

## SEROLOGICAL STUDIES DURING THE 1953 EPIDEMIC OF INFLUENZA A IN NEW YORK STATE

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(With 4 Figures in the Text)

A number of workers have shown that antibodies to the influenza A viruses which are demonstrable in the sera of normal adults undergo periodic fluctuations in titre related to epidemic occurrence of the disease. The rise in antibodies accompanying infection and demonstrable by neutralization, agglutination-inhibition and complement-fixation tests is used as a method of diagnosis which is admitted to be of greater sensitivity than actual recovery of virus from the throat. Studies of the population during an epidemic have also revealed the existence of subclinical infection with rise in antibodies comparable to that occurring in those suffering clinical illnesses. But surveys of sera from large samples of the population show no general upward shift in antibody levels unless an actual epidemic occurs (Martin, 1940). The studies made by Francis, Magill, Rickard & Beck (1937), Hoyle & Fairbrother (1937), Rickard, Lennette & Horsfall (1940) and Martin (1940) also indicate the relative impermanence of the enhanced antibody levels consequent upon an epidemic. A relatively rapid decrease in antibody is shown both by the neutralization and complement-fixation tests during the 3-6 months after an epidemic and then a slower fall occurs until the next epidemic again causes a rise in titres. There have, however, been relatively few studies on large samples of populations situated in different geographical areas before and during an outbreak.

The study of the spread of influenza in different parts of the world has thus far depended upon recovery of actual strains of influenza virus from garglings of clinical cases of influenza. Such studies as those made by the World Health Organization suggest that a geographical spread of a particular strain or group of strains does in fact occur and that an epidemic of influenza may originate from a distant focus of infection (Chu, Andrewes & Gledhill, 1950; Isaacs & Andrewes, 1951). It was felt that a serological study based upon the examination of sera from a cross-section of the population might reveal the chronological occurrence of influenza virus A infection even more accurately than the isolation of virus. Such a study might, moreover, demonstrate the existence of subclinical infection in an area where an outbreak was undetected clinically. It was hoped that some light on the mode of spread of influenza might thereby be obtained. The present study was begun in December 1952 at a time when influenza had not been reported to be present in New York State, or for that matter in the United States as a whole. Because of the delay in dissemination of information and isolation of virus, it was

not known that an epidemic had in fact begun in December, although it was then located in the Middle Western States, and outbreaks in New York State were not detected clinically before January 1953.

#### METHOD OF STUDY

Sera were obtained from hospital patients in five different centres. These centres are shown on Fig. 1, an outline map of New York State. They comprised:

(i) Albany—a town of about 125,000 people on the main artery of communication from New York City to the West.

(ii) Saranac Lake, Lake Placid and Tupper Lake—small communities in the Adirondacks, largely cut off from other places during the winter except that at week-ends visitors arrive by train from New York City for winter sports.



Fig. 1.

(iii) St Lawrence County—an area of small towns and villages on the northern side of the Adirondacks separated from Canada by the St Lawrence river.

(iv) Watertown—a small township to the west of the Adirondacks chiefly in contact with the western parts of New York State.

(v) Cooperstown—a rural community with relatively poor contact with other areas.

The pathologists in all these areas collected sera obtained for routine Wassermann test irrespective of the clinical diagnosis and which did not react in the complement-fixation test for syphilis. Batches of these sera were received weekly at the Laboratories of the New York State Department of Health at Albany. The

sera, which were re-inactivated at 56° C. for 30 min. before test, were stored frozen at -5° C. until use. The sera were examined by the method of complement-fixation with 'soluble' influenza virus A antigen based on the method of Hoyle (1948). The 'soluble' antigen was prepared from the allantoic membranes of hens' eggs inoculated intra-allantoically with PR8 virus. After harvesting, the membranes were frozen and thawed, ground to a pulp and centrifuged. Supernatant fluid was frozen and dried after preliminary absorption with fowl red cells to remove virus particles. The antigen was standardized by the method of titration of antigen and also of serum using convalescent human serum samples obtained in 1951.

The technique of the complement-fixation reaction was a modification of that introduced by Wadsworth, Maltaner & Maltaner (1931, 1938) and Wadsworth (1939, 1947) for the routine diagnosis of syphilis and other infections. The complement, amboceptor and sheep red blood cell suspension were prepared and standardized according to Wadsworth (1947), and the volumes of the reagents used were the same.

