

Age-Specific Prevalence of Complement-Fixing Antibodies to Sixteen Viral Antigens: A Computer Analysis of 58,500 Patients Covering a Period of Eight Years

Pentti Ukkonen, Tapani Hovi, Carl-Henrik von Bonsdorff, Pekka Saikku, and Kari Penttinen

Department of Virology, University of Helsinki, Helsinki, Finland

The age-specific prevalence of CF antibodies against 16 viral antigens was determined by using the computerized data registry of the routine diagnostic laboratory of the authors' department. The material consisted of data based on serum specimens from about 58,500 patients. All ages from newborn infants to 90-year-olds were represented. The sera had been collected and tested with a CF screening test over a period of 8 years (1971-1978). Several different antibody prevalence patterns were distinguished in regard to the rapidity and timing of the initial increase of the prevalence, as well as to the mode of later changes in prevalence. For most respiratory viruses a rapid increase of the prevalence was seen through the childhood continuing, for some of them, up to the 30s (influenza A and coronavirus), while rather variable patterns were found in the older age groups. Herpes simplex and cytomegaloviruses showed, interestingly, another type of pattern: a slow increase of prevalence continuing through the whole age range. The frequency of herpes simplex antibodies reached 90% by the age of 80 years. Antibody levels against any antigen in infants less than one-month-old were equal to those in 20- to 40-year-old adults, and the expected rapid decrease of antibodies took place within the first 6 months of life. Possible influences of epidemics and repeated exposures to different viruses (external boosting), and of latent or chronic infections (internal boosting), as well as of technical variations, on the observed prevalence patterns are discussed.

Key words: viral antibodies, complement fixation, aging, maternal antibodies

INTRODUCTION

There are already many serologic surveys from the 1950s describing the age-specific frequencies of viral antibodies, and, in general, the prevalence of viral antibodies in population seems to increase with advancing age during childhood and

Accepted for publication June 22, 1983.

Address reprint requests to Dr. Pentti Ukkonen, Department of Cell Biology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

in the teens, and then gradually decrease in older people. However, most of the older studies have limitations, such as small numbers of studied sera and that all age groups from birth to senescence are not usually included. Also, sera may not represent the whole underlying population, and generally only a couple of viral antigens have been used in one study. Therefore, it has been difficult to compare the seroepidemiology of different viral infections.

The data from the routine diagnostic laboratory of the authors' department have been stored by computer since 1970 [Ukkonen et al, 1979]. In complement fixation (CF) serology, a screening test with 15 to 20 antigens was performed annually on 5000 to 9000 patients in the years 1971 to 1978. Apart from the immediate benefit in more effective finding of specific diagnosis because of the broad coverage, a screening test like this provides valuable epidemiological information.

In the present paper we report the age-specific prevalences of 16 viral antibodies during 8 years, which may reveal at what age infections with different viruses mainly occur. We have also attempted to correlate year-to-year changes in antibody prevalences to the known occurrence of the respective viral diseases. Similar analysis from the same material for *Mycoplasma pneumoniae* [Pönkä and Ukkonen, 1983] and chlamydia antibodies will be reported separately.

MATERIALS AND METHODS

Patients

Our department is responsible for studying more than 50% of all blood specimens drawn in Finland for serological diagnosis of viral infections. About 80% of the specimens are coming from different hospitals and the remainder from outpatient clinics. Geographically, all parts of the country are well covered, with the exception of the southwestern district served by another major laboratory. Therefore, the patients represent fairly well the general Finnish population. The present study is based on data collected in the screening test for CF antibodies during the years 1971–1978. The data were obtained from the computer files as described [Ukkonen et al, 1979]. The total number of patients studied was about 58,500. The results are presented as grouped in four 2-year periods, each consisting of about 11,000 to 18,000 patients, and in 16 age groups, which, in one 2-year period, had 100 to 2700 patients each (Table I). The numbers of patients tested varied with different antigens, as some antigens were temporarily absent from the screening test (Table II).

Screening of Viral Antibodies

In diseases whose symptoms might be caused by several different agents, such as respiratory infections, the clinicians usually choose a complement fixation screening test. In this test, the second specimen of paired sera, and in some cases the single serum available, is assayed at dilutions 1:8 and 1:16 by complement fixation against about 15 viral antigens, and *Mycoplasma pneumoniae*, chlamydia, and toxoplasma antigens. Specimens positive in the test at the 1:16 dilution, are then further titrated at least up to 1:512, and in case of paired sera, together with the first specimen. In the present study, the test results of the second serum specimen were used, if paired sera were available.

TABLE I. Number of Patients in Each Age Group and in the Four 2-Year Periods

Age group	Year of study			
	1971-1972	1973-1974	1975-1976	1977-1978
< 1 Month	333	323	370	593
1-3 Months	221	252	244	353
4-6 Months	103	158	143	179
7-11 Months	146	270	287	365
12-23 Months	349	428	469	712
2-3 Years	384	514	444	654
4-6 Years	451	631	530	753
7-10 Years	568	724	782	925
11-20 Years	1,073	1,431	1,585	1,779
21-30 Years	1,922	2,299	2,670	2,710
31-40 Years	1,389	1,758	1,966	2,382
41-50 Years	1,298	1,712	1,721	1,909
51-60 years	1,245	1,528	1,681	1,906
61-70 Years	1,074	1,370	1,420	1,586
71-80 Years	498	684	727	911
81+ Years	100	176	172	211
All	11,154	14,258	15,211	17,928

The total number of studied patients was 58,551.

TABLE II. Numbers of Patients Tested With Each Viral Complement Fixation Antigen

Viral antigen	No. of studied patients	Remarks
Influenza A	58,536	
Influenza B	58,551	
Parainfluenza 1	48,918	Not used in 1976
Parainfluenza 3	35,275	Not used in 1974-1976
Respiratory syncytial	56,933	Only 9554 tested in 1971-1972
Corona	16,183	Used from 1977
Mumps	58,551	
Measles	58,551	
Adeno, type 7	58,551	
Rota	17,537	Used from 1977
Coxsackie B5	53,831	Only 8110 tested in 1971-1972
Polio 1	33,387	Not used in 1974-1976
Polio 2	40,031	Not used in 1977-1978
Herpes simplex	58,543	
Varicella-zoster	25,314	Only 7859 tested in 1971-1972, not used in 1973-1976
Cytomegalo	58,512	

Significantly lower numbers are explained under "Remarks."

