

Cyclical patterns and predictability in infection

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An enthusiast does not always realize that what is of profound interest to himself may evoke only an amused tolerance in others... I cannot of course write too vividly of the interest which this study of epidemics has brought to me personally, quite apart from the conviction that it must inevitably lead in some small way to an addition to our knowledge of epidemic disease.

William Norman Pickles M.D., *Epidemiology in Country Practice* (1939).

INTRODUCTION

Many infections, especially viral infections, show a certain periodicity which can be wholly or partly predictable. It is important to be able to recognize these patterns because anticipating changes in incidence should lead to better diagnosis, treatment and control of infection. In this review patterns of some viral and other infections in England and Wales which have been observed from laboratory reports over a period of 21 years, from 1967 to 1987, are described.

SOURCES OF DATA

Laboratory Reports

Since 1967 all Public Health Laboratories in England and Wales, a number varying from 62 to 52 during this period, and most NHS microbiology laboratories have reported all viral as well as certain other microbiologically-confirmed infections to a central epidemiology unit of the Public Health Laboratory Service. Between 1967 and 1976 this was the Epidemiological Research Laboratory and in 1977 the surveillance functions of this unit were passed on to the Communicable Disease Surveillance Centre. The data are reported weekly on specially designed forms. Laboratories complete and post their forms on a Friday and the collection, analysis and interpretation of the week's data by epidemiologists begin on the following Monday. By Friday of the same week, the 'response', in the form of a printed Communicable Disease Report, is ready for posting to the reporting laboratories and to many others concerned with the investigation, diagnosis, treatment and prevention of infection in England and Wales and many countries abroad. Items of special interest, such as reports of outbreaks and periodical interpretative analyses of laboratory data, are included as 'Special Reports' in each issue. Thus within 8 days of reporting, the source laboratory receives a tabulated, analysed summary of prevalent infectious disease in the country, with appropriate interpretation as necessary. Since 1975 the statistics have been computerized, and quarterly and annual tabulations are available.

As the laboratories have provided most of the data on which this review is based, it may be pertinent to examine the limitations and strengths of these laboratory-based statistics. The reporting laboratories do not usually have a defined catchment population; moreover the investigating habits of GPs and hospital doctors tend to vary widely, both within and between areas. For example it has been found that the physical proximity of a general practice to a laboratory is very likely to stimulate use of that laboratory, even more than providing an efficient transport service for specimens (Tillett & Thomas, 1981). The age of the patient, as well as the severity of illness, are also likely to influence use of a diagnostic service. Technical problems – such as the ease with which a laboratory can diagnose an infection, the cost of the investigation and the availability of reagents, the taking and transport of the specimens and the technical competence of the laboratory in making a diagnosis – as well as a laboratory's research interests, all contribute to variation between, and possibly within, laboratories in what they eventually report to CDSC. Finally the reporting itself, both in quality and completeness, may vary from time to time between and within laboratories. In spite of all these apparent disadvantages, however, laboratory reports have provided a valuable source of information on infectious disease in the country. Clinically, they provide a scientific basis to diagnosis, treatment and investigation. Epidemiologically they provide coherent and on the whole, consistent information on trends in infection in the country. Furthermore they add 'qualitative' detail to other sources of information. For example, laboratory reports provide information on the type, subtype and variant of influenza virus causing an epidemic of what would otherwise be clinical influenza.

In the data reported to CDSC there is a lag phase of, on average, 7–10 days between the date the specimen was taken and the date of reporting, which may need to be taken into account when interpreting the data.

Other sources of information

Notifications

As in many other countries, there is a list of infections which doctors are required to notify. In England and Wales, doctors notify cases to the local authority, thus providing information for local prevention and surveillance. These notifications are collated each week and sent to the centrally based Office of Population Censuses and Surveys, where they are further collated, analysed and then published, so providing statistics for national surveillance. Notifications have the advantages of providing data over a considerable length of time and of covering the whole country. The disadvantages are that only a short list of the more serious infections are notifiable; they tend to cover broad diagnostic categories such as food poisoning and, until recently, 'infective jaundice' (to many of which laboratory data provide an important extra dimension); being primarily clinically based, they may be inaccurate; and are often incomplete.

From the point of view of surveillance the importance of the incompleteness and the inaccuracy of notification for common diseases is often overstressed. Few reporting systems are complete, and provided that trends are discernible in time,

