These have in fact been incorporated into the SAMDC's latest set of guidelines.

So, with the exception just mentioned, the same conclusion has emerged in this section as in the previous sections: an HIV test cannot permissibly be performed without the informed consent of the person tested, in any case in which that consent can be sought.

We are most grateful to the other members of the Committee for the lively and interesting discussions that led to the formulation and unanimous acceptance of these guidelines.

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SPECIAL ARTICLE

Benefits and limitations of the Witwatersrand influenza and acute respiratory infections surveillance programme

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Objective: To establish an ongoing active surveillance programme for acute respiratory infections in general, and influenza in particular.

Design: A network of 16 sentinel primary health care providers furnished morbidity information and clinical specimens for virus characterisation supplemented by school absenteeism and regional mortality data.

Setting: General practices, hospital outpatient departments and staff clinics in the Witwatersrand area.

Participants: Subjects treated for acute respiratory infections by 7 general practitioners, 1 specialist pulmonologist, 4 paediatric outpatient departments, 1 mine hospital and university, factory and institutional staff clinics. Absenteeism data were obtained from 8 primary and 6 high schools in the region (representing 9 000 pupils).

Outcome measures: Morbidity information and strain characterisation of influenza isolates as well as other viral respiratory pathogens, school absenteeism, seasonal excess mortality.

Results: The most sensitive indicator of influenza activity was virus isolation, which gives an earlier warning signal of an impending epidemic than morbidity or absenteeism parameters. Both morbidity and school absenteeism provided quantitative indicators of the severity of the epidemic. Mortality from all causes showed characteristic winter increases in the 65-year-old and older population which were not seen in younger individuals. Circulating influenza viral strains matched the strains recommended for the vaccine in 1991 and 1992, but not in 1993.

Conclusions: The course and extent of the annual winter influenza epidemic can be charted by means of an active surveillance programme, with sentinel primary health care providers furnishing morbidity data and clinical material from which virus isolations can be made. Antigenic characterisation of the isolates demonstrated that circulating strains may not match recommended strains in northern hemisphere-formulated vaccines and stresses the need for a southern hemisphere vaccine formulation for South Africa. Absenteeism information provides an indicator of the impact of influenza on the economy and excess mortality data emphasise the need for routine immunisation of the elderly.

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Influenza is an enigmatic disease. The virus is one of the most contagious of all infectious organisms, and a new strain of influenza can appear and spread with dramatic swiftness causing acute pandemics of vast proportions. However, the epidemics generally last no longer than 12 weeks and affect no more than 50% of susceptibles in a population before mysteriously disappearing. Not surprisingly, outlandish theories of the origin of influenza have been published, such as Hoyle and Wickramasinghe's hypothesis (quoted by Henderson and Perry)[1] that new influenza strains arise from virus-bearing comets which continuously bombard Earth.

At a more down-to-earth level, influenza remains one of the major causes of morbidity and mortality in humans. In the USA up to 20 000 deaths may be ascribed to the virus and in major epidemic years this figure may even exceed 40 000.[2] The cost of epidemics is staggering — in the USA alone, annual productivity losses have been estimated at over $700 million, and direct hospitalisation costs exceed $300 million.[2]

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Active surveillance programmes have been established in many developed countries in an attempt to monitor influenza epidemics,[3] and the World Health Organisation itself maintains a network of over 120 national reference laboratories throughout the world. These programmes have two objectives.

The first is to obtain influenza virus isolates for antigenic characterisation so that tailor-made vaccines with corresponding antigens can be prepared annually. The second is to quantify the extent and chart the course of the epidemic as well as anticipate the course that it is likely to take, so that appropriate interventions can be planned.

The influenza laboratories of the National Institute for Virology serve as one of the National Institutes of Influenza of the WHO. The Viral Watch Programme of the Institute was established in 1984 to obtain influenza isolates and measure influenza epidemics in this country.[4] Over the past 2 years, parameters of influenza activity such as mortality data and respiratory morbidity indices have been added to the programme's activities. In this article the value of the programme in charting and forecasting the course of influenza epidemics, particularly over the past 2 years, is reviewed.

