5198) per patient [4][5].

2. Epidemiology of Human *S. suis* Infections in Thailand

In Thailand, *S. suis* infection was first described in 1987 in Bangkok, with two cases of meningitis [6]. Before the largest outbreak of human *S. suis* infection occurred in Sichuan province, China in 2005 [7], sporadic human cases had been reported in several provinces in Thailand, especially in the north [8][9][10][11][12][13][14]. One outbreak with 10 fatal cases due to septic shock was documented in 2000 in Lamphun province, northern Thailand, well before the largest outbreak occurred in China [14]. That study demonstrated that all cases were healthy men aged 40–49 years who were clustered during the same period and geographic area [14]. All cases had a history of chronic alcohol use and the consumption of raw pork or pig's blood dishes prior to their illness [14].

National guidelines for human *S. suis* infections are not yet available in Thailand. However, the practice of *S. suis* recruitment in the public health system is conducted using the R506 system (a daily case report of communicable diseases) of the Ministry of Public Health that was initiated after the first large outbreak in 2007. As shown in **Figure 1**, human cases reported in the system showed an increasing trend during 2011–2021. Although the number of cases dropped in 2022, annual data were only up until September. Notably, these reported cases were submitted by the hospital network where they could identify this bacterium. Thus, misidentification of *S. suis* as other bacteria might have occurred, and this would not have been reported in that system [15][16][17][18]. Therefore, the reported human *S. suis* cases registered in the R506 system may be lower than the real situation.

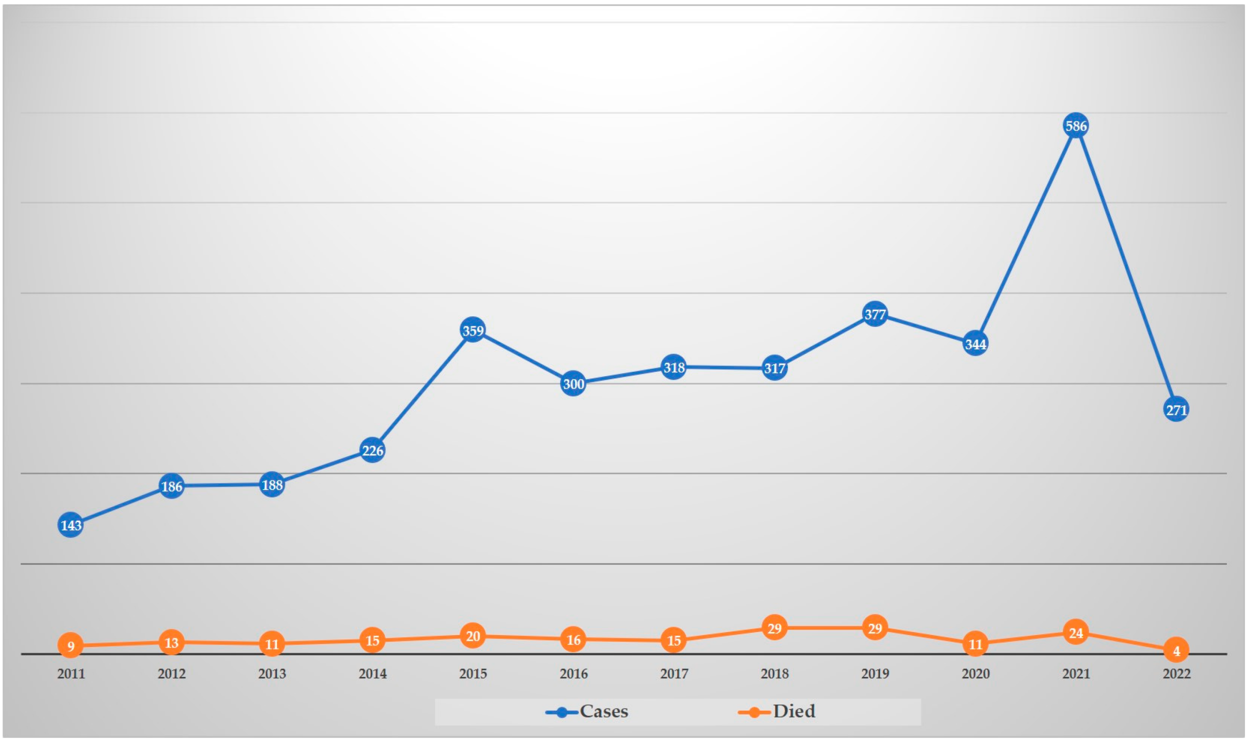

Figure 1. Human *S. suis* cases in Thailand 2011–2022 reported in R506 system by the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health. For 2022, data are provided only up to September.