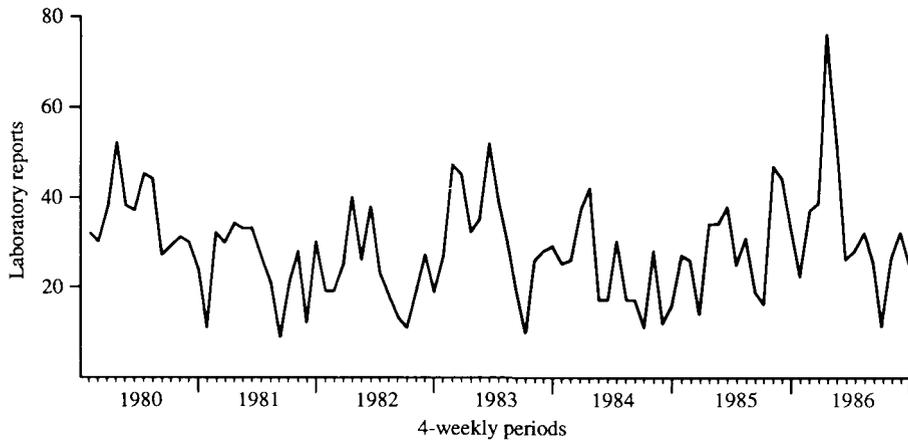


Fig. 1. Rhinovirus: laboratory reports 1980-6.

place and person, it can be argued that the basic requirements of a notification and surveillance system are met. The trends for most common notifiable diseases are also sufficiently consistent to suggest that the diagnoses are mostly accurate, as in the example of whooping cough (see below).

General practitioner reporting system

A third useful source of information on infectious disease in England and Wales is the clinical reporting system run by the Royal College of General Practitioners since 1966 (Fleming & Crombie, 1985). About 40 practices covering a population of about 200 000 report every new diagnosis each week to the RCGP Research Unit in Birmingham. As each reporting practice also provides an age and sex distribution of the practice population, this is the only source of information on infectious diseases with an inbuilt facility to provide a rate. Like notifications, RCGP data are based on clinical diagnoses; they are useful for ascertaining morbidity (consultation) rates of diseases and clinical syndromes not covered by notifications, and for which laboratory reports may be of limited value, such as influenza, chickenpox, mumps and the common cold. The population covered however is small and the distribution of reporting practices patchy.

PERIODICITY OF INFECTIONS

Endemic

Many infections show no regular annual and seasonal variation. Cytomegalovirus (CMV) and herpes simplex virus are characteristic of this group. The rhinoviruses, which are reported untyped, also show little annual variation although there is some evidence of a mild seasonal pattern, with an increase in April/May (Fig. 1). Any significant deviation from the endemic pattern of any of this group of organisms would most likely signify either an artifact, such as an increase in laboratory interest in the organism, easier diagnostic methods, or an increased incidence of an underlying disease. Thus an increasing incidence of

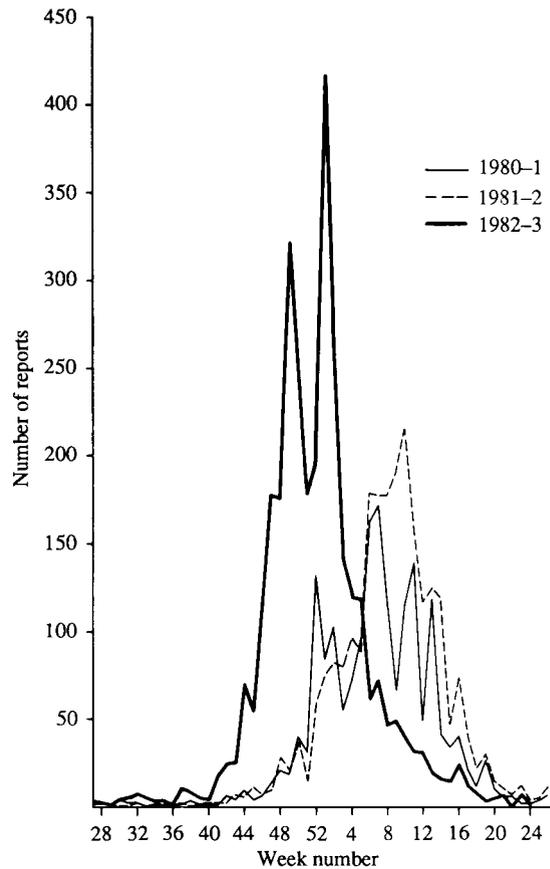


Fig. 2. Respiratory syncytial virus: laboratory reports 1980/1 to 1982/3.

AIDS, and probably other immunosuppressive conditions such as bone marrow and other types of transplant surgery, has been associated with an increase in CMV infections. The 'endemic' viruses are generally quite useful in monitoring the 'diagnostic background' of laboratory reporting – for example a sudden decrease in reporting of these viruses is usually associated with events such as bank holidays, and changes in epidemic virus infections can be assessed against this type of change.

