J. Hyg., Camb. (1978), **80**, 249
Printed in Great Britain

Excess mortality from influenza in a large urban population, Rome, Italy, 1956–76*

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(*Received* 8 *August* 1977)

SUMMARY

Influenza activity was studied in the Rome population from 1956 to 1976 by analysis of mortality from respiratory causes and from all causes. During cold weather months, type A influenza virus was associated, as a rule, with epidemic excess deaths at two year intervals while type B virus was prevalent twice during epidemic excess mortality periods. Excess absenteeism from work and virus isolation data were also compared with epidemic excess mortality during four consecutive years. The evidence obtained indicated that influenza virus isolation alone does not represent a reliable index of epidemic influenza activity in this population. The proportion of deaths attributed to respiratory causes consistently increased in every epidemic, the most pronounced increases occurring during large epidemics. The break-down by age of deaths from respiratory causes in the course of two epidemic periods showed that the percentage distribution of deaths was essentially the same as in non-epidemic periods. This evidence indicates that the same factors influencing the age-related distribution of mortality from respiratory causes during non-epidemic periods, probably affect the fatal outcome of influenza during epidemics.

INTRODUCTION

The monitoring of excess deaths due to respiratory causes, as originally indicated by Farr (1885), remains a useful indirect measure of influenza activity, since other surveillance techniques based on case reporting (Langmuir & Housworth, 1969; Rubin & Gregg, 1975), analysis of excess absenteeism (Dowdle, Coleman & Gregg, 1974) and laboratory study (Volpi *et al.* 1976; Marine, McGowan & Thomas, 1976) are not completely adequate for characterizing influenza epidemics (Dowdle *et al.* 1974). In fact, even though it is important to look at all these factors to obtain a comprehensive picture of the problem the analysis of the mortality phenomenon, *per se*, can provide a quantitative appreciation of the

* This work was supported by contract No. 77.00276.84 within the 'Progetto Finalizzato Virus' of the C.N.R., Italy.

severity of influenza epidemics (Langmuir & Housworth, 1969; Rocchi, Ragona, De Felici & Muzzi, 1974) and, through the measure of the statistical significance of excess mortality (Housworth & Langmuir, 1974), it also makes it possible to compare the relative intensity of different epidemics.

The purpose of this paper is to present an analysis of some mortality characteristics of influenza epidemics in a large urban population during 21 consecutive years in which data on influenza virus isolation were available.

In this study data on absenteeism from work referring to several epidemic and non-epidemic periods are also compared with those on mortality and on virus isolation.

MATERIALS AND METHODS

Population and mortality

The urban population of Rome consisted of 2781993 inhabitants at the time of the census of 1971. Data on the yearly number of residents and the monthly deaths from all causes for the period 1956 to 1976 were taken from the 'Notiziario statistico mensile' of the municipality. Deaths from respiratory causes (ICD category 460–6, 470–4, 480–6, 490–3) (World Health Organization, 1967) for the period 1956 to 1970 were also taken as monthly data from the same source, while those for the years 1971 to 1976 were obtained week by week directly from the municipal statistics service, and were recorded according to age distribution. The monthly data were transformed by linear interpolation into 4-week values. The method of Serfling (Eickoff, Sherman & Serfling, 1961; Serfling, 1963) was employed to calculate both the expected number of deaths and the threshold distinguishing significant deviations in excess. The expected number of deaths from all causes and the corresponding epidemic threshold were calculated for the periods 1956 to 1966 and 1964 to 1976, while the expected number of deaths from respiratory causes and the corresponding epidemic threshold were calculated for the periods 1956 to 1964, 1964 to 1971 and 1970 to 1976 because of the different secular trend showed by mortality during these series of years.

