Influenza- and respiratory syncytial virus-associated adult mortality in Soweto

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Background. Influenza and respiratory syncytial virus (RSV) infections cause seasonal excess mortality and hospitalisation in adults (particularly the elderly) in high-income countries. Little information exists on the impact of these infections on adults in Africa.

Objectives. To estimate influenza- and RSV-related adult mortality, stratified by age and hospitalisation in Soweto.

Study design. A retrospective hospital-based study in Soweto from 1997 to 1999 to estimate influenza- and RSV-related excess all-cause deaths and hospitalisation using a rate-difference method. The study was based on influenza seasons of varying severity, provided by surveillance data.

Results. Influenza seasons were significantly associated with excess mortality in adults across all 3 years, except for 18 - 64-year-olds in 1998. Excess mortality was highest in those ≥65 years of age: 82.8/100 000 population in the mild 1997 season and 220.9/100 000 in the severe 1998 season. Influenza significantly increased adult medical hospitalisation in the severe 1998 season alone. RSV did not significantly affect mortality or hospitalisation.

Conclusion. Influenza-related mortality was substantial and disproportionately affected the elderly. Influenza vaccination for the elderly warrants consideration. The RSV-related burden was not significantly increased but merits observation over a longer period.

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Influenza is a major cause of seasonal excess mortality and hospitalisation in adults, particularly the elderly, in temperate climates and in subtropical areas.[1-9] There is little information on the burden of influenza among adults in Africa. An outbreak in Madagascar in 2002 had a high attack rate and a mortality of 2.5%.[10] Regular active surveillance for influenza to define seasons and infecting types is conducted in only a few African countries, including South Africa.[11] Knowledge of the local burden of influenza is important to assess the potential benefits of a vaccination programme.

Respiratory syncytial virus (RSV) epidemics, which often overlap with the influenza season, cause significant morbidity and mortality in adults, especially the elderly.[3-7,12] Studies of both influenza and RSV infections typically employ indirect methods because neither infection is routinely confirmed virologically.[1-7,13]

Soweto has a temperate climate with summer rainfall. Viral surveillance data from South Africa from 1997 to 1999 revealed influenza seasons of varying severity. We aimed to determine influenza- and RSV-associated mortality and hospitalisation among adults and to stratify these results by ages ≥65 years and 18 - 64 years.

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Methods

Study design and study population

Ours was a retrospective cohort study of adults admitted to the Department of Medicine, Chris Hani Baragwanath Hospital, Soweto, from January 1997 to December 1999. To calculate mortality and hospitalisation attributable to influenza or RSV, we used differences by calendar year between the rates of these events when the viruses were circulating, and the rates when neither virus was present above baseline levels.

Study site

Chris Hani Baragwanath Hospital is a 2 700-bed public sector hospital serving Soweto. The Department of Medicine had 883 adult medical beds and an average of 27 000 hospitalised patients per year. The hospital had paper-based information systems with no back-up. There was no classification system for discharge diagnoses. The background rate of HIV-infected adults in the medical wards was 26% in 1997 and 31% in 1999. About 80% of the population of South Africa does not have private medical insurance.

Viral surveillance and definitions of study periods

Influenza and RSV seasons were based on weekly isolations of the viruses at the National Institute of Virology, Johannesburg, which has a sentinel network. Specimens were also supplied from a study of children hospitalised at Baragwanath Hospital.[14,15]

Influenza and RSV seasons were defined as the period of at least 2 consecutive weeks in which each week accounted for ≥3% of total annual isolates respectively. The baseline period was defined as periods of at least 2 consecutive weeks in which both influenza and RSV isolations were <2% of the annual total.

Mortality and hospitalisation data

The numbers of adult and paediatric patients who died in the hospital were extracted from the mortuary register and classified by week. The numbers and ages of adults from the medical wards were recorded. All-cause mortality was used as there were insufficient data in many patients' clinical records to enable cause of death or predisposing disorder to be accurately assigned. The number of all-cause adult medical hospitalisations per week was extracted from the admission ward register. The data for age and reasons for hospitalisation were incomplete.

