An outbreak of Asian flu in a "closed" population which had been adequately protected by prior vaccination is reported. The soil in which the outbreak developed was provided by unvaccinated newcomers. The authors discuss the significance of their finding.

ASIAN INFLUENZA: ISOLATED OUTBREAK WITHIN A LARGE CLOSED POPULATION

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A SHARPLY localized outbreak of febrile illness occurred in February, 1960, in a single building of an institution with 25 widely separated patient buildings.* The evolution of this epidemic, the serologic findings in acute and convalescent serums, the isolation and identification of the etiologic agent, and the finding that unvaccinated individuals may have served as the focal point for the outbreaks, are the subject of this report.

Clinical Findings and Approach to the Problem

Sixteen patients fell suddenly ill between noon and 4:00 p.m. on February 5, 1960. The major symptoms were high fever, chills, flushed face, sore throat, paroxysmal coughing, nausea, and diarrhea. Prostration in some patients was extreme and parenteral fluids were administered. Physical examinations failed to reveal localizing signs, and the presumptive diagnosis of a viral disease was made. In the hope of future identification, nasal and pharyngeal swabs were taken on ten of the ill patients, and saline suspensions prepared which were sealed into glass ampules and stored at −60° C. Blood specimens were drawn from the same patients, serum harvested and stored at −20° C.

The following day, all patients were reexamined and although a few new patients had fallen ill during the night, there were still no localizing evidences of disease. Some of the originally ill patients were brighter and their fevers had abated.

The daily occurrence of illness is shown in Figure 1. The cases of fever that antedated the "outbreak" on February 5, probably represent the true beginning of the epidemic, but the explosive occurrence of illness in 16 patients identified the situation. Febrile illness of variable duration (Figure 2) in 64 of the 275 patients in this building during a period of approximately one month represents a 23 per cent attack rate.

Materials and Methods

Serologic Tests

The hemagglutination-inhibition (HI) test with the modification that the 18th embryonated egg passage of A/Jap 305/57 is used as antigen has been reported previously.[1-3] Hemagglutinin ob-

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tained from this egg passage level is not susceptible to nonspecific inhibitors frequently demonstrable in serum. Four-week convalescent serums from the same ten patients from whom acute phase serums were obtained were analyzed for hemagglutination - inhibition antibody (HAI) titers against Asian influenza virus.

The HAI titers were supplemented with complement-fixing antibody (CFA) tests using A/Jap 305/57 (anti-V) as antigen[4] and neutralizing antibody (NA) determinations. NA titers were determined with embryonated eggs infected with approximately 100, 50 per cent infectious doses (ID 50) of A/Jap 305/57 virus.

Virus isolation attempts were carried out as follows: A portion of each saline swab suspension was treated with 500 units of penicillin and 250 micrograms of streptomycin per ml and injected into both the allantoic and amniotic cavities of embryonated chicken eggs. Following incubation at 36.5° C for 72 hours, fluids from both these cavities were examined for the presence of hemagglutinins with chicken erythrocytes. Two additional embryo passages of combined allantoic and amniotic fluids were made before a specimen was considered negative for virus content.

Results

Data summarized in Table 1 show that there were sharp rises in Asian influenza HAI, CFA, and NA titers in the majority of the patients. All the titers for any particular test were determined in a single day's run. The finding of no HAI antibodies in the acute phase serums of seven of nine patients and no CF (anti-V) antibodies in eight of ten patients was in sharp contrast to the serologic findings in patients 2 and 3. Such negative serologic responses were unanticipated since our hospital population was exposed to Asian influenza in 1957, was totally vaccinated with monovalent Asian influenza vaccine in 1957, and again with polyvalent influenza vaccine in 1958. Review of the histories of these patients indicated that whereas patients 2 and 3 had been previously immunized, the other patients had entered the hospital subsequent to any of the aforementioned influenza experience.