In this study, the epidemic period was defined as the time, including one or more 4-week periods, during which mortality from respiratory causes exceeded the epidemic threshold. For each epidemic period the following indexes of mortality were calculated: rate of excess deaths from all causes and respiratory causes per million residents, i.e. the difference between the observed and the expected rate in the period (Langmuir & Housworth, 1969); proportion of deaths attributed to respiratory causes, i.e. the ratio of the observed number of deaths from respiratory causes to the observed number from all causes multiplied by 100, the corresponding expected percentage incidence being calculated from the figures of the expected mortality. The relative intensity, a statistic which provides a relative measure of the intensity of excess mortality during epidemics, was also calculated as described by Housworth & Langmuir (1974).

Absenteeism

Data on the number of employees and figures referring to daily illness absences for the period September 1971 to July 1975 were taken from the public transport service of Rome. The number of employees consisted of 12142 in 1971, and progressively increased to 16037 in 1975. Daily absenteeism rates were cumulated in 4-week values. The expected level of absenteeism and the epidemic threshold were calculated by the method devised by Serfling to obtain the expected mortality (Serfling, 1963). Rate of excess absenteeism per hundred employees was obtained from the difference between the observed and the expected rate of daily absences.

Virus isolation

Data on influenza virus isolation were obtained through the courtesy of Dr I. Archetti, World Health Organization National Influenza Centre, Istituto Superiore di Sanità, Italy. Specimens for virus isolation are referred to this laboratory over the year from hospitals and from general practitioners when individual patients or epidemic cases of influenza and acute respiratory infections are observed. The data reported in this paper refer to influenza virus isolation in Rome: these data are used to identify the serotypes prevailing during the epidemic excess mortality periods.

RESULTS

Figures 1–3 depict the curves of the observed and expected number of deaths from all causes and from respiratory causes and indicate the time periods when influenza virus strains were isolated in Rome.

The periodicity of the seasonal variation of the observed mortality is evident. Peaks exceeding the epidemic threshold stand out, with few exceptions, both in the graphs of mortality from respiratory causes and in the graphs of mortality from all causes, deaths from respiratory causes demonstrating in a more evident way the epidemic excesses. During epidemic excess deaths periods, as a rule, influenza virus strains were isolated, except for the epidemic periods of January 1957, December 1962 and July 1971. Circulation of influenza virus, however, was demonstrated several times during the winter season, when no significant increase of deaths from respiratory causes was shown: for example, type B influenza virus strains were isolated in January 1959, March 1971 and December 1973, and type A influenza virus in February and March 1962, February 1966, January 1969, December 1971 and January 1972, February and March 1974 and in March 1976.

Table 1 gives the figures for excess mortality, relative intensity and the proportion of deaths attributed to respiratory causes for the 15 epidemics recorded from 1956 to 1976. During the 12 years of Asian influenza A(H2N2) virus activity, the highest rates of excess mortality were registered in 1957 and in 1967–8, i.e. when the original virus strain (A/Singapore/1/57) and the last antigenic variant (A/Tokio/3/67), respectively, were demonstrated in Italy. The maximum rate of excess mortality (355·3 and 530·6 per million from respiratory and from all causes, respectively) after the introduction of A(H3N2) Hong Kong influenza virus in Italy was observed in the winter of 1969–70. Excess deaths associated with type B

