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Epidemiological features of parainfluenza virus infections: Laboratory surveillance in England and Wales, 1975–1997

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Abstract. Hospital laboratory reports of parainfluenza virus (PIV) infections from England and Wales between 1975 and 1997 were analysed with regard to PIV type and seasonality, and in addition, those between 1985–1997 with regard to age, sex and clinical features. Laboratory-based surveillance data highlight striking differences in the seasonality of different PIV types. PIV-3 reports demonstrated a clear annual epidemic cycle, with a peak usually occurring in late spring or summer, whereas peaks of PIV-1 and PIV-2 occurred at one or two year intervals, in the late autumn or early winter. PIV-4 also occurred most frequently in the late autumn or early winter, but a clear epidemic cycle could not be identified. Laboratory surveillance data also provide insight into the age and disease distribution of PIV infection in children and indicate severity of PIV infection in immunosuppressed adults. Of 8221 PIV reports received between 1985–1997, PIV-3 accounted for 70.8%, PIV-1 for 17.2%, PIV-2 for 7.5%, and PIV-4 for 1.1%; 64.1% of reports came from infants under one year, 24.4% from children aged 1–4 years and 7.2% from individuals aged 5 years or older, with an excess of males in all age groups. Bronchiolitis, croup and pneumonia occurred in association with all PIV types. In children under 1 year, PIV-2 infections were more likely to be associated with bronchiolitis than infections with other PIV types. In children under 15 years, croup was more frequently associated with PIV-1 and PIV-2 than with PIV-3 or PIV-4. In 392 (7.2%) of the reported PIV infections between 1989 and 1997 an underlying condition was implicated, which included immunosuppression or chronic cardiac or pulmonary disease. Considerable morbidity is associated with PIV infections in infants and young children and would make the widescale use of a vaccine a valuable public health intervention. Surveillance information is essential to guide the development and use of preventive measures as well as to monitor their effectiveness.

Key words: Epidemiology, Parainfluenza virus, Respiratory diseases, Seasonality, Surveillance

Introduction

Lower respiratory tract infections (LRTIs) are one of the leading causes of mortality and disability worldwide [1]. Human respiratory viruses, such as influenza viruses, respiratory syncytial virus (RSV), adenovirus, and parainfluenza viruses (PIVs), contribute substantially to the burden of respiratory infections in all age groups [1–3], but particularly in the very young and in the elderly.

Human PIVs are an important cause of acute respiratory infections and predominantly affect infants and young children [4–11]. They have been associated with a variety of upper and lower respiratory syndromes including rhinitis, otitis, laryngotracheobronchitis or croup, bronchiolitis, and pneumonia [2, 3, 5, 9] as well as asymptomatic infections. A high percentage of the population have been infected by the age of 2, although reinfection is common throughout life, because infection does not necessarily confer protective immunity. The severity of infection decreases with increasing age, which may reflect altering physiology and anatomy of the maturing respiratory tract, as well as gradual accumulation of neutralising antibody [9].

PIV1-4 are members of the *Paramyxoviridae* and have a single stranded negative sense RNA genome. The virus envelope contains two glycoproteins: the haemagglutinin-neuraminidase (HN) and the fusion (F) proteins, to which the major antibody response is generated. Four major serological types have been identified: PIV-1 to 4, although PIV-1 and 3 and PIV-2 and 4 are genetically more closely related to each other, than to other PIV types [8].

PIVs have also recently been identified as a cause of nosocomial outbreaks involving paediatric, geriatric [12, 13], and bone marrow transplant wards [14].

PIVs, in particular PIV-3, have been also recently been associated with acute pneumonia, persistent infection and high mortality in immunosuppressed patients, including transplant recipients and patients undergoing chemotherapy, suggesting an enhanced pathogenicity of human PIV in these groups of patients [14, 15].

Therefore, it was of some interest to determine whether the changing patterns of chemotherapy for cancer, improvements in organ transplantation and identification of other immunosuppressive diseases or conditions, such as HIV infection, have had any impact on the detection or severity of PIV infections reported in a national surveillance scheme in the last decade. We present an analysis of laboratory reports of PIV infections from England and Wales, with regards to PIV type, age, sex and clinical features of illness, including underlying conditions of the patients over the period 1985–1997, and with regards to seasonality, over the period 1975–1997.

Methods

National laboratory reporting scheme for England and Wales

In the national laboratory reporting scheme for England and Wales, the network of Public Health Laboratory Service (PHLS) diagnostic and reference laboratories, as well as over 200 National Health Service (NHS) microbiology laboratories report identifications of bacteria, viruses and other pathogens from clinically significant infections to a central database held at the PHLS Communicable Disease Surveillance Centre (CDSC), Colindale, London, [16, 17]. The laboratory reports include information about specimen type, diagnostic method, and demographic details. Reports received after 1988 contained additional clinical and epidemiological information, in the form of semi-structured or free text. For some laboratories using electronic systems, prompts for specific clinical features e.g. bronchiolitis, croup and pneumonia were available.