Excess events

The effects of influenza and RSV were estimated by using a rate-difference method.[5-7,16] For each calendar year, the average number of events (death or hospitalisation) per week was calculated for the baseline and the influenza or RSV season. The excess events per week were calculated by subtracting the baseline rates from the rates during an influenza or RSV season. These results were expressed as a percentage increase. The excess rate per week was multiplied by the total number of weeks of influenza or RSV predominance to give a total number of events in the season. The excess number of events was applied to the Soweto population (based on the 1996 census) to give rates per 100 000 population.

Statistical analysis

Descriptive statistics were calculated using STATISTICA (StatSoft, Version 6, Tulsa, USA). The squared coherence, which describes the strength of association in time series analysis, is reported at a frequency of 52 weeks across all 3 years in the dataset. Differences between means, together with the 95% confidence interval (CI) of these differences, were calculated using Confidence Interval Analysis (C.I.A., version 2.1.2 Build 50, University of Southampton, UK).

Ethical approval

This study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand.

Results

Influenza and RSV seasons

The weekly isolations are represented in Fig. 1. The severe (and early) 1998 influenza season was essentially RSV-free and was sandwiched for comparison between the mild 1997 influenza season with a separate RSV season and the moderately severe 1999 season with an overlapping RSV season. Influenza subtype A/Sydney/5/97-like H3N2 was dominant in all three seasons.

Mortality

The squared-coherency between influenza season and all-cause adult medical mortality was 0.90 (Fig. 2). Modelling for lag periods at the end of a season did not affect the results (results not shown). In Table I, all-cause mortality for the entire hospital (adult and paediatric) and all-cause mortality for the adult medical department are presented. There were slightly more than 100 deaths per week for the hospital in the baseline period of each study year, of which approximately 60 occurred in the adult medical wards. In all three influenza seasons, total hospital deaths and adult medical deaths were significantly increased. RSV-associated mortality was not significantly increased in any year.

Table I shows all-cause mortality for patients ≥65 years old in the adult medical wards. Mortality increased by 80% in the severe 1998 influenza season and was significant across all influenza seasons. The elderly accounted for 31%, 64% and 42% of deaths in 1997, 1998 and 1999, respectively. All-cause deaths for those aged <65 years significantly increased in the mild

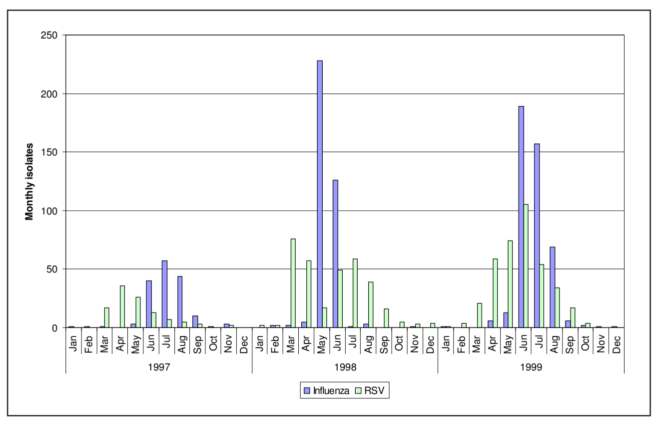

Fig. 1. Seasonal distribution of influenza and RSV isolates 1997 - 1999 by week and month.

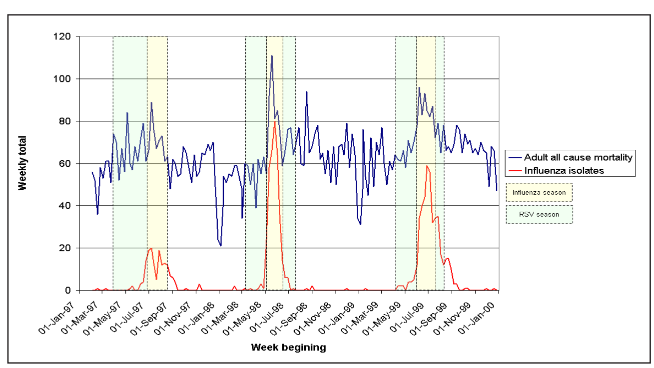

Fig. 2. Weekly influenza isolates and all-cause adult medical mortality.