The national annual crude incidence is 0–0.381 per 100,000 persons [18]. A study in Nakhon Phanom province (northeastern Thailand) documented an annual incidence of 0.1–2.2 cases per 100,000 population for 2006–2012 [18]. This differed from a study in 2010 that estimated human cases to be 730 per year in northern Thailand, with an incidence of 6.2 per 100,000 of the general population [19]. The reasons for these different rates are still unknown, but ethnicity, tribe, cultural behavior, and lifestyle might all influence the *S. suis* infection rate [3].

3. Genotypes of Thai Human *S. suis* Strains

As shown in **Table 1**, for *S. suis* isolated from patients in Thailand, serotype 2 (93.4%) was dominant, followed by serotypes 14 (5.2%), 24 (0.6%), 5 (0.4%), 4 (0.1%), 9 (0.1%), 31 (0.1%), and unencapsulated (0.1%), respectively [17][20][21][22][23]. MLST classified serotype 2 into five CCs: CC1, CC25, CC28, CC104, and CC233/379. Of these, CC1 is a major CC of human *S. suis* infection in this country and ST1 is the main ST in CC1 [21], while serotype 14 was classified to only CC1, with ST105 predominant [21][23]. For serotype 2, ST104, ST25, ST28, and ST233 were the main STs in CC104, CC25, CC28, and CC233/379, respectively. Notably, STs 1 and 104 for serotype 2 are the predominant STs in Thai human infections, and CC104, CC233/379, and CC221/234 are found exclusively in Thailand [20][21][24].

Table 1. Distribution of genotypes of *S. suis* isolates from humans.

Serotype	Clonal Complex	Sequence Type	Reference
2	1	1, 11, 105, 126, 144, 298, 337	[17][18][19][20][21][22][23][25][26][27][28][29] https://pubmlst.org/organisms/streptococcus-suis (accessed on 5 October 2022)
	25	25, 102, 103, 380, 381, 395, 515, 516	
	28	28, 382	
	104	101, 104, 391, 392, 393, 512, 513, 514	
	233/379	233, 379, 1656, 1713	
	1687/1688	1687, 1688	
	Singleton	232, 236	
4	94	94	

Serotype	Clonal Complex	Sequence Type	Reference
5	221/234	221	
	Singleton	181, 235	
9	16	16	
14	1	11, 105, 127	
24	221/234	221, 234	
31 (Unencapsulated)	221/234	221	
Unencapsulated serotype 2 or 1/2	28	28	

Although most cases of Thai human *S. suis* infections had a history of consumption of raw pork dishes, there was no direct evidence or laboratory investigation to confirm or prove the *S. suis* strains in the raw pork dishes that were eaten because none of the raw pork dishes remained after consumption. Indirect investigation was conducted with *S. suis* isolated from slaughterhouse pigs. Three studies showed *S. suis* strains isolated from pigs in Thailand had genotypic profiles of PFGE, RAPD, MLST or combined techniques identical to the *S. suis* strains from humans [30][31][32]. For example, Kerdsin and colleagues (2020) demonstrated that 70.4% of isolates of *S. suis* serotypes 2 and 14 from slaughterhouse pigs revealed STs and PFGE patterns identical to the human isolates [30]. Similarly to Maneerat et al. (2013), the finding showed most of *S. suis* serotype 2 isolates collected from human patients and pigs (diseased and asymptomatic) in different regions of Thailand had the same of ST, RAPD, and virulence-associated gene profile [31]. Such indirect evidence suggests the genetic relationships and confirms the possibility of zoonotic transmission of *S. suis* isolates from pigs to humans for certain STs, especially ST1 and ST104, as well as proving that slaughterhouse pigs are a reservoir of pathogenic human *S. suis* strains.