Laboratory methods

During the period of this study, the main laboratory methods of diagnosis of PIV infection were virus isolation, direct immunofluorescence (DIF) and complement fixation test (CFT) serology. Isolation of PIV 1–4 was usually by inoculation of clinical specimens, onto primary rhesus monkey kidney cells provided by either the European Cell Culture Collection, Porton, England, or onto VERO (African Green Monkey) cells. Identification of PIV growth was usually by haemadsorption followed by either neutralisation using immune antisera or commercially available type or subtype-specific fluorescent (FITC conjugated) antibodies. Identification of PIV infection normally occured as part of a screen for respiratory viruses, but is likely to have been under ascertained as many appropriate specimens may not have beeen tested for the presence of PIVs.

Data analysis

PIV reports received during the years 1975 to 1997 were extracted from the database for analysis. The main data items were: virus type (PIV 1–4, or untyped), age and sex of patient, date of specimen collection, specimen type and test method, and Regional Health Authority (RHA) of source laboratory. Aggregated data was used for the period 1975–1984, in the form of counts of PIV reports by virus type and week of specimen collection. This provided a dataset covering a 23-year time period for the analysis of seasonal and annual patterns. Additional clinical and epidemiological information was available on reports received between 1989 and 1997, which was used to identify patients with specific clinical symptoms or syndromes associated with PIV infection, and patients with particular underlying conditions. It was not possible to differentiate the reports into those derived from hospitalised patients and those derived from outpatients, but it is assumed that most (>90%) of the reports relate to hospitalised patients.

Rates of reported infections were estimated using mid-year population estimates by RHAs for the years 1990–1995, supplied by the Office for National Statistics (ONS). Where appropriate, comparisons of numbers or proportions in different groups were made using χ^2 tests.

Results

A total of 8221 PIV laboratory reports were received between 1985 and 1997, of which 97.8% related to specimens taken in this time period. Thirty-four (0.4%) reports of specimens collected in 1984 were also included in the analysis unless stated otherwise. For 145 (1.8%) reports, the date of specimen collection was not known, and these were also included in analyses which did not require knowledge of date of specimen.

PIV-1 accounted for 17.2% of all reports between 1985 and 1997 (1417), PIV-2 for 7.5% (619), PIV-3 for 70.8% (5819), and PIV-4 for 1.1% (88) (Figure 1). For 278 (3.4%) reports the virus type was not known. Virtually all (8136 or 99.0%) detections of PIV were in respiratory specimens. Other specimens included blood or serum (21), cerebrospinal fluid (CSF) (11), genitourinary secretions (5), faeces (4), heart (2), and eye swabs (1). Five reports of CSF isolates related to an outbreak of meningitis associated with PIV-3 infection in a neonatal unit in 1993, but in most cases there was no further information with which to qualify the reports of identifications in non-respiratory specimens, and it is likely that some of these reports represent misreporting of site. The site or type

