JOURNAL OF CLINICAL MICROBIOLOGY, Oct. 1984, p. 833–835
0095-1137/84/100833-03$02.00/0

Vol. 20, No. 4

Sporadic Occurrence of Zoonotic Swine Influenza Virus Infections

CLIFFORD C. DACSO,[1] ROBERT B. COUCH,[1]* HOWARD R. SIX,[1] JAMES F. YOUNG,[2]† JOHN M. QUARLES,[3] AND JULIUS A. KASEL[1]

Influenza Research Center, Department of Microbiology and Immunology, Baylor College of Medicine, Houston, Texas 77030[1]; Department of Microbiology, Mount Sinai School of Medicine, New York, New York 10029[2]; and Department of Microbiology, Texas A & M University, College Station, Texas 77844[3]

Received 14 May 1984/Accepted 5 July 1984

Two infections by swine influenza virus, antigenically similar to A/New Jersey/76 (H1N1) virus, were detected during community epidemics with other influenza viruses. The swinelike viruses were obtained during virological surveillance of acute respiratory illnesses, and the clinical symptoms of these two patients were similar to those caused by other respiratory viruses. Both patients reported contact with swine a few days before onset of illness, but in one case it was brief. Serological studies suggested that one patient may have transmitted the virus to his roommate, but spread into the community was not indicated.

Type A influenza virus was first isolated from swine in 1931 (8). Retrospective serological surveys for antibody to this virus indicate that viruses bearing similar antigens were responsible for the 1918 influenza pandemic. Since then, swinelike influenza viruses have regularly caused epizootics among swine (12), but until recently, evidence for infections in humans has been mostly limited to serological data among persons with exposure to swine (3, 5, 10). Sporadic cases of infection and illness caused by swinelike viruses have been reported recently, and in 1976 a localized outbreak of infection and illness caused by a swinelike virus occurred at Fort Dix, N.J. (7, 9, 11).

This report describes two cases of swine influenza virus infections that were detected in southeastern Texas during epidemics of influenza in human populations. Swine influenza virus was isolated from both cases.

(Under the new classification scheme, viruses isolated from animals other than humans are not distinguished from viruses circulating in humans. Thus, HswlN1 viruses now belong in the H1N1 subtype [2].)

Case 1. A 20-year-old college student was in good health before 19 February 1979, when he experienced sudden onset of an acute illness consisting of fever to 39°C, headache, coryza, and pharyngitis. On day 2 of illness, he visited the student health center, a throat swab specimen was obtained, and symptomatic therapy was given. On day 3 of illness, he was hospitalized overnight in the health center because of continued fever. Recovery was thereafter uneventful. He was clinically well 5 days after the onset of symptoms.

The throat swab specimen of the patient yielded a hemadsorbing agent in primary rhesus monkey kidney tissue culture, but indirect immunofluorescent identity tests with antisera to current influenza strains (A/USSR/90/77 [H1N1] [A/USSR], A/Texas/1/77 [H3N2], and B/Hong Kong/5/72) were negative. Allantoic fluid harvested from a passage of the agent in 10-day-old embryonated chicken eggs contained a hemagglutinating agent that was identified as an A/New Jersey/8/76 (H1N1)-like virus (A/NJ) in hemagglutination inhibition (HI) tests. This identity was confirmed by the World Health Organization Collaborating Laboratory for Influenza in Atlanta, Ga., and it was given the strain designation A/Texas A & M/26/79 (A/TAM). Sera obtained 2 and 5 months after the illness episode revealed a fall in serum HI antibody from 1:16 to 1:4 to A/TAM virus and 1:8 to <1:4 to A/NJ virus. The titer of antibody to A/USSR virus was 1:4 in both sera, and complement fixation antibody was not detected in either serum.

Comparison of the viral proteins from the A/TAM strain to those derived from other type A viruses indicated that it most closely resembled viruses isolated from swine (Fig. 1). The protein patterns for strains representative of the H1N1 and H3N2 subtypes circulating in human populations at that time are shown in lanes 1 and 2, respectively. The A/TAM isolate (lane 3) was distinguished from these strains by a double nucleoprotein band and by a smaller nonstructural 1 protein. These characteristics were also observed in a Fort Dix swinelike isolate, A/New Jersey/11/76, and in a contemporary swine isolate, A/Swine/Wisconsin/355/76, as shown in lanes 4 and 5, respectively. Nucleotide-sequencing studies have recently shown that the smaller molecular size of the nonstructural 1 protein is the result of large deletions in the amino acid sequence at the carboxy termini due to spontaneous nonsense mutations resulting in premature termination of the proteins (6).