The optimal antigen dose was determined in the presence of three and four and one-half 50% units of complement using twofold serial dilutions of immune serum (1:8-1:256) and antigen (1:2-1:256) with suitable controls. The optimal amount of antigen was considered to be that dilution which gave the maximum degree of fixation.

All sera were first examined by a screening test in which one or two dilutions only of serum (1:4 and 1:16) were used with the optimal dose of antigen. Fixation was performed for 1 hr. at 37° C. using four and one-half 50% units of complement. Sera giving any degree of fixation at 1:4 dilution ('positive' sera) were then re-tested in serial twofold dilutions (1:4-1:64) with the appropriate optimal dilution of antigen and three 50% units of complement with fixation for 24 hr. at from 3 to 6° C. Controls of known positive sera, normal antigen, complement, antigen alone, the test sera alone, and sensitized cells were included in each group of tests.

The results were evaluated in terms of the number of 50% units of complement fixed, and were expressed as the extrapolated values for twofold serial dilutions of serum based on the conversion factors established for the complement-fixation test for syphilis (Wadsworth, 1947). For each batch of sera those giving any degree of fixation in the screening test were regarded as 'positive' provided that the controls were satisfactory. Those giving no fixation at 1:4 dilution of serum were classified as 'negative'. Individual titres of sera grouped as 'positive' were calculated on the cold-fixation test for comparison with each other and with the results obtained with certain other samples.

A series of forty-one pairs of sera which were obtained from patients with proven influenza A in institutional outbreaks in New York State were also examined. These patients had all exhibited at least a threefold increase in antibody titre with the usual allantoic fluid C.F. test as used in routine influenza virus diagnosis in the Laboratories of the New York State Department of Health. The convalescent sample of serum was compared with that obtained in the acute stage of illness, and all sera were re-examined by the cold-fixation test with 'soluble' antigen as outlined above.

A further sixty-five single specimens of serum which had failed to exhibit any degree of fixation with soluble antigen in the 1 hr. screening-test were also examined by the cold-fixation method in order to establish possible antibody titres in sera originally classified as 'negative'.

Finally, fifty sera collected in a State school in Syracuse during March 1953, 7 weeks after a localized epidemic from which influenza virus A was recovered, were tested by the screening technique and by full titration as above in order to indicate the results likely to be obtained in an area of true epidemicity of the virus. The sera were collected at random irrespective of a history of recent influenza.

No attempt was made to study influenzal antibodies against the influenza B viruses.

RESULTS

Table 1 shows the results of the complement-fixation screening-test on all the batches of sera collected from the six different areas during the entire period of the study. The results of sera received during individual weeks from December 1952 to March 1953 were consolidated into 4-week periods. All sera giving evidence of fixation of complement at 1:4 dilution of serum are included as 'positive', the percentage of the totals being expressed in the separate column. It is necessary to consider separately the results from the different areas.

Table 1. *Results of the influenza A complement-fixation test used as a screening procedure with single specimens of serum from different geographical regions in New York State*

	Albany			Watertown			Cooperstown		
	No. tested	No. pos.	% pos.	No. tested	No. pos.	% pos.	No. tested	No. pos.	% pos.
1953									
Four-week periods, weeks beginning:									
14 Dec.-4 Jan.	249	18	7.2	—	—	—	96	12	12.5
11 Jan.-1 Feb.	198	16	8.0	310	31	10.0	326	17	5.2
8 Feb.-1 Mar.	151	13	8.6	264	44	16.6	387	40	10.3
8 Mar.-29 Mar.	86	17	19.7	59	7	11.8	121	19	15.7
Single collections of sera:									
May	148	23	15.5	—	—	—	—	—	—
June	99	11	11.1	—	—	—	—	—	—
July	70	4	5.7	90	1	1.1	—	—	—
Sept.	100	5	5.0	—	—	—	—	—	—
Total numbers of sera	1101			723			930		
	St Lawrence County			Saranac Lake, etc.			Syracuse School		
	No. tested	No. pos.	% pos.	No. tested	No. pos.	% pos.	No. tested	No. pos.	% pos.
1953									
Four-week periods, weeks beginning:									
14 Dec.-4 Jan.	88	8	9.1	19	3	15.7	—	—	—
11 Jan.-1 Feb.	130	9	6.9	159	22	13.2	—	—	—
8 Feb.-1 Mar.	483	38	7.8	99	14	14.1	50	22	44.0
8 Mar.-29 Mar.	125	18	14.4	3	1	33.3	(single collection 7 weeks post-epidemic)		
Total numbers of sera	826			280			50		