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1997 season and the overlapping 1999 season (Table II). RSV season excess deaths were not significant in either age group.

Table II shows the excess death rates/100 000 population for Soweto adults. For those ≥65 years of age, the excess mortality rate was 220.9/100 000 in the severe 1998 season, and 82.8/100 000 in the mild 1997 season.

Hospitalisation

The mean weekly hospitalisation in the adult medical wards in the baseline period increased from 561 in 1997 to 596 in 1998 and 611 in 1999. Only in the 1998 influenza season alone was there a significant increase in weekly admissions to 678 – an increase of 14% (95% CI 8 - 20%). This increase in admissions in the 1998 influenza season was 88.4/100 000 population. No significant RSV-related increase was found (data not shown).

Discussion

In our 3-year study, influenza seasons were significantly associated with excess all-cause mortality in adults (except in 18 - 64-year-olds in 1998), particularly in the elderly, and with excess all-cause medical hospitalisation in the severe 1998 season only. RSV did not significantly affect mortality or hospitalisation.

The occurrence of the severe 1998 H3N2 influenza season sandwiched by the mild 1997 season and the intermediate 1999 season provided a useful period for studying the impact of influenza seasons on hospitalisation and mortality in a previously unstudied community and country. After taking the RSV seasons into consideration, the 1999 season was compromised by the marked overlap of the two seasons, i.e. one could not place as much store on the results from 1999 owing to the overlap of RSV and flu.

We used a rate-difference method to estimate the effects of influenza and RSV season on hospitalisation and mortality as we had only three seasons to consider.[5] A potential weakness is that this method does not control for seasonal effects. Against this significant confounder was the early epidemic in 1998 and that RSV covered similar periods and was not found to have a significant impact. As in most other studies, the viral seasons were based on surveillance data and the infections were not directly confirmed.

The mortality in the elderly in 1998 of 221/100 000 is among the highest recorded. In the developed world, all-cause mortality in the elderly ranges from 116 to 136/100 000 but mortality is smoothed out over a number of seasons.[3,6-8] In the USA, ≥90% of deaths occur in those aged ≥65 years. In Soweto, this ranged from 31% to 64% by year, largely because the elderly represented only 6% of adults. There was a significant influence on mortality in those aged 18 - 64 years in 1997 and 1999 at a similar rate to the 6.4 - 12.5/100 000 found in those aged 50 - 64 years in developed countries.[3,6-8,16]

Although the impact of RSV on mortality did not reach significance, the rates in the elderly of 70.2 - 110.5/100 000 are

Table I. All-cause deaths for the entire hospital and for adult medical patients ≥65 years of age and <65 years of age per week and per season for influenza and RSV 1997 - 1999

			Entire hospital				Adult medical wards				≥65 years of age				<65 years of age			
Year	Period	Duration in weeks	Mean / week	SD	% increase	95% CI	Mean / week	SD	% increase	95% CI	Mean / week	SD	% increase	95% CI	Mean / week	SD	% increase	95% CI
1997	Baseline	28	101	17	-		58	11	-		17	4	-		40	8	-	
1997	Influenza	9	117	11	16%	3 to 28	70	9	21%	7 to 34	21	5	24%	0 to- 41	48	8	20%	5 to 35
1997	RSV	11	105	13	4.%	–15 to 8	66	9	14%	–26 to 2	20	5	18%	–41 to 0	45	8	13%	–18 to 3
1998	Baseline	34	101	19	-		60	14	-		15	5	-		45	12	-	
1998	Influenza	7	128	26	27%	11 to 44	80	19	33%	12 to 53	27	8	80%	53 to 113	52	12	16%	–7 to 38
1998	RSV	12	109	11	8%	–20 to 4	62	11	3%	–18 to 12	17	5	13%	–40 to 7	44	8	–2%	–16 to 18
1999	Baseline	34	105	17	-		63	11	-		14	4	-		48	10	-	
1999	Influenza	7	123	12	17%	4 to 30	85	8	35%	22 to 49	23	6	64%	63 to 93	61	5	27%	10 to 42
1999	RSV	12	110	12	5%	–14 to 6	68	7	8%	–19 to 3	18	4	29%	–43 to 7	50	6	4%	–15 to 10
All groups		154	107	18			64	13			17	6			46	10		

