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Infection with influenza A/Victoria virus in Houston families, 1976

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SUMMARY

In 1976, an epidemic caused by infections with an influenza virus antigenically similar to A/Victoria/75 (H3N2) occurred in Houston, Texas. During this outbreak, 37 families (155 members) enrolled in the Houston Family Study were under observation. The families lived throughout the metropolitan area (Houston, Texas), and were representative of low income groups. The overall frequency of infection in family members was 27·7%. The frequency of infection was the highest for infants under one year of age and for their older siblings, 14 (37·8%) of 37 and 17 (33·3%) of 51, respectively. Eighteen (48·6%) of the 37 families had at least one infected member. Twelve of the 18 'infected' families had school aged children, whereas only three of the 19 'non-infected' families had school aged children ($P < 0·01$). These infected families were also larger and had increased household density (persons/rooms). The levels of pre-existing HI antibodies to A/Victoria/75 and A/Port Chalmers/73 were inversely related to frequencies of infection and illness associated with A/Victoria/75 virus. Three children required hospitalization as direct consequence of their infection with this H3N2 influenza virus. Antibody response to infection was related to previous experience with antigenically-related influenza A (H3N2) viruses according to Francis', 'doctrine of original antigenic sin.'

INTRODUCTION

As part of the surveillance program of the Influenza Research Center at Baylor College of Medicine, a longitudinal family study was initiated in 1975. During January 1976, an epidemic of influenza caused by influenza A/Victoria/75 (H3N2) – like viruses occurred in Houston, Texas (Glezen & Couch, 1978). Virus was first isolated from an ill person in early January, and the epidemic peaked during the second week of February. This epidemic had been preceded in 1975 by an epidemic caused by influenza A/Port Chalmers/73 (H3N2)-like viruses. During

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the 1976 outbreak, 37 families in the Houston Family Study were under observation. This report concerns A/Victoria/75 infection and illness among those families and family members.

MATERIALS AND METHODS

Family recruitment

Families who lived throughout the metropolitan area were enrolled in the study at the time of birth of a newborn infant. They were recruited from patients seeking obstetric care at the public hospital which serves low income families of Houston and Harris County, Texas, an area containing about two million people. The first family was enrolled in January 1975 and enrolment proceeded steadily throughout the year at a rate of three or four families per month. A home visit prior to delivery of the newborn infant was made by a physician and nurse or physician assistant to explain the study and obtain informed consent of both parents for participation of the family.

Virologic surveillance

Upon enrollment into the study, a blood sample of 5 ml was obtained from the father, mother and siblings. A cord blood was obtained at the time of delivery and additional samples were obtained from the infant at birth, four, eight, and twelve months of age. Blood samples also were obtained from older siblings and parents in October 1975 and April 1976.

Each family was contacted weekly during the respiratory disease season. A nasal wash specimen for virus isolation (Hall & Douglas, 1975) was obtained from each infant followed from birth at each home visit, well-baby care clinic visit, and at the time of each respiratory illness. Older siblings and adults were cultured, if possible, whenever an illness was reported or an influenza virus was isolated from a family member.

Signs and symptoms of each respiratory illness were recorded along with the results of cultures on a standard form precoded for computer analysis. In addition, forms were completed each year which describe the individuals in each family and the epidemiologic and environmental factors for each household.

Virologic and serologic tests

Methods for isolation and identification of influenza viruses were performed as described (Baxter, Couch & Greenberg, 1977). Paired serum specimens were tested for haemagglutination-inhibiting (HI) antibody to influenza A viruses using A/Victoria/3/75 (H3N2), A/Port Chalmers/1/73 (H3N2), and A/Hong Kong/1/68 (H3N2) antigens by a standard microtitre procedure (Dowdle, Kendal & Noble, 1979). A/England/42/72 (H3N2) virus was not included because the available antigen was sensitive to nonspecific serum inhibitors that were not removable by treatment with receptor destroying enzyme. Neutralization tests for antibody against A/Victoria/3/75 (H3N2) virus were performed as described on a selected set of sera (Dowdle *et al.* 1979).