(i) *Albany*

The largest number of sera came from the Albany area and chiefly from the Albany hospital which admits patients from Albany and adjacent regions of New York State. The percentage of positive sera increased from the previous levels of 7.2, 8.0 and 8.6 to 19.7 during March 1953. Subsequent sera collected during 3-day periods in each of the months of May, June, July and September showed a decreasing percentage of positive results—15.5, 11.1, 5.7 and 5.0. The results suggested that infection of the community with influenza virus A occurred during or before March, and this agreed with reports from practitioners suggesting that sporadic instances of influenza-like illnesses were prevalent in March. A strain of influenza virus A was in fact recovered at the Albany Hospital from the garglings of a medical student ill with influenza on 9 February. Yet, no localized outbreaks of influenza occurred in schools, students or groups of nurses, and it seems probable that if as many as 10 % of the population were affected by the virus, then most of the infections were subclinical. The rapid fall of antibodies by July to a level similar to that found in the first collections of sera was interesting and suggested that the positive results obtained with the latter sera might have been due to recent infections rather than to antibodies persisting from previous epidemics.

Compared with the published results of other authors, and particularly with those of Martin (1940), Rickard *et al.* (1940), and Hoyle & Fairbrother (1947), the percentage of positively reacting specimens in the early and later batches of sera was low. Thus the usual figure quoted for sera reacting at a dilution of 1:4 or higher for an inter-epidemic period is 20–30 %, whereas our figure was 5–9 %. This could have been due to technical or to real differences. As no reports have been made on large-scale serum surveys conducted since 1947 when the so-called influenza A prime viruses first appeared in America, there may have been a real alteration in the antibody levels in the population detected by the soluble antigen since the earlier surveys were made. Certainly, the results obtained with convalescent sera and with the institutional sera from Syracuse detailed below did not suggest that the sensitivity of the screening test used was inadequate.

(ii) *Watertown*

The highest percentage of positive sera (16.6) was obtained with those collected during February, and the January and March figures (10.0 and 11.8 respectively) were similar to the results in Albany before March. The occurrence of influenza-like illnesses in the Watertown area during January was notified in the last week of the month, and an attempt was made to recover virus from three patients visited on 27 January. The illnesses in these patients were not regarded as typical of influenza clinically and no virus was recovered. Serum specimens were obtained in the acute phase of illness, but not subsequently so that there was no serological evidence to support the clinical diagnosis. No increase in absenteeism from school was noted however in the Watertown areas, and if influenza did in fact occur in January or February, it seems to have been sporadic in incidence. Nevertheless, influenza A was identified in an Army camp adjacent to the Watertown area where a high

incidence of acute respiratory disease occurred in the week ending 14 January shortly after the arrival of troops from another area (personal communication, Armed Forces Epidemiological Board, Washington). Influenza A infections were also identified in the latter camp during the first week of January before the troop movements. Admixture of troops from the camp with civilians in Watertown was occurring when the town was visited on 27 January and the possibility of spread of influenza A to the town from 14 January onwards seems definite.

Exceptionally few positive sera were identified in samples collected in July, and no conclusions concerning the rate of decline of antibodies in this area seem permissible.

(iii) *Cooperstown*

The percentage of positive sera fluctuated month by month in the Cooperstown area, the highest level being reached in March. In this month also influenza-like illnesses were reported in the town and environs, but no outbreak was considered by practitioners to have occurred. Because the sera collected in December and early January gave a higher percentage of positive results (12.5) than those collected during the succeeding 4 weeks, the hospital records were consulted. No indication was obtained that ten of the twelve individuals whose sera had given complement-fixation had suffered from recent influenza, the hospital diagnoses being respectively: fracture, fractures, pregnancy (with delivery), vertigo, haematemesis, tiredness, myocardial infarction, cirrhosis hepatis (in a patient with chronic pulmonary fibrosis), asthma and collapse of the left upper lobe and pulmonary fibrosis following virus pneumonia 2 months previously. Apart from the three latter patients, who each exhibited respiratory disease, the other patients had no history of recent infection of the respiratory tract.

