Laboratory surveillance of viral meningitis by examination of cerebrospinal fluid in Cape Town, 1981–9

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SUMMARY

Nine years accumulated laboratory data derived from the culture of the cerebrospinal fluid of 11 360 aseptic meningitis cases were retrospectively reviewed to establish the epidemiology of viral meningitis in Cape Town. Virus was isolated from 3406 of the cases (91% enteroviruses and 9% mumps).

Five major summer viral meningitis episodes were documented: two of echovirus 4 (706 and 445 cases), echovirus 9 (223), coxsackie A9 (104) and one of unidentified enterovirus (324 cases – probably echo 9). Although coxsackie B was endemic, clusters of one or other type were dominant at any one time. Mumps was endemic. Sixty-two percent of all viral cases were < 5 years old. The median ages of 4 and 5 years in echoviruses 9 and 4 (the epidemic strains) contrasted with that of 1 year in coxsackie B (with many cases < 3 months old). Mumps peaked at 3–4 years of age. Males dominated overall, particularly in mumps.

INTRODUCTION

In South Africa viral meningitis is not generally notified, and epidemiological data are scanty. The few published records of viral meningitis have been confined to single outbreaks or comparatively small numbers of cases [1–8]. Large numbers of patients with meningitis attend the outpatient departments of hospitals in South Africa. The laboratories of the teaching hospitals associated with the University of Cape Town Medical School receive for investigation approximately 900 cerebrospinal fluid specimens (CSFs) per month. We decided to intensify virological investigation of this resource as part of the routine diagnostic service.

This paper is a retrospective review of 9 years' accumulated data which enabled us to ascertain the frequency and aetiology of viral meningitis in our community and also to evaluate age and sex distribution patterns and virus recovery rates.

MATERIALS AND METHODS

A case of aseptic meningitis was defined as one with clinical features of meningitis and with a CSF specimen containing any polymorphonuclear cells or more lymphocytes than $2 \times 10^6/l$ and no identified bacterial or non-viral cause.

Initial specimens from such cases were routinely forwarded from the bacteriology laboratories serving four teaching hospitals in Cape Town. These State hospitals, the Red Cross War Memorial Children's Hospital, Groote Schuur, Somerset and Victoria Hospitals, serve a predominantly low socio-economic group. Seventy percent of the specimens originated from the General Medical Outpatients Department of the Children's Hospital. This department has an annual attendance of approximately 140 000 patients (55 % males). Age, race, sex, clinical data, CSF cells, chemistry and microbiology results were indicated on the request forms with variable degrees of completeness. Seventy-five percent of the cases were from the ethnic group of mixed origins (coloured), 19 % from the black and 6 % from the white ethnic groups. There was a 7 % increase in the proportion of blacks in 1987-9 which coincided with a large influx of black people from the rural areas to urban Cape Town.

Culture

The CSF specimens were received in the virus laboratory 1-3 days after lumbar puncture and generally only the clear supernatant fluid was forwarded for viral culture. Viral isolation was accomplished by standard inoculation of pairs of cell cultures of primary vervet monkey (*Aethiops cercopithecus*) kidney cells (MK), HeLa cells and human embryo (whole or lung) fibroblasts (HFs) and by inoculation into suckling mice. Since insufficient CSF was received from 70 % of the cases to complete all four investigations, preference was given to MK, HFs, HeLa and mouse inoculation in that order (30 % were inoculated only into MKs). Viral isolates were identified by cytopathic effects on stained coverslips and/or mouse histopathology and typed by microneutralization techniques using specific antisera (coxsackie B 1-6, coxsackie A9 and echovirus types 4, 9, 11). Enterovirus not thus identified in 1981 to March 1983 were examined by neutralization using the Lim Benyesh-Melnick intersecting pools of antisera A to H (courtesy of the World Health Organisation, Geneva). These intersecting pools were unfortunately not available from March 1983 to 1985 and only very sparingly thereafter. Isolates producing an enterovirus-like cytopathic effect and not further identified were termed 'enteroviruses not fully identified' (entero n.f.i.). Polioviruses were sought by combined P1, P2 and P3 antisera (provided by the National Institute of Virology, Johannesburg) in the years 1981-4. Thereafter this was discontinued partly because poliovirus is exceptional in the CSF in clinical polio and partly because the disease has become rare in our community with universal polio immunization. Mumps was confirmed by an indirect fluorescent antibody technique with commercial antisera (Flow).