Definition of infection and illness

A family member was defined as having been infected with A/Victoria virus if (*a*) virus was isolated from a nasal wash or throat swab specimen, (*b*) a fourfold rise in HI antibody to any one of the three antigens listed above occurred, or (*c*) a fourfold rise in neutralizing antibody against A/Victoria/75 virus was observed. The pre- and post-epidemic serum specimens from each person were tested simultaneously. Illnesses were attributed to influenza A/Victoria infection when virus was isolated from specimens obtained during the illness, and in the case of infection detected by antibody rise only, when illness was temporally associated with virus isolation in a family contact. Otherwise, the most severe illness of the epidemic period was assumed to have been related to the A/Victoria infection.

RESULTS

Virologic and serologic evidence of infection in family members

The 37 families under observation during the A/Victoria epidemic contained 155 members. Eighteen families with a total of 84 members included at least one family member with infection, and 19 families (71 members) were without evidence of infection. The overall infection rate among all family members was 27·7%. Infection rates (Table 1) for the age groups < 1, 1–4, and 5–14 were approximately the same, 37·8%, 33·3%, and 33·3%, respectively; adults, who represented approximately 40% of the family member population, had an infection rate of 18% (12/67). All virus isolations from family members occurred during the month of February, although the epidemic started in January and ended in March. During the month of February, 40 cultures were obtained from ill persons, and 13 (32·5%) yielded influenza A/Victoria/75 isolations. Thus, 13 of the 43 infections detected were documented by isolation of virus, seven of these 13 isolates were obtained from infants under one year of age. Each person with a virus isolation also had a seroconversion by HI and/or neutralization tests.

As noted in Table 1, among children less than one year of age, eight had a fourfold rise in HI antibody to A/Victoria/75 alone, five to A/Victoria/75 and A/Port, Chalmers/73, but none to A/HK/68 virus. Among children one to four years old, the HI antibody response included A/HK/68 in two of six children, but, in the five to nineteen year olds and the adults, a rise in antibody to A/HK/68 occurred in most. Only one adult had a fourfold rise in HI antibody to A/Victoria/75 antigen only. One other adult had a fourfold rise in neutralizing antibody only (to A/Victoria/75), and this person also had an illness associated with isolation of virus.

Patterns of illness

The highest incidence of symptomatic infection (85·7%) was seen in children under one year of age (Table 2). Only two of the 14 infected infants, two and nine months of age, were asymptomatic. Most of the infants had uncomplicated febrile upper respiratory illness but one required hospitalization for studies to rule out occult bacterial infection. Lower respiratory tract involvement occurred in three

Table 1. *Number of persons infected with influenza A/Victoria/75 virus as determined by serum HI antibody rise*

Age group (years)	No. of persons	No. with virus isolation	HI antibody rises to indicated virus*				Neut antibody rises to Vic	Total infected (%)
			Vic	Vic and PC	Vic, PC and HK	PC and HK		
0–1	37	7†	8	5	—	—	—	14 (37·8)
1–4	21	0	2	2	1	1	1	7 (33·3)
5–19	30	3	1	—	3	3	3	10 (33·3)
20–29	47	2	—	—	2	6	—	8 (17·0)
30–47	20	1	1	—	—	2	1	4 (20·0)
Totals	155	13	12	7	6	12	5	43 (27·7)

* Vic = A/Victoria/3/75 (H3N2), PC = A/Port Chalmers/1/73 (H3N2), HK = A/Hong Kong/1/68 (H3N2).
† Virus was isolated from one infant from whom serum was not available for study.

