Community study of role of viral infections in exacerbations of asthma in 9-11 year old children

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Abstract

***Objective*—To study the association between upper and lower respiratory viral infections and acute exacerbations of asthma in schoolchildren in the community.**

***Design*—Community based 13 month longitudinal study using diary card respiratory symptom and peak expiratory flow monitoring to allow early sampling for viruses.**

***Subjects*—108 Children aged 9-11 years who had reported wheeze or cough, or both, in a questionnaire.**

***Setting*—Southampton and surrounding community.**

***Main outcome measures*—Upper and lower respiratory viral infections detected by polymerase chain reaction or conventional methods, reported exacerbations of asthma, computer identified episodes of respiratory tract symptoms or peak flow reductions.**

***Results*—Viruses were detected in 80% of reported episodes of reduced peak expiratory flow, 80% of reported episodes of wheeze, and in 85% of reported episodes of upper respiratory symptoms, cough, wheeze, and a fall in peak expiratory flow. The median duration of reported falls in peak expiratory flow was 14 days, and the median maximum fall in peak expiratory flow was 81 l/min. The most commonly identified virus type was rhinovirus.**

***Conclusions*—This study supports the hypothesis that upper respiratory viral infections are associated with 80-85% of asthma exacerbations in school age children.**

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BMJ 1995;310:1225-8

Introduction

Patients having an acute attack of asthma often give a history of a "cold" before the onset of the exacerbation. Despite numerous studies, however, the cause of most exacerbations of asthma remains controversial. With the exception of asthma epidemics such as those associated with soya beans in Barcelona,[1] there is little evidence to implicate aeroallergens as provoking agents.[2,3] The weighted average detection rates of viruses during exacerbations of asthma were 24% for incidental studies and 31·9% for prospective studies in children and 13·3% in adults.[4] This compares with a rate of 3% in asthmatic patients when free of symptoms.[5-8] Several studies have observed a temporal relation between viral infections and asthma exacerbations,[9-16] while others have found associations between severity of wheezing illness and rate of viral detection.[12-14,17,18] These studies are weakened by low rates of detection,[11,14] particularly of rhinoviruses and coronaviruses, which together cause about two thirds of common colds,[19,20] and by a lack of objective measures to define the exacerbations being studied. We conducted a detailed 13 month longitudinal study to investigate the association of viral infections with exacerbations of asthma in 9-11 year old children in Southampton using the polymerase chain reaction to increase sensitivity of detection.[21,22]

Respiratory symptoms recorded during the study

Upper respiratory symptoms	Lower respiratory symptoms
Runny nose	Cough during the day
Sneezing	Cough during the night
Blocked or stuffy nose	Wheeze during the day
Itchy, sore, or watery eyes	Wheeze during the night
Sore throat	Difficulty breathing or shortness of breath
Hoarse voice	Not fit to go to school because of chest problems (score 2)
Fever or shivery	
Headaches or face aches	
Aches or pains elsewhere	

Subjects and methods

We invited the 186 children aged 7-9 years from the Southampton area who had completed a previous study on bronchial hyperreactivity in children with wheeze or persistent cough,[23] to take part in a study on the role of viral infections in asthma. A total of 114 children, then aged 9-11 years (62 boys and 52 girls), enrolled for this study, which lasted 13 months from 3 April 1989 to 7 May 1990. Children or their parents recorded the peak expiratory flow rate twice daily, and daily upper and lower respiratory tract symptoms were scored from 1 (mild) to 3 (severe) and summated. The box lists the symptoms included. Parents telephoned the investigators if the upper or lower respiratory scores totalled 4 or more, if peak expiratory flow fell by more than 50 l/min from the child's usual value, or if the parent subjectively felt that the child was developing a cold. The child was then visited at home by one of the investigators within 48 hours to obtain specimens for virological testing. Drug treatment and baseline peak expiratory flow were assessed over the first two weeks of the diary card recordings. The study was approved by the Southampton hospitals joint ethics subcommittee.