Epidemiological observations. During the week before onset of acute illness, the patient had served as an attendant at the swine barn of a major regional livestock show. He slept in the livestock area and reported contact with over 2,000 swine; he recalled none of them as being ill, although 1 pig had died of an unknown cause. The patient was an animal science student and denied having ever received an influenza vaccine.

The patient's only close contact during the illness period was with his roommate, who denied any respiratory illness. Sera obtained at the same time as the patient's revealed HI antibody titers of 1:32 for A/TAM and A/NJ virus and 1:16 for A/USSR virus in both the early and late serum. The roommate was also an animal science major and had had frequent contact with swine in the past. The relative significance of a titer of 1:32 in this population was evaluated by determining serum HI antibody titers in 71 other animal science students (Table 1). Five students had antibody to A/NJ virus, but three of these also had antibody to A/USSR virus, and two reported prior vaccination with A/NJ-inactivated vaccine. The estimated past exposure of the student to swine was not related to detection of A/NJ antibody. Thus,

* Corresponding author.
† Present address: Department of Molecular Genetics, Smith Kline & French Laboratories, Philadelphia, PA 19479.

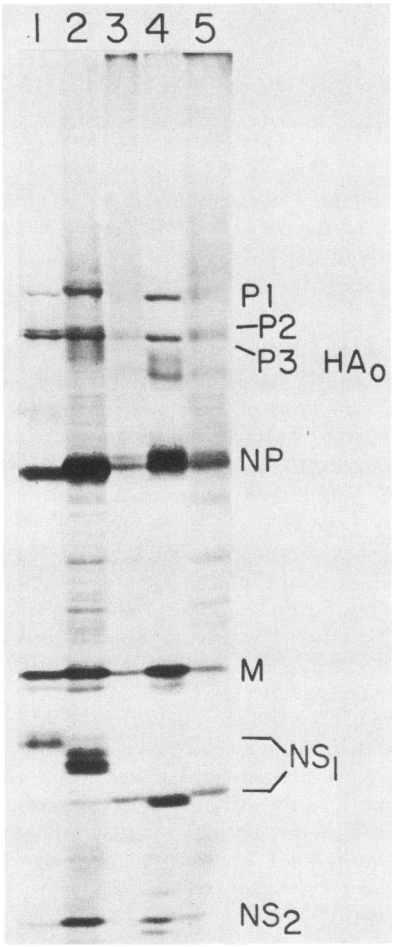

FIG. 1. Autoradiogram of sodium dodecyl sulfate-polyacrylamide gel electrophoresis patterns of ^{35}S-labeled influenza virus protein. MDCK cells were infected with virus in a medium containing [^{35}S]methionine (6). The cells were then solubilized with sodium dodecyl sulfate and β-mercaptoethanol and boiled for 3 min, and the proteins were separated on linear 7 to 14% polyacrylamide gels. Lanes 1 through 5 contained proteins derived from A/Maryland/2/80 (H1N1), A/Bangkok/1/79 (H3N2), A/New Jersey/11/76 (H1N1), A/TAM, and A/Swine/Wisconsin/355/76 (H1N1), respectively. HA_0, Hemagglutinin; NP, nucleoprotein; M, matrix protein; NS_1 and NS_2, nonstructural 1 and 2 proteins.

a titer of 1:32 was unusual and suggested that a transmission between roommates may have occurred.

Virological surveillance was being conducted at the university, and throat swab specimens were collected from students seeking medical attention for febrile respiratory diseases. During the surveillance period, 435 specimens from other students with febrile respiratory disease were tested for influenza virus, and 90 yielded virus which were A/Brazil/11/78 (H1N1)-like viruses. The isolate from the patient occurred during the last week of a 5-week influenza outbreak; no other isolate of swine virus were obtained before or after that period.