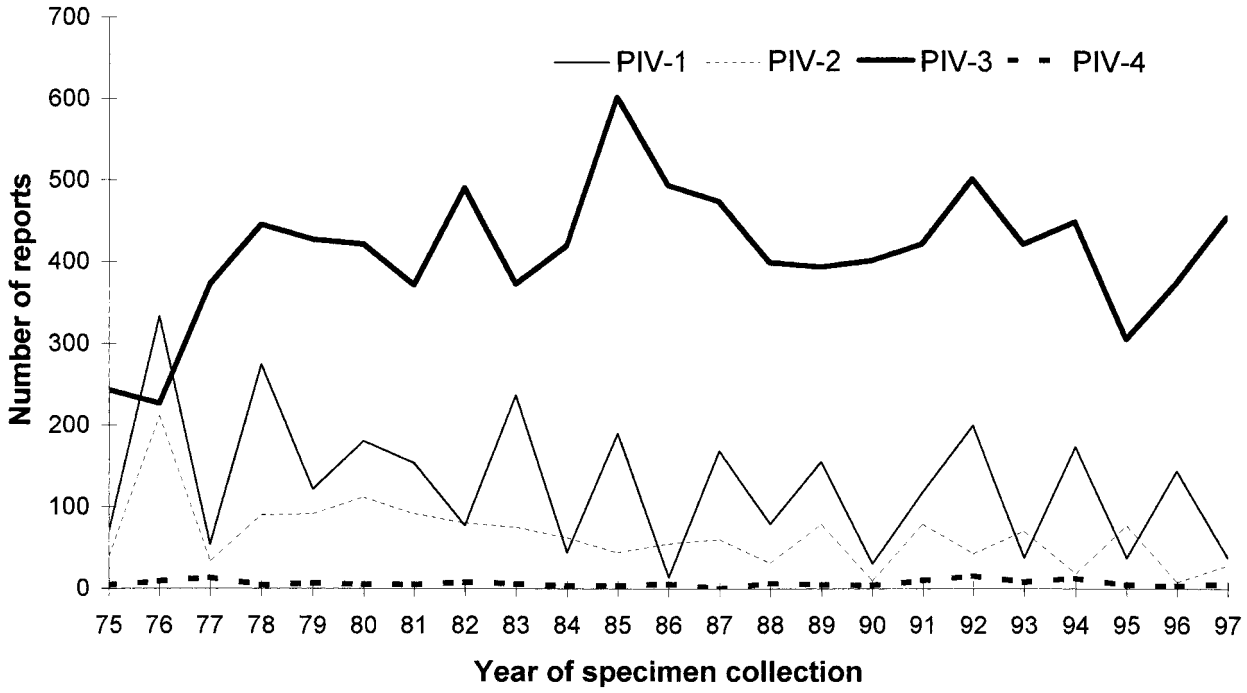

Figure 1. Laboratory reports of parainfluenza virus (PIV) types 1–4, by year of specimen collection, England and Wales, 1975–1997.

of the specimen was not specified for 41 reports (0.4%).

The method of PIV identification was available for reports received after 1988 (5463 in total). For PIV-1, PIV-2 and PIV-3 the proportion of all infections identified by virus isolation was similar, averaging 75% (3850 reports), while DIF accounted for 23% (1182 reports). In contrast, virus isolation accounted for only 19 (27%) of 70 PIV-4 reports, whereas DIF accounted for 51 (73%). Demonstration of specific CFT antibody was reported in 17 (0.3%) cases, and no method was specified for 91 (1.7%) PIV reports.

Seasonal patterns

Numbers of PIV reports by week of specimen collection for a 22-year period during the years 1975 to 1997 are shown in Figure 2. PIV-1 was detected in each year of the study period, but major peaks occurred, usually in the last quarter of the year, and generally in alternate years. Biennial peaks were seen in even numbered years between 1975 and 1978; in odd numbered years between 1981 and 1991; and again in even numbered years between 1992 and 1997. Peaks occurred each year between 1978 and 1981, while in 1991 the two-yearly pattern was disrupted by a peak in the first half of the year.

PIV-2 reports also tended to peak in the last quarter of the year, and during the study period alternated between a yearly cycle (1978–1987) and a two-yearly cycle with peaks in even numbered years (1976–1978) or odd numbered years (1987–1995).

PIV-3 reports demonstrated a clear annual epidemic pattern (Figure 2), with peaks occurring between April and August (spring or summer), with relatively small numbers reported during the winter months (December to March).

Weekly numbers of PIV-4 reports were too small to reveal a clear epidemic pattern; however plotting reports by week number for the study period as a whole (Figure 3), a seasonal pattern was observed for PIV4, with infections being detected most frequently between weeks 41 and 4 (October to January) and least often between weeks 13 and 36 (April to August). In this respect PIV-4 infections showed a very similar seasonality to PIV-1 and PIV-2. These contrasted markedly with that of PIV-3, which was isolated most frequently between weeks 13 and 32 (April to July).

Regional distribution

There were wide regional variations in the numbers and rate of PIV reports received over the study period, probably reflecting differences in virus isolation and detection procedures, rather than true differences in incidence. The crude mean annual rate ranged from 6.2 per million population (Mersey RHA) to 32.2 per million population in Northern RHA.

Age and sex

The age of the patients was known for 7730 (94.0%) reports between 1985 and 1997, and in a further 199 (2.4%) reports, a semi-quantitative age-group, such as 'child', 'adult', or 'elderly' was given. No information on age of patient was available for 292 (3.6%) reports.