RESULTS

General

Viruses were isolated from 3406 of the 11360 cases of aseptic meningitis investigated from 1981-9 (Table 1). Omitting the first 4 months of 1981 when surveillance was incomplete, the monthly median of cases investigated was 97 (range 40-336; May 1984, December 1989) and of cases with virus was 27 (range 5-144; June 1984, December 1989). Fig. 1 shows that aseptic and enteroviral

Fig. 1. Seasonal incidence of viral meningitis. Cumulative totals of cases by month, 1981–9.

meningitis peak in the summer months whereas mumps peaks both in autumn and in the early summer months. Ninety-one percent (3098) of the cases with virus in the CSF (viral meningitis) yielded enterovirus and 9% (308) mumps. Echoviruses (echo) constituted 52% (1598) of the enteroviruses with 75% (1205) of the echoviruses further identified as echovirus type 4 (echo 4), 19% (299) as echovirus 9 (echo 9) and 6% (94) as a further 16 other echo types (Table 1). Coxsackie B (cox B) accounted for 11% (347) of the enteroviruses, coxsackie A9 (cox A9) 4% (127) and the remaining 33% (1026) were not further identified (entero n.f.i.). No other viruses were isolated.

Temporal distribution

There were periods when particular viruses predominated among the isolates. Four of these periods involved more than 100 cases of viral meningitis and there were 11 smaller clusters with between 14 and 44 cases. The former were associated with echo 4 (twice), echo 9 and cox A9 and the latter with cox B, and echo types 4 and 11. Echo 4, echo 9 and cox A9 overlapped in the summer months of 1985–6. Other than a considerable rise in numbers of entero n.f.i. isolates towards the end of 1989 and a slight increase in numbers during the summer, there was no clustering in time of the remaining enteroviruses to suggest significant outbreaks. Mumps meningitis occurred endemically throughout the 9 years.

Major episodes

Echovirus 4 (Fig. 2). The first echo 4 episode of 706 cases, which lasted 18 months, commenced in May 1981, peaked in the summer months (November 1981 to April 1982, 527 cases), declined in the following winter (June to August) and ended in October 1982. Only 7 cases were identified in the following 33 months. The second episode in 1986/1987, although smaller (445 cases), was of longer duration (34 months). In the 8 months prior to this period small numbers of cases

Table 4. *Male:female sex ratios in viral meningitis by age and aetiology. Ratio (number) of cases in each age/aetiological group*

Virus	Months		Years					Total
	< 6	6-11	1-4	5-9	10-14	15-24	25 +	
V.M.*	1.2 (328)	1.6 (256)	1.6 (1046)	1.8 (687)	1.7 (176)	0.9 (62)	1.1 (60)	1.6 (2615)
Mumps	2.0 (6)	4.7 (17)	2.9 (149)	3.1 (91)	M§ (11)	0 (0)	M (2)	3.2 (276)
Enterot†	1.2 (322)	1.5 (239)	1.5 (897)	1.7 (596)	1.6 (165)	0.9 (62)	1.0 (58)	1.5 (2339)
Echo†	1.5 (82)	1.4 (95)	1.4 (401)	1.6 (335)	1.6 (108)	1.0 (45)	0.7 (37)	1.4 (1103)
CoxA9	F (3)	1.6 (13)	1.3 (54)	1.5 (35)	M (3)	2.0 (3)	4.0 (5)	1.5 (116)
CoxB	0.9 (91)	1.7 (33)	1.8 (130)	1.1 (43)	1.1 (19)	1.0 (4)	M (4)	1.4 (324)

* Viral meningitis (with virus from the CSF).
† Includes enteroviruses not fully identified (796 cases).
‡ All echo virus types.
§ M, males only.
|| F, females only.

Fig. 2. Monthly incidence of cases of echo 4, echo 9, and enterovirus not fully identified, 1981–9.

(2–6) were identified every month. The main episode commenced in April 1986 (10 cases) and peaked in the late winter months and spring months (July, August and September 1986). Thereafter the monthly number of cases decreased more or less uniformly to the end of 1987.