Case 2. In February 1980, a 6-year-old healthy boy who lived in suburban Houston experienced an acute onset of fever, coryza, pharyngitis, and otitis media. In addition, he experienced a brief episode of diarrhea. A throat swab specimen taken by his physician was submitted for virus culture, and an A/NJ-like virus was identified in HI tests as described above. Again, protein analysis suggested that the virus was of swine origin, and the identity was confirmed by the World Health Organization Collaborating Laboratory for Influenza. The physician declined the request for a specimen of the patient's serum.

Epidemiological findings. The patient had no history of close environmental exposure to swine, but he had visited a large regional livestock show 2 days before the onset of his illness. Although he visited the swine area, his parents denied that he had had any physical contact with animals during that visit.

No respiratory illness occurred in the parents or sibling in the time period surrounding the patient's illness. Sera obtained 6 weeks after the episode from both parents and the office nurse who obtained the throat swab specimen were negative for A/NJ antibody.

During the 1979 to 1980 respiratory disease season, specimens were obtained from individuals seeking health care in Houston from selected public clinics and private physicians as part of community surveillance maintained by the Influenza Research Center. A total of 342 specimens yielded influenza viruses similar to B/Singapore/222/79, and 6 yielded influenza A/Brazil/11/78 (H1N1)-like viruses. No other isolates of H1N1 viruses were obtained.

Discussion. Two cases of acute swine influenza virus infection in humans were documented. Both patients reported contact with swine; in one case it was intensive, and in another it was brief. Secondary transmission from these cases to immediate contacts may have occurred but could not be documented; no spread occurred in the populations surveyed. Thus, the cases appear to be sporadic, isolated infections. Illnesses were clinically indistinguishable from those caused by other respiratory viruses, including other influenza viruses. Beare and Craig (1) previously reported that A/NJ virus given by intranasal inoculation to volunteers produced a clinical syndrome similar to that resulting from infection with other H1N1 viruses.

Evidence of infection of humans with swine virus has been suggested from serological studies in the past, but occurrence of any illness was uncertain. Isolation of swine virus from a human was first reported in 1974; the subject was a 14-year-old boy with Hodgkin's disease who had died of viral pneumonia (9). In 1976 a localized outbreak of swine virus infection among U.S. Army recruits occurred at Fort Dix, N.J. (11). Swinelike virus was isolated from five recruits with acute respiratory illness, in one case from the lung of a recruit who died with pneumonia. Serological assessment subsequently provided evidence that ca. 500 recruits were infected with this virus in a 4-week period. Although the swine virus clearly spread from person to person at Fort Dix, the outbreak did not spread to neighboring civilian areas. Three additional isolates were obtained

TABLE 1. Prevalence of HI antibody titers to H1N1 viruses among animal science students in 1980

Test virus	No. (%) with the following titer[a]:		
	<4–4	8–16	≥32
A/TAM[b]	66 (96)	3 (4)	0 (0)
A/NJ	65 (93)	5 (7)	0 (0)
A/USSR	57 (83)	12 (17)	2 (3)

[a] Titers are expressed as the reciprocal of the serum dilution that inhibited hemagglutination.

[b] Two sera were not tested with the A/TAM virus, and one of these was not tested with the A/NJ virus because of insufficient volume.

in 1976 from persons with acute influenza, and each had contact with swine on a midwestern farm. Secondary transmission to one other person from these cases was suggested by serological studies. More recently, swinelike virus was recovered from an immunocompromised child who had died from viral pneumonia and who had no known contact with swine (7). The child was thought to have acquired the virus by person-to-person transmission, but serological evaluation of patient contacts suggested that if further spread of the virus occurred, it was minimal. Thus, it appears that swine influenza virus can be transmitted from swine to humans and cause acute influenza, including pneumonia, but such human infections appear to have limited potential for spreading to other humans.