Table II. Annual excess deaths/100 000 population in Soweto, based on the 1996 census, for influenza and RSV for the entire hospital, and for adult medical deaths as a whole and by age ≥65 and <65 years, 1997 - 1999

			Influenza		RSV	
Burden	Year	Population	*N* excess events	Rate/10^5	*N* excess events	Rate/10^5
Hospital mortality	1997	894 113	140	15.7	46	5.1
	1998		193	21.6	94	10.5
	1999		127	14.2	59	6.6
Adult medical mortality	1997	648 240	110	17.0	88	13.6
	1998		139	21.4	22	3.4
	1999		156	24.1	60	9.3
Mortality ≥65 years	1997	39 833	33	82.8	37	92.9
	1998		88	220.9	28	70.2
	1999		65	163.2	44	110.5
Mortality <65 years	1997	608 407	72	11.8	51	8.4
	1998		50	8.2	0	0
	1999		88	14.5	16	2.6

similar to those of high-income countries.[3,5-7,12] The burden of RSV warrants further study across more seasons in this setting.

The increase in influenza-associated mortality across all seasons was not mirrored in hospitalisation figures; this may be partly explained by the increasing number of patients admitted over the years of the study, mostly owing to HIV-related disease, which might have caused a loss of seasonality.

There are limitations to this study, which was conducted in a paper-based system without back-up data sources or disease classifications. It was performed in a single, large hospital, the only public sector hospital in Soweto. Approximately 80% of the population does not have medical aid cover for private sector health services, and most of them would use public hospitals. We did not adjust the population denominator for those who might have accessed private medical care or used other hospitals, as there was no information on which to base such adjustment. Some people would have died at home. People from outside Soweto might have used this hospital, as a Soweto address was needed to ensure hospitalisation. In our opinion, the excess rates in this study would represent a minimum estimate for the effect of influenza in Soweto. The influenza and RSV seasons overlapped in 1999 and the effects of each season could not be separated. The seasons were discrete in 1997 and 1998; in those years, only influenza-attributable increases reached significance, and modelling for lag periods at the end of a season did not affect the results. Inadequate data precluded a study of hospitalisation by age and consideration of influenza- and RSV-related conditions. Growing numbers of HIV-related admissions might have affected excess hospitalisation and possibly mortality data. HIV infection may exacerbate the severity of influenza[17] but, because few patients had been tested, we did not use data on HIV infection.

South Africa's guidelines for using influenza vaccine focus on the elderly and people with high-risk conditions.[18] As far as we could ascertain, there was almost no usage of influenza vaccine in the community of Soweto during this study. Therefore, influenza vaccine should be provided to the elderly of Soweto until new strategies or vaccines become available. Controversy surrounds evidence for the degree of effectiveness of influenza vaccine in the elderly.[19,20] A long-term study of a defined home-based (i.e. non-institutionalised) community designed to answer some criticisms of previous studies, demonstrated a 27% reduction in the risk of hospitalisation for pneumonia or influenza, and a 48% reduction in the risk of death.[21] A case control study on the effectiveness of influenza vaccination in the elderly over one season was done by a South African private medical funding organisation. The research results were inconclusive, owing to a relatively mild season, limitations inherent in the study design and potential confounders.[22] Since the influenza season in the southern hemisphere occurs after that in the northern season, the match between circulating viruses and vaccine strains is generally better. A vaccination programme in this vaccine-naïve population could answer some of the remaining questions on the effects of vaccination of the elderly.

Conclusion

Influenza had an important effect on mortality among adults in Soweto, particularly those ≥65 years old, across seasons of varying severity. Its effect on hospitalisation was significant only in the most severe season. An influenza vaccination programme targeting the elderly appears to be a logical outcome of this study.

Surveillance data were provided by Barry Schoub and Jo McAnerney of the National Institute of Communicable Diseases. Triclinium CRO (contract research organisation), Dorothy Hlatshwayo and Mark Rubery assisted with data collection. Sanofi-Pasteur supported the study.

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