(iv) *St Lawrence County*

The samples of sera obtained from this area were drawn from hospitals serving a series of small towns and villages situated in a more widely scattered fashion than in the other areas. Again, the highest percentage of positive sera occurred in March (14.4) and the positive results before March were like those in the Albany area. No outbreaks of influenza were recorded at any time in St Lawrence County but a sporadic case of influenzal pneumonia was notified in March.

(v) *Saranac Lake region*

The sera obtained in this area were less numerous than from other areas because of the smallness of the population. Saranac Lake, Lake Placid and Tupper Lake hospitals all contributed samples obtained routinely on admission to hospital, and in addition a number of sera were obtained by Dr William Y. L. Chen of the Bureau of Epidemiology and Communicable Disease Control of the New York State Department of Health. The latter sera, 70 in all, were collected at random during a field study designed to throw some light on the epidemiological events in this area.

The high percentage of positive sera (15.7) obtained during and after the first week of January suggested the occurrence of influenza in this area. A mild out-

break of upper respiratory infection had in fact occurred among patients and staff at the Ray Brook State Tuberculosis Hospital at Saranac Lake during the first week in January. The hospital was visited on 20 January and garglings and sera were collected from a number of patients with acute respiratory disease in addition to tuberculosis. Although most of these patients had been ill for 3 days or more, two strains of influenza virus A were recovered without difficulty by inoculation of the garglings into embryonated eggs by the amniotic route. Serological tests confirmed the existence of influenza A in six of seven patients who were tested. Also at this time (20 January), cases of clinically typical influenza were visited at Lake Placid and strains of virus were recovered from specimens from two patients who also developed serological responses. There was thus no doubt at all that influenza A was present in the Saranac—Lake Placid region during the early weeks of January 1953. The field study carried out by Dr Chen during the first week of February was designed to estimate the percentage of clinical illnesses possibly due to influenza in random samples of the population at Saranac Lake, Lake Placid and Tupper Lake. It was found that some 14–17% of the surveyed populations in the two former areas, but only 5% at Tupper Lake, had experienced illnesses suggesting influenza during the 6 weeks prior to the study. However, separate analysis of the serological results obtained with the various batches of sera from hospital or random collections in the three areas did not suggest any comparable difference in exposure to influenza virus A. Thus during January and February, 10.5% of 152 sera from Saranac Lake, 19% of 74 sera from Lake Placid and 16.1% of 44 sera from Tupper Lake were positive in the complement-fixation test. No clues were obtained during the field survey concerning the origin of influenza in the area but cases of influenza were first noted immediately after Christmas 1952, a season when a considerable influx of visitors from New York City and elsewhere was experienced.

(vi) *Syracuse*

An outbreak of influenza occurred in a State School in Syracuse during January 1953 and influenza virus A was identified by Dr Seymour S. Kalter in throat washings collected on the 14th of the month. Fifty sera were collected at random on 5 March. The percentage of positive results (44%) in these sera contrasts with the percentages elsewhere obtained by the more random method of sampling. The sera had been collected in order to provide experience of the findings likely in a group of individuals who had recently experienced an outbreak of influenza. Many of those providing serum specimens had not suffered clinical attacks of influenza during the outbreak. In view of these results it seems clear that the sensitivity of the complement-fixation screening test employed during the study was reasonably good.

ANTIBODY TITRES IN THE VARIOUS SERA

In addition to the determination of the crude percentage of sera showing a reaction to any degree in the 1 hr. complement-fixation test, the determination of the absolute titre of antibodies was carried out as a possible source of additional information. The antibody titres of sera titrated by the method of complement-fixation

in the cold room overnight were expressed as numbers of 50% doses of complement which would be fixed by undiluted serum. These were obtained from the higher dilutions of serum still giving fixation of complement, by the conversion factor used for the complement-fixation test for syphilis (Wadsworth, 1947). Forty-one