4. Antimicrobial Susceptibility

Other studies have revealed that Thai *S. suis* isolates were susceptible to penicillin [13]. This contrasted with Nakaranurack et al. (2017), who reported that 6 out of 11 Thai *S. suis* isolates were intermediately resistance to penicillin, whereas cefotaxime and vancomycin were completely susceptible [33]. However, a study in 2021 demonstrated that 448 *S. suis* isolates recovered from human infections in Thailand had 8.2% intermediate resistance to penicillin, while they were all susceptible to cefepime and ceftriaxone [34].

Resistance to tetracycline (98.2%), clindamycin (94%), erythromycin (92.4%), and azithromycin (82.6%) with the resistance genes *tet(O)* and *ermB* were the predominant determinant genes of tetracycline and erythromycin (also macrolide-lincosamide–streptogramin B (MLS_B)) resistance detected in 448 *S. suis* isolates [34]. Resistance to tetracycline appeared common in *S. suis* from human infections worldwide [35][36][37][38][39], whereas the resistance

4. Thongsawad, S. Burden and Epidemiological Characterisations of Streptococcus suis in Chiang Mai, Thailand. Ph.D. Thesis, The University of Edinburgh, Edinburgh, UK, 2016.
5. Rayanakorn, A.; Ademi, Z.; Liew, D.; Lee, L.-H. Burden of disease and productivity impact of Streptococcus suis infection in Thailand. PLoS Negl. Trop. Dis. 2021, 15, e0008985.
6. Phuapradit, P.; Boongird, P.; Boonyakarnkul, S.; Niramarnsakul, S.; Pongliktmongkol, S.; Vorachit, M. Meningitis caused by Streptococcus suis in humans. Intern. Med. 1987, 3, 120–122.
7. Yu, H.; Jing, H.; Chen, Z.; Zheng, H.; Zhu, X.; Wang, H.; Wang, S.; Liu, L.; Zu, R.; Luo, L.; et al. Streptococcus suis study groups. Human Streptococcus suis outbreak, Sichuan, China. Emerg. Infect. Dis. 2006, 12, 914–920.
8. Teekakirikul, P.; Wiwanitkit, V. Streptococcus suis infection: Overview of case reports in Thailand. S. Asian J. Trop. Med. Public Health 2003, 34 (Suppl. 2), 178–183.
9. Vilaichone, R.K.; Vilaichone, W.; Nunthapisud, P.; Wilde, H. Streptococcus suis infection in Thailand. J. Med. Assoc. Thai. 2002, 85 (Suppl. 1), S109–S117.
10. Donsakul, K.; Dejthevaporn, C.; Witoonpanich, R. Streptococcus suis infection: Clinical features and diagnostic pitfalls. S. Asian J. Trop. Med. Public Health 2003, 34, 154–158.
11. Suankratay, C.; Intalapaporn, P.; Nunthapisud, P.; Arunyingmongkol, K.; Wilde, H. Streptococcus suis meningitis in Thailand. S. Asian J. Trop. Med. Public Health 2004, 35, 868–876.
12. Rusmeechan, S.; Sribusara, P. Streptococcus suis meningitis: The newest serious infectious disease. J. Med. Assoc. Thail. 2008, 91, 654–658.
13. Wangkaew, S.; Chaiwarith, R.; Tharavichitkul, P.; Supparatpinyo, K. Streptococcus suis infection: A series of 41 cases from Chiang Mai University Hospital. J. Infect. 2006, 52, 455–460.
14. Fongcom, A.; Pruksakorn, S.; Mongkol, R.; Tharavichitkul, P.; Yoonim, N. Streptococcus suis infection in northern Thailand. J. Med. Assoc. Thail. 2001, 84, 1502–1508.

rates to erythromycin was low in Thailand, Hong Kong, and Vietnam [35][36][40]. Although *tet(O)* is prevalent in human *S. suis* in Thailand, the *tet(M)* genes is more widespread in humans with *S. suis* in China and Vietnam [36][38]. The *ermB* gene was predominant in human isolates in Vietnam and Thailand, while *mefA* was present in Hong Kong [34][36]. This may indicate differences in the local spread of tetracycline and erythromycin-resistance genes among human *S. suis* isolates in different countries or geographical regions.