Patients and methods

Structure of the Viral Watch Programme

In 1993 the Witwatersrand Viral Watch Programme comprised 16 centres — a mine hospital, 4 paediatric outpatient departments, 7 general practitioners, 1 specialist pulmonologist, a university students' clinic, a factory clinic and the staff clinic of the National Institute for Virology. The centres represent a cross section of socio-economic classes, age and race groups, and institutionalised and non-institutionalised individuals. Patients are selected by Viral Watch doctors on the basis of clinical presentation of acute respiratory symptoms with or without pyrexia, rather than on the surveillance definition of influenza of the WHO.[5] A throat swab is taken from each patient and sent in transport medium to the laboratory within 24 hours, as described previously.[4] During 1993, 13 of the Viral Watch centres also maintained a register of all patients with any acute respiratory symptoms. A weekly acute respiratory morbidity index (ARMI) was calculated by division of the total number of incidents per week by the number of participating centres.

Indirect indices of influenza activity

In addition to the ARMI data provided by the Viral Watch Programme, other parameters examined were school absenteeism and mortality data. School absenteeism has been monitored annually since 1987. In 1993, 9 000 pupils in 8 primary schools and 6 high schools were monitored. The schools were telephoned on a weekly basis for the number of pupils absent each week. A weekly absenteeism rate per 1 000 pupils was calculated by the formula (number absent ÷ total number of pupils) x 1 000. Monthly mortality figures for 1992 and 1993 were from two old age institutions in Johannesburg and monthly mortality rates for the municipal region of Johannesburg were kindly supplied by the Johannesburg City Health Department.

Virus isolation and typing

Specimens were processed and typed as described previously[4] except that MDCK cells were now used for tissue culture isolation instead of the vervet monkey kidney cells and HeLa cells used previously. All specimens were inoculated intra-amniotically into 12-day-old embryonated eggs and MDCK cell cultures. The eggs were incubated for 3 days at 34°C and amniotic fluid was examined by haemagglutination (HA), with 0,5% guinea pig and fowl red blood cell suspensions in 0,85% saline. Positive fluid was inoculated into the chorio-allantoic membrane of 10-day-old embryonated eggs and incubated for 2 days at 34°C. Negative fluid was re-passaged intra-amniotically in 12-day-old embryonated eggs before being discarded as negative.

Specimens inoculated into MDCK cell cultures in Eagle's MEM supplemented with 2% fetal calf serum were incubated for 21 days at 33°C and tested for HA with guinea pig cells as above.

Chorio-allantoic or tissue culture fluid was typed by HA inhibition, with reference sera kindly supplied by Dr J. Skehel of the WHO Influenza Centre, National Institute for Medical Research, Mill Hill, London. The sera were first treated with receptor-destroying enzyme (Phillips Duphar) in a 1:6 dilution, serially doubly diluted and then mixed with an equal volume of the allantoic fluid or tissue culture fluid containing 8 HA units, and incubated at room temperature for 1 hour. A 0,5% suspension of fowl red blood cells in 0,85% saline was added and after 45 minutes at room temperature the HA inhibition titre was measured as the highest dilution giving complete inhibition of HA. Positive isolates were also sent to Dr J. Skehel for confirmatory typing.

Results

In 1991 and 1992 virus isolation was more efficient from actively recruited (Viral Watch) specimens derived mainly from the community (77 of 235 specimens (32%) in 1991 and 82 of 236 specimens (35%) in 1992) compared with routine clinical specimens derived mainly from hospitalised patients (42 of 217 (19%) in 1991 and 27 of 148 specimens (18%) in 1992). In 1993, however, isolation rates from Viral Watch (43 of 209 (21%)) and routine clinical specimens (30 of 130 (23%)) were similar. In 1992, which was anecdotally reported by the sentinel physicians to be a 'severe' year, isolations commenced unusually early in April and continued for a prolonged time — until September, in contrast to the anecdotally 'milder' 1993 season when isolates were made in a more restricted period of time — from June until August (Fig. 1). The influenza strains isolated and typed by the WHO reference centre in London are shown in Table I together with the WHO recommended vaccine strains for the preceding northern hemisphere winter which were also used for the following winter season for vaccines in South Africa. In 1991 and 1992 all the influenza isolates matched the recommended vaccine strains. However the 1992 - 1993 recommended strains which were used for the 1993

vaccines in South Africa were discordant in respect of H_3N_2 influenza strain; the recommended H_3N_2 vaccine strain was thus A/Beijing/353/89-like whereas all the H_3N_2 isolates made in that year were of a new and significantly different variant, A/Beijing/32/92 (H_3N_2).