Table 2. *Distribution of C.F. titres obtained with various sera*

Category of sera	Serum titres expressed as units of complement							Total nos.
	< 8	8-19	20-39	40-59	60-79	80-99	100 and over	
Cases of influenza:								
Acute sera	32	7	1	1	—	—	—	41
Convalescent sera	—	—	9	8	3	7	14	41
Sera found negative in screening test	43	20	2	—	—	—	—	65
Sera collected seven weeks post-epidemic	28	2	8	10	1	1	—	50

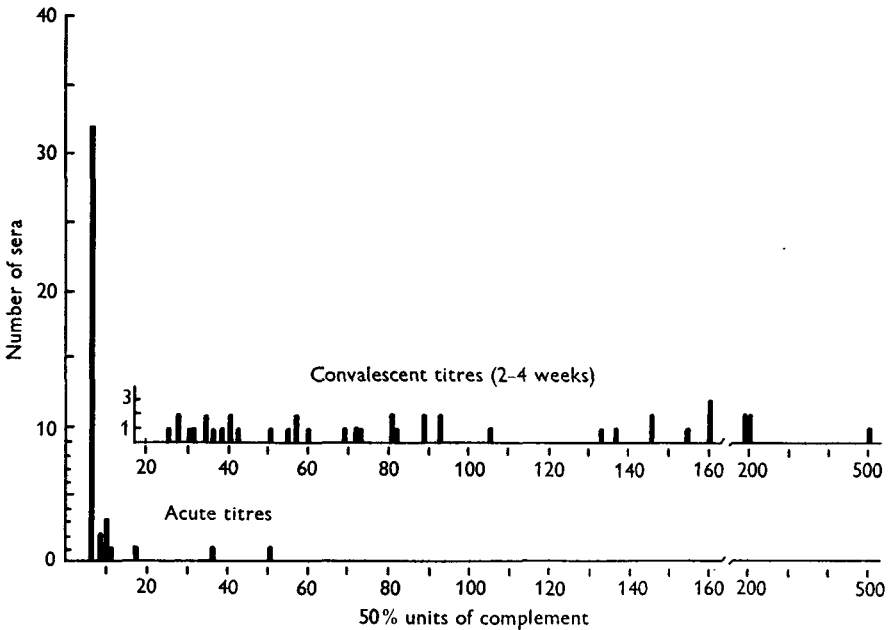


Fig. 2. Pairs of sera from forty-one cases of proven influenza A.

pairs of sera from cases of influenza A which gave at least a threefold rise of antibody between acute and convalescent specimens, were used to establish the levels to be expected in the immediate post-infection state by the cold-fixation test. Table 2 and Fig. 2 show the distribution of titres for the group of forty-one acute specimens and the forty-one convalescent specimens separately. The range of antibody titre in the acute specimens was from zero (thirty-two samples) to fifty, whereas sera from the same individuals during convalescence gave titres from 25 to 497. Fourteen of the sera exhibited titres in excess of 100, but only one gave a titre in excess of 200.



Table 2 also shows the results obtained by the cold-fixation test with 65 sera not giving fixation after 1 hr. in the water-bath at 37° C., all of which had titres below 25. Twenty-two of 50 sera obtained 7 weeks after the epidemic of influenza A in the Institution at Syracuse gave fixation in the screening test and these showed antibody titres ranging from 8 to 88, of which 17 fell in the ranges of 30 and over. However, many of the individuals from whom these sera were obtained were young adolescents and their titres cannot be regarded as necessarily indicative of levels which might be expected in adults at the corresponding time after infection.