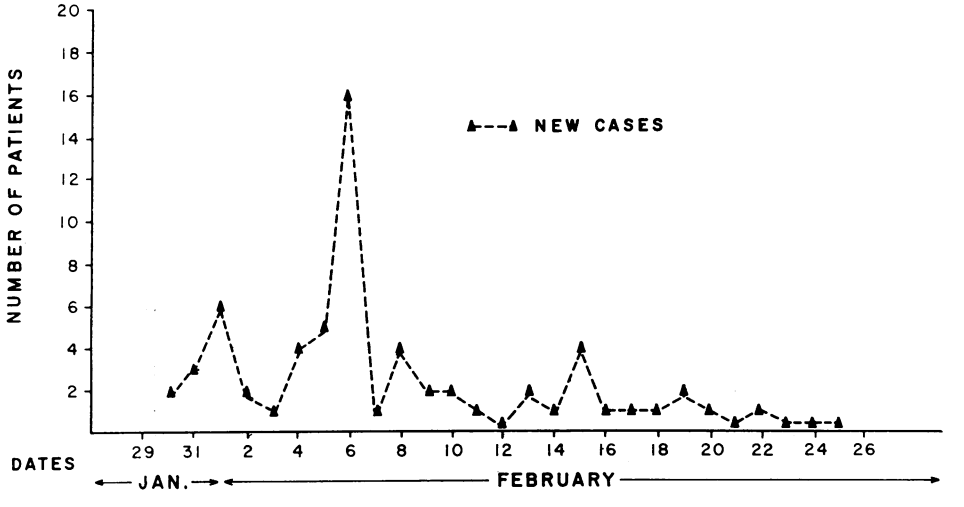

Figure 1—Incidence of Illness During Epidemic

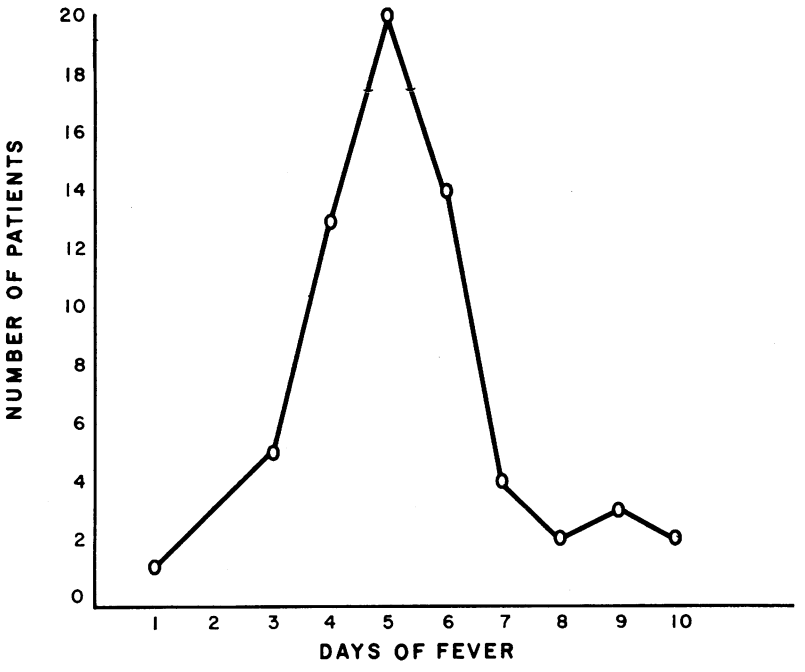

Figure 2—Duration of Individual Febrile Illnesses During Epidemic

Table 1—Asian Influenza Virus Antibody Titers of Patients with Upper Respiratory Illness During February, 1960