Echovirus 9 (Fig. 2). The 1984–6 echo 9 episode of 223 cases, which lasted for approximately 19 months, was biphasic. Following the identification of 4 cases in the early spring months of August–October 1984, the monthly number of cases rapidly increased to a peak in January and February 1985 (85 cases). The prevalence subsided during the cooler months of May to November and increased to a secondary peak in December 1985/January 1986 (28 cases). Although no echo 9 cases had been identified in the preceding 19 months, during the following 21 months (March 1986–November 1987) echo 9 continued to be isolated sporadically (44 cases).

Coxsackie A9 (Fig. 3). The 7-month-long cox A9 episode of 104 cases commenced in October 1985, peaked in December/January (48 cases) and ended in April 1986. Cases of cox A9 meningitis were identified only occasionally before, but not after, this period.

Enterovirus not fully identified (Fig. 2). From September to December 1989 the number of enterovirus isolates rose to a total of 288 of which 277 were not further

Fig. 3. Monthly incidence of cases of coxsackie A9, coxsackie B and mumps, 1981–9.

identified. This higher prevalence, which continued into 1990 for a further 7 months with a peak in the summer of 1989/90, included more cases (926 cases) than the first echo 4 episode (1990 data not given). Later, 43 random samples taken during this period were all identified as echo 9 and this suggested this may have been an echo 9 episode.

Minor episodes

Coxsackie B (Figs. 3 and 4). Cox B viruses were isolated throughout the 9 years but time clustering only became clear when they were typed individually. Nine clusters of 14–44 cases were noted of which types 1, 2, 3 and 5 accounted for two clusters each and cox B4 only one. Only one type of cox B appeared to predominate at any one time, but there was occasional overlapping (e.g. in 1989 the observed cox B peak was associated with types 1, 3 and 5).

Echovirus (Fig. 2 and Table 1). Echo 4 reappeared as a small cluster in the first 7 months of 1989 and 16 cases of echo 11 meningitis were detected in the first 4 months of 1989.

Mumps (Fig. 3)

There were two broad periods of increased mumps activity. In the 5 years 1981–5 a mean of 2 cases were identified per month (range 0–7) with a total of 114 cases. In the 16 month period of September 1986 to December 1987 the monthly

Fig. 4. Monthly incidence of cases of coxsackie B1 to B5, 1981-9.

Table 2. Age distribution of 3227 viral meningitis cases. Percentage (number) of the total cases in each aetiological group

Virus	Cases	Age						
		< 6 m	6-11 m	1-4 y	5-9 y	10-14 y	15-24 y	25+y
VM*	3227	13.0 (420)	8.9 (287)	39.8 (1286)	25.7 (830)	7.1 (230)	3.0 (97)	2.4 (77)
Mumps	301	2.3 (7)	6.0 (18)	53.5 (161)	33.9 (102)	3.6 (11)	0 (0)	0.7 (2)
Enterot†	2926	14.1 (413)	9.2 (269)	38.4 (1125)	24.9 (728)	7.5 (219)	3.3 (97)	2.6 (75)
Echo 4	1111	7.9 (88)	6.8 (76)	34.8 (387)	30.5 (339)	10.8 (120)	5.0 (56)	4.0 (45)
Echo 9	292	9.6 (28)	6.8 (20)	41.8 (122)	27.0 (79)	8.6 (25)	3.8 (11)	2.4 (7)
Echos‡	86	17.4 (15)	17.4 (15)	41.9 (36)	17.4 (15)	5.8 (5)	0 (0)	0 (0)
Cox A9	124	4.8 (6)	9.7 (12)	46.0 (57)	29.0 (36)	3.2 (4)	3.2 (4)	4.0 (5)
Cox B1	74	25.7 (19)	9.4 (7)	50.0 (37)	6.7 (5)	5.4 (4)	0 (0)	2.7 (2)
Cox B2	57	14.0 (8)	12.3 (7)	50.9 (29)	17.5 (10)	3.5 (2)	1.7 (1)	0 (0)
Cox B3	96	39.6 (38)	13.5 (13)	30.2 (29)	13.5 (13)	3.1 (3)	0 (0)	0 (0)
Cox B4	28	14.3 (4)	3.6 (1)	42.8 (12)	25.0 (7)	7.1 (2)	3.6 (1)	3.6 (1)
Cox B5	80	28.7 (23)	8.7 (7)	35.0 (28)	13.7 (11)	8.7 (7)	2.5 (2)	2.5 (2)
Cox B6	1	0 (0)	0 (0)	100 (1)	0 (0)	0 (0)	0 (0)	0 (0)
AM§	10671	16.2 (1728)	10.7 (1144)	34.8 (3714)	19.3 (2065)	6.8 (731)	4.9 (527)	7.1 (762)

* Viral meningitis (with virus from CSF).
† Includes enteroviruses not fully identified (977 cases).
‡ All echos other than types 4 and 9.
§ Aseptic meningitis (all cases investigated, with and without virus).