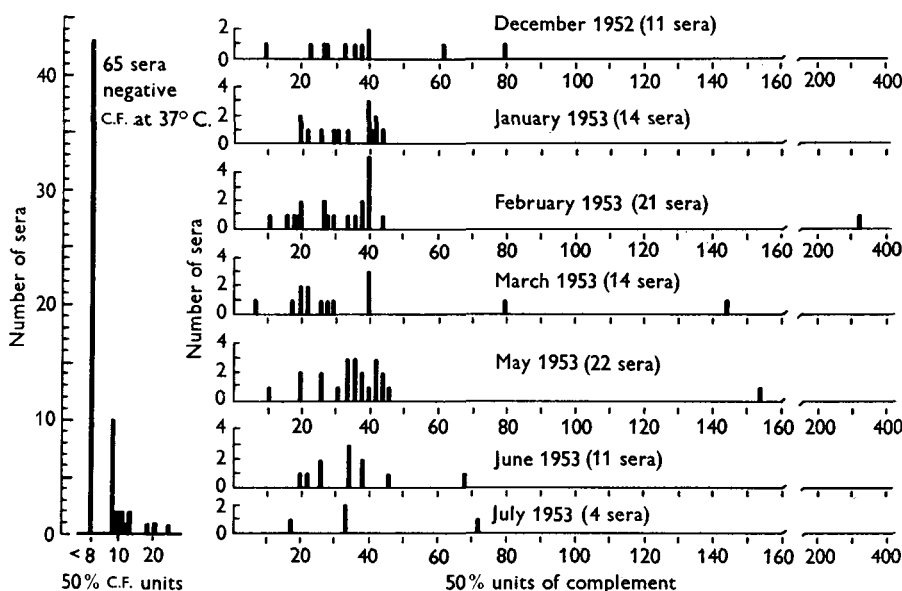


Fig. 3. Distribution of C.F. titres in sera from Albany.

Nevertheless, the results obtained with the sera from proven cases of influenza, which were mostly in adults, were thought to provide a valid basis for comparison with the results in the sera from various towns at various times. For instance, although no level which was statistically valid as an indication of the convalescent state could be established because of the wide range of titres, it appeared likely that antibody titres in excess of 100 would often indicate a relatively recent attack of influenza A.

Table 3 gives the distribution of antibody titres obtained with the sera found positive by the screening test and re-titrated in the cold-fixation method. In a few instances, insufficient serum was available for the second test, but the majority of the specimens could be examined. Figs. 3 and 4 show the data for Albany and Watertown, respectively, and also the results of performing the overnight cold fixation test on 65 sera found not to give fixation of complement in the 1hr. screening test. From this table and the figures it is seen that the range of antibodies in the various batches of sera from any one area did not alter with time as greatly as

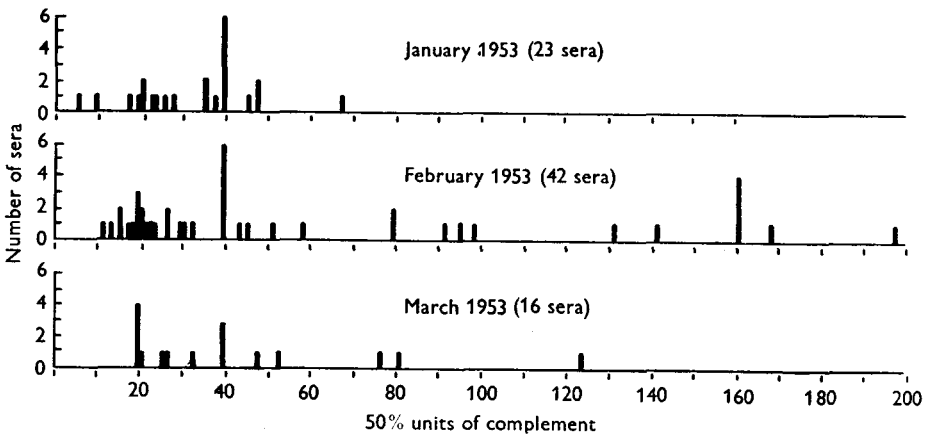


Fig. 4. Distribution of C.F. titres in sera from Watertown.

Table 3. *Distribution of C.F. titres obtained with sera found positive in the screening test*