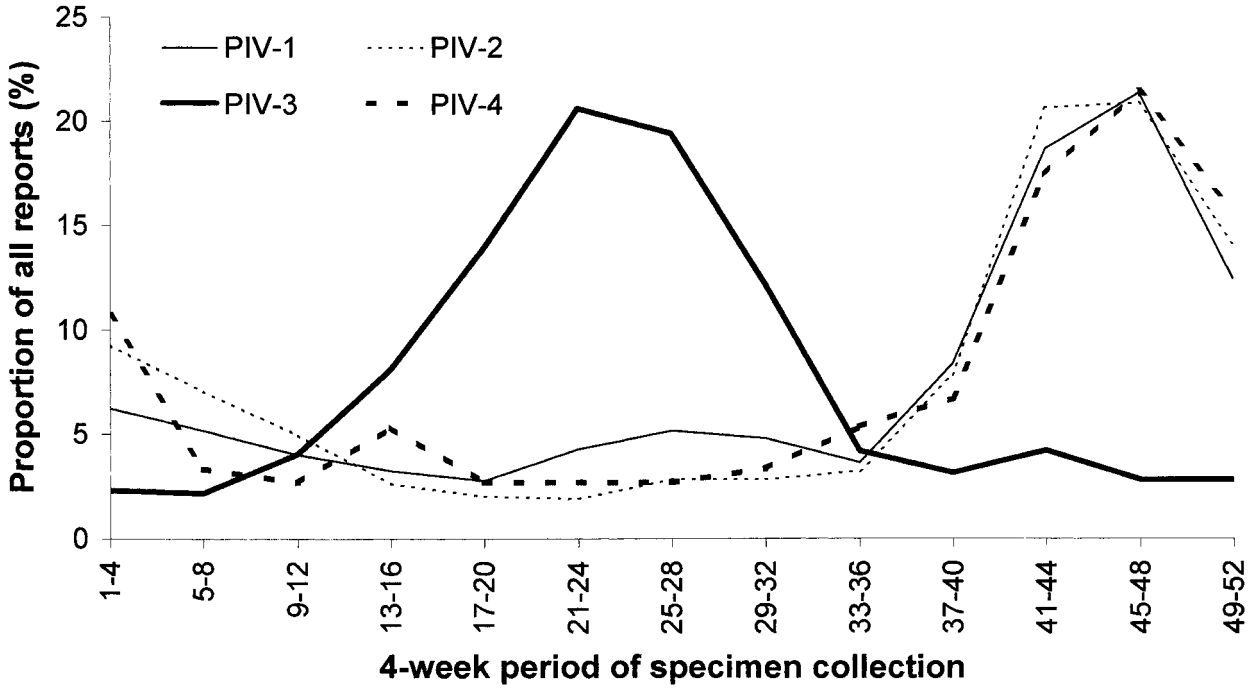

Figure 2. Laboratory reports of parainfluenza virus (PIV) types 1–4 by week of specimen collection: England and Wales 1975–1997. Five-week moving averages.

Of the PIV reports with known age, 6839 (88.5%) were from children under five years, 4956 (64.1%) were from infants under one year, and 2824 (36.5%) were from infants under six months. Only 186 (2.4%) reports came from patients aged 45 years or over.

The age distribution of patients differed significantly between PIV types (Figure 4): a higher proportion of PIV-3 and PIV-4 reports were from children aged under one year (68%) compared with PIV-1 and PIV-2 reports (53%) ($p < 0.0001$).

Sex was known for all but 146 (1.8%) reports: 4874 (59.3%) were male and 3201 (38.9%) were female. An excess of reports from males was seen in all age groups, and there was no significant difference in the sex distribution between PIV types.

Clinical features

Information on diagnosis or symptoms associated with PIV infection was available for 1902 (34.8%) reports received between 1989 and 1997, of which 97.9% were respiratory symptoms (Table 1). Bronchiolitis, croup, and pneumonia were the most common respiratory diagnoses and accounted for 75.6% of reports in which a diagnosis or symptom was given.

Bronchiolitis was most likely to be reported in infants under one year old (23.8% of all reports in this age group), and least likely to be reported in patients aged over 14 years (2.3%) ($p < 0.0001$). This pattern was seen for all PIV types (data not shown). Among children aged under one year, bronchiolitis was more frequently associated with PIV-2 infection (35.3% of PIV-2 reports) than with other PIV types (23.3% of PIV-1, 3 and 4 reports combined) ($p = 0.03$).

Croup was most likely to be reported in children aged 1–4 years (11.7% of all reports in this age group) and was more likely to be reported with PIV-1 and PIV-2 infections (22.8% and 24.5%, respectively) than with PIV-3 and 4 infections (5.8% and 8.3%, respectively) ($p < 0.0001$). A similar association of PIV-1 and PIV-2 with croup was seen among children aged under one year ($p = 0.006$), and for children aged 5–14 years ($p < 0.0001$).

Pneumonia was most likely to be reported in persons aged over 15 years (10.5% of all reports in this age group) and least likely to be reported in children aged under 1 year (2.5%, $p < 0.0001$). PIV-3 accounted for 73.6% (131/178) of reported cases of pneumonia (Table 1). Of PIV-3 infections 11.4% were associated with pneumonia, compared with 7.8% of PIV-1 infections and 4.8% of PIV-2 infections where clinical information was available.