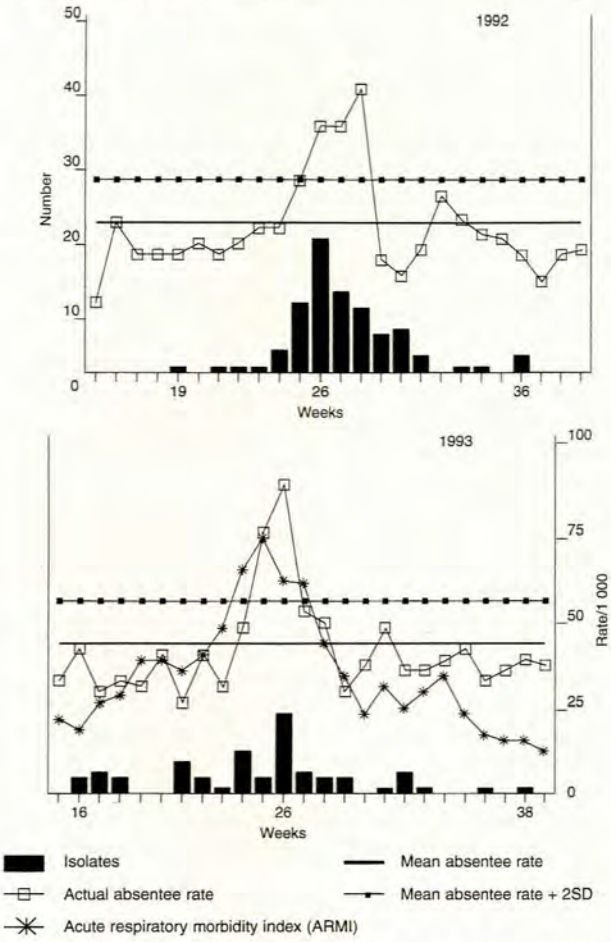

Fig. 1. Influenza isolations, and absenteeism and morbidity data for 1992 and 1993.

Table I. Concordance of vaccine recommendations with influenza virus isolates

Year	WHO vaccine strain recommendations	Local influenza isolates typed by the WHO
	1990-1991 recommendations[12]	
1991	(i) A/Guizhou/54/89 (H_3N_2)-like	41 x /Taiwan/1/86* (H_1N_1)
	(ii) A/Singapore/6/86 H_1N_1)-like	1 x A/Singapore/6/86 (H_1N_1)
	(iii) B/Yamagata/16/88-like	5 x B/Panama/45/90*
	1991-1992 recommendations[13]	
1992	(i) A/Beijing/353/89 (H_3N_2)-like	39 x A/Washington/15/91* (H_3N_2)
	(ii) A/Singapore/6/86 (H_1N_1)-like	4 x A/Hong Kong/25/90* (H_3N_2)
	(iii) B/Yamagata/16/88 OR B/Panama/45/90-like	2 x A/Beijing/353/89 (H_3N_2) 5x A/England/261/91* (H_3N_2) 24 x B/Quingdao/102/91* 1 x B/Victoria/2/87
	1992-1993 recommendations[14]	
1993	(i) A/Beijing/353/89 H_3N_2)-like	21 x A/Beijing/32/92 (H_3N_2)-like
	(ii) A/Singapore/6/86 (H_1N_1)-like	
	(iii) B/Yamagata/16/88 OR B/Panama/45/90-like	3 x B/Panama/45/90

*Variant strains antigenically very similar to corresponding vaccine strain.

The weekly school absenteeism rates for 1992 and 1993 and the ARMI for 1993 are shown in Fig. 1. In both 1992 and 1993 virus isolation proved to be a considerably more sensitive indicator of the influenza epidemic. In 1992, virus isolates commenced some 6 weeks before the rise in the weekly absenteeism rate and the peak of virus isolation in week 26 preceded by 3 weeks the peak of absenteeism. Similarly, in 1993, virus isolations commenced some 3 weeks before the absenteeism peak. In both years biphasic absenteeism curves were observed, with a second peak occurring about 5 - 6 weeks after the first and coinciding with a second round of virus isolation. The curve of the ARMI for 1993 approximated the absenteeism curve although it peaked about 2 weeks earlier (Fig. 1).