Table 2. *Clinical manifestations of influenza A/Victoria/75 infection by age*

Age group (years)	Number infected	Number with indicated illness			
		None	Afebrile URI*	Febrile URI	Lower respiratory disease
0–1	14	2	2	7†	3‡
1–4	7	5	1	1	—
5–19	10	7	—	3§	—
20–29	8	5	1	2	—
30–47	4	2	—	—	2

* Upper respiratory illness.
† One hospitalized with unexplained fever, later developed URI.
‡ One hospitalized with pneumonia.
§ One hospitalized with associated encephalitis.

infants aged five, seven and nine months of age: the seven month old, who had severe croup with stridor accompanied by pneumonia, was hospitalized. The majority of infections in older children and adults were recorded as asymptomatic. These data may not, however, reflect the true incidence of minor illness in the older age groups since some family members, particularly school aged children and working parents, were not always available for cultures and clinical examinations. Two adults developed acute bronchitis and a six year old boy was admitted to the hospital with an encephalitis-like illness. The latter illness began with fever and upper respiratory symptoms followed soon by a grand mal convulsion. His cerebrospinal fluid contained 36 mononuclear cells per mm^3 and his electroencephalogram showed diffuse slowing. Influenza A/Victoria/75 virus was isolated from his respiratory secretions and his paired sera demonstrated seroconversion in HI antibody tests to this virus. He had an uneventful complete recovery.

Infection and illness in relation to pre-existing serum antibody

Pre-epidemic HI antibody titers were available for 154 of the 155 family members (pre-epidemic serum was not available for one infant). The levels of pre-existing HI antibodies to A/Victoria/75 and A/Port Chalmers/73 were inversely related to frequencies of infection and illness associated with A/Victoria/75 virus (Wilcoxon, $z = -1{\cdot}92$ and $-1{\cdot}75$ for A/vic, $z = -2{\cdot}70$ and $-2{\cdot}06$ for A/PC, $P < 0{\cdot}05$, one tail); however, this relationship was not significant for antibodies to A/HK/68 virus (Table 3).

Factors related to the occurrence of infection in the family unit

Available data on factors which might be related to the occurrence of infection in families were compared for families including one or more infected members ($N = 18$) and families with none infected ($N = 19$). Although there was no statistically significant difference in the age distribution for the two groups of families (Wilcoxon test $z = 0{\cdot}2154$), there was a significant difference in the number of children in school or day care (24/84) among infected family members

Table 3. *Frequency of infection and illness attributed to influenza A/Victoria/75 virus among a group of Houston families in relation to pre-existing serum antibody to different H3N2 viruses*

Pre-existing HI titre	A/Victoria/75			A/Port Chalmers/73			A/Hong Kong/68		
	No. tested	No. (%) infected	No. (%) ill	No. tested	No. (%) infected	No. (%) ill	No. tested	No. (%) infected	No. (%) ill
< 10	64	23 (36)	12 (19)	52	20 (39)	10 (19)	69	22 (32)	11 (16)
10	63	15 (24)	9 (14)	54	16 (30)	10 (19)	35	9 (26)	6 (17)
20	21	4 (19)	1 (5)	28	5 (18)	1 (4)	25	6 (24)	2 (8)
⩾ 40	6	1 (17)	0 (0)	20	2 (10)	1 (5)	25	6 (24)	3 (12)

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Table 4. *Frequency of infection and illness attributed to influenza A/Victoria/75 virus among persons in families with and without children attending school or day care*

Family status	Number of persons	Number of infections	Number of illnesses
With school children	78	30 (38·5%)	15
Without school children	77	13 (16·9%)	7

as compared to non-infected family members (4/71) ($\chi^2 = 9{\cdot}6$, $P < 0{\cdot}01$). Distribution of pre-epidemic HI antibody to A/Victoria, A/Port Chalmers, and A/Hong Kong virus for the two family groups were compared. No difference was detected in the distribution of pre-existing HI antibody titres in the two groups of families for any of the three viruses. Similarly, when antibody distributions were compared according to age of family members, no difference between 'infected' and 'non-infected' families was detected.

All families were from low income (but not indigent) groups and no relationship of infection to geographic location in the city of Houston was noted. The racial and ethnic distribution in the infected families were ten black, four white, and four Mexican–American, as compared to nine black, eight white, and two Mexican–American among the non-infected families.