After each report the investigator took a nasal aspirate and diluted it in 10 ml of virus transport medium,[21] 8 ml of which was frozen in dry ice and stored at −70°C. The remainder was used to prepare six cytospin slides, which were fixed and stored at −20°C for later analysis. A 100 μl finger prick blood

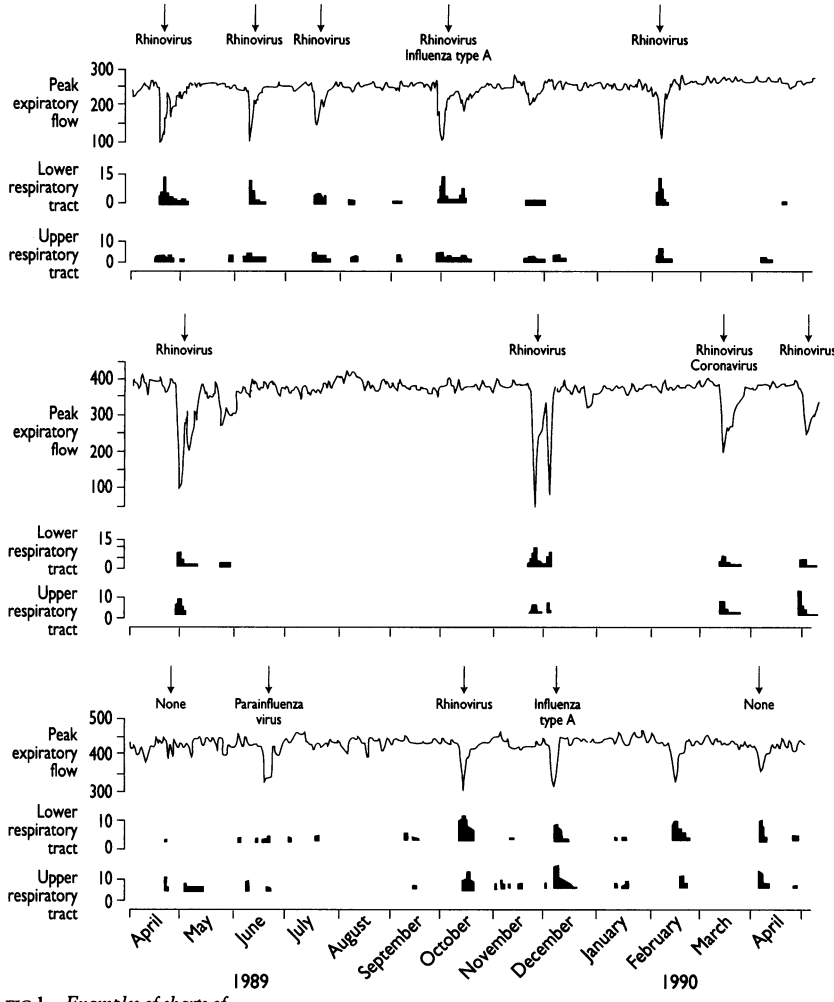

FIG 1—*Examples of charts of peak flow recordings and respiratory symptom scores for three children taking part in the study. The horizontal axis represents the 13 months of the study*

sample was taken at the time of the report and two to three weeks later. Serum was diluted and stored at 4°C.

We also asked children who had reported episodes to provide a further sample during June to September 1991, when they had not had any upper or lower respiratory symptoms in the preceding two weeks. Sixty five children agreed to provide samples. Rhinorrhoea was induced,[21] and sampling and storage methods were identical to those described above.

DETECTION OF VIRUSES

Nasal aspirates were cultured in Ohio HeLa, HEp-2, and clone 16 cells.[24] Samples collected between 1 November 1989 and 18 January 1990 (during an influenza type A epidemic in Britain) were also cultured in MDCK cells, and if parainfluenza virus infection was suspected from the results of immunofluorescence or serology, aspirates were cultured in LLC-MK_2 cells. The cytopathic effect of an isolate was confirmed by electron microscopy (coronavirus), acid stability testing (rhinovirus),[25] immunofluorescence (adenovirus, respiratory syncytial virus, and parainfluenza virus), or haemadsorption (influenza virus).[26]

Picornavirus (rhinovirus and enterovirus) polymerase chain reaction—Duplicate 50 μl aliquots from all samples were taken from two tubes and analysed on different days. Reverse transcriptase polymerase chain reaction and internal probe hybridisation were carried out.[21]

The coronavirus polymerase chain reaction was used to analyse 80 samples with sufficient remaining clinical material in which no virus was detected after all other tests, 10 samples known to be positive for coronavirus (both 229E and OC43) by enzyme immunoassay, and 10 known to be positive for other viruses. The nested reverse transcriptase polymerase chain reactions used primers specific to the nucleocapsid genes of 229E or OC43.[22] Samples were analysed singly with positive results confirmed in duplicate.

Immunofluorescence—Respiratory syncytial virus, adenovirus, and influenza virus type A were detected by direct immunofluorescence (Novo Biolabs, Cambridge). Parainfluenza virus types 1-3 were detected by indirect immunofluorescence with polyclonal antibodies against all three types (Barbara Young, Royal Victoria Infirmary, Newcastle). Testing was carried out on cytospins from nasal aspirates and the results confirmed on tissue culture cells.