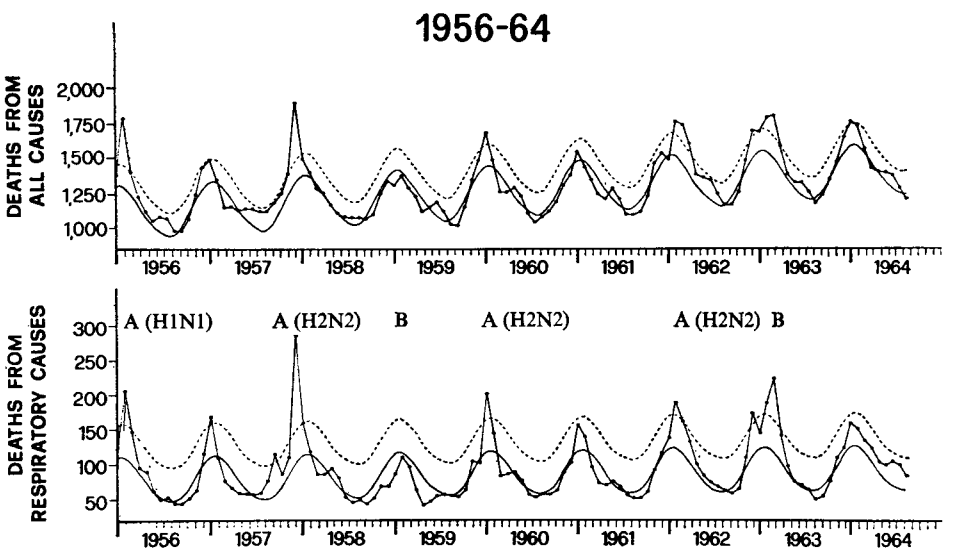

Fig. 1. Deaths in Rome, 1956–64. ●—●, Observed; ——, expected; – – –, epidemic threshold.

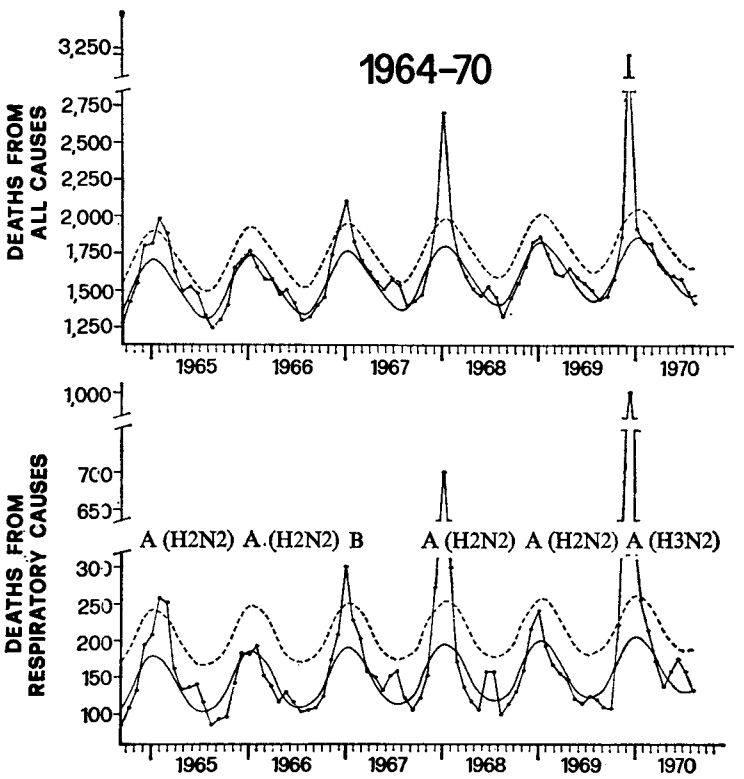

Fig. 2. Deaths in Rome, 1964–70. Symbols as in Fig. 1.