Patient Number	Asian Influenza Virus Vaccine	Antibody Titers (Reciprocal)					
		Hemagglutination Inhibition		Complement-Fixing		Neutralizing	
		Acute	Conv.	Acute	Conv.	Acute	Conv.
1	None	—	—	<2	8	—	—
2	3/5/58 1/9/59	32	64	64	48	10	10
3	10/18/57 1/7/59	16	16	6	8	20	20
4	None	<2	32	<2	16	—	—
5	None	<2	1024	<2	128	10	60
6	None	<2	128	<2	32	10	80
7	None	<2	64	<2	48	10	40
8	None	<2	256	<2	128	10	20
9	None	<2	32	<2	12	—	—
10	None	<2	32	<2	16	10	20

The serologic responses following illness in seven patients clearly indicated Asian influenza as the probable cause of the epidemic. Further, however, Table 2 shows that virus isolates were recovered from the nasopharyngeal swabs of patients 2, 4, 5, and 10. The serums of patients 2, 4, 5, and 9 were tested against all four virus isolates in a single HI test. (Serum from patient 10 had been used up by previous testing so serum from patient 9 was substituted.) The acute phase serum sample of patient 2 showed an appreciable HAI titer (1:40) against all isolates and this patient had been previously vaccinated with Asian influenza vaccine. Although Asian influenza virus was isolated from the nasopharyngeal swab of this patient taken at the time of acute illness, no rise in HAI titer was detected in the convalescent serum. In contrast to this finding, patients 4, 5, and 9, who had not been previously vaccinated showed no antibodies in the acute serums, but significant rises in Asian influenza HAI titers occurred in response to their illnesses. The situation with respect to patient 3 was identical with that of patient 2 except that virus was not isolated.

The acute and convalescent serums of patients 2, 4, 5, and 9 showed comparable levels of Asian influenza antibodies when the newly isolated strains of virus and a known reference strain of Asian influenza virus were used as antigens (Table 2). None of the virus isolates were susceptible to nonspecific inhibitors of hemagglutination as evidenced by lack of reactivity with acute serum samples of patients 4, 5, and 9. The same HAI titers were obtained using a standard rooster Asian influenza reference serum* and the four newly isolated strains. Finally, quantitatively similar CFA titers (1:32 – 1:64) were observed when a reference A/Jap 305/57 (anti-V) guinea pig serum was tested with the four newly isolated strains and the reference strain as antigens.†

The foregoing laboratory studies leave little doubt that the observed outbreak was due to the Asian influenza virus

* The authors are indebted to Major E. L. Buescher, chief, Department of Virus Diseases, Walter Reed Army Hospital, Washington, D. C., for having supplied the reference serum.

† The authors are indebted to Dr. Florence Lief, Childrens Hospital; Philadelphia, Pa., for having supplied this reference serum.

NOTE: No CF reaction occurred when PR-8 and Lee influenza virus strains were employed as antigens with this serum.

Table 2—Asian Influenza Virus Hemagglutination-Inhibition Antibody Titers Determined with Homologous and Heterologous Virus Isolates

Virus	Hemagglutinin: Detected in Egg Passage	Hemagglutinin: Titer	Hemagglutination-Inhibition Antibody Titers (Reciprocal): Serum No. 2 Acute	Serum No. 2 Conv.	Serum No. 4 Acute	Serum No. 4 Conv.	Serum No. 5 Acute	Serum No. 5 Conv.	Serum No. 9* Acute	Serum No. 9* Conv.	Ref. Serum A/Jap 305/57
No. 2	3	256	40	40	<2	20	<2	160	<2	40	400
No. 4	2	256	40	20	<2	20	<2	160	<2	40	400
No. 5	2	128	40	40	<2	40	<2	320	<2	40	800
No. 10	1	128	40	40	<2	20	<2	160	<2	80	800
Ref. A/Jap 305/57			40	20	<2	20	<2	320	<2	40	400

* Serum No. 10 not available in sufficient amount for testing.