TABLE III. Viral Antigens Used in the Complement Fixation Screening Test During the Years 1971 to 1978

Viral antigen	Period when used	Source	Manufacturer
Influenza A	1971-78	Chorioallantoic membrane cells (S-antigen)	Orion Diagnostica, Espoo, Finland
Influenza B	1971-78	Chorioallantoic membrane cells (S-antigen)	Orion Diagnostica
Parainfluenza 1	1971-75	Allantoic fluid (V-antigen)	Orion Diagnostica
	1977-78	Chorioallantoic membrane cells (S-antigen)	Orion Diagnostica
Parainfluenza 3	1971-73	U cells ^a	Own production
	1977-78	Vero cells ^b	Orion Diagnostica
Respiratory syncytial	1971-75	U cells	Own production
	1976-78	Vero cells	Orion Diagnostica
Corona (strain OC43)	1977-78	Newborn mouse brain	Own production ^f
Mumps	1971-78	Allantoic fluid (V-antigen)	Orion Diagnostica
Measles	1971	U cells	Orion Diagnostica
	1972-78	Vero cells	and own production
Adeno (type 7)	1971-74	Bristol-HeLa cells	Own production
	1975	MRC-5 cells ^c	Own production
	1976-78	Bristol-HeLa cells	Orion Diagnostica
Rota (NCDV) ^d	1977-78	BS-C-1 ^b or LLC-MK ₂ cells ^b	Own production ^g
Coxsackie B5	1971-72	MK ₂ cells	Own production
	1973-76	GMK cells ^b	Central Public Health Laboratory, Helsinki, Finland
Polio 1	1977-78	LLC-MK ₂ cells	Own production
	1971-73	U cells	Own production
	1977-78	LLC-MK ₂ cells	Own production
Polio 2	1971-76	U cells	Own production
Herpes simplex	1971-78	BS-C-1 cells	Own production
Varicella-zoster	1971-72	GMK-cells	Own production
	1977-78	HES cells ^e	Orion Diagnostica
Cytomegalo	1971-73	HES cells	Own production
	1974-77	MRC-5 cells	Own production
	1978	HES cells	Orion Diagnostica

^aContinuous human amnion cells.

^bContinuous monkey kidney cells.

^cDiploid strain of human embryonic lung cells.

^dBovine rotavirus, Nebraska calf diarrhea virus strain.

^ePrimary human embryonic skin cells.

^fRiski et al (1977a).

^gvon Bonsdorff et al (1978).

Complement Fixation Test (CF)

The test was performed on microtitration plates, as described [Riski et al, 1977b]. Two units of complement and four units of antigen were used. The first specimen dilution was 1:8, and in this study, the results are expressed as prevalence (%) of antibody titers \geq 1:8. Crude antigen preparations were used (Table III). In

case of antigens derived from cell cultures, the infected cells with full cytopathic effect were broken by repeated freezing and thawing, centrifuged, and sonicated. The adenovirus antigen used in 1976 to 1978 was prepared from the culture medium instead of infected cells. Chorioallantoic membranes (influenza A and B, parainfluenza type 1; S-antigens) from 13-day-old chicken embryos, infected at the 11th day, were homogenized and ultracentrifuged, and the concentrated supernatant was used as CF antigen. Mumps and parainfluenza type 1 V-antigens were allantoic fluid from 12- to 13-day-old chicken embryos, infected at the 8th and 11th day, respectively.

Other

The numbers of virologically (by virus isolation or serology) diagnosed cases in Finland during the years 1971 to 1978 (Fig. 8) were obtained from the files of the Central Public Health Laboratory, Helsinki.

RESULTS AND DISCUSSION

Antibodies in Infants

The prevalence of CF antibodies (titers $\geq 1:8$) in infants less than 1 month old was equal to or slightly less than that of adults aged 21 to 40 years, a group that includes most of the females in the childbearing age. During the following months the proportion of positive reactors rapidly decreased, reflecting the loss of transplacentally acquired maternal antibodies (Figs. 1-7).

Rotavirus antibodies were found more often in infants less than 1 month old (38%) than in 21- to 40-year-old adults (27%). This could indicate that the mothers of small children have higher levels of rotavirus antibodies than the other people at the same age, possibly due to frequent exposure to rotavirus from infected children. Another possibility is that the higher prevalence of antibodies in children is a reflection of frequent rotavirus infections in the newborns themselves.

Respiratory Viruses

Different respiratory viruses (influenza A and B, parainfluenza types 1 and 3, respiratory syncytial, and coronavirus) showed antibody prevalence patterns with many similarities but also contained certain differences. For all of them, a rapid increase in prevalence took place in the childhood. Antibodies to parainfluenza and respiratory syncytial viruses reached their respective peak prevalence values by the age of 10 years while the prevalences of antibodies to the influenzaviruses and coronaviruses continued to increase during early adulthood (Figs. 1-3). Year-to-year differences in the prevalence patterns were typical of each antigen and will be commented on the following.

The prevalence of influenza A antibodies showed an increase over all age groups from 1973/1974 to 1975/1976 (Fig. 1). The increase was seen already between the figures of 1973 and 1974 (not shown). No likely explanation for this change can be given. The main epidemiological features in Finland during the study period were as follows: In 1969 to 1970 an epidemic was caused by H3N2 type, no epidemic occurred in 1971, and from 1972 to 1978 moderate size epidemics took place every year. The epidemic in 1978 was caused mainly by type H1N1, while all the previous epidemics were due to type H3N2 [Pyhälä and Visakorpi, 1979].

The increase in prevalence of influenza B antibodies between 1971/1972 and 1973/1974 (Fig. 1) coincides with the epidemic of 1974 but correlation between

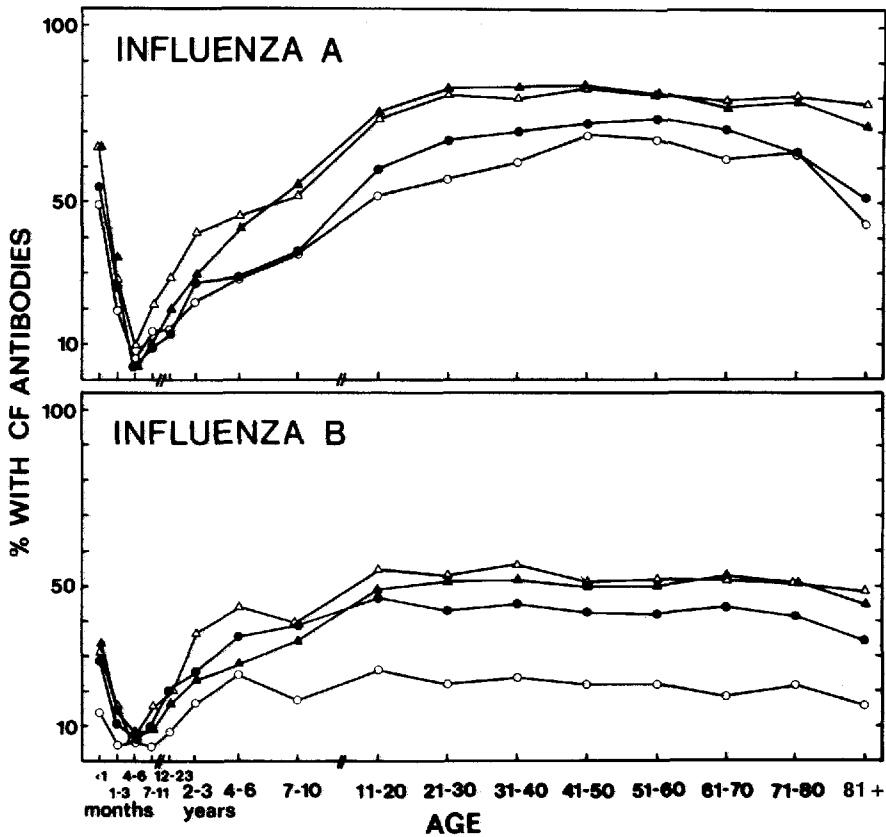


Fig. 1. Age-specific prevalences of complement-fixing (CF) antibodies (titers $\geq 1:8$) to influenza A and B viruses in patients screened with sixteen viral antigens during the years 1971-1978. The numbers of tested patients are given in Tables I and II. The prevalence curves represent four 2-year periods: 1971-1972 (\circ), 1973-1974 (\bullet), 1975-1976 (\triangle), and 1977-1978 (\blacktriangle).

documented epidemics and the observed overall antibody prevalence scores may not be that simple (Fig. 8). Namely, the increase in antibody prevalence had started already in the year 1973 with very few documented influenza B cases in the country.