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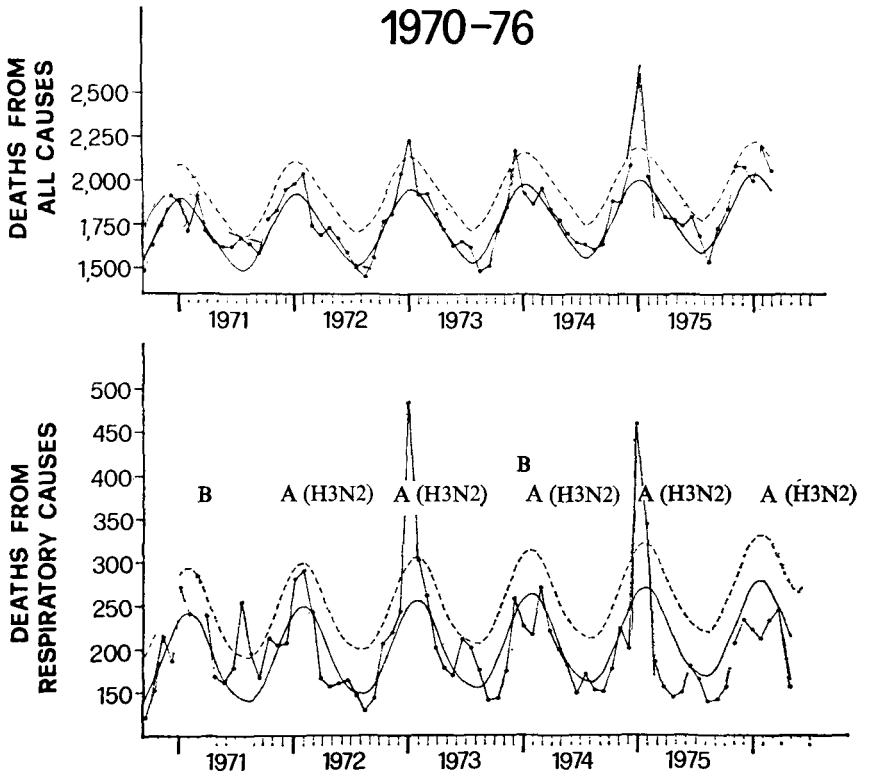

Fig. 3. Deaths in Rome, 1970–6. Symbols as in Fig. 1.

influenza virus epidemics were recorded twice from 1956 to 1976, but circulation of this virus type in the urban population was usually detected at four-yearly intervals. In February and March 1963 and in January 1967, when type B influenza virus could be looked on as the causative agent of the epidemic, the rate of excess mortality from respiratory causes was 75·2 and 42·6 per million, respectively.

From 1956 to 1976 the epidemic periods, with few exceptions, had relative intensities for respiratory causes greater than for all causes. In addition, during several epidemic periods, in which the observed pattern of deaths from all causes did not stand out from the epidemic threshold (Figs. 1–3), the intensity for all causes was not significant. The highest levels of relative intensity both for respiratory and all causes were recorded during the two major epidemic increases of deaths occurring in December 1967 to February 1968 and in December 1969 and January 1970. The proportion of deaths attributed to respiratory causes consistently increased in every influenza epidemic which was recorded from 1956 to 1976 (Table 1). However, most pronounced increases of the proportion of deaths from respiratory causes, twice as great as the expected figures, occurred when both Asian and Hong Kong influenza virus strains produced the first epidemic in the population, i.e. in autumn and winter 1957 and in winter 1969–70 respectively. Small or minimal increases of the proportion of deaths from respiratory causes were registered in several small-size excess deaths periods, associated with A(H2N2) and B type influenza virus outbreaks.

Table 1. *Excess mortality from respiratory causes and from all causes, relative intensity and proportion of deaths attributed to respiratory causes during fifteen epidemic excess periods*