The distribution of families by size was significantly different for 'infected' and 'non-infected' families (Wilcoxon, $z = 2{\cdot}25$, $P < 0{\cdot}05$). Eleven of 18 infected families included five or more persons while only three of 19 non-infected families were that large ($\chi^2 = 8{\cdot}07$, $P < 0{\cdot}01$). This greater number of family members among 'infected' families was also reflected in household density (persons/room); the distribution of families by housing density was significantly different (Wilcoxon $z = 2{\cdot}58$, $P < 0{\cdot}05$). Among the infected families, 10 of 18 families averaged more than 1·0 person per room in the family dwelling, whereas only four of 19 families in the non-infected group averaged greater than 1·0 person per room ($\chi^2 = 4{\cdot}68$, $P < 0{\cdot}05$). Similarly, 12/18 'infected' and 3/19 'non-infected' families contained at least one child in school or day care ($P = < 0{\cdot}01$, Fisher's Exact Test).

Table 4 shows the frequency of infection and illness in families with and without school age children. Among 78 persons living in households including children attending school or day care facilities, there were 30 (38·5%) infections, whereas only 13 (16·9%) infections occurred among 77 persons living in households without school children ($\chi^2 = 7{\cdot}5$, $P = < 0{\cdot}01$). The importance of children housed in day care facilities as introducers of infection can be supported by direct observations. Two infants, ages 10 months and two years, were housed in the same day care nursery. They both developed febrile illnesses on the same day and influenza virus was isolated from one of the infants. Some 36 hours later, the mother of these two infants developed a febrile respiratory illness and subsequent serologic evidence of infection with A/Victoria virus. In two other households the first person ill was also a child in day care.

Five of the 18 'infected' families had only one member with documented infection and these included one infant, one toddler, one school child, one mother

who did not work outside the home, and one father who was on military duty in Louisiana but home every weekend. In the families with more than one person infected it was not possible to clearly assign the index case because many infections were detected by antibody rise only and could not be timed precisely; however, the circumstances suggest that a school child was the index case in four families, a child in day care in three families and a parent in three families. Of the latter three families, two included only preschool children not in day care. The index case in the remaining three families was uncertain.

In three families, respiratory illnesses in infected members were more than seven days apart suggesting reintroduction of infection; this would result in suggesting 21 primary or co-primary infections among the 18 'infected' families. Twenty-two secondary infections occurred among 63 contacts yielding a secondary attack rate of 34·9 %.

DISCUSSION

The infection rate of 27·7 % for influenza A/Victoria/75 in our families was similar to that (32·3 %) reported for families in New Zealand (Jennings & Miles, 1978), infected with A/Port Chalmers/73. The illness rates by age were higher in the latter study. This probably occurred because those investigators included temporally-associated illness without documented infection and because we probably were not made aware of some illnesses in our families, particularly in school children or working adults. Influenza A/Port Chalmers/73 and A/Victoria/75 viruses were sequentially occurring H3N2 variants of the original H3N2 prototype virus A/Hong Kong/68. Therefore, the older children and adults in these two family studies had probably experienced prior infection with other influenza A (H3N2) viruses.

Other reported infection rates have been somewhat higher. An infection rate of 54·7 % and an illness rate of 40·9 % was observed in the Cleveland Family Study (Jordan *et al.* 1958) during the first epidemic caused by Asian influenza virus (H2N2). In studies designed to evaluate amantadine, Galbraith observed a family infection rate of 45·8 % among those given a placebo during an intensive H2N2 epidemic in 1967 (Galbraith *et al.* 1969*a*) and 48·5 % during the initial H3N2 epidemic in 1969 (Galbraith *et al.* 1969*b*).

Use of the epidemic virus (A/Victoria) only for detecting HI antibody responses would have underestimated our infection rate. Francis (1955) showed that the virus of a subtype causing first infection appeared to have an orienting effect on the antibody response to antigenically-related viruses encountered later with reinforcement of early antibodies occurring at the time of subsequent infections. This led to the concept of 'original antigenic sin'. This phenomenon was observed in the Houston Family Study. Infants under one year of age whose first exposure to influenza virus was A/Victoria/75 usually had a fourfold or greater rise to the A/Victoria haemagglutinin antigen alone, whereas older children and adults, whose exposure to earlier H3N2 variants could have been multiple, had significant antibody rises either to multiple antigens (A/Victoria, A/Port Chalmers, and/or A/Hong Kong) or to the earlier infecting strains (A/Port Chalmers, and/or A/Hong Kong).