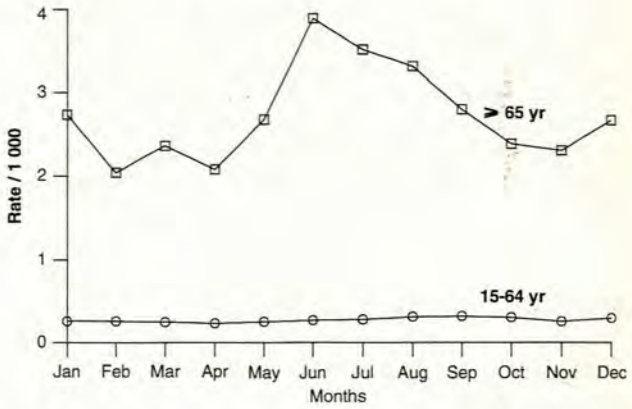

Fig. 2. Mortality data in the Johannesburg municipal area supplied by the Department of Health, Housing and Urbanisation of the City of Johannesburg.

Mortality figures for the two old age institutions monitored are shown in Table II. Although there was a tendency for increased mortality in the winter months, these did not appear to be significant because of the small numbers involved. Both institutions had also extensively immunised their residents — approximately 75% each for both institutions. The monthly mortality rates for the municipal area of Johannesburg are shown in Fig. 2 and demonstrate a clear winter increase in the over-65-year age group, peaking in June/July, while the curve for the 15 - 64-year age group shows no seasonal variation.

Table II. Mortality figures from two old-age institutions

	Institution A (N = 570)		Institution B (N = 457)	
Month	1992	1993	1992	1993
J	12	7	1	1
F	7	8	5	0
M	12	8	1	2
A	5	11	1	1
M	12	12	2	2
J	18	16	3	3
J	25	12	7	3
A	12	10	0	5
S	7	10	2	2
O	8	11	3	2
N	10	8	0	2
D	5	15	3	

Discussion

Influenza surveillance programmes have been established in many countries. Some of them, e.g. those of the Centers for Disease Control in Atlanta and the Influenza Research Center in Houston in the USA,[6] the GROG (Regional Influenza Surveillance Group) in France,[7] the 'spotter' physician network of the Royal College of General Practitioners in the UK,[8] and the Brussels Institute of Hygiene and Epidemiology in Belgium,[9] have developed programmes of considerable size and sophistication with large numbers of 'spotter' physicians reporting relatively detailed data to central processing units. The WHO has appealed for as many countries in the world as possible to establish influenza surveillance programmes and possibly network with each other through an electronic database.[10]

There are 4 major objectives of an influenza surveillance programme. The first is to be able to have an early detection system of an influenza outbreak so that the health care system can be adequately prepared. The second is to facilitate the estimation of the likely impact of a forthcoming epidemic. The third is to collect influenza isolates both for outbreak and patient diagnostic purposes, as well as to provide strains for antigenic analysis for planning the composition of vaccine. The last is to be able to delineate groups that will be at special risk for influenza and its complications so that they can be earmarked for vaccination if they are not already on the existing recommended list for vaccination.

The structures of influenza surveillance programmes vary from country to country although in general most of the monitoring parameters are similar. These parameters vary intrinsically in sensitivity and specificity, and their reliability depends on the enthusiasm of the sentinel doctors who collect the data as well as the representativeness of the surveillance programmes.

Virus isolation remains the cornerstone of all influenza surveillance programmes. The simultaneous isolation of influenza virus and monitoring of non-viral parameters, such as respiratory morbidity, are the only guarantee of the specificity of the programme given the nonspecificity of clinical presentation of influenza. In addition, virus isolation was shown to be the most sensitive of all parameters, preceding the rise in other parameters by several weeks.[6,7,9] Several of the surveillance programmes have also added serological investigations: blood specimens are taken before and after an epidemic to determine the prevalence of significantly increased titres in paired sera, which is usually determined by the haemolysis-in-gel technique.[6,7,11] In our Viral Watch Programme virus isolation was also shown to be the most sensitive of the monitoring parameters with detection of virus preceding the increase in absenteeism by 3 - 6 weeks. The diagnostic value of virus isolation was also shown by the demonstration that the second phase of the epidemic in both 1992 and 1993 was coincident with the second round of influenza virus isolation.