5. Public Health Control

Kerdsin et al. (2022) mentioned that sociocultural factors, including cultural, religious, and societal behaviors and attitudes associated with the consumption of raw pork or pig's blood play an important role in human infections [3]. Therefore, effecting a reduction in the human *S. suis* cases in Thailand requires a multidimensional approach involving the government and community sectors. Enforcement is required of meat inspection regulations and hygiene practices at pork processing facilities, as well as conducting food safety campaigns, establishing an educational program on preventing this infection, and reducing behavior regarding the consumption of raw pork or pig's blood dishes.

Another study in Thailand showed the effectiveness of a food safety campaign [41]. Overall, this campaign led to a marked decrease in the annualized incidence of human *S. suis* disease, from 6.4/100,000 persons in 2010 (before the campaign implementation) to 2.7/100,000 persons in 2011, then to 2.0/100,000 persons in 2012, and finally to 3.5/100,000 persons in 2013 [41]. Finally, early diagnostics in *S. suis* suspected patients using rapid alternative methods rather than traditional culture (a gold standard but slower) could facilitate prompt treatment and reduce the mortality rate, as well as prompt epidemiological investigation [42][43][44][45].

6. Conclusions

Thai human *S. suis* isolates have diversified in serotypes and STs, with serotype 2 and STs 1 and 104 being the majority in Thailand. In addition, serotype 14 with ST105 is also prevalent in the country. β-Lactam antibiotics can be used in empirical treatment for human *S. suis* infections; however, intermediate resistance to penicillin has been reported. This should be of concern and should be carefully monitored. Thai *S. suis* strains have been reported to be highly resistant to macrolide and tetracycline.

Reducing human *S. suis* disease is Thailand requires a multidimensional approach combining government and public health efforts through policy, regulations, and education, and active community involvement to effect behavioral changes that are evidence-based but culturally sensible and acceptable, along with the implementation in health-care systems of more rapid diagnostics and more relevant screening tools.

15. Le, H.T.T.; Sugiyama, N.; Duangsonk, K.; Tharavichitkul, P.; Osawa, R. Phenotypic and PCR-based identification of bacterial strains isolated from patients with suspected Streptococcus suis infection in northern Thailand. Jpn. J. Infect. Dis. 2012, 65, 171–174.

16. Tarini, N.M.A.; Setiabudy, M.; Susilawathi, N.; Fatmawati, N.; Mayura, I.; Darwinata, E.; Sudiariani, N. Misidentification of S. suis as a Zoonotic Agent. Open Access Maced. J. Med. Sci. 2019, 7, 2309–2312.

17. Hatrongjit, R.; Kerdsin, A.; Gottschalk, M.; Takeuchi, D.; Hamada, S.; Oishi, K.; Akeda, Y. First human case report of sepsis due to infection with Streptococcus suis serotype 31 in Thailand. BMC Infect. Dis. 2015, 15, 392.

18. Prapasiri, P.; Owusu, J.T.; Thammathitiwat, S.; Ditsungnoen, D.; Boonmongkon, P.; Sangwichian, O.; Prasert, K.; Srihapanya, S.; Sornwong, K.; Kerdsin, A.; et al. Streptococcus suis Infection in Hospitalized Patients, Nakhon Phanom Province, Thailand. Emerg. Infect. Dis. 2015, 21, 345–348.

19. Takeuchi, D.; Kerdsin, A.; Pienpringam, A.; Loetthong, P.; Samerchea, S.; Luangsuk, P.; Khamisara, K.; Wongwan, N.; Areeratana, P.; Chiranairadul, P.; et al. Population-Based Study of Streptococcus suis Infection in Humans in Phayao Province in Northern Thailand. PLoS ONE 2012, 7, e31265.

20. Kerdsin, A.; Dejsirilert, S.; Puangpatra, P.; Sripakdee, S.; Chumla, K.; Boonkerd, N.; Polwichai, P.; Tanimura, S.; Takeuchi, D.; Nakayama, T.; et al. Genotypic Profile of Streptococcus suis Serotype 2 and Clinical Features of Infection in Humans, Thailand. Emerg. Infect. Dis. 2011, 17, 835–842.

21. Kerdsin, A.; Akeda, Y.; Takeuchi, D.; Dejsirilert, S.; Gottschalk, M.; Oishi, K. Genotypic diversity of Streptococcus suis strains isolated from humans in Thailand. Eur. J. Clin. Microbiol. Infect. Dis. 2018, 37, 917–925.