Table 3. *Age distribution in two echo 4 episodes. Percentage (number) of total cases in each episode*

	Episode 1 1981-2 (631 cases)	Episode 2 1986-7 (407 cases)
< 6 months	5.5 (35)	11.0 (45)
6-11 months	5.7 (36)	7.4 (30)
1-4 years	31.5 (199)	37.8 (154)
5-9 years	36.0 (227)	24.3 (99)
10-14 years	10.9 (69)	11.0 (45)
15-24 years	5.1 (32)	5.4 (22)
25+ years	5.2 (33)	2.9 (12)

mean rose to 5.5 cases (range 2-11) with a total of 88 cases. In 1988, mumps activity decreased (29 cases), but in 1989 (73 cases) the monthly mean rose again to 6.1 (range 1-11). This continued into the first 4 months of 1990 and then decreased again (1990 data not given).

Age distribution (3227 Cases) (Table 2)

Age was given in 10671 cases of aseptic meningitis of which 3227 yielded virus. Eighty-seven percent (2823) of all confirmed viral cases were < 10 years old and 62% (1993 cases) were < 5 years old. By year, of the < 5 year olds, the greatest number of cases occurred in the first year of life (< 1 year of age, 707 cases; 1 year, 325; 2 years, 306; 3 years, 358; and 4 years of age 297 cases). One third (223) of the < 1 year age group were < 3 months old and 35 were < 1 month old (1% of total cases).

From the age of 5 years onwards the numbers of cases decreased steadily. Over 45 years of age only 7 of the 196 cases investigated yielded a virus (all echovirus). Some significant variations in the age distribution patterns were observed with individual viruses as detailed below.

Mumps (301 cases)

Range: 1 month-34 years. Median: 4 years.

Children aged between 2 and 6 years accounted for 68% (206) of the mumps cases with a peak at 3 years of age. Below 9 months and above 15 years mumps meningitis was uncommon. Two cases were under 3 months old.

Echovirus (1459 cases)

Range: 6 days-67 years. Echo 4 median: 5 years, echo 9 median: 4 years.

In echo meningitis 82% (1220) of all the cases were < 10 years old and 53% (787) were aged < 5 years. Six were under 1 month of age (all echo 4). Echovirus accounted for 68% of all cases above 14 years of age, although only 8% (119) of echo meningitis cases were in this age group. Table 3 shows the age distribution of cases in the two echo 4 episodes. The age distribution patterns of echovirus types 4 and 9 were similar. The other echoviruses (which were largely non-epidemic) differed in that they occurred in the younger age groups (e.g. 35% were aged < 1 year compared to 15% and 16% for echos 4 and 9 respectively).

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Virus	Months			Years					Total
	< 6	6-11		1-4	5-9	10-14	15-24	25+	
V.M.*	1.2 (328)	1.6 (256)		1.6 (1046)	1.8 (687)	1.7 (176)	0.9 (62)	1.1 (60)	1.6 (2615)
Mumps	2.0 (6)	4.7 (17)		2.9 (149)	3.1 (91)	M§ (11)	0 (0)	M (2)	3.2 (276)
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Echo†	1.5 (82)	1.4 (95)		1.4 (401)	1.6 (335)	1.6 (108)	1.0 (45)	0.7 (37)	1.4 (1103)
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* Viral meningitis (with virus from the CSF).

† Includes enteroviruses not fully identified (796 cases).

‡ All echo virus types.

§ M, males only.

|| F, females only.

Coxsackie A9 (124 cases)

Range: 21 days–35 years. Median: 3 years.

The cox A9 age distribution pattern was similar to that of echo meningitis but the proportions were slightly lower in the age groups of < 6 months and 10–14 years. Two cases were less than 1 month old.