Epidemic

Annual cycles

Many infections undergo cycles lasting 1, 2, 3 or even 4 years. Those that occur every year tend to exhibit the most marked seasonal variation. Thus the respiratory syncytial virus (RSV) has a strong winter incidence and almost disappears in summer and autumn. Numbers of reports of RS virus begin to rise in about December but do not usually increase steeply until the New Year, with a peak usually between February and March. The periodicity of RSV is probably the most predictable of all virus patterns. In 1982 however, for no apparent reason, the outbreak occurred 2 months earlier than usual (Fig. 2). (A similar

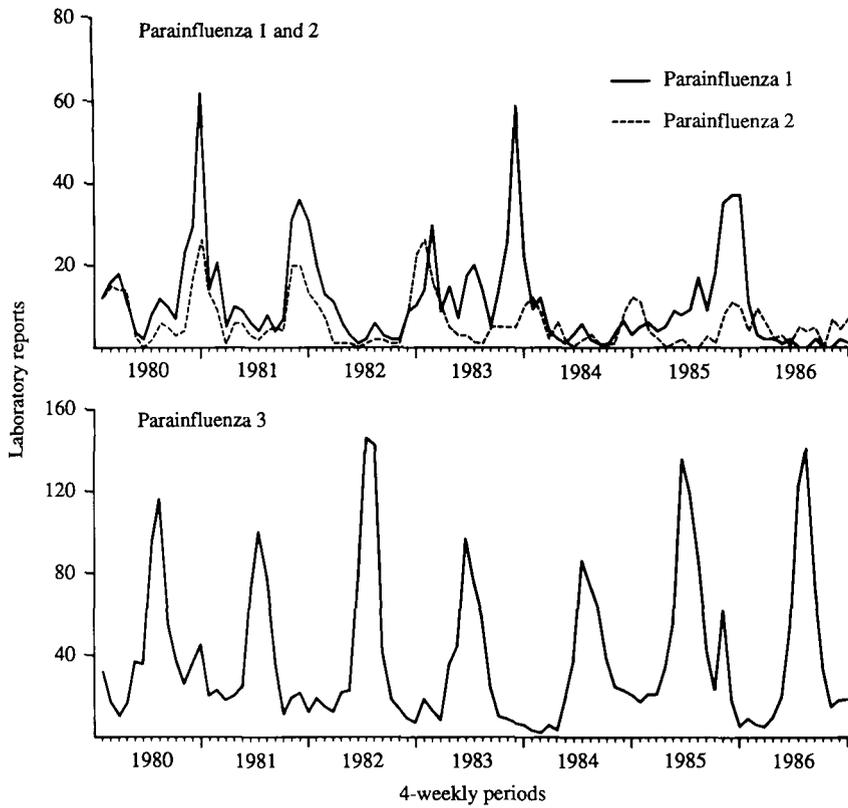


Fig. 3. Parainfluenza viruses: laboratory reports 1980–6.

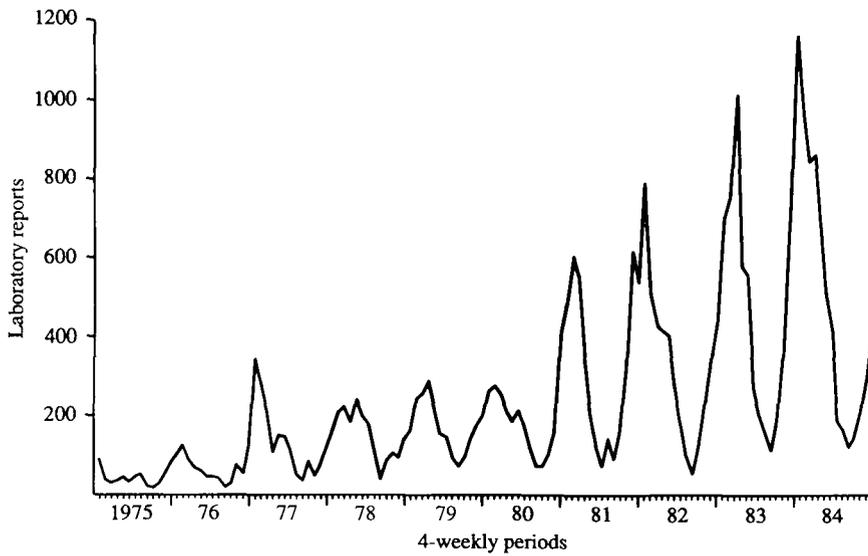


Fig. 4. Rotavirus: laboratory reports 1975–84.

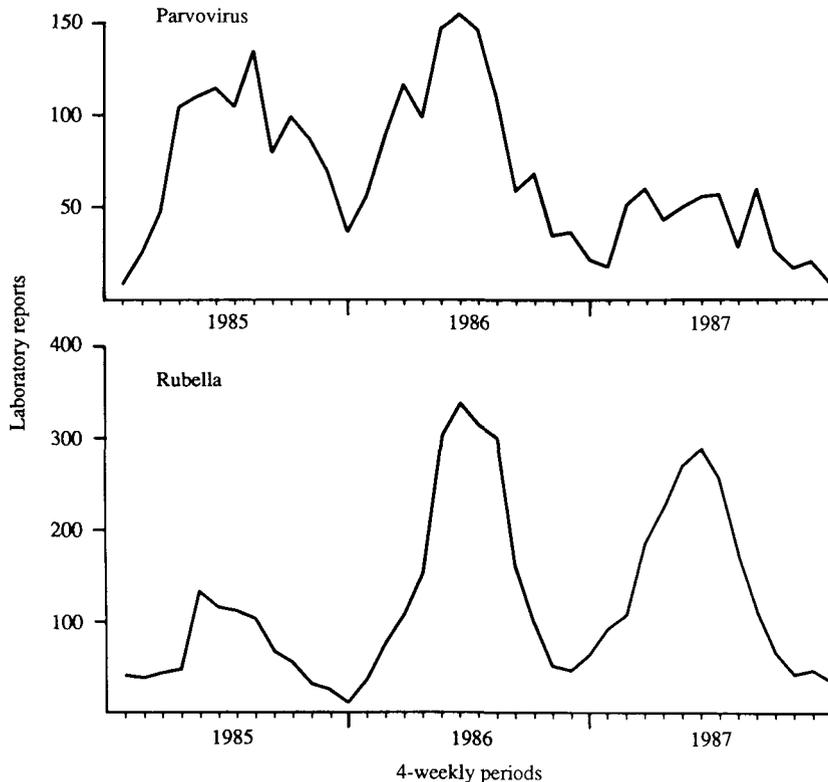


Fig. 5. Parvovirus B19 and rubella: laboratory reports 1985-7.

break in the pattern occurred last winter, 1988/89.) In Scotland, the pattern for RSV infection from 1967 was virtually identical to that in England and Wales until in 1979 a small outbreak occurred not in winter but in summer (Communicable Disease Surveillance Centre and Communicable Diseases (Scotland) Unit 1980). In England only the Northern region followed the Scottish pattern; the rest of the country followed the usual periodicity. These two inexplicable changes in the pattern of RSV infection were the more remarkable given the usual predictability of the virus and were accompanied by some changes in the age distribution of reported cases which are discussed further below.

Parainfluenza type 3 virus, unusually for a respiratory virus, has a summer peak, although infections are reported through most of the year (Fig. 3). One of the gastroenteritis viruses, the rotavirus, has a strong winter pattern which became apparent even from the time when laboratories first began to report these infections, despite the number of reports increasing rapidly over the first few years (Fig. 4). The regularity of the pattern of rotavirus reporting has been remarkable, with numbers increasing in September or October to a peak some time between February and April before returning to the baseline in about August.

Rubella infection has a predictable seasonal pattern, with a peak in June or July, but the size of each outbreak is generally unpredictable (Fig. 5). Although large epidemics are infrequent, it has been known for one large outbreak to follow another, as in 1978 and 1979 (Tobin *et al.* 1985). The seasonal pattern for rubella

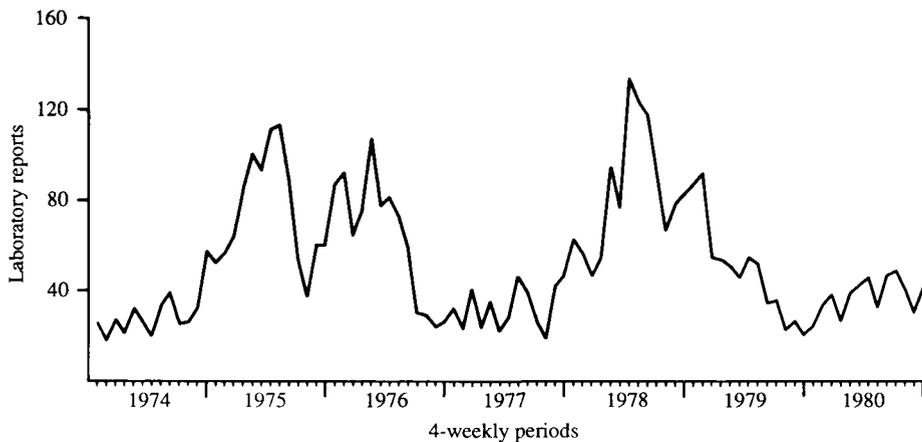


Fig. 6. Mumps virus: laboratory reports 1974–80.

is similar to that for parvovirus B19 (Fig. 5) and it is unfortunate, especially for the future monitoring of the effects of MMR on rubella, that these two infections can be easily confused clinically.

Cycles of 2–3 years

Some of the virus infections with a longer periodicity also have regular patterns of recurrence. The parainfluenza viruses types 1 and 2, unlike type 3 from which they are clinically indistinguishable, exhibit a periodicity quite different from the regular summer and autumn peaks of the type 3 virus. Both viruses cause winter outbreaks, but they do so every 2 years (Fig. 3). Only one exception has occurred to this pattern since 1967, and this is shown in Fig. 3 when the 1981/82 outbreak was larger and the 1982/83 outbreak smaller, than expected and the cycle changed so that alternate years from 1983/84 became the times of high incidence. The winter outbreaks of the parainfluenza viruses 1 and 2, unlike those of the RSV, tend to peak before the end of the year (Fig. 3). These curious differences in the periodicity and seasonality of the three essentially very similar parainfluenza viruses are unexplained.

The mumps virus causes outbreaks every year, with the peaks tending to occur in spring, but the periodicity of this infection is unusual as, superimposed on this seasonal regularity, one can discern a pattern of 2 years of larger outbreaks succeeded by 1 year of a smaller outbreak (Fig. 6).

Measles had a marked biennial cycle until 1968, when the vaccine first began to be used routinely. Death certifications suggest that this biennial pattern was present for at least 100 years.

Longer cycles

Whooping cough and *Mycoplasma pneumoniae* are examples of infections that exhibit cycles of 4 years. Furthermore they tend to coincide. Whooping cough however usually shows a clear '2 year high–2 year low' pattern (Fig. 7) while *M. pneumoniae* takes about 2 years to reach a peak, and a further 18 months to return to the baseline where it remains for a further 12 months or so before rising again (Fig. 8). We should expect the next outbreak of *M. pneumoniae* in the winter of

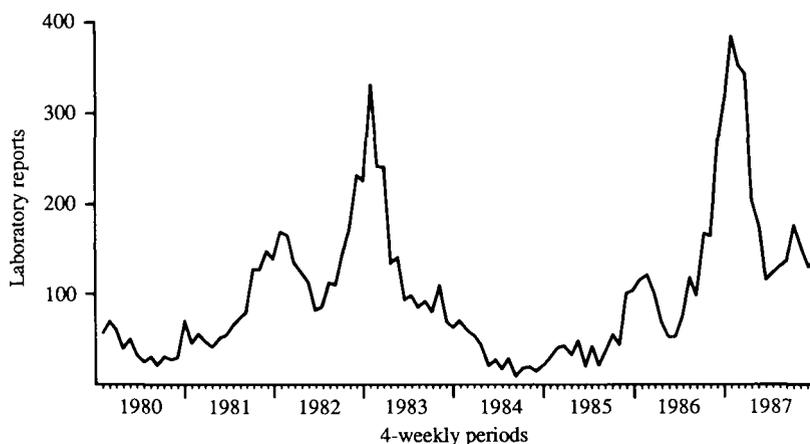


Fig. 8. *Mycoplasma pneumoniae*: laboratory reports 1980–7.

1990/1, with the reports beginning to rise in 1989. The next whooping cough outbreak will also begin in the summer of 1989, and reach its peak in the winter of the following year, 1990/1. Both with whooping cough and *M. pneumoniae* there is usually a small subsidiary peak in the winter preceding the main peak (Figs. 7 and 8), suggesting that both these infections have a mild seasonal tendency.

The magnitude of each whooping cough outbreak appears to be determined by the immunity status of the population as achieved by vaccination. The periodicity on the other hand is not apparently affected by the size of the susceptible population. Thus when the catastrophic fall in vaccination uptake rates occurred from around 78% in the early part of the 1970s to 38% in 1976 the next outbreak did not occur earlier than expected, although it was considerably larger than previously. The subsequent steady increase in whooping cough vaccination uptake rates since 1975 to 68% in 1986 reduced the size of the 1985/6 epidemic but not its timing. With measles on the other hand mass vaccination appears to have removed the classical biennial cycles of this infection.

Figure 7 illustrates how the three main sources of data on whooping cough show almost identical periodicity; the magnitude of the outbreaks also correlate well. This suggests that the two clinical sources of information on whooping cough (notifications and RCGP) probably reflect true whooping cough, as they correlate well with the laboratory isolates of *Bordetella pertussis*.

Another organism that appears fairly regularly to cause outbreaks at long intervals is coxsackie virus A 16, the most common agent of hand foot and mouth disease. Outbreaks have been recorded in 1967, 1970, 1973, 1977/8, 1980, 1983, and 1986 but the recent outbreaks have been less easily discernible because the numbers of isolations reported by laboratories during this time have decreased. Perhaps this is because of financial cutbacks and less demand for viral confirmation of a disease that is easily recognized clinically.

Resurgent epidemics

Some viruses which cause occasional (and unpredictable) outbreaks lasting less than 1 year sometimes cause an outbreak stretching over 2 or more years. It is



Fig. 9. Adenovirus type 7: laboratory reports 1972-5.

often possible to predict this 'second' or resurgent part of the epidemic if the first year's outbreak fails to reach the baseline for that virus after the first peak. In the summer of 1973 an outbreak of adenovirus type 7 occurred (Fig. 9). Reporting did not return to normal levels for that virus by the end of the year, and the virus caused another epidemic in 1974. Some epidemiological features of this outbreak have been described (Epidemiological Research Laboratory, 1973*d*). In 1974, echovirus type 19 produced a similar pattern (Fig. 10) and the resurgence of the outbreak in 1975 was successfully predicted (Epidemiological Research Laboratory, 1975). An example of an echovirus epidemic, that of type 30 in 1986, in which reporting by laboratories did reach the normal levels for that virus by the middle of winter, is shown (Fig. 11). One would expect the outbreak to be over and indeed the virus did not return with any frequency in 1987. A review of the epidemiological features of the echoviruses is in preparation.

The 'random' viruses

There remains a group of viruses, which includes the influenza A and B viruses, outbreaks of which have so far resisted most attempts to predict them. As the influenza A virus in particular tends to produce an outbreak nearly every year, forecasts of 'influenza this year' are generally correct. The magnitude of an epidemic has been rather more difficult to predict, as indeed have many other factors associated with this virus. The seasonal patterns have been only a little more predictable. Influenza A commonly produces outbreaks in early or mid winter but, especially in recent years, has been prevalent in spring and even in summer. Influenza B virus is not much more consistent and tends to cause outbreaks in late winter, spring or early summer. It was confidently expected that the emergence of a new subtype of influenza A would lead to a pandemic within 1 or 2 years, and that the emergence of a new influenza subtype would totally supplant a circulating subtype, but the reappearance of the H1N1 virus in 1977

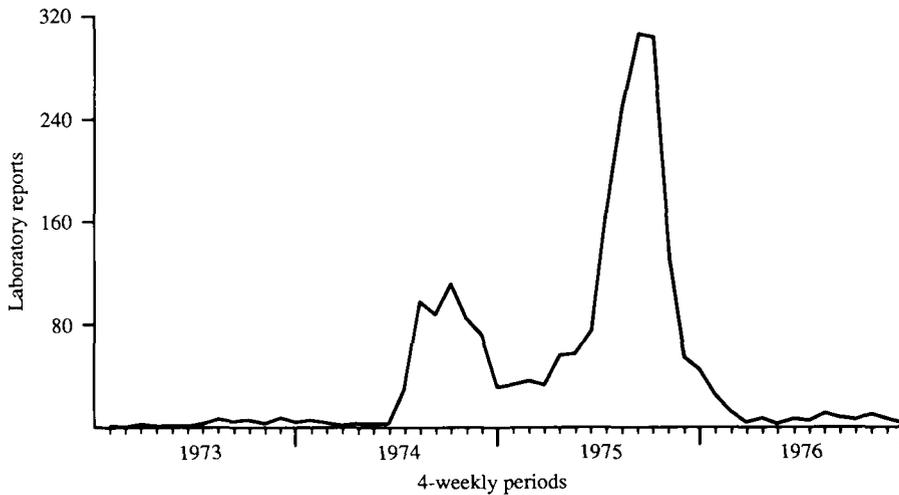


Fig. 10. Echovirus type 19: laboratory reports 1973–6.

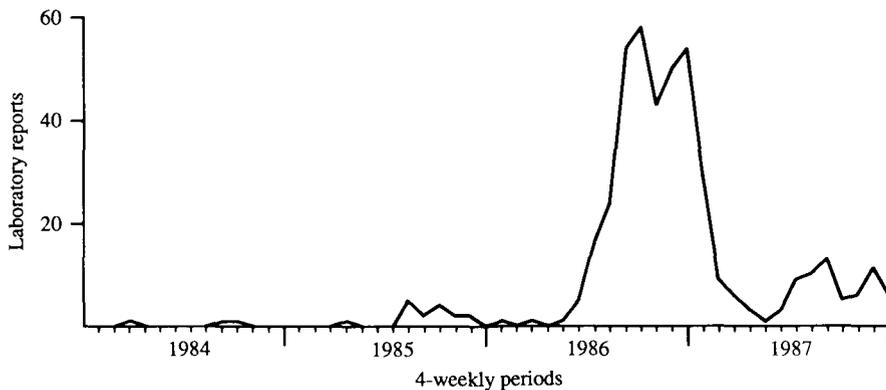


Fig. 11. Echovirus type 30: laboratory reports 1984–7.

about 20 years or so after it stopped causing human infection in 1956, did not create a large pandemic; and it has co-existed peacefully with the already circulating H3N2 subtype for more than 10 years. Longini, Fine & Thacker (1986) claim that some Russian work on mathematical modelling showed good concordance between prediction and observation in the course of the influenza A H3N2 pandemic in 52 major cities of the world in 1968–9. There has not been another pandemic since then to confirm the value of this modelling method.

Periodicity, seasonality and age

For viruses with short cycles, changes in periodicity can be linked with changes in patient-age. The parainfluenza viruses, as already described, fall into two groups: type 3 with an annual pattern and types 1 and 2 with a biannual pattern. The age distribution of the patients from whom these viruses have been isolated shows (Fig. 12) that a greater proportion of infections is diagnosed in children under 1 year of age with parainfluenza type 3 than with types 1 and 2. Moreover

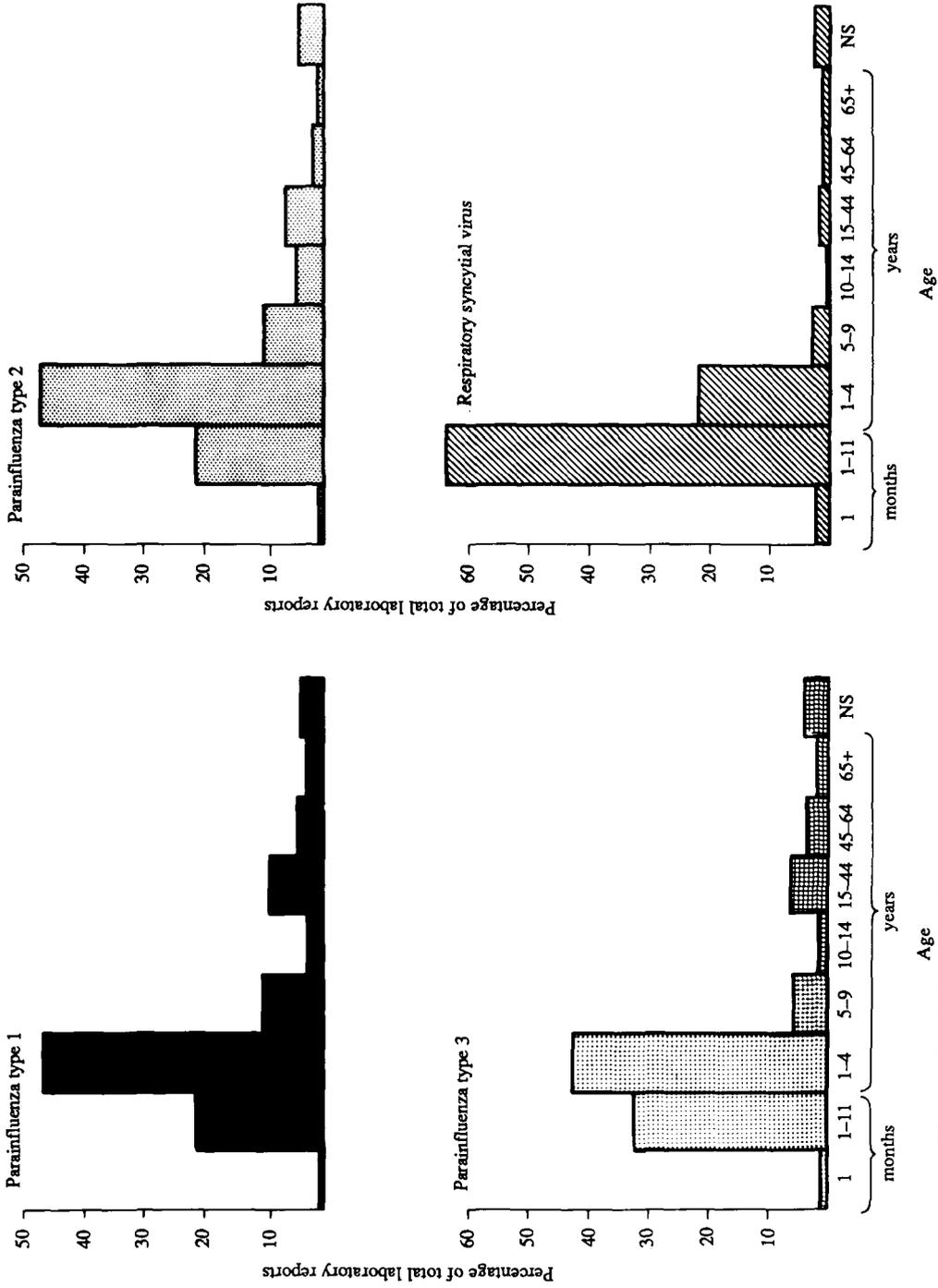


Fig. 12. Parainfluenza and respiratory syncytial viruses: age distribution of laboratory-diagnosed infections.

Table 1. *RS virus, age distribution by (quarter) 1981-4*

Quarter (year)	Total reports	< 1 year (%)	Range (%)
First (81, 82, 84)	5740	4276 (74.5)	73.4-74.9
Fourth (81, 83)	668	488 (73.1)	71.4-73.8
Fourth 1982	1619	1328 (82.0)	—
First 1983	1520	1116 (73.4)	—

Table 2. *RS virus: proportion of reports in under 1-yr-olds 1981/2-83/4*

Epidemic year (weeks 27-26)	Interval between median weeks	Age					6-11 months	Total (all ages)
		< 1 week	1-3 weeks	1-2 months	3-5 months	6-11 months		
		Number (%)						
81/2	—	0 (0.0)	53 (3.3)	468 (29.3)	612 (38.4)	462 (29.0)	1594	
82/3	44	3 (0.1)	87 (3.7)	792 (33.7)	820 (34.9)	647 (27.5)	2349	
83/4	58	2 (0.1)	111 (4.4)	803 (31.9)	873 (34.7)	730 (29.0)	2519	

the age distribution for type 1 and type 2, which have identical periodicity, is closely similar. The RS virus, with its large epidemics every year, affects predominantly those under 1 year of age. When, in Scotland and the Northern Region of England, the RS virus failed to produce a significant outbreak in the winter of 1979, the age distribution for RS virus infection in Scotland curiously was altered in the year before (Communicable Disease Surveillance Centre, Communicable Diseases (Scotland) Unit, 1980) when there was a lesser than expected proportion of cases in those aged under 1 year and a greater than expected proportion in those aged 25 years and over. In England in 1982/3 however, when the outbreak of RS virus infection occurred about 2 months earlier than usual, in the fourth quarter of 1982 82.0% of cases reported were under 1 year of age compared with an expected proportion of 73.1% of cases in this quarter (Table 1). By the first quarter of 1983 however the proportion of those under 1 was back to 'normal' (Table 1).

An analysis of changes in age distribution of RS infection in the under 1-year-olds (Table 2) has been conducted for three epidemic periods 81/2 to 83/4, using an epidemiological year (week 27 to week 26). The times between epidemics have been calculated by counting the interval between the median week of each outbreak. When an outbreak occurred after a short interval (82/3) there was a shift in the age distribution to the 1-2 m age group, and a shift back to 6-11 m after a long interval (83/4).

DISCUSSION

Many of these cyclic and seasonal variations in infection shown by the laboratory reporting system were described in 1973 in the epidemiology reports from the Epidemiological Research Laboratory in *The British Medical Journal*: the parainfluenza and RS viruses (Epidemiological Research Laboratory,

1973*a, b*), adenovirus type 7 (Epidemiological Research Laboratory, 1973*d*), hand, foot and mouth disease (Epidemiological Research Laboratory, 1973*c*). The cyclic pattern of *M. pneumoniae* in the UK was described in 1974 (Noah), similar periodicity having already been noted in Denmark (Lind, 1971). Such cycles of *M. pneumoniae* infection have since been shown to occur throughout Scandinavia and they appear to run approximately in parallel with those in the UK (Noah & Urquhart, 1980). Variations in incidence with similar periodicity occur in Australia and New Zealand for *M. pneumoniae* (Noah & Urquhart, 1980), as well as for the parainfluenza and RS viruses, with parainfluenza 1 and 2 in April/May, parainfluenza 3 in November/December, and RS virus in June, 1 or 2 months after parainfluenza types 1 and 2 (Communicable Disease Intelligence, 1981). The seasonal patterns are thus consistent with those in England and Wales. The seasonal patterns of RS virus and parainfluenza viruses 1, 2 and 3 do not appear to be different in USA (Glezen *et al.* 1984; Kim *et al.* 1973; Monto, Bryan & Rhodes, 1974; Monto, 1973) though a study in Michigan (Monto, 1973) stated that parainfluenza type 3 occurred in the autumn. The data provided in this paper, however, suggest that the type 3 virus is indeed a summer virus. The alternating short and long intervals between peaks of RS virus infection described in USA (Monto, Bryan & Rhodes, 1974) do not seem to occur in England and Wales or Scotland (Noah & Urquhart, 1980). Localized surveys of children with acute respiratory infections have confirmed the patterns described here for the parainfluenza and RS viruses (Buchan, Marten & Kennedy, 1974; Martin, Gardner & McQuillin, 1978; Hope-Simpson, 1981). In Norway (Anestad, 1982, 1987) the variations in incidence of the parainfluenza and RS viruses are similar to ours, but the 'interference' noted between these viruses and influenza A virus has not been seen in our data. The changes in age described in this review suggest that periodicity is an important factor in determining the age distribution of certain infections; or perhaps the periodicity is partly dependent on the age distribution of susceptibles?

It is probable that the patterns described here may only occur during periods of social and demographic stability, and may change at times of great behavioural or social upheaval.

Knowledge of variations in incidence of infection is important for several reasons. It should be helpful both to the clinician and the microbiologist in making a diagnosis. It should also be helpful in making decisions about treatment. Planning for outbreaks could be easier to rationalize, and preventive strategy should be influenced for the better by a knowledge of epidemic behaviour.

Allowances for periodicity of infection will need to be made in research projects: a 1-year study of, say, respiratory infection in a community would be difficult to interpret without prior awareness of the phase of the whooping cough/*M. pneumoniae* cycles in which the survey was conducted.

Knowledge of cyclic variation in infections may help to generate hypotheses about chronic and other diseases in which secular variation has also been noted: these include anencephalus and spina bifida (Maclean & Macleod, 1984), thyrotoxicosis, which was attributed to seasonal variation in iodine intake (Phillips, Barker & Morris, 1985), cryptorchidism (Jackson & Swerdlow, 1986), cardiovascular mortality (Baker-Blocker, 1982; Bainton, Moore & Sweetnam,

1977), sudden infant death syndrome (Helweg-Larsen, Bay & Mac, 1985), and insulin-dependent diabetes (Gleason *et al.* 1982). The seasonality found in deaths from asthma (Khot & Burn, 1984) is similar to that for parainfluenza type 3. Using laboratory data from the PHLIS, Gabriel *et al.* (1976) were able to show a correlation between influenza B and renal transplant rejection and between adenovirus infection and renal graft rejection. In reviewing such associations, it is often helpful to see if the association holds good during times of unexpected changes in incidence. Alderson (1985) has written a comprehensive and useful review of season and mortality.

Like William Pickles, I hope that the reader's 'amused tolerance' will have been sustained to this point.

Each laboratory identification reported represents a considerable amount of careful work by the laboratory, and their essential part in the infection surveillance system in England and Wales is gratefully acknowledged. I am grateful also to Sarah Fowle for assistance with the analysis of age.

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