Serology—We obtained antigens for enzyme immunoassays for coronavirus 229E and OC43 from the Medical Research Council Common Cold Unit; for respiratory syncytial virus, adenovirus, and parainfluenza virus type 1 from University Microbiology, Southampton; for parainfluenza virus types 2 and 3, from Virion, and for influenza virus type A from the Public Health Laboratory Service, London. Samples were analysed in duplicate except for parainfluenza virus type 2, influenza virus, and adenoviruses, which were analysed singly; equivocal or positive results were confirmed in duplicate. Standard methods were used, and a twofold rise in titre was taken as significant. For coronavirus, however, a difference of more than 2 standard deviations of log antibody units between acute and convalescent samples was used.[27]

ANALYSIS OF DATA

The data from the whole 13 months for each child were plotted to allow visual inspection for patterns of illness (fig 1). All clinical data and virus detection results were coded and entered on to a computer and checked against originals.

An episode was defined as two or more days with symptom scores above the median for that child (or peak expiratory flow at or below the 10th centile) preceded by one day at or below the median (above the 10th centile) and followed by two days at or below the median (at or above the median). A reported episode of lower respiratory tract symptoms or fall in peak expiratory flow was considered to coincide with an observed episode if it occurred within seven days of the observed episode. For upper respiratory tract symptoms reported and observed episodes were considered to coincide if the reported episode was during or up to seven days after the observed episode. Severity was expressed as the maximum total score during the episode for upper and lower respiratory tract episodes and as the largest drop from the median expiratory flow rate for peak expiratory flow episodes. The duration of an episode was taken as the time from the initial fall in peak expiratory flow or rise in symptoms to the day when they returned to the median value.

Normally distributed data are summarised by mean (SD) and skewed data by median (interquartile range). The Mann-Whitney U test was used to compare continuous data between subgroups. Different episodes in the same child were treated as independent. Results were not altered by use of models including a random child effect to allow for non-independence of multiple episodes or reports from the same child. For the 65 children who had samples taken while asymptomatic the number of signals positive for picornavirus by polymerase chain reaction was compared in the asymptomatic samples and in the first symptomatic sample for each child by McNemar's test. Fortran programming was used to adjust peak expiratory flow for height[23] and to define episodes. Statistical analyses were done with the statistical package SPSS.

Results

A total of 108 children (58 boys) completed the study. Six children took bronchodilators regularly and

15 as required; 18 took prophylactic inhaled steroids or disodium cromoglycate; and three took theophyllines. The median baseline peak expiratory flow was 312 (264-350) l/min. Sixty two children were atopic,[28] 42 had had asthma diagnosed, and 52 had reported wheeze in the original questionnaire.[23]

SYMPTOMS AND PEAK EXPIRATORY FLOW EPISODES

There were many unreported episodes of respiratory symptoms and diminished peak expiratory flow (fig 1, table I). During the 13 months the mean (SD) number of episodes per child was 4·13 (1·66) for a fall in peak expiratory flow, 5·33 (4·99) for lower respiratory tract symptoms, and 7·24 (4·47) for upper respiratory tract symptoms. The median (interquartile range) total duration of the episodes per child each year was 64 (44-79), 30 (11-56), and 39 (22-70) days respectively. The median number of days a year that lower respiratory tract symptom scores of at least moderate severity were recorded was 16 (7-35).

The seasonal patterns of reported and unreported episodes were similar (fig 2). However, the severity and duration of reported episodes were significantly greater than those of unreported episodes ($P < 0·001$, table I). The median maximal percentage fall from baseline in peak expiratory flow was 26% and 13·8% for reported and unreported episodes respectively. A fall of 30-120 l/min (9·6%-38·5% from baseline) was recorded in 120 (78%) reported peak expiratory flow episodes and a fall of over 120 l/min (>38·5% from baseline) in 26 (17%) episodes. Cough, wheeze, or shortness of breath of at least moderate severity was recorded in 169 (85%) of the reported lower respiratory tract symptom episodes.

There were 292 reported episodes from 96 of the 108 children. The mean number of reports was 2·5 per child a year, and the maximum number of reports was eight (five children). Satisfactory (0·5-1·5 ml mucus) nasal aspirate samples were obtained from the children for all 292 reported episodes and for all 65 samples from children when asymptomatic.

The median delay between reduction in peak expiratory flow and onset of upper respiratory tract or lower respiratory tract symptoms was one day, the delay being two or more days in 54/117 (46%) upper respiratory and 39 (33%) in lower respiratory tract episodes. Lower respiratory tract and upper respiratory tract symptoms were usually reported on the same day, but upper respiratory tract symptoms preceded lower respiratory tract symptoms by one day or more in 41 (35%) of episodes. There was no significant difference in time between the onset of the episode and specimen collection between those with and without viruses detected (median 2 (1-4) and 2 (1-5·3) days respectively, $P = 0·42$). Specimens were collected within four days after the onset of an episode in 221/276 (80%) cases.