22. Takamatsu, D.; Wongsawan, K.; Osaki, M.; Nishino, H.; Ishiji, T.; Tharavichitkul, P.; Khantawa, B.; Fongcom, A.; Takai, S.; Sekizaki, T. Streptococcus suis in humans, Thailand. Emerg. Infect. Dis. 2008, 14, 181–183.

23. Kerdsin, A.; Oishi, K.; Sripakdee, S.; Boonkerd, N.; Polwichai, P.; Nakamura, S.; Uchida, R.; Sawanpanyalert, P.; Dejsirilert, S. Clonal dissemination of human isolates of Streptococcus suis serotype 14 in Thailand. J. Med. Microbiol. 2009, 58, 1508–1513.

24. Kerdsin, A.; Hatrongjit, R.; Wongsurawat, T.; Jenjaroenpun, P.; Chopjitt, P.; Boueroy, P.; Fittipaldi, N.; Zheng, H.; Gottschalk, M. Genomic Characterization of Streptococcus suis Serotype 24 Clonal Complex 221/234 From Human Patients. Front. Microbiol. 2021, 12, 812436.

25. Brizuela, J.; Kajeekul, R.; Roodsant, T.; Riwload, A.; Boueroy, P.; Thaipadungpanit, J.; Jenjaroenpun, P.; Wongsurawat, T.; Batty, E.; van der Putten, B.; et al. Streptococcus suis

outbreak in Thailand caused by an emerging zoonotic strain with acquired multidrug resistance. Microb. Genom. 2022; accepted.

26. Kerdsin, A.; Gottschalk, M.; Hatrongjit, R.; Hamada, S.; Akeda, Y.; Oishi, K. Fatal Septic Meningitis in Child Caused by Streptococcus suis Serotype 24. Emerg. Infect. Dis. 2016, 22, 1519–1520.
27. Kerdsin, A.; Dejsirilert, S.; Sawanpanyalert, P.; Boonnark, A.; Noithachang, W.; Sriyakum, D.; Simkum, S.; Chokngam, S.; Gottschalk, M.; Akeda, Y.; et al. Sepsis and spontaneous bacterial peritonitis in Thailand. Lancet 2011, 378, 960.
28. Kerdsin, A.; Takeuchi, D.; Gottschalk, M.; Hamada, S.; Akeda, Y.; Oishi, K. A human case of Streptococcus suis infection caused by an unencapsulated strain. JMM Case Rep. 2014, 1, e002329.
29. Kerdsin, A.; Hatrongjit, R.; Gottschalk, M.; Takeuchi, D.; Hamada, S.; Akeda, Y.; Oishi, K. Emergence of Streptococcus suis serotype 9 infection in humans. J. Microbiol. Immunol. Infect. 2017, 50, 545–546.
30. Kerdsin, A.; Takeuchi, D.; Nuangmek, A.; Akeda, Y.; Gottschalk, M.; Oishi, K. Genotypic Comparison between Streptococcus suis Isolated from Pigs and Humans in Thailand. Pathogens 2020, 9, 50.
31. Maneerat, K.; Yongkiettrakul, S.; Kramomtong, I.; Tongtawe, P.; Tapchaisri, P.; Luangsuk, P.; Chaicumpa, W.; Gottschalk, M.; Srimanote, P. Virulence Genes and Genetic Diversity of Streptococcus suis Serotype 2 Isolates from Thailand. Transbound. Emerg. Dis. 2013, 60 (Suppl. 2), 69–79.
32. Tharavichitkul, P.; Wongsawan, K.; Takenami, N.; Pruksakorn, S.; Fongcom, A.; Gottschalk, M.; Khanthawa, B.; Supajatura, V.; Takai, S. Correlation between PFGE Groups and mrp/epf/sly Genotypes of Human Streptococcus suis Serotype 2 in Northern Thailand. J. Pathog. 2014, 2014, 350416.
33. Nakaranurack, C.; Puttilerpong, C.; Suwanpimolkul, G. A Decennium of Etiology and Antimicrobial Susceptibility Patterns in Patients with Infective Endocarditis at a University Hospital, Thailand. Jpn. J. Infect. Dis. 2017, 70, 295–300.
34. Bamphensin, N.; Chopjitt, P.; Hatrongjit, R.; Boueroy, P.; Fittipaldi, N.; Gottschalk, M.; Kerdsin, A. Non-Penicillin-Susceptible Streptococcus suis Isolated from Humans. Pathogens 2021, 10, 1178.
35. Bojarska, A.; Molska, E.; Janas, K.; Skoczynska, A.; Stefaniuk, E.; Hryniewicz, W.; Sadowy, E. Streptococcus suis in invasive human infections in Poland: Clonality and determinants of virulence and antimicrobial resistance. Eur. J. Clin. Microbiol. Infect. Dis. 2016, 35, 917–925.
36. Hoa, N.T.; Chieu, T.T.; Nghia, H.D.; Mai, N.T.; Anh, P.H.; Wolbers, M.; Baker, S.; Campbell, J.I.; Chau, N.V.; Hien, T.T.; et al. The antimicrobial resistance patterns and associated determinants in