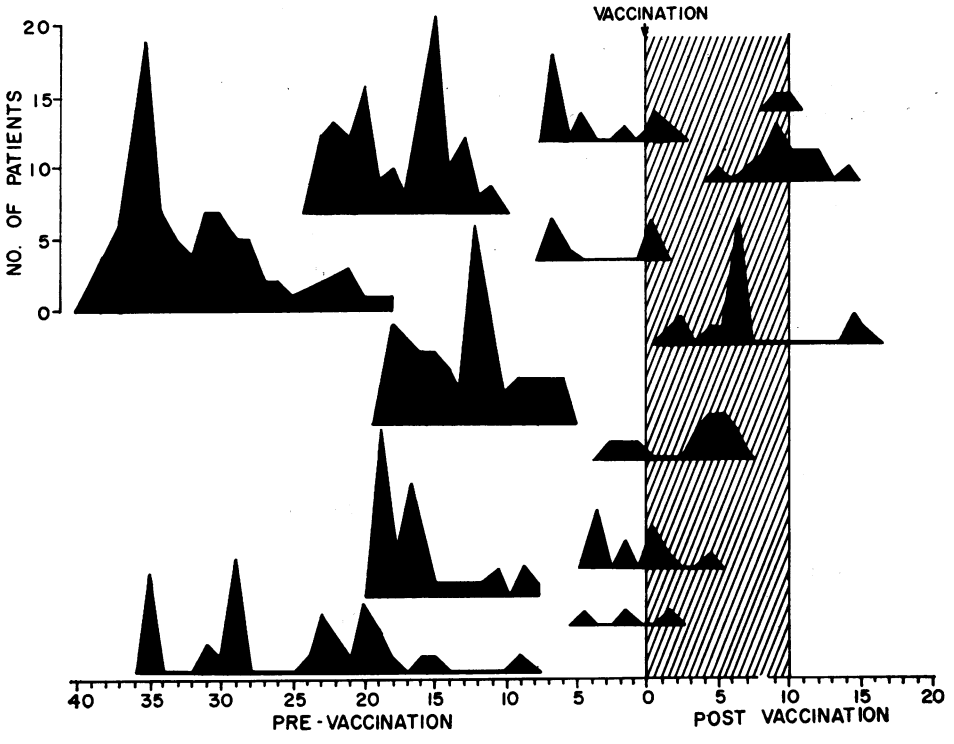

Figure 3—Asian Influenza 1957: Pattern of Incidence of New Cases by Building

and that the strain of virus isolated was antigenically similar to or identical with strains isolated during the 1957 pandemic.

Discussion

The "single building" outbreak reported here stands in sharp contrast to the "multibuilding" epidemic in this same institution during the fall of 1957. As a result of the advance notice of the expected occurrence of Asian influenza (1957) and the ample evidence of disease in the surrounding community, the entire institutional population was carefully observed for occurrence of febrile illnesses. In the presence of an epidemic the occurrence of fever and disability has been regarded as a rough index of attack rate by a prevalent cause of disease.[5] The differing patterns of febrile illnesses in 13 of the 25 buildings that house the hospital population are shown in Figure 3. Total hospital vaccination with monovalent Asian influenza virus vaccine concurrently with the epidemic was too late to affect the occurrence of illness during the first wave of disease.

In 1958 the entire population of the hospital was revaccinated with polyvalent influenza virus vaccine. In the autumn of 1959 only the diabetic, tuberculous, and elderly patients were immunized, since significant residual Asian influenza HAI titers were detected in a large sample of the hospital population.[3] Although Asian influenza was predicted for 1959-1960, few cases were identified by virus isolation in our

metropolitan area and widespread community disease was not noted; hence it was not suspected that influenza was causing the outbreak in a single building of an institution with such a concentrated influenzal vaccine and epidemic history. The circumstances that made possible the taking of blood and the obtaining of nasopharyngeal swabs that permitted identification, long after the fact, were more or less fortuitous.