Coxsackie B (336 cases)

Range: 5 days–36 years. Median: 1 year.

The age distribution pattern of cox B differed from that of the other identified enteroviruses (i.e. the 1613 cases due to cox A9 and echoviruses). The cox B cases tended to be younger: 38 % (127) of all cox B cases were < 1 year of age in contrast to 16 % (260) for the others. Moreover 48 % (61) of the < 1 year olds were aged < 3 months compared to 23 % (61) for the others. In the 1–4 year age group the proportions were similar, whereas over the age of 5 years cox B cases were proportionately less common.

The age patterns in cox B meningitis varied with the different types. These differences were most prominent in the age group of < 1 year (e.g. 18 % of all cox B4 cases were < 1 year of age against 53 % in the case of cox B3; see Table 2). Cox B1 and B3 had substantial proportions of cases < 3 months of age (18 % (13) and 31 % (30) of all cox B1 and all cox B3 cases respectively).

Sex distribution (Table 4)

The overall ratio of males to females was similar whether the aetiology of the aseptic meningitis was known (1·61 : 1, 2615 cases) or unknown (1·5 : 1, 7660 cases). In viral meningitis male predominance decreased in the > 14 years age groups. In mumps meningitis, males were strongly predominant in all age groups whereas in echo meningitis cases they predominated only in those under 15 years (above 25 years there was a slight predominance of females). In contrast, in cox B meningitis males were only clearly predominant in the 6 months to 4 years age groups.

Virus recovery rate (percentage of CSFs from which a virus was isolated)

There was an overall rate of 30 % (Table 1). Monthly rates ranged from 9 % (June 1984) to 49 % (March 1982: echo 4). Monthly rates of greater than 40 % were observed only at times of high prevalence. The virus recovery rate varied with age and ranged from 10 % (25 years and above) to 40 % (5–9 year olds). In four age groups in the < 1 year olds recovery rates were similar (range 22 % (9–11 months) to 27 % (6–8 months). Virus recovery rates were similar in the three ethnic groups. In a sample of 208 cases with white cell counts of $< 10 \times 10^6/l$ virus recovery rate was 10 %, in 111 cases with counts of $> 1000 \times 10^6/l$ the rate was 25 % and in 3997 cases with counts of between 10 and $1000 \times 10^6/l$ the rate was 32 %.

DISCUSSION

Since viral meningitis is generally a benign disease [9] only few specimens from isolated cases or closed community outbreaks were received for viral studies in our

laboratory prior to 1981. Sporadic data or short studies of viral meningitis are of limited value and may be misleading. For example, we have now shown that the 1981 'winter' outbreak of echo 4 meningitis reported by Potter and colleagues in Cape Town [5] was the start of a widespread summer echo 4 meningitis episode which peaked in 1981/82. Enteroviral infections have been reported in the summer and autumn months in temperate climates of both the Northern and Southern hemispheres [9-12] but less so in tropical climates [9, 10]. We found a temperate pattern in Cape Town which has a mediterranean climate. Mumps occurs mainly in winter/spring and in 2-7 year cycles in temperate zones [9, 13]. We were unable to show any regular seasonal or cyclic pattern of mumps meningitis although combined monthly totals showed peaks in early summer and autumn (Fig. 3). However, Donald and colleagues showed only a spring/early summer peak on combined monthly totals in a 4-year study of 49 cases near Cape Town [8]. (Mumps immunization is most unlikely in the study populations.)

Many types of echovirus [14] including 4 [15-19] and 9 [20, 21] have been reported as common causative agents of viral meningitis epidemics. In South Africa, echo 4 associated outbreaks were reported in 1957 in Johannesburg [1] and in 1960 in Worcester [2, 3], and echo 9 was implicated in cases reported in Durban from 1953-60 [4]. These were the only echo types identified in large numbers in our laboratory during the 9 years reviewed. The acute epidemic features and age groups attacked in the 1981-2 episode suggested the pattern of a virus strain re-introduced into an antigenically naive community. In addition, there was anecdotal evidence that viral meningitis was widespread at that time. CSF specimens are rarely received from areas outside Cape Town, but in 1981-2 CSF specimens were received from 235 aseptic meningitis cases domiciled in a wide geographical area up to 1154 kilometres from Cape Town. The 30 viruses isolated were all echo 4. In Cape Town we found that echo meningitis, and indeed all viral meningitis, occurred at a considerably younger age than in the United Kingdom [22]. We found echo meningitis prominent in children aged < 5 years (53% of all echo cases) and less common in > 15 year olds (8%). These proportions contrast with the values of 20% and 44% respectively, derived from data of the Public Health Laboratories of the United Kingdom (1978-82) [12, 22]. In a 10-year study of viral meningitis in Edinburgh [12] the peak incidence in the 5-10 year age group contrasts with our 1-4 year age peak. Our study confirms the rarity of viral proven meningitis over the age of 45 years [12, 22].