Streptococcus suis isolated from humans in southern Vietnam, 1997–2008. BMC Infect. Dis. 2011, 11, 6.

37. Marie, J.; Morvan, H.; Berthelot-Hérault, F.; Sanders, P.; Kempf, I.; Gautier-Bouchardon, A.V.; Jouy, E.; Kobisch, M. Antimicrobial susceptibility of Streptococcus suis isolated from swine in France and from humans in different countries between 1996 and 2000. J. Antimicrob. Chemother. 2002, 50, 201–209.
38. Ye, C.; Bai, X.; Zhang, J.; Jing, H.; Zheng, H.; Du, H.; Cui, Z.; Zhang, S.; Jin, D.; Xu, Y.; et al. Spread of Streptococcus suis sequence type 7, China. Emerg. Infect. Dis. 2008, 14, 787–791.
39. Chang, B.; Wada, A.; Ikebe, T.; Ohnishi, M.; Mita, K.; Endo, M.; Matsuo, H.; Asatuma, Y.; Kuramoto, S.; Sekiguchi, H.; et al. Characteristics of Streptococcus suis isolated from patients in Japan. Jpn. J. Infect. Dis. 2006, 59, 397–399.
40. Chu, Y.W.; Cheung, T.K.; Chu, M.Y.; Tsang, V.Y.; Fung, J.T.; Kam, K.M.; Lo, J.Y. Resistance to tetracycline, erythromycin and clindamycin in Streptococcus suis serotype 2 in Hong Kong. Int. J. Antimicrob. Agents 2009, 34, 181–182.
41. Takeuchi, D.; Kerdsin, A.; Akeda, Y.; Chiranairadul, P.; Loetthong, P.; Tanburawong, N.; Areeratana, P.; Puangmali, P.; Nakayama, T.; Yamamoto, K.; et al. Impact of a Food Safety Campaign on Streptococcus suis Infection in Humans in Thailand. Am. J. Trop. Med. Hyg. 2017, 96, 1370–1377.
42. Nga, T.V.T.; Nghia, H.D.T.; Tu, L.T.P.; Diep, T.S.; Mai, N.T.H.; Chau, T.T.H.; Sinh, D.X.; Phu, N.H.; Chau, N.V.V.; Campbell, J.; et al. Real-time PCR for detection of Streptococcus suis serotype 2 in cerebrospinal fluid of human patients with meningitis. Diagn. Microbiol. Infect. Dis. 2011, 70, 461–467.
43. Nakayama, T.; Zhao, J.; Takeuchi, D.; Kerdsin, A.; Chiranairadul, P.; Areeratana, P.; Loetthong, P.; Pienpringam, A.; Akeda, Y.; Oishi, K. Colloidal gold-based immunochromatographic strip test compromising optimised combinations of anti-S. suis capsular polysaccharide polyclonal antibodies for detection of Streptococcus suis. Biosens. Bioelectron. 2014, 60, 175–179.
44. Zhang, X.; Wu, Z.; Wang, K. Diagnosis of Streptococcus suis Meningoencephalitis with metagenomic next-generation sequencing of the cerebrospinal fluid: A case report with literature review. BMC Infect. Dis. 2020, 20, 884.
45. Thu, I.; Tragoolpua, K.; Intorasoot, S.; Anukool, U.; Khamnoi, P.; Kerdsin, A.; Tharinjaroen, C.S. Direct detection of Streptococcus suis from cerebrospinal fluid, positive hemoculture, and simultaneous differentiation of serotypes 1, 1/2, 2, and 14 within single reaction. Pathogens 2021, 10, 996.