TABLE I—*Number, type, severity, and duration of reported and unreported episodes, from symptom and peak expiratory flow rate diaries. Values are medians (interquartile ranges) unless stated otherwise*

Type of episode	Reported	Unreported	Total
Upper respiratory tract:			
No of episodes	253	529	782
Duration (days)	7 (4-12)	4 (2-7)	5 (3-8)
Severity (symptom score)	6 (4-8)	3 (2-3)	3 (2-5)
Lower respiratory tract:			
No of episodes	200	376	576
Duration (days)	7 (5-12)	4 (2-7)	5 (3-9)
Severity (symptom score)	4 (3-7)	2 (1-3)	2 (2-4)
Peak expiratory flow:			
No of episodes	153	293	446
Duration (days)	14 (7-24)	8 (4-18)	10 (5-21)
Severity (maximum fall from median, l/min)	81 (54-107)	43 (29-67)	52 (33-85)

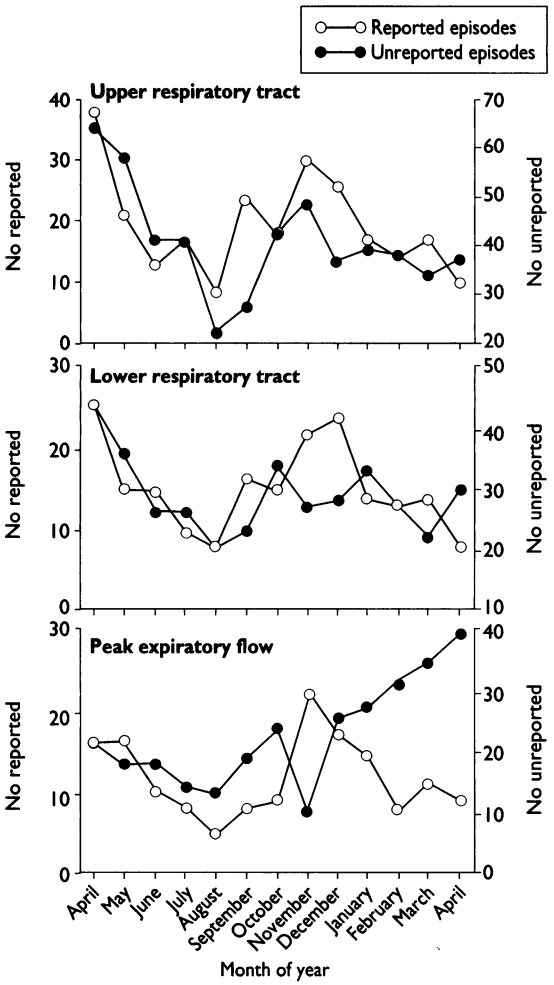

FIG 2—*Seasonal patterns of reported and unreported respiratory symptom and peak expiratory flow episodes*

TABLE II—*Viruses detected during reported respiratory episodes*

Virus	Method of detection: Polymerase chain reaction	Culture	Immunofluorescence	Antibody rise by ELISA	Total
Rhinovirus/enterovirus	146	47			147*
Coronavirus	17	14		21	38
Influenza viruses		14	10	20	21
Parainfluenza Viruses 1, 2, and 3		6	6	18	21
Respiratory syncytial virus		6	6	12	12
Other		2	1	2	3

*84 found to be rhinovirus on further testing; remainder were unidentified picornaviruses.
ELISA = enzyme linked immunosorbent assay.

VIRAL DETECTION

Viruses were detected in 226 of 292 reported episodes (77%); in 14 (4·8%) two viruses were detected, and in one three viruses were detected (fig 1). Picornaviruses were detected in 147 episodes, coronaviruses in 38, influenza and parainfluenza viruses each in 21, and respiratory syncytial virus in 12 (table II). Of the picornaviruses detected, 84 were rhinoviruses, and one had characteristics of both enterovirus and rhinovirus and has not been finally classified. The remaining 62 could not be cultured but are likely to be rhinoviruses, as most enteroviruses culture easily.

Viruses were detected in 161 (81%) reported episodes of lower respiratory tract infection and 125 (80%) reported falls in peak expiratory flow. For episodes with respiratory tract symptoms or falls in peak flow, or with both, viral infections were detected in 80-85% (table III). The highest detection rate was in reported episodes of wheeze, cough, and upper respiratory tract symptoms together with a fall in peak expiratory flow. Presence of