Time period	Prevailing influenza virus type	Rate of excess per million		Relative intensity		Proportion of deaths from respiratory causes (%)	
		Respiratory causes	All causes	Respiratory causes	All causes	Observed	Expected ($\pm 2\sigma$)
Feb. 1956	A(H1N1)	55·0	279·5	3·5	4·3	11·6	8·5 (±1·4)
Jan. 1957	n.d.*	31·4	85·6	2·1	1·4†	11·3	8·2 (±1·5)
Oct. 1957	A(H2N2)	33·0	77·5	2·2	1·3†	9·6	5·1 (±1·4)
Dec. 1957	A(H2N2)	101·4	315·6	6·7	5·1	15·1	7·5 (±1·4)
Jan. 1960	A(H2N2)	41·7	119·4	3·1	2·2	11·9	8·0 (±1·4)
Feb.–Mar. 1962	A(H2N2)	51·6	238·8	2·9	3·3	9·9	7·9 (±1·0)
Dec. 1962	n.d.*	29·4	94·0	2·4	1·9†	10·1	7·3 (±1·3)
Feb.–Mar. 1963	B	75·2	238·7	4·4	2·7	11·4	7·8 (±1·0)
Feb.–Mar. 1965	A(H2N2)	66·0	287·7	3·1	5·1	13·1	10·8 (±1·1)
Jan. 1967	B	42·6	134·1	3·0	3·5	14·4	10·9 (±1·5)
Dec.–Feb. 1967–68	A(H2N2)	271·8	532·2	11·1	8·2	19·3	10·8 (±0·9)
Dec.–Jan. 1969–70	A(H3N2)	355·3	530·6	18·5	10·3	26·6	10·8 (±1·0)
July 1971	n.d.*	39·7	60·3	3·5	1·7†	13·5	9·0 (±1·5)
Jan. 1973	A(H3N2)	83·0	182·7	7·5	5·2	21·7	12·8 (±0·4)
Jan.–Feb. 1975	A(H3N2)	94·8	302·2	6·2	6·2	17·4	12·5 (±0·3)

* n.d.: Not determined.

† Intensities not exceeding 1·96 standard deviation units are not considered statistically significant ($P > 0·05$).

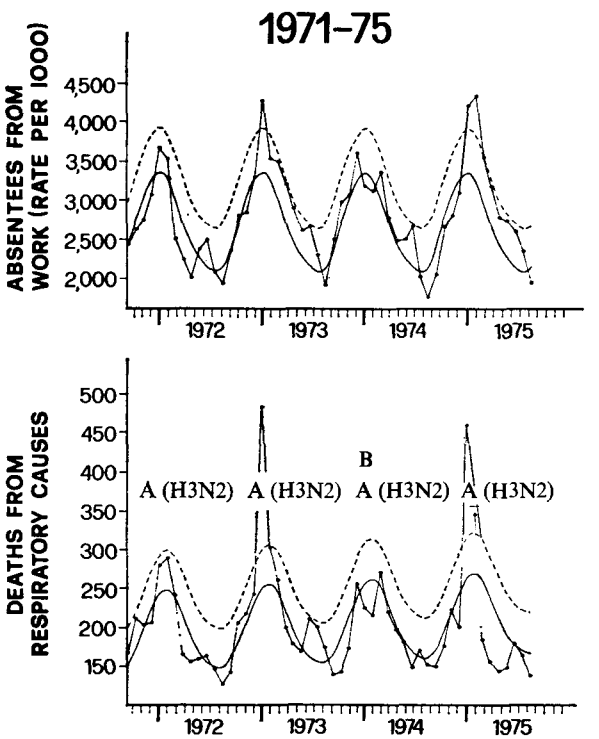

Fig. 4. Absenteeism from work in the municipal transport service and deaths from respiratory causes in Rome, 1971–5. Symbols as in Fig. 1.

Table 2. *Observed and expected percentage distribution by age groups of mortality from respiratory causes during two epidemic winter periods*

		Percentage distribution of mortality from respiratory causes			
		Jan. 1973		Jan.–Feb. 1975	
Age group (years)	Population (1000s)*	Observed	Expected ($\pm 2\sigma$)	Observed	Expected ($\pm 2\sigma$)
0–4	239·3	3·93	4·05 (±1·22)	2·23	4·39 (±0·92)
5–19	651·3	0·62	0·51 (±0·34)	0·62	0·41 (±0·28)
20–39	836·9	0·83	0·61 (±0·40)	0·50	0·56 (±0·34)
40–49	397·7	0·62	1·20 (±0·68)	1·36	1·53 (±0·56)
50–59	283·4	5·37	5·35 (±1·38)	2·61	4·55 (±0·94)
60–69	223·9	20·45	17·89 (±2·38)	15·14	17·36 (±1·72)
70–79	112·4	34·30	32·88 (±2·94)	34·62	32·63 (±2·12)
80–89	34·8	29·13	31·00 (±2·90)	34·48	30·99 (±2·08)
⩾ 90	3·1	4·75	6·86 (±1·58)	8·44	7·61 (±1·20)

* Census of 1971.