Non-respiratory symptoms were cited in 50 reports of PIV infection, although in 48 of these a PIV was identified in a respiratory specimen. Gastrointestinal symptoms such as diarrhoea or vomiting accounted for 18 of the reports of extra-respiratory symptoms, and rashes for 14. Neurological symptoms included febrile convulsions (5), confirmed or suspected meningitis (4), meningism (3), and Guillain–Barré syndrome (2). PIV-3 infection was associated with all four reports of meningitis, two of the three reports of meningism, and the two reports of Guillain–Barré syndrome. PIV-3 was isolated from CSF in two cases

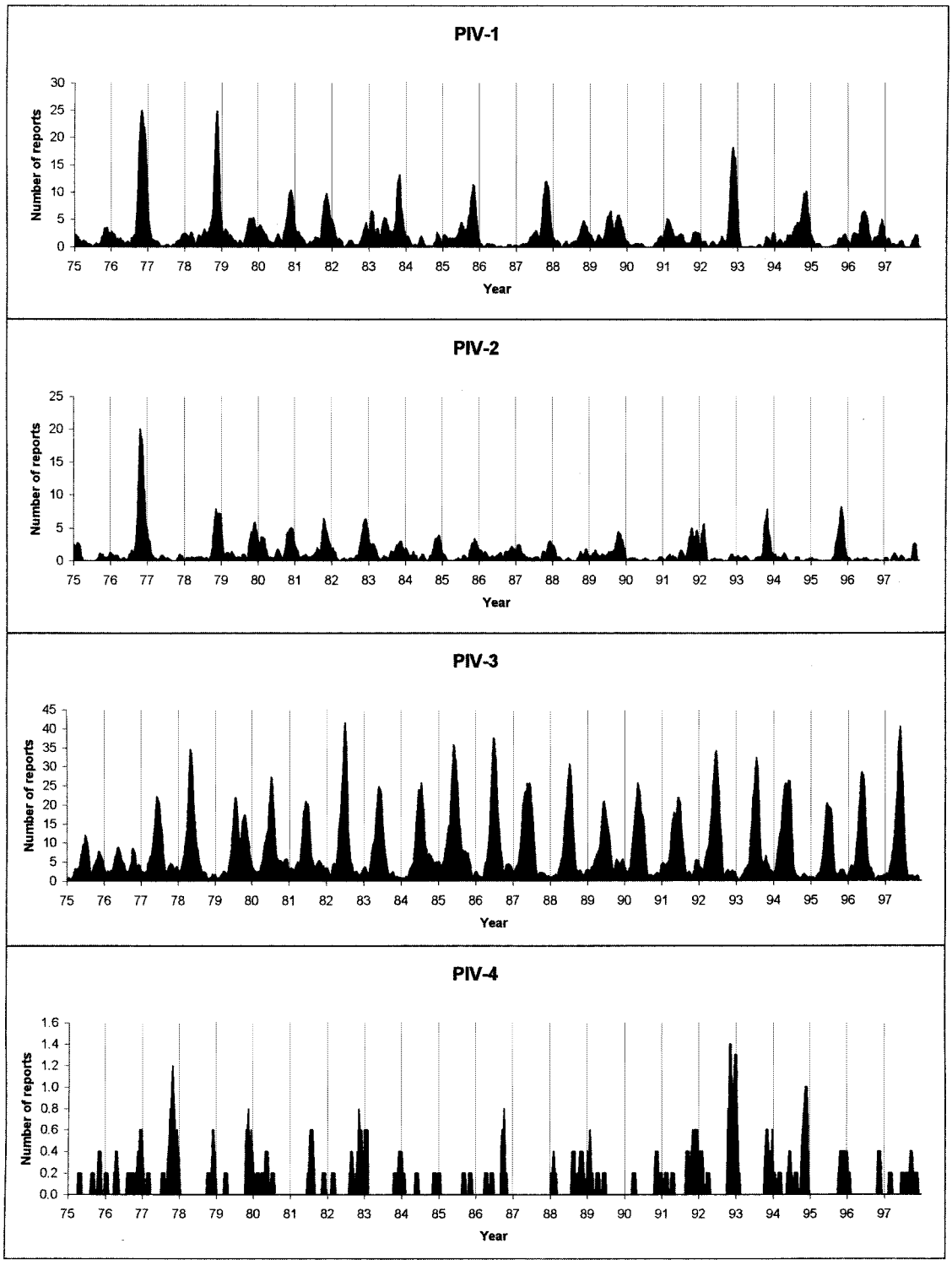

Figure 3. Relative seasonal distribution of parainfluenza infections: England and Wales, 1975–1997.

of meningitis. One report of meningism was associated with PIV-1 infection. Lymphadenopathy was mentioned in two reports, and myocarditis in two reports of PIV-2 infection.