Unlike those of the influenza viruses, the prevalence of antibodies detected with parainfluenza type 1 and 3 antigens began to decrease at about 10 years of age (Fig. 2). The relatively low levels of antibodies obtained by type 3 antigen in 1971-1973 may be due to differences in antigen preparations compared to those used in 1977-1978 (Table III). The fall in antibody prevalence with parainfluenza I antigen in 1977 was apparently related to the use of S antigen instead of V antigen (Table III). Comparison with previous studies is difficult, as most of these had been performed with neutralization or haemagglutination inhibition tests, and all age groups are not represented [Golubjatnikov et al, 1975; Jennings, 1971; Jensen et al, 1962; Parrott et al, 1962].

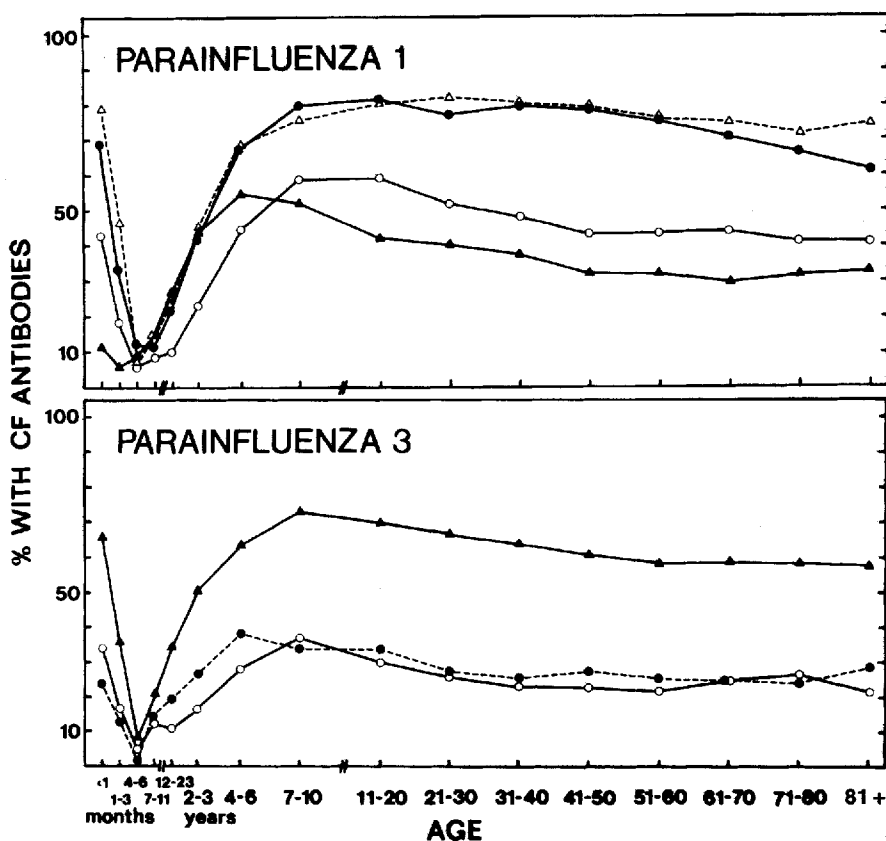


Fig. 2. Age-specific prevalences of CF antibodies to parainfluenza type 1 and 3 antigens. Symbols and other details are as in Figure 1. The broken line represents only 1 year: 1975 in case of parainfluenza 1, and 1973 in case of parainfluenza 3.

The frequency of antibodies to respiratory syncytial virus (RSV) was characterized by a rapid increase up to the age of 6 years, and only a slight decrease in adults (Fig. 3). This observation is in accordance with the known epidemiology of RSV. While causing major illness only in infants and elderly people, it spreads through all age groups during epidemics, mostly by subclinical infections [Cooney et al, 1975; Henderson et al, 1979; Parrott et al, 1973].

Epidemics of RSV infections occurred in Finland every second year during the study period. The epidemic in 1973 to 1974 probably caused the observed increase in antibody prevalence in all age groups; the overall positivity was 15% in 1973, but 78% in 1974 (Fig. 8). Other studies on RSV antibodies by CF have resulted in very different frequencies. Hornsleth and Volkert [1964] found only 23% with antibodies at the age of 15 years. On the other hand, an almost identical prevalence pattern compared with our investigation was reported from London [Hambling, 1964]. These differences are most likely due to presence or absence of widespread epidemics

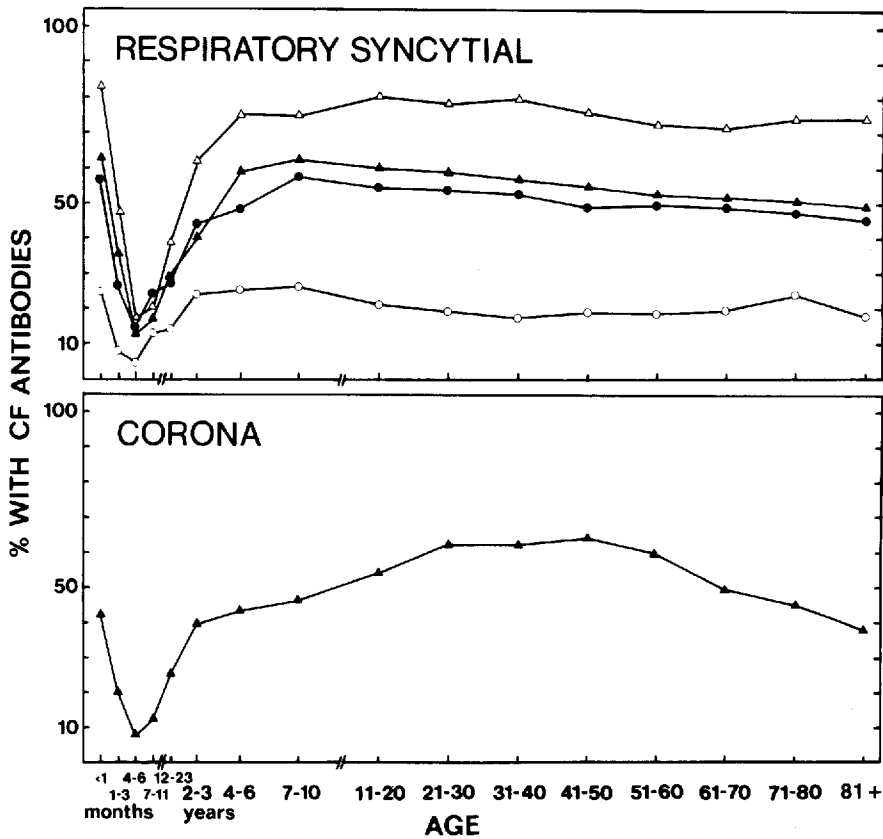


Fig. 3. Age-specific prevalences of CF antibodies to respiratory syncytial and corona viruses. Symbols and other details are as in Figure 1.

during the study, which can clearly be seen in our material covering a period of 8 years. It is interesting to note that despite the apparent heavy epidemic in 1977 to 1978, the prevalence of RSV antibodies decreased steadily from 1976 (73%) to 1978 (45%). One explanation for this might be that most of the documented RSV cases during the last epidemic were from the southwestern district of Finland not served by this laboratory.