An inverse relationship between pre-existing HI antibody and occurrence of infection and illness with the same influenza virus has been demonstrated in several instances for persons undergoing artificial challenge (Hobson *et al.* 1973). Similar findings have been reported for naturally occurring infection and illness among adults (Farnik & Bruge, 1961; Francis *et al.* 1946; Davenport *et al.* 1955; Meiklejohn *et al.* 1955; and Greenberg *et al.* 1974) and school children (Sugiura *et al.* 1970). The majority (69/84) of members of infected families in the Houston Family Study had HI antibody titres to A/Victoria/75 of $\leqslant 10$. Higher HI antibody titres to A/Victoria and/or A/Port Chalmers were associated with protection of individual family members; however, no such relationship existed for the more distant H3N2 variant, A/Hong Kong/68. Jennings & Miles (1978) showed that pre-existing antibody to both A/England/72 and A/Port Chalmers/73 correlated with protection against A/Port Chalmers/73 infection, but they did not test their subjects for antibody against A/Hong Kong/68.

The infants in our families represented a uniquely susceptible group because most were over four months of age at the time of the epidemic and beyond the age that low levels of passively acquired antibody would have provided protection (Puck *et al.* 1980). Moreover, a serologic survey prior to the epidemic had indicated a low frequency of serum antibody among prospective mothers. Fourteen of 18 infants in families with infection were infected with A/Victoria virus and 12 had clinically apparent illness; three had lower respiratory tract disease and two required hospitalization. In addition, febrile seizures and CSF pleocytosis, which occurred in a six-year-old boy, not uncommonly accompany influenza A virus infections in children (Glezen, Paredes & Taber, 1980). Such complications are usually overlooked in assessing the impact of epidemic influenza; the cost of hospitalization of this child plus the two infants mentioned above was approximately $6000.

The risk of hospitalization for infants from low income families residing in Harris County during this epidemic was estimated to be four per 1000 live births during the A/Victoria epidemic (Glezen *et al.* 1980). The mortality rate for hospitalized infants was 7·5% demonstrating that influenza infection represents a serious threat for young infants.

Three determinants characterized those families who were infected with A/Victoria virus: family size, density, and the presence of school age children and/or children in day care facilities. These three characteristics were closely related and could not be clearly separated one from another. The 'infected' families were the largest families and, therefore, had the greatest number of school age children (and children in day care), and the family dwellings had less room per person than those of the 'non-infected' families. Thus, these larger families had a greater number of potential 'introducers' of infection into the family, as well as a size and density that may have contributed to intra-familial spread of infection. In an outbreak of influenza caused by Hong Kong variant, Hope-Simpson (1970) noted that the household was more favourable than the community for spread of this variant. In some other influenza outbreaks (Dunn *et al.* 1959, and Rosenstock, 1960), higher attack rates were also associated with increasing family size, but in one (Green, 1959), differences in family size had no apparent effect on incidence of

infection in families. Jordan (1960) has suggested that observed attack rates in the larger families could have been as much a function of the age of the children in the family as of the number of individuals.

In our family study, the increased incidence of infections in families with school children suggested that the school child is the introducer of infection into the family unit – a conclusion shared by investigators for the New Zealand and Cleveland family studies. Analysis of community surveillance data for Houston (Glezen & Couch, 1978) revealed that during the early stages of the A/Victoria outbreak an inordinately high proportion of culture-proven cases occurred among school children and school absenteeism peaked early in the course of the epidemic. Similar observations were made (Philip, 1961) in suburban Washington families with influenza A (1953) and influenza B (1952, 1955). These combined observations support the belief that school children are important disseminators of infection in the community.

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