The value of virus isolation in obtaining strains which can be characterised for the planning of vaccine formulation was shown by comparison of virus isolations each year with the vaccine formulations (Table I). The strains which are incorporated into South African vaccines are those recommended for the northern hemisphere winter by the WHO for the preceding winter season 6 months previously. In most years new viral strains initially circulate during winter in the more populous northern hemisphere and then move down to the southern hemisphere winter 6 months later. Thus, the vaccine formulation would usually correspond to the circulating viral strains in South Africa and this indeed occurred in 1991 and 1992. However, in 1993 the vaccine formulation for the 1992/93 northern hemisphere season contained A/Beijing/353/89 as its H_3N_2 strain, while the H_3N_2 strain which actually circulated in South Africa was a new strain which was antigenically significantly different, A/Beijing/32/92. This emphasises the need for a southern hemisphere influenza vaccine manufacturing facility which can rapidly manufacture vaccines using strains corresponding to those circulating in this hemisphere.

The measurement and charting of respiratory morbidity are subject to considerable error depending on the degrees of indirectness of the parameters that are being measured. The WHO clinical surveillance definition of influenza is that of an acute febrile ($\geq$ 38°C) respiratory illness usually accompanied by prostration and cough, with or without myalgia or sore throat.[10] This has led to considerable underdiagnosis[3] either because episodes do not come to medical attention, diagnostic criteria are imprecise or, as we found, the imposition of complex questionnaires dampens the enthusiasm of busy sentinel physicians. More streamlined morbidity indicators such as total respiratory illness which may, at first sight, appear to be less specific, turn out, in practice, to be more accurate and reliable indicators of the influenza disease burden. Indirect indicators, such as absenteeism, form a part of all influenza surveillance programmes because these data are relatively easy to obtain. School absenteeism may provide an earlier alerting signal of an influenza epidemic compared with adult worker absenteeism because epidemics of respiratory infections in children always precede those in adults. It was demonstrated over 40 years ago that the incidence of acute respiratory infections was twice as high in adults who lived with school age children than in adults who did not.[15] Other indirect parameters used include visits to hospitals or emergency rooms[3,6,7] and consumption of pharmaceuticals, such as cough preparations, decongestants, antihistamines and antibiotics.[7] Each of these has a similar value as an adjunct to the composite picture of an influenza epidemic. These non-virological parameters can, however, be misleading with regard to influenza activity, in the absence of confirmation by virus isolation.[6]

Mortality has been used for many years to estimate the impact of influenza, especially in the elderly population. Excess mortality, i.e. the number of deaths recorded in excess of the number expected on the basis of past experience, is commonly used as an indicator of the severity of influenza.[5] It has been shown, however, that methods used both to predict baseline as well as to record excess mortality, considerably underestimate the effects of influenza on mortality.[3,5] Seasonal mortality figures from all causes are probably a better indicator of influenza activity than influenza mortality itself.[9] The mortality rates in Johannesburg demonstrated a clear winter peak in the over 65-year-old population, confirming that this group should be routinely immunised against influenza. In order to use excess mortality as a measure of the impact of influenza, mortality

rates over many years need to be utilised to determine baseline as well as excess mortality levels. In our study mortality figures on their own over the past few years contributed little to our knowledge of the extent of influenza.

An epidemic of influenza is diagnosed on both virological criteria (the proof of the presence of influenza virus) together with epidemiological criteria (based on the presence of these nonspecific indicators). A number of definitions of an epidemic or an epidemic threshold have been devised. For example, the rise of the monthly incidence of influenza-like illness beyond 400 per 100 000 inhabitants[16] or the isolation of influenza from at least 10% of submitted samples,[7] or an excess of cases of influenza-like illness and nonspecific acute respiratory illness for 2 consecutive weeks above the epidemic threshold.[9]

The success of the influenza surveillance programme depends directly on the interest and enthusiasm of the sentinel doctors and the programme is an example *par excellence* of how primary care physicians and biomedical laboratories can co-operate and collaborate in a particularly important preventive medical venture.

Our sincere thanks to all the sentinel doctors who assisted so enthusiastically with the Witwatersrand Viral Watch Surveillance Programme, as well as the principals and secretaries of all the schools included in the absenteeism surveillance programme. We would also like to thank Ms Magda de Beer of the Department of Health, Housing and Urbanisation of the City of Johannesburg, and Dr J. Lundie and Sr E. Joss for providing mortality data for the two homes for the aged studied.

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