The overall impression of cox B endemicity in the community, suggested by the high frequency and young age incidence of cox B infections, was at variance with the behaviour of individual cox B types. These appeared in discrete episodes with no obvious regular pattern. No one type was continuously present. These 'waves of infection' are similar to those reported earlier by Gear and Measroch [23]. A degree of geographical localisation of types was suggested by the identification of an extensive cox B3 epidemic in Johannesburg in 1984 [24] when type 5 predominated in Cape Town. We found that a single type of cox B dominated in both meningitis cases and non-meningitis cases at any one time with cox B3 the type most frequently identified both during the study period and the 11 years prior to it (unpublished). Over the same period of time, types 1, 2, 4 and 5 were isolated from the non-meningitis cases in fairly equal numbers (data not given).

Therefore our paucity of cox B4 meningitis was intriguing and at variance with a report where it was identified in approximately one quarter of cox B cases [25]. Our impression that in our community viral meningitis is primarily a disease of the young was further substantiated by the age distribution patterns of both cox B and mumps. Three quarters of all our cox B cases were < 5 years old in contrast to the approximate one quarter reported in Glasgow [25]. The very young age incidence of cox B3 in particular is striking and merits further study. If the age distribution of mumps meningitis is representative of mumps in general, then both the median (4 years) and the peak age (3 years) observed suggests that mumps is acquired at an earlier age in our community than in the Northern hemisphere (5–9 years) [13].

The present study confirms the previously reported male predominance in viral meningitis cases < 15 years of age, especially in mumps, and this dominance declines in the older groups [7, 12, 16, 21].

Virus recovery rates of up to 57 % from CSFs have been reported in outbreaks [3, 20, 26]. Our lower isolation rates of between 30 % and 48 % may have resulted from the very wide spectrum of material included by our selection criteria, and the handicap of prior passage through a bacteriology laboratory, with resultant delay (48 hours) and variable depletion of quantity and quality of CSF in each case.

We chose to examine CSFs because of their ready availability and the high significance of virus isolation from this source. However, examination of CSFs alone limits the study to viruses which are readily isolated from the CSF by current techniques. Examination of further specimens would generate additional associated viral isolates whose causal roles may be difficult to interpret. Thus in 1981 we received throat and rectal swabs from 92 cases in addition to CSFs. Echoviruses were isolated from the CSFs of 11 of these cases and a further 25 cases yielded a range of viruses from combined throat and rectal swabs. These swabs identified 13 more cases with echovirus as well as cases with herpes simplex virus, poliovirus, adenovirus and cytomegalovirus.

It is our laboratory policy to identify all viral isolates as far as possible. However, isolation of an enterovirus may be relatively simple but further identification can be very demanding. Some isolates remained unidentified because they defied attempts to identify them and they pose a particular challenge. In the latter years of the survey the numbers of enteroviruses isolated overwhelmed the modest resources of a routine diagnostic service in a developing country (e.g. 872 enteroviruses isolated between September 1989 and June 1990 (1990 data unpublished)). Although complete identification of enteroviruses for epidemiological purposes is ideal, it does not contribute significantly to patient management. Random sampling for identification was the only practical means of establishing the dominant virus (echo 9).

Our laboratory survey has identified episodes of infection although it was inherently limited by the nature of the data (e.g. case selection criteria, lack of denominators and scant clinical information) and was thus unable to provide a full epidemiological picture of disease in the community. It provided useful information not otherwise available to clinicians and other laboratories. (Most of the raw data in this paper has been reported monthly in a surveillance bulletin of South African virus laboratories.)

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