Both isolates of swine virus reported here were obtained during community epidemics with other influenza viruses. Spread of swine virus from the present cases into the community may have been limited by the dominance of other influenza strains circulating at the time. It has been speculated that a concurrent epidemic of H3N2 viruses may have limited spread at Fort Dix by some mechanism of viral interference. Host immunity was probably not a contributing factor because other H1N1 viruses have regularly produced epidemic diseases in these same populations since their appearance in 1977. All the factors that influence transmissibility of influenza viruses between individuals have not been defined; it is likely that viral factors are involved, and it appears that swine influenza virus lacks these factors. In this regard, analysis of the isolates indicated that the genes were similar to isolates from swine (J. Young, personal communication). The potential for swinelike viruses to acquire "transmissibility" factors would be through genetic reassortment with other type A influenza viruses. Genetic exchange between viruses of two type A subtypes (H1N1 and H3N2) circulating simultaneously in humans has been previously documented (4, 13), and mixed infections with viruses of both subtypes have been reported. However, despite the simultaneous circulation of viruses of both subtypes in human populations since 1977, such occurrences appear to have been rare events. Although sporadic infections of humans with swine influenza viruses have clearly occurred when other type A viruses were epidemic in the population, on two occasions (Fort Dix and Texas A & M) progeny infections with viruses possessing swine surface antigens that would indicate transmissibility among humans comparable to human viruses did not occur.

This work was supported by Public Health Service contract AI-32685 from the National Institute of Allergy and Infectious Disease. Support for J.F.Y. was from grant AI-11823 to Peter Palese.

We thank Kay Brown for typing the manuscript.

LITERATURE CITED

1. **Beare, A. S., and J. W. Craig.** 1976. Virulence for man of a human influenza A virus antigenically similar to "classical" swine virus. Lancet **ii**:4–5.
2. **Centers for Disease Control.** 1980. Influenza nomenclature. Morbid. Mortal. Weekly Rep. **42**:514–515.
3. **Kendal, A. P., G. R. Noble, and W. R. Dowdle.** 1977. Swine influenza viruses isolated in 1976 from man and pig containing two coexisting subpopulations with antigenically distinguishable hemagglutinins. Virology **82**:111–121.
4. **Nakajima, S., N. J. Cox, and A. P. Kendal.** 1981. Antigenic and genomic analysis of influenza A (H1N1) viruses from different regions of the world, February 1978 to March 1980. Infect. Immun. **32**:287–294.
5. **O'Brien, R. J., G. R. Noble, B. C. Easterday, A. P. Kendal, D. M. Shasby, D. B. Nelson, M. A. W. Hattwick, and W. R. Dowdle.** 1977. Swine-like virus infection in a Wisconsin farm family. J. Infect. Dis. **136**(Suppl):S390–S396.
6. **Parvin, J. D., J. F. Young, and P. Palese.** 1983. Nonsense mutations affecting the length of the NS1 nonstructural proteins of influenza A virus isolates. Virology **128**:512–517.
7. **Patriarca, P. A., A. P. Kendal, P. C. Zakowski, N. J. Cox, M. S. Trantman, J. D. Cherry, D. M. Auerbach, J. McCusker, R. R. Belliveau, and K. D. Kappus.** 1984. Lack of significant person-to-person spread of swine influenza-like virus following fatal infection in an immunocompromised child. Am. J. Epidemiol. **119**:152–158.
8. **Shope, R. E.** 1931. Swine influenza. III. Filtration experiments and etiology. J. Exp. Med. **54**:373–385.
9. **Smith, T. F., E. O. Burgert, Jr., W. R. Dowdle, G. R. Noble, R. J. Campbell, and R. E. Van Scoy.** 1976. Isolation of swine influenza virus from autopsy lung tissue of man. N. Engl. J. Med. **295**:708–710.
10. **Thompson, R. L., M. A. Sande, R. P. Wenzel, C. H. Hoke, Jr., and J. M. Gwaltney.** 1976. Swine influenza infection in civilians. N. Engl. J. Med. **294**:714–715.
11. **Top, F. H., Jr., and P. K. Russell.** 1977. Swine influenza A at Fort Dix, New Jersey (January–February 1976). IV. Summary and speculation. J. Infect. Dis. **136**(Suppl):S376–S380
12. **Woods, G. T.** 1972. Evidence for periodicity of swine influenza in Illinois—1963 to 1970. Am. Rev. Respir. Dis. **106**:535–540.
13. **Young, J. F., and P. Palese.** 1979. Evolution of human influenza A viruses in nature: recombination contributes to genetic variation of H1N1 strain. Proc. Natl. Acad. Sci. U.S.A. **76**: 6547–6551.