	Serum titres expressed as units of complement							Total
	< 8	8-19	20-39	40-59	60-79	80-99	100 and over	
Albany. Weeks beginning:								
14 Dec.-4 Jan.	—	1	11	4	1	1	—	18
11 Jan.-1 Feb.	—	3	7	6	—	—	—	16
8 Feb.-1 Mar.	—	1	5	5	—	—	1	12
8 Mar.-29 Mar.	1	1	7	3	—	1	1	14
May	—	1	13	7	—	—	1	22
June	—	—	9	1	1	—	—	11
July	—	1	2	—	1	—	—	4
Sept.	—	—	—	5	—	—	—	5
Watertown. Weeks beginning:								
11 Jan.-1 Feb.	1	4	12	11	1	1	1	31
8 Feb.-1 Mar.	—	5	15	11	—	5	8	44
8 Mar.-29 Mar.	—	—	3	2	1	—	—	6
Cooperstown. Weeks beginning:								
14 Dec.-4 Jan.	—	4	7	1	—	—	—	12
11 Jan.-1 Feb.	—	7	8	1	—	—	—	16
8 Feb.-1 Mar.	—	17	11	9	—	—	1	38
8 Mar.-29 Mar.	—	—	9	5	2	1	2	19
St Lawrence County. Weeks beginning:								
14 Dec.-4 Jan.	—	—	6	2	—	—	—	8
11 Jan.-1 Feb.	—	1	3	4	—	—	1	9
8 Feb.-1 Mar.	—	8	15	2	3	2	8	38
8 Mar.-29 Mar.	1	1	9	5	—	—	2	18
Saranac Lake, Lake Placid, Tupper Lake. Weeks beginning:								
14 Dec.-4 Jan.	—	1	2	—	—	—	—	3
11 Jan.-1 Feb.	—	1	7	8	3	1	2	22
8 Feb.-1 Mar.	—	2	8	1	1	1	1	14
8 Mar.-29 Mar.	—	1	—	—	—	—	—	1

might have been anticipated. Nevertheless, isolated sera with titres in excess of 100 were encountered, as is shown in Table 4.

Table 4

Town	Dates of individual sera with titres in excess of 100	Approximate time of occurrence of influenza based on the screening test
Albany	24 Feb.; 9 Mar.; 12 May	Mar.
Watertown	4, 9, 12, 18, 23, 25, 26, 28 Feb.; 3 Mar.	Feb.
Cooperstown	25 Feb.; 13 Mar. (two)	Mar.
St Lawrence County	2, 26 Feb.; 2, 4 (four); 5, 6, 11 (two) Mar.	Mar.
Saranac Lake and Lake Placid	20 Jan. (two); 26 Feb.	Jan.

It seems almost certain that the individuals from whom these sera had been collected had suffered attacks of influenza in the previous 2 weeks and the chronological agreement between the highest percentage of positive sera and the few sera with high titres as shown in Table 4 is good. In fact, it seems possible that the occurrence of high antibody titres could be used as a crude method of case-finding indicative of the whereabouts of the influenza virus. Much more doubtful is the significance of the general range of antibodies in sera found positive in the screening test. It is still an open question whether these results suggest that virus was present in the community well before the peak in positive sera or not, and it will be necessary to continue these studies during inter-epidemic periods or at least for 6 months before an epidemic before any further statement can be made.

#### DISCUSSION

A previous serological study of influenza was made in New York State in 1945-6 with sera collected originally for the Wassermann test but which were tested also with influenza virus antigens (Dalldorf & Rice, 1947). Paired sera from cases of clinical influenza occurring in December 1945 showed antibody rises with influenza virus B but not with influenza virus A antigens. The sera, collected at random, were pooled in groups of five and over 300 serum pools collected from June 1945 to February 1946 were tested. The influenza virus A complement-fixation titres were highest in the pools of sera collected in June to August 1945 and lowest in the pools collected in January and February 1946. With influenza virus B, however, the titres were lowest in June to August 1945 and highest in the pools of sera collected during January and February 1946. These findings were thought to be consistent with infection of the community with influenza virus B in December 1945. Allantoic fluid antigens were used in this study.

The present work was begun in December 1952 in an attempt to study the mode of occurrence of influenza virus A infection during an expected A epidemic. Serum specimens obtained from individuals were tested rather than serum pools in order to detect the occasional high-titred sample. The soluble antigen was used because

it was considered to be capable of detecting serological changes in human sera as a result of exposure to influenza A viruses regardless of minor antigenic differences between the individual virus strains.

Four hospital regions were selected, three of which were remotely situated from New York City where the heaviest concentration of population in the State exists. The small communities in the Adirondacks grouped around Saranac Lake, Lake Placid and Tupper Lake, were known however to be subject to periodic intermingling with individuals from New York City who entered the area regularly at week-ends and holidays. It seemed possible that these communities might become infected as a result of the influx of population and that a spread to the more northerly villages and towns of the St Lawrence County might then occur. The choice of Watertown to the west of the Adirondacks, and Cooperstown to the west of Albany was made on the assumption that these would be equally liable to infection from either west or east, and that both areas were in less close contact with New York City or other large aggregations of population than was Albany. Although no sera were collected from New York City, the fact that several laboratories in the city were conducting research on acute respiratory disease made it seem likely that evidence concerning the occurrence of influenza virus infection in the city could be made available.