Underlying diseases

In 392 (7.2%) reports received between 1989 and 1997 (Table 2), an underlying disease or condition was cited which may have increased the risk of serious complications of PIV infection. Immunosuppression was cited in 275 (70%) of these reports, and the most common causes were malignancies (98), organ transplantation (130), and HIV infection (18). Underlying respiratory conditions reported include broncho-pulmonary dysplasia (16), cystic fibrosis (11), asthma (6), and other chronic or congenital conditions (4). Cardiac conditions reported were mainly congenital heart disease or other conditions

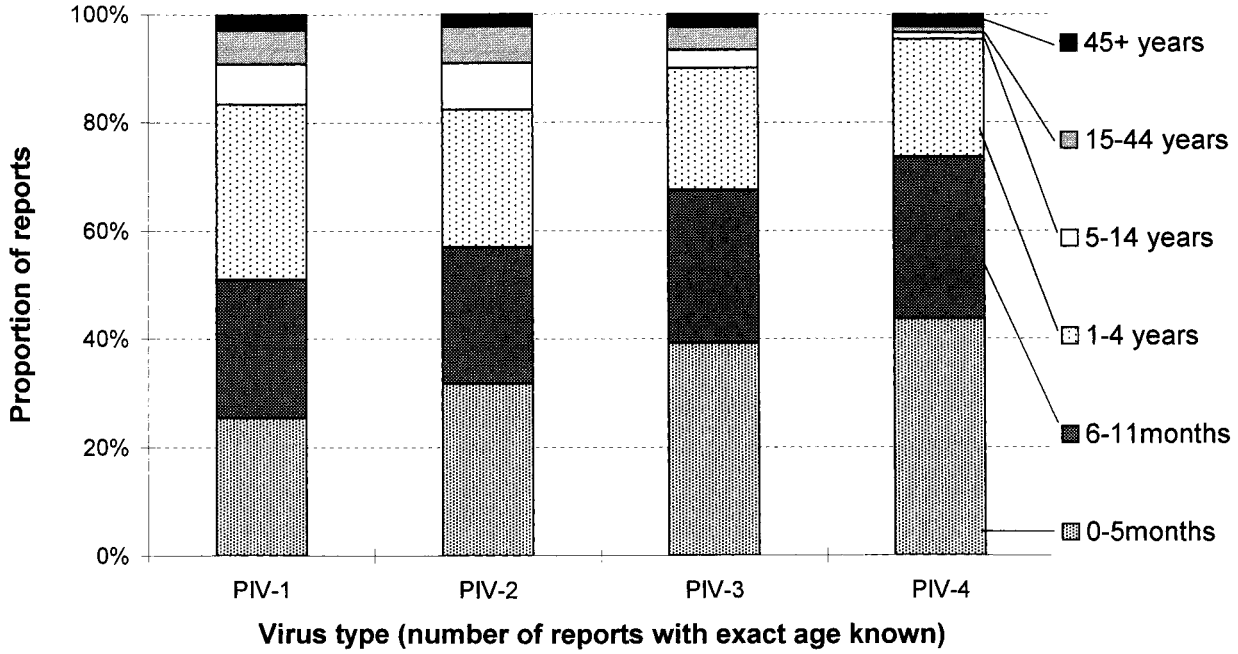

Figure 4. Age distribution of PIV laboratory reports: England and Wales 1985–1997.

requiring surgery. The number of reports of PIV infection in immunosuppressed patients increased from 13 in 1989 to 51 in 1992, but no systematic increase was seen thereafter, and in 1997 immunosuppression was mentioned in only seven reports. PIV-3 infection accounted for 269 (68.8%) of the reports of patients with underlying diseases or conditions.

Mortality

Between 1985 and 1997, death was reported in association with 28 cases of PIV infection. PIV-3 accounted for 20 cases, PIV-2 for four cases, PIV-1 for two cases, and PIV type was not determined in two cases. Sixteen deaths were in children under one year, seven in children aged 5–14 years, and three were in persons aged 15 or over. In three cases the patient was reported to have underlying cardiac or respiratory disease, and in six cases the patient was immunocompromised. The extent to which PIV infections directly contributed to death could not be determined from the data available.

Discussion

Surveillance data from hospital laboratory-based reporting schemes tend to capture the more serious spectrum of disease due to viral infections. For PIV infections, this includes severe bronchiolitis in infants, infections in immunosuppressed patients and atypical PIV infections such as extra-respiratory infections. PIV infection may be more likely to be identified in infants and children with severe disease and in patients with underlying diseases such as haematological malignancies or organ transplants, since these groups of patients often undergo extensive investigations and may also have a higher viral load

Table 1. Symptoms and diagnoses reported in association with parainfluenza infection, 1989–1997