The incidence of upper respiratory illness throughout our hospital population during the winter of 1959-1960 was remarkably low, and similar clinical observations were made in a number of nearby closed hospitals that had been solidly immunized against influenza. Accordingly, the attack rate of 23 per cent (64 patients) in this sharply circumscribed epidemic was all the more unusual. Of the 275 patients in the building, 219 were vaccinated and 56 (20 per cent) were not vaccinated by reason of recent admission to the hospital. Of the 64 patients who were ill, 40 were vaccinated and 24 (38 per cent) were unvaccinated. The attack rate of 23 per cent in this single building outbreak was comparable to the 22 per cent attack rate observed in 1957 when the entire population was regarded as susceptible.

Sixteen patients falling ill in a single day marked the "explosive" onset of an epidemic and serums of ten of these patients were studied. Seven of these ten patients failed to show detectable HAI or complement-fixation (anti-V) titers in acute phase serums, and five of these seven had insignificant neutralizing antibodies. It would appear that there was in this building a small susceptible group that probably served as a focus for an outbreak within a population, 80 per cent of which had been vaccinated against influenza. The high attack rate at least suggests that the virulence of the infecting virus was sufficient to override the immunity of some of the vaccinated patients who had titers ordinarily regarded as protective. In retrospect, it would have been highly desirable to study serologically the entire population of the building, but at the time of the outbreak, no one remotely suspected Asian influenza and the etiology of the epidemic was established many months after the fact.

The likelihood of such a group of susceptible individuals occurring in the future has been reduced by the establishment of a policy that all newly admitted patients be vaccinated with polyvalent influenza vaccine, 1 ml subcutaneously at time of admission and 1 ml again at six or eight weeks.

Illness that was clinically indistinguishable from that of the foregoing group of seven patients, occurred in patients 1, 2, and 3 (Table 1). Patient 2 had a titer of 1:32 at the time of onset of illness and an insignificant rise was observed in the four-week convalescent serum, despite Asian influenza virus being isolated from the nasopharyngeal swab. Patient 3 also had a pre-illness titer and showed no rise at four weeks despite illness identical to patient 2. Patient 2 had a titer of 1:32 which is greater than the 1:14 regarded by some as indicating immunity[6] and comparable to those regarded as protective by others.[7] Perhaps, as many contend, HAI titers are an index of immune response and not a measure of protection. It is possible that patient 2 was a carrier of Asian influenza virus and was actually suffering from some other febrile disease. The carrier state of influenza has been mentioned, but few facts are available.

The attack rate of 64 of 275 (23 per cent) in a closed population that had been better than averagely vaccinated was unusually high. Although only 10 of the 64 sick patients were studied serologically or culturally, there seems to be no reasonable doubt that the circumscribed outbreak observed was en-

tirely or predominantly due to Asian influenza.

Summary and Conclusions

A sharply circumscribed outbreak of febrile illness, with an attack rate of 23 per cent occurred in one of 25 buildings that house a closed population of 4,600 persons. This outbreak was identified by virus isolation and serologic studies as due to Asian influenza. The explosive illness in a single building was in sharp contrast to the general freedom from febrile illnesses of the large hospital population during this same period.

An epidemic of Asian influenza in this population was unexpected, since this disease hit the institution in 1957-1958 with an attack rate of 22 per cent, and subsequently an active vaccination program has been carried out in 1958 and 1959. The absence of Asian influenza antibodies in serums from patients in this epidemic led to the discovery that these patients were recent admissions to the hospitals and had escaped the general vaccination programs. It is strongly recommended that patients admitted to closed population hospitals be vaccinated against influenza at the time of admission. The need for further definition of the protective level of influenza antibodies is indicated and the question of a carrier state in patients who have high antibody titers is raised.

During the winter of 1959-1960 there were few clearly identified epidemics of Asian influenza in the mid-Atlantic states, and for this reason the sharply defined epidemic within our closed population has special interest.

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