In fact, though localized outbreaks of influenza A occurred in Army camps, institutions and colleges of New York State from January onwards, no recognizable clinical epidemic developed in the various large towns. The total number of deaths and deaths from pneumonia and influenza in the up-state cities of Albany, Schenectady, Utica, Syracuse, Buffalo and Yonkers likewise showed no rise indicative of an influenza epidemic. Rochester, N.Y., did however experience an increase in mortality during the last week of February, but in view of the rise of 15% or more of deaths experienced in other parts of the United States it seems clear that New York State as a whole had no comparable epidemic experience. The major purpose of this study, which was a correlation of epidemiological and serological findings during a true epidemic of influenza, was therefore defeated. However, the information already detailed above indicates that community infection with influenza virus A actually occurred at various times in all the various areas which were studied.

A strain of influenza virus A was recovered from a sporadic case of acute respiratory disease in New York City at the Hospital of the Rockefeller Institute in the week beginning 4 January by Dr David A. J. Tyrrell (personal communication), and during the next week sporadic cases of influenza were detected clinically in the Saranac Lake and Lake Placid area and strains of influenza virus A were recovered by us on 20 January. Although virus strains were not recovered from other areas where serum studies were being made, the detection of occasional high-titred sera and the change in the percentage of sera giving fixation of complement with influenza A antigen indicated that the virus was active in all these communities. The time of occurrence of community infection was probably during early February in the Watertown area, and in March in Albany, St Lawrence County and Cooperstown. The fact that the population in the Albany area showed evidence of infection

nearly 2 months later than that of the Adirondacks is of epidemiological interest. Both rail and road communications between Albany and New York City are extensive but apparently did not lead to an appearance of influenza in Albany for 2 months after the first occurrence of the virus infection in New York City. The occurrence of the small outbreak in the Adirondacks shortly after the recovery of virus in New York City suggests that the influx of visitors into a relatively sparsely populated area is indeed effective in leading to a dissemination of the virus. On the other hand, this dissemination never led to any serious degree of epidemicity and the more northerly villages and towns of St Lawrence County were unaffected for a further 2 months. The fact that none of the batches of sera from the five areas under study gave as high a percentage of positive results as did the samples collected after a real epidemic at the Institution in Syracuse again supports the view that the community infection was essentially sporadic. The absence of clinical outbreaks suggests that such infection was largely subclinical. The widespread occurrence of influenza A in New York State in 1951 may perhaps have been responsible for failure of the virus to become established in 1953.

The view is held by some that influenza epidemics do not in fact originate from a spreading infection by the virus but that the latter is essentially endemic in the population. Though the present data do not enable a decision to be made on this point, the fact that the earliest batches of sera collected in towns such as Albany contained individual specimens with quantitative titres little different from those found in March or subsequently may be significant. The rapid decline in the percentage of positive sera after March 1953 is consistent with the findings of other authors and may indeed suggest that influenza infection was present in the community before December 1952. The available evidence suggests that antibody detected in the complement-fixation test by the 'soluble' influenza virus antigen does not last long and this was one reason for selecting this rather than the virus antigen. Until more data are available on the decline of antibody to the 'soluble' antigen after infection, it would be unwise to depart from the traditional view that the sera collected during a pre-epidemic or inter-epidemic period and which react in the complement-fixation test are derived from individuals infected during the previous epidemic. Meanwhile, it seems possible that the events recorded in human populations and which are interpreted as being due to spread of virus with subsequent epidemicity of infection only provide a partial picture of what actually occurs. Virus may normally be disseminated by subclinical infection and epidemics of clinical influenza may be due to circumstances which favour rapid passage of virus and a gain in some character like the exaltation of virulence which occurs under laboratory conditions. It is clear that further large-scale studies of sera from communities in inter-epidemic as well as epidemic periods may be helpful in outlining more precisely the mode of spread of the influenza viruses.

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