Diagnosis/symptoms	Number of reports					
	PIV-1 (%)	PIV-2 (%)	PIV-3 (%)	PIV-4 (%)	Untyped (%)	All types (%)
Information available[a]	404 (42.2)	183 (44.1)	1204 (32.1)	22 (31.4)	88 (33.1)	1902 (34.8)
Bronchiolitis	167 (17.5)	88 (21.1)	669 (17.8)	14 (20.0)	43 (16.2)	981 (18.0)
Croup	115 (12.0)	59 (14.1)	99 (2.6)	2 (2.9)	8 (3.0)	283 (5.2)
Pneumonia	34 (3.6)	9 (2.2)	141 (3.8)	3 (4.3)	5 (1.9)	192 (3.5)
Other respiratory symptoms	82 (8.6)	27 (6.5)	279 (7.4)	4 (5.7)	32 (12.0)	424 (7.8)
Non-respiratory symptoms	12 (1.3)	4 (1.0)	33 (0.9)	0 (0.0)	1 (0.4)	50 (0.9)
No information available	553 (57.8)	233 (55.9)	2549 (67.9)	48 (68.6)	178 (66.9)	3561 (65.2)
Total[a]	957	417	3753	70	266	5463

[a] Categories given for diagnosis/symptoms were non-exclusive. Twenty-four reports had more than one diagnosis/symptom stated.

Table 2. Underlying conditions reported in association with parainfluenza infection, 1989–1997

Underlying condition	Number of reports					
	PIV-1 (%)	PIV-2 (%)	PIV-3 (%)	PIV-4	Untyped	All types
Respiratory disease	0 (0.0)	3 (9.4)	29 (10.8)	2	3	37
Cardiac disease	7 (9.7)	1 (3.1)	28 (10.4)	0	2	38
Immunosuppression	61	23	181	4	6	275
(malignancy)	(23) (31.9)	(8) (25.0)	(65) (24.2)	(1)	(1)	(98)
(transplant)	(32) (44.4)	(8) (25.0)	(84) (31.2)	(2)	(4)	(130)
(HIV/AIDS)	(1) (1.4)	(3) (9.4)	(14) (5.2)	(0)	(0)	(18)
(other/not specified)	(5) (6.9)	(4) (12.5)	(18) (6.7)	(1)	(1)	(29)
Preterm infant	3 (4.2)	3 (9.4)	24 (8.9)	0	0	30
Other	1 (1.4)	2 (6.3)	7 (2.6)	1	0	11

or shed virus for long periods of time, making detection easier. Clinical data including diagnoses and underlying conditions were available from only 38% of reports received between 1989 and 1997, and consequently there may be biased representation of certain underlying conditions.

Notwithstanding these remarks, PIVs were the fourth most commonly identified viral agent of acute respiratory infections, after RSV, influenza and adenoviruses, in the national laboratory reporting system for England and Wales during 1985–1997 (data not shown). This finding is consistent with population-based studies of children which have shown that after RSV, PIVs are the second most commonly identified agents of viral LRTI [2, 3, 8]. In a recent population-based survey of acute respiratory infections in children under five years over a 20-year period, PIVs accounted for 17.4% of positive viral cultures [16]. PIV virus isolates were also the leading viral agent associated with acute otitis media and upper respiratory tract infections, second to RSV in LRTI, and third behind RSV and influenza in cases with fever $>39\,^{\circ}C$ [16].

The seasonal pattern reported for all PIV types is probably an accurate representation of the seasonal trends of community-acquired PIV infections in England and Wales during the 23-year study period. Laboratory-based surveillance data highlight striking differences in the seasonal pattern of PIV infections in England and Wales. PIV-3 infections, which represent 71% of all reports over the study period, were mainly reported during the summer months, while, PIV-1 PIV-2 and PIV-4 occurred mainly in the winter (January–February) or late autumn (November–December). PIV-3 infections have demonstrated a regular annual cycle, whereas with PIV-1 and PIV-2 infection peaks often occurred at two year intervals, or occasionally at one or three years. Studies from Northern America, Finland and Australia have revealed similar seasonal patterns for PIV-3 infections [8, 18–23], although the seasonality of PIV-1 and 2 has not been so clearly delineated.

Cross-sectional studies have shown that over 50% of children under one year have antibodies against PIV, higher estimates being reported with PIV-3, particularly among infants under 6 months [18, 24, 25]. The presence of PIV antibodies may reflect early PIV infection, but interpretation of such studies may be complicated because of the presence of maternal antibodies in neonates and infants. Nevertheless, such data suggest a higher penetrance of PIV-3 than PIV-1 or 2 in children under 1 year. The reasons for this are not apparent, but could reflect differences in the rate of loss of maternal antibodies, differences in transmissibility of PIV types or reflect the different annual seasonality seen with PIV-3 compared with the less frequent periodicity of PIV-1 and PIV-2.