Figure 4 shows the curves of the expected and observed rates of absenteeism recorded among the public transport employees for the period September 1971 to July 1975. The curve of deaths from respiratory causes, as given in Fig. 3, is also shown for reference in the chart. Two significant peaks exceed the threshold of

https://doi.org/10.1017/S0022172400053602 Published online by Cambridge University Press

absenteeism in 1973 and in 1975, contemporaneously with the epidemic excesses of deaths from respiratory causes in the general population. In January 1973 and in January and February 1975 rates of excess absenteeism reached 92·3 and 195·8 per hundred employees and rates of excess mortality from respiratory causes reached 83·0 and 94·8 per million. The epidemics of 1973 and of 1975 were associated with the A(H3N2) antigenic variants A/England/42/72 and A/Port Chalmers/1/73, respectively.

Table 2 gives the data on percentage distribution of mortality from respiratory causes by age groups for the two last epidemic periods (January 1973, January and February 1975). The figures of the expected percentage distribution, i.e. averaged data derived from corresponding periods of non-epidemic years (1971, 1972, 1974, 1976) are also given for comparison. No relevant difference in the percentage distribution by age of deaths appears between epidemic and non-epidemic periods.

DISCUSSION

A total of fifteen epidemic increases of mortality occurred in Rome from 1956 to 1976. They are more clearly indicated by the peaks of deaths from respiratory causes than by the mortality peaks from all causes, even though the real impact of large influenza epidemics on the population is shown in its full evidence by the rates of excess deaths from all causes. In fact, the rate of excess deaths from respiratory causes from 1956 to 1976 accounts for less than one third of the excess mortality from all causes. This indicates that mortality from epidemic influenza can be underestimated when its evaluation is based on respiratory diseases deaths rather than on mortality from all causes.

Epidemic increases of deaths related to type A influenza virus outbreaks recurred in Rome at intervals of 2 to 3 years. Circulation of type B influenza virus was detected every four years and it was associated with epidemic excess mortality during two winter seasons.

The measure of the statistical significance of the excess mortality, indicated as relative intensity (Housworth & Langmuir, 1974), allowed a further quantification of the effect of influenza epidemics in Rome. This index correlates fairly well with the rate of excess, both for deaths from respiratory and from all causes. The limitation in the use of relative intensity in the present study is due to the fact that three different curves were prepared to describe the expected mortality levels for the twenty-one years under study. In these circumstances, the comparison of the relative intensities has to be confined to the epidemics included within the same curve (Housworth & Langmuir, 1974).

The proportion of deaths attributed to respiratory causes showed pronounced variations during the epidemic periods, high values being associated, as a rule, with large epidemic excesses of deaths rather than with small or minimal epidemics. These data indicate the existence of an appreciable variability in the pathological expression of influenza virus infection in different outbreaks (Masterson, 1969; Burk, Schaffner & Koenig, 1971; Mulder & Hers, 1972).

This study shows that in the course of two periods of epidemic excess mortality,

where data by age group were examined, the break-down by age of deaths from respiratory causes has a distribution similar to that of non-epidemic years. This evidence confirms that influenza mortality from respiratory causes is prevailingly concentrated among age groups from 60 years onward; it also suggests that the same factors, which determine the age-related difference in the pattern of distribution of mortality from respiratory causes during non-epidemic periods, affect the fatal outcome of influenza infection during epidemic excess death periods.

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