Antibodies to coronavirus reached a high prevalence, more than 60% by the age of 30 years (Fig. 3). This shows that coronavirus infections are common, and they occur during a long period of life. These infections are apparently mild, which explains the unexpectedly low numbers of serologically diagnosed infections in contrast to the high antibody prevalence [Riski and Hovi, 1980].

Mumps

The prevalence of mumps antibodies differed slightly from parainfluenza virus antibodies: A rapid increase starting at 6 months tended to continue up to 20 years of age; thereafter the prevalence slowly decreased (Fig. 4). It should be mentioned that vaccination against mumps with a killed vaccine in Finland is carried out only in

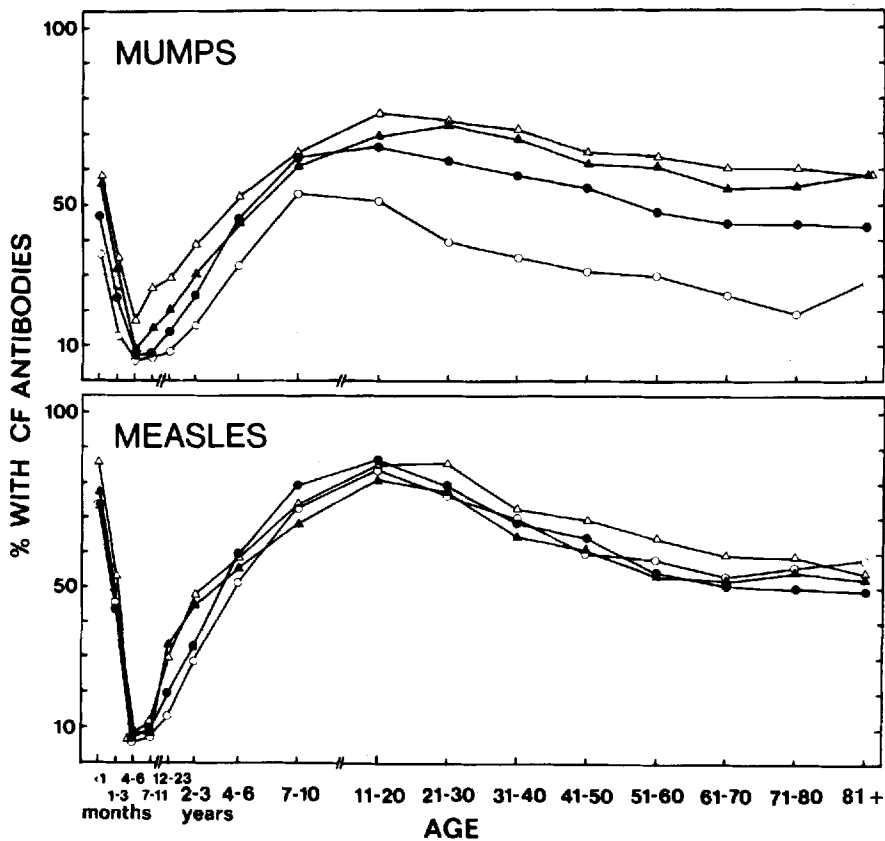


Fig. 4. Age-specific prevalences of CF antibodies to mumps and measles viruses. Symbols and other details are as in Figure 1.

conscripts in the Defence Forces around the age of 20 years [Penttinen et al, 1968]. The observed similarity to parainfluenza viruses was somewhat unexpected, as mumps infection is thought to induce a lifelong immunity in most cases, whereas the parainfluenza viruses do not. However, the persistence of CF antibodies to mumps may be an indication of repeated external boosting by contacts with the virus irrespective of the clinical immunity status. The similarity of the antibody frequencies against paramyxoviruses may also partly be due to antigenic cross-reactions [DeMeio and Walker, 1957; Lennette et al, 1963; Penttinen and Cantell, 1967].

There were two epidemics of mumps during the study period: in 1971, and in 1975 to 1976. The former epidemic was preceded by a low prevalence of antibodies and was followed, as expected, by an increase in the prevalence numbers through all age groups (Figs. 4 and 8). During the latter epidemic, an increase in the antibody prevalence was clearly seen only in children between 12 months and 3 years of age (Fig. 8), although mumps infection with the characteristic clinical symptoms (parotitis, meningitis) is not common at this age. However, it is known that in children below 5 years, mumps virus infections are often present with only respiratory symptoms [Cooney et al, 1975] and, therefore, may not be recognized as mumps.

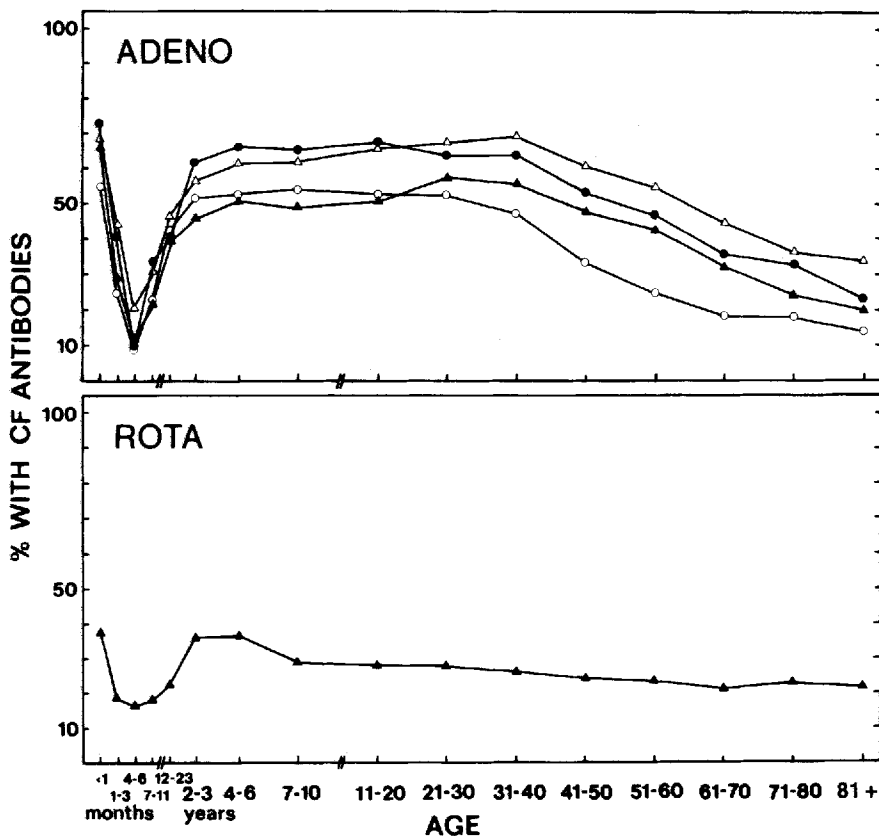


Fig. 5. Age-specific prevalences of CF antibodies to adeno and rota viruses. Symbols and other details are as in Figure 1.

Measles

Measles antibody prevalence differed from that of other paramyxoviruses in two respects: There was practically no interannual variation, and a distinct decrease in prevalence occurred after the age of 30 years (Fig. 4). The first feature suggests that the antigen has not much changed during the study period, and on the other hand, it is in agreement with the fact that measles is constantly circulating in the population instead of causing intermittent widespread epidemics. The declining antibody prevalence in adults is in agreement with the results of a 5-year follow-up study where the CF antibody titers lowered significantly during the first year after measles infection [Bech, 1960].

Vaccination of children with live measles vaccine began in Finland in 1975. Most children are vaccinated at the age of 12 to 16 months. The effect of vaccination on the prevalence curves (earlier increase in prevalence) is apparent in the age groups 1 to 3 years (years 1975 to 1978 vs 1971 to 1974).

Adenovirus

Antibodies against adenovirus appeared early; after 6 years of age there was no more increase in prevalence. Another characteristic feature was the prominent de-

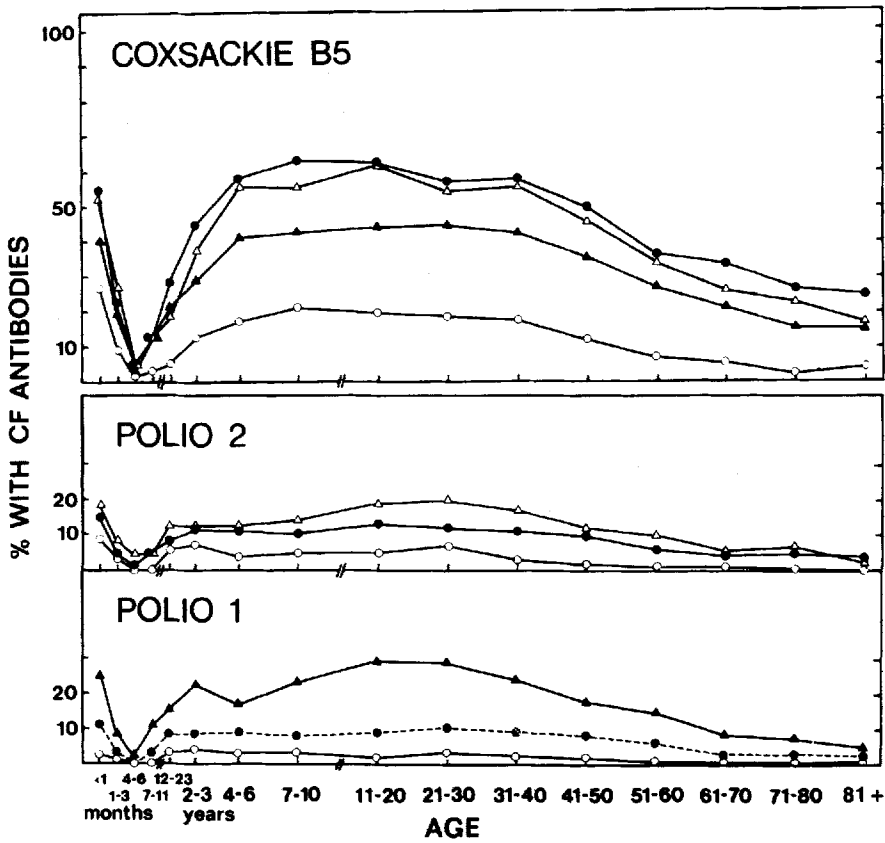


Fig. 6. Age-specific prevalences of CF antibodies to coxsackie B5 and polio type 1 and type 2 antigens. The broken line represents only 1 year, 1973 (polio 1). Symbols and other details are as in Figure 1.

crease in antibody frequency of adults beginning at the age of 40 years (Fig. 5). The drop was even steeper than that found for measles antibodies. A similar trend for adenovirus antibodies has also been reported from Jamaica [Jennings, 1971]. From the results it could be suggested that external boosting, which is likely to occur at all ages, as adenovirus infections are common in population, no longer stimulates the CF antibody formation in the older age groups. Neutralizing antibodies probably present in adults may prevent the boosting of CF antibodies. On the other hand, decreasing contacts with children may also result in fewer external boosting occasions in the older age groups.

Rotavirus

Antibodies to rotavirus were found at a relatively low frequency, which contrasts with the common occurrence of rotavirus infections during childhood (Fig. 5). This suggests that the CF antibodies are of short duration as, on the other hand, they regularly develop during gastroenteritis caused by rotavirus [von Bonsdorff et al, 1978]. In our material, the rotavirus antibodies were acquired somewhat later than in a previous study with a similar antigen [Blacklow et al, 1976]. Although the maximal

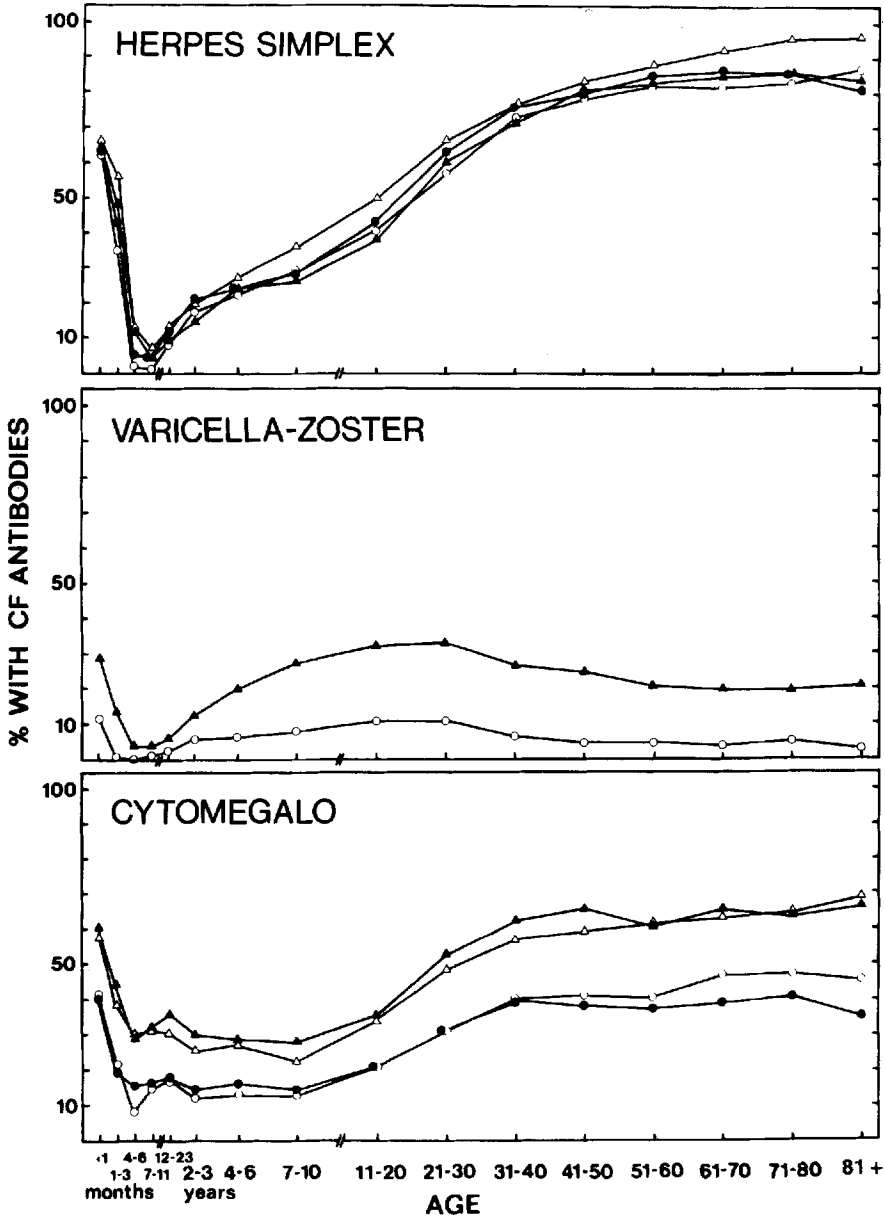


Fig. 7. Age-specific prevalences of CF antibodies to herpes group viruses. Symbols and other details are as in Figure 1.

prevalence was rather low (about 35% at the age of 4 years), the minimal frequency after loss of maternal antibodies remained relatively high (about 15%) compared with most other antiviral antibodies. This is in agreement with the frequent occurrence of rotavirus infections in early childhood. The period of increasing antibody prevalence was shorter (up to 4 years of age) than with any other antigen in this study (Fig. 9).

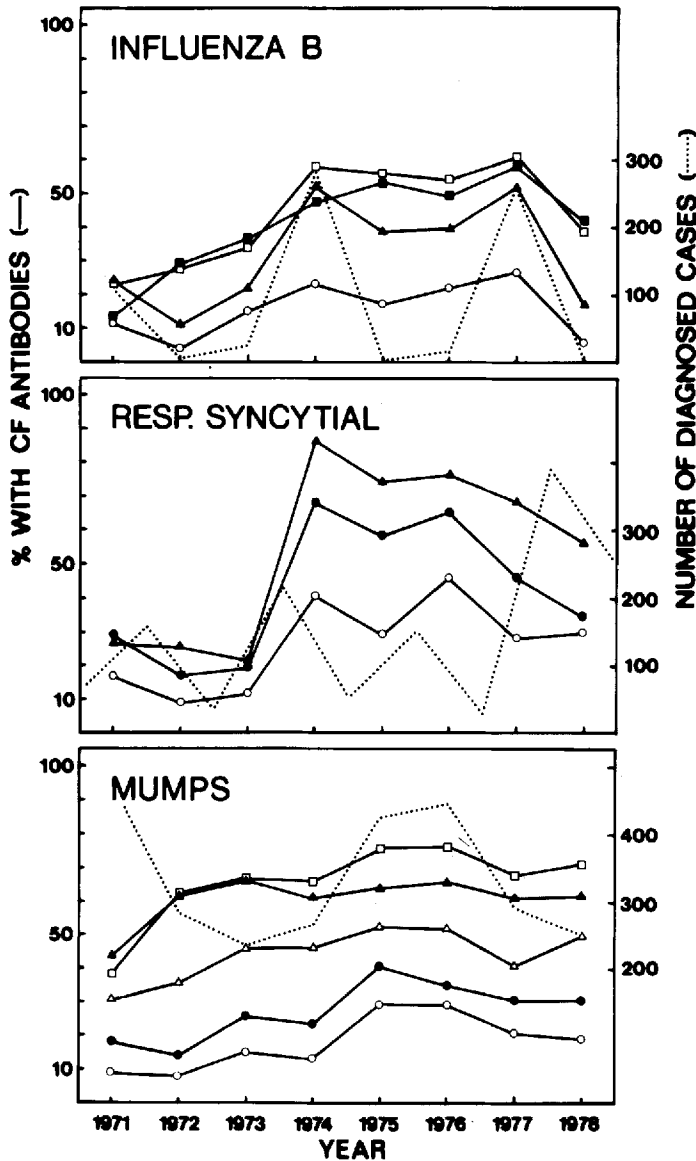


Fig. 8. Associations of virologically diagnosed (by serology and/or virus isolation) influenza B, respiratory syncytial, and mumps virus infections (. . . .) with the respective CF antibody prevalences (—) in selected age groups (showing the clearest changes) during the years 1971-1978. Age groups: 12-23 month olds (o), 2-3 year olds (•), 4-6 year olds (△), 7-10 year olds (▲), 11-20 year olds (□), and 41-50 year olds (■).

Enteroviruses

The antibody prevalence measured by coxsackie B5 antigen revealed a pattern similar to that observed with adenovirus, suggesting that enterovirus infections are common during the first 6 years of life in this population (Fig. 6). The overall increase in antibody prevalence (7% in 1971, 53% in 1974) was probably caused by

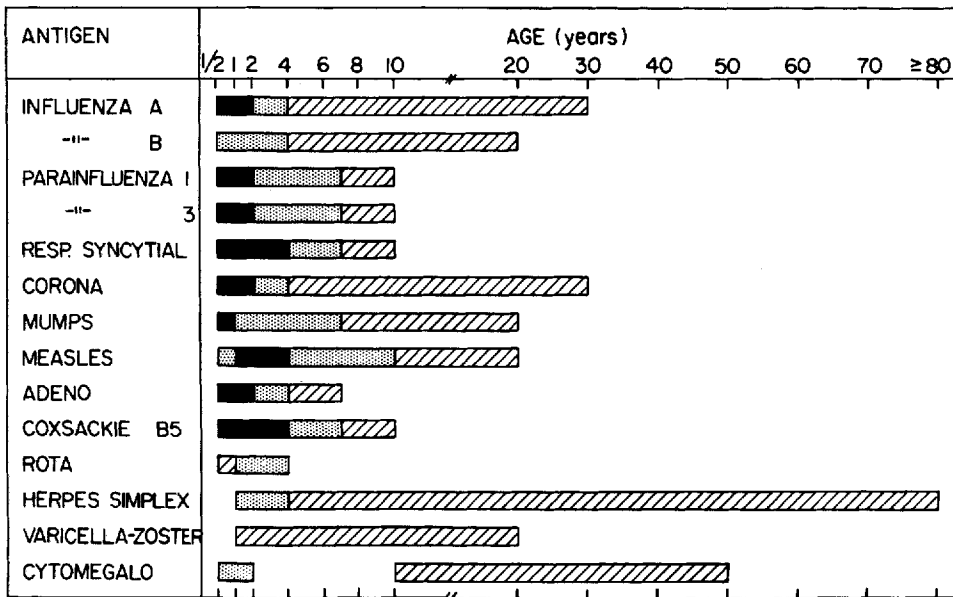


Fig. 9. Periods of increasing prevalence of CF antibodies against 14 viral antigens based on data shown in Figures 1-7. The horizontal columns demonstrate the rate of increase in prevalence percentage: █ > 10%, ▒ 5-10%, ▨ < 5% increase per 1 year of age.

an improved antigen preparation, as the number of virologically diagnosed diseases caused by enteroviruses did not change during the study years (not shown).

No poliomyelitis cases have occurred in Finland since 1964. All Finnish children have been vaccinated with inactivated polio virus vaccine (types 1, 2, and 3) from the year 1960. Therefore, the antibodies measurable by polio CF antigens (Fig. 6) are in part raised by vaccination. Other enterovirus infections may also contribute to antibody prevalence measured in the polio virus complement fixation test, because of antigenic cross-reactions.

Herpesviruses

Herpes simplex virus. Antibodies to herpes simplex virus had a unique prevalence pattern. Antibodies were acquired relatively rapidly from 6 months to 4 years of age, after which the increase was slow but continued up to the age of 80 years, when 85-95% of the patients had antibodies (Figs. 7 and 9). Similar patterns have been reported by other investigators [Holzel et al, 1953; Smith et al, 1967; Wentworth and Alexander, 1971], although the oldest age groups were not included in all studies. The continuous increase of herpes simplex antibody frequency fits well with the fact that after primary infection, the virus remains latent in the nervous system. In this case, the latent infection or, rather, the reactivations seem to booster efficiently the CF antibody formation. Another distinct feature was that virtually no annual variation of antibody prevalence occurred during the 8 years. This is an indication of the nonepidemic nature of herpes simplex infection as well as of the stability of the CF test for herpes simplex antibodies.

Varicella-zoster virus. The antibody prevalence was generally low compared with the fact that most people have varicella during childhood (Fig. 7). The CF antibodies must disappear rapidly after primary infection, and therefore the CF test is a poor indicator of a past varicella infection. In a previous study, an increasing antibody prevalence was observed in old people, but only 9 to 20 patients were included in these age groups, and therefore, the results may not be representative of whole populations [Tomlinson and MacCallum, 1970]. Higher antibody frequencies in adults (50–60%) have been reported by other authors [Wentworth and Alexander, 1971; Tomlinson and MacCallum, 1970], and a big difference within our study was also seen between the years 1971 to 1972 (6.5%) and 1977 to 1978 (24%). This variation was probably caused by changes in the antigens used (Table III) rather than by epidemiological circumstances.

Cytomegalovirus. The slow and late acquisition of cytomegalovirus antibodies (Fig. 7) was similar to that reported earlier [Hanshaw, 1966; Leinikki et al, 1972; Stern et al, 1965; Wentworth and Alexander, 1971]. The increase in antibody prevalence appeared at two ages: A short period of rising antibodies was observed between 6 months and 2 years of age, then the prevalence remained steady up to the teen ages, when another period of increasing antibody frequency took place. Cytomegalovirus is known to infect most people primarily before 1 year of age [Leinikki et al, 1972], which is in agreement with the first peak in our prevalence curve. Thereafter, the increase of antibody frequency cannot be taken as a reflection of primary cytomegalovirus infections but it may result from boosting effects of reactivated infection. The increase in prevalence after 10 years of age is probably associated with sexual activity; hormonal changes (eg, pregnancy) may also play a role.

It may well be that with most members of the herpesvirus group, the primary infection as such does not induce longlasting CF antibodies, and that the relatively late increases of antibody positivity in our material reflect the accumulated effect of several boosters coming internally by reactivation of latent infections (in the case of varicella-zoster, herpes simplex, and cytomegalovirus), and possibly externally (repeated exposure to varicella at school age, and to herpes simplex and cytomegalovirus with increasing sexual activity).

GENERAL DISCUSSION

Methodological Considerations

Changes in methodology are important factors affecting the results of any survey covering a period of several years. In our study, all the CF tests were performed in the same laboratory, with the same working procedures, and in many cases, with identical antigen preparations through the whole period. A good indicator of the stability of the principal method was the prevalence of herpes simplex virus antibodies since the age-specific prevalences were unchanged during 8 years.

Great interannual variations with some antigens, without obvious epidemiological reasons, can be interpreted as difficulties in the standardization of these antigens. In this group of "poor" antigens we would include parainfluenza, coxsackie B5, polio, varicella-zoster, and cytomegalovirus antigens. The level of antibody positivity was not, however, essential in this survey, but instead, the prevalence pattern was considered to be the most informative point. Irrespective of the varying overall

TABLE IV. The Prevalence Patterns of Complement-fixing Antibodies to Different Viral Antigens (see Figs. 1-7)

Age group	Change in antibody prevalence	Viral antibodies
Children	Rapid and early increase	Influenza A, parainfluenza, respiratory syncytial, corona, mumps, measles, adeno, coxsackie B
	Intermediate rate increase	Influenza B, rota, (polio)
	Slow and/or late increase	Herpes simplex, cytomegalo, varicella-zoster
Adults	Definite decrease	Adeno, coxsackie B, (polio), measles, corona
	Slight decrease	Parainfluenza, respiratory syncytial, mumps, rota, varicella-zoster
	No change	Influenza A and B
	Increase	Herpes simplex, cytomegalo (slight increase)

antibody prevalences, the age-specific prevalence patterns did not significantly change during the 8 years, as exemplified by cytomegalovirus antibodies.

Patient Material

Although the serum samples studied were obtained from patients with suspected viral infection, we consider that the general population was fairly well represented for the prevalence of antiviral antibodies. The rationale for this is based on the use of the screening test with nearly 20 viral antigens: The percentage of recent infections caused by a given virus under study was negligible, as the screening test was applied for the diagnosis of a great number of different infections. From the computer files we found that the total number of acute viral infections (rising antibody titers in paired sera) was about 10% in this material. The most common diagnosis was influenza A, which accounted for 1-3% of the patients, while the other virus diagnoses were found in less than 1% of the patients. This means that in the case of influenza A, 97%-99% of the patients did not have a recent influenza A infection at the time of study and could be regarded as "normal" population. The respective percentages for the other viruses were more than 99%. Furthermore, the patients were not selected for socioeconomic class due to the public health care system in Finland, and because our laboratory serves all types of hospitals and polyclinics, representing about two-thirds of the whole population. However, the fact that about 80% of the patients were from hospitals and only 20% from outpatient clinics diminishes the value of this material as a representative of normal population and may result in erroneous interpretations of some of the results.

Antibody Prevalence Patterns

For most viral antigens the antibody levels by CF are known to decrease relatively soon after primary infection. Therefore, the period of increasing antibody prevalence might be considered to reflect at what age infections mainly occur (sum-

marized in Fig. 9). Both primary and reinfections may contribute to this part of the prevalence curve. The persistence of antibodies in adults is much more difficult to explain as it is probably a net result of several factors typical of each infective agent. These factors include the capability to induce chronic and latent recurring infections (herpes group), repeated epidemic exposures (influenza A and B), and antigen cross-reactions (paramyxoviruses; enteroviruses). It is clear that neutralization test and probably radioimmunoassay and enzyme immunoassay would be proper methods to determine the cumulative proportion of the population that has experienced a given virus infection.

In spite of variations in the overall antibody prevalences, the characteristic age-specific prevalence patterns for any given viral antibody remained fairly constant from year to year. Patterns typical of each antigen are evident in Figures 1-7 and are arbitrarily arranged in groups in a summary table (Table IV). The specific patterns shown by the herpesviruses can be explained by the unique biological features of these viruses. Whether the more modest differences between the patterns of antibody prevalences of all the other antigens reflect any true biological differences between the respective viral infections, cannot be judged by the available information.

ACKNOWLEDGMENTS

The authors thank Ms. Helena Norrila for secretarial help, and Mr. Pekka Pulkkinen, B.Sc., for advice in computer use and the data registry.

REFERENCES

- Bech V (1960): Titers of complement-fixing measles antibodies in human sera collected from one to five years after illness. *Acta Pathologica Microbiologica Scandinavica* 50:81-88.
- Blacklow NR, Echeverria P, Smith DH (1976): Serological studies with reovirus-like enteritis agent. *Infection and Immunity* 13:1563-1566.
- von Bonsdorff C-H, Hovi T, Mäkelä P, Mörttinen A (1978): Rotavirus infections in adults in association with acute gastroenteritis. *Journal of Medical Virology* 2:21-28.
- Cooney MK, Fox JP, Hall CE (1975): The Seattle virus watch. VI. Observations of infections with and illness due to parainfluenza, mumps and respiratory syncytial viruses and *Mycoplasma pneumoniae*. *American Journal of Epidemiology* 101:532-551.
- DeMeio J, Walker DL (1957): Demonstration of antigenic relationship between mumps virus and hemagglutinating virus of Japan. *Journal of Immunology* 78:465-471.
- Golubjatnikov R, Allen VD, Olmos-Blancarte MP, Inhorn SL (1975): Serologic profile of children in a Mexican highland community: Prevalence of complement-fixing antibodies to *Mycoplasma pneumoniae*, respiratory syncytial virus and parainfluenza virus. *American Journal of Epidemiology* 101:458-464.
- Hambling MH (1964): A survey of antibodies to respiratory syncytial virus in the population. *British Medical Journal* 1:1223-1225.
- Hanshaw JB (1966): Cytomegalovirus complement-fixing antibody in microcephaly. *New England Journal of Medicine* 275:476-479.
- Henderson FW, Collier AM, Clyde WA, Denny FW (1979): Respiratory-syncytial virus infections, reinfections and immunity. *New England Journal of Medicine* 300:530-534.
- Holzel A, Feldman GV, Tobin JO, Harper J (1953): Herpes simplex. A study of complement-fixing antibodies at different ages. *Acta Paediatrica* 42:206-214.
- Hornsleth A, Volkert M (1964): The incidence of complement-fixing antibodies to the respiratory syncytial virus in sera from Danish population groups aged 0-19 years. *Acta Pathologica Microbiologica Scandinavica* 62:421-431.
- Jennings R (1971): Adenovirus, parainfluenza virus and respiratory syncytial virus in the sera of Jamaicans. *Journal of Hygiene (Cambridge)* 70:523-529.

- Jensen KE, Peeler BE, Dulworth WG (1962): Immunization against parainfluenza infections. *Journal of Immunology* 89:216-226.
- Leinikki P, Heinonen K, Pettay O (1972): Incidence of cytomegalovirus infections in early childhood. *Scandinavian Journal of Infectious Diseases* 4:1-5.
- Lennette EHF, Jensen FW, Guenther RW, Magoffin RL (1963): Serologic responses to parainfluenza viruses in patients with mumps virus infection. *Journal of Laboratory and Clinical Medicine* 61:780-788.
- Parrott RH, Vargosko AJ, Kim HW, Bell JA, Chanock RM (1962): Myxoviruses: Parainfluenza. *American Journal of Public Health* 52:907-917.
- Parrott RH, Kim HW, Arrobio JO, Hodes DS, Murphy BR, Brandt CD, Camargo E, Chanock RM (1973): Epidemiology of respiratory syncytial virus infection in Washington, D.C. II. Infection and disease with respect to age, immunologic status, race and sex. *American Journal of Epidemiology* 98:289-300.
- Penttinen K, Cantell K (1967): Parainfluenza 1 (Sendai) antibodies and mumps vaccination. *Annales Medicinæ Experimentalis Fenniae* 45:202-205.
- Penttinen K, Cantell K, Somer P, Poikolainen A (1968): Mumps vaccination in the Finnish Defence Forces. *American Journal of Epidemiology* 88:234-244.
- Pönkä A, Ukkonen P (1983): Age-related prevalence of complement-fixing antibody to *Mycoplasma pneumoniae* during an 8-year period. *Journal of Clinical Microbiology* 17:571-575.
- Pyhälä R, Visakorpi R (1979): Influenza A (H1N1) viruses of the 1977/1978 outbreak: Isolation and haemagglutination properties. *Journal of Hygiene (Cambridge)* 82:91-98.
- Riski H, Hovi T (1980): Coronavirus infections of man associated with diseases other than common cold. *Journal of Medical Virology* 6:259-265.
- Riski H, Hovi T, Väänänen P, Penttinen K (1977a): Antibodies to human coronavirus OC43 measured by radial haemolysis in gel. *Scandinavian Journal of Infectious Diseases* 9:75-77.
- Riski H, Pyrhönen S, Wager O, Penttinen K (1977b): Lack of measurable complement-fixing antibodies against viral antigens. *Acta Pathologica Microbiologica Scandinavica, Section B* 85:167-173.
- Smith IW, Peutherer JW, MacCallum FO (1967): The incidence of *Herpesvirus hominis* antibody in population. *Journal of Hygiene (Cambridge)* 65:395-408.
- Stern H, Elek SD (1965): The incidence of infection with cytomegalovirus in a normal population. *Journal of Hygiene (Cambridge)* 63:79-87.
- Tomlinson AH, MacCallum FO (1970): The incidence of complement-fixing antibody to varicella-zoster virus in hospital patients and blood donors. *Journal of Hygiene (Cambridge)* 68:411-416.
- Ukkonen P, von Bonsdorff C-H, Penttinen K (1979): Use of computer in the evaluation of virus diagnostics. Abstracts of the XVII Symposium of the European Association against Virus Diseases, Munich, September 1979.
- Wentworth BB, Alexander ER (1971): Seroepidemiology of infections due to members of the herpesvirus group. *American Journal of Epidemiology* 94:496-507.