PIV-1 was more likely to be associated with croup than PIV-2 or PIV-3 over the study period. This confirms the findings of an eleven-year survey of 851 cases of croup, which identified PIV-1 as the leading aetiological agent associated with croup (48.1%), followed by PIV-3 (17.5%) and RSV (10%) [26]. PIV-3 was more likely to be associated with bronchiolitis and pneumonia than other PIV types, and is consistently the most frequently reported PIV type associated with bronchiolitis and pneumonia [2, 4, 8, 19–22, 25–27]. Together, these data suggest that the tropism of PIV-3 within the respiratory tract may be slightly different to that of PIV-1 and PIV-2, a speculation which might account for the different disease spectrum seen.

The national surveillance scheme identified 50 reports of PIV infection between 1989 and 1997 associated with extra-respiratory symptoms (in addition to respiratory symptoms) of which 12 were neurological, including meningitis, and febrile convulsions. From two of these 12 cases, PIV-3 was isolated from CSF of infants less than six months old. Reports of isolation of PIV in CSF in occasional case histories provides limited evidence of PIV neurotropism [29–32]. Together, the cases reported to the national surveillance scheme described here and the published data, suggest that PIV infection could be considered as a rare (and possibly underdiagnosed) cause of

acute neurological illness in young children, particularly if there are associated respiratory symptoms. Rashes described in association with PIV infection were not described morphologically in the data analysed, and cannot therefore classified further. Some of the rashes described may be the result of co-infection with other viral or bacterial pathogens or may represent idiosyncratic reactions to PIV infection.

Seven per cent of PIV reports involved immunosuppressed patients over the period 1989–1995. In view of the biases discussed above, these data may not represent the true proportion of PIV infections affecting immunosuppressed persons in England and Wales. Nevertheless, they do provide a more accurate description of the spectrum of underlying conditions which are known to be associated with life threatening PIV infections: transplant recipients, patients with haematological malignancies or with human immunodeficiency virus (HIV) infection, or patients who have undergone cardiorespiratory surgery. Pneumonia was the most common clinical diagnosis reported in this population and 64% of these reports were associated with PIV-3. In addition, five out of 26 deaths reported were in patients with immunosuppressed conditions, highlighting the severity of PIV related diseases in the immunocompromised host. However, the small numbers of reports provide too little power to determine any significant trends in the occurrence of PIV infections in immunosuppressed patients over the period studied.

Case series, prospective cohort studies and outbreak reports have provided new insight into the susceptibility of immunosuppressed hosts to community acquired viral infections or re-infections including RSV, influenza and parainfluenza virus [33–35]. HIV sero-positive children [36], bone marrow transplants or patients with haematological malignancies [14, 37–42], organ transplant recipients [43–46], and patients who have undergone pulmonary or cardiovascular surgery may be affected by PIV infections or re-infections [47]. High fatality rates associated with PIV related pneumonia have been reported in all these groups of patients. It is likely that there was an underestimate of the number of deaths associated with PIV in this reporting system, because mortality information was not available at the time of reporting PIV detection.

Elderly people without any immunosuppressive conditions can be affected by PIV infection [48], and PIV infections have been associated with outbreaks in residential facilities [13]. High attack rates have been observed during PIV outbreaks in acute care units for immunosuppressed patients and in residential facilities for the elderly, providing evidence of the need to implement rapid control measures in order to prevent the spread of life-threatening PIV infections in wards or residential facilities [14, 37–42].

Laboratory-based and population-based surveillance data have provided consistent estimates of the burden of PIV infections in infants and children and its cost [49]. Therefore efforts have been made to develop PIV vaccines. Following disappointing results from inactivated PIV-3 vaccine trials in animals [50, 51], PIV-3 subunit vaccines have been developed and found effective at protecting animals against live virus challenge [52]. Live attenuated human and bovine PIV-3 vaccines have already been found to be immunogenic, safe, and phenotypically stable in infants and children [53, 54], so that efficacy trials are likely to be conducted in the near future. Prospective population-based surveys on PIV infections provide an appropriate setting for a vaccine field efficacy trial [18, 55].

Laboratory-based surveillance provides continuous insight into seasonal patterns of PIV infections and trends over time in individuals affected by PIV with regards to age, sex and underlying conditions. Surveillance data may be strengthened by better ascertainment of patients' details and underlying conditions such as those related to immunosuppression. The increasing recognition that hospitalised adults may be seriously affected by nosocomial PIV infection among the elderly and immunosuppressed patients highlights the need for appropriate virological surveillance in specialised wards and residential facilities in order to implement rapid control measures [56–59].

Any vaccination program aimed at reducing PIV associated morbidity and mortality, will require both community and laboratory based surveillance of PIV infection to identify the population that would benefit from active prevention, and to measure the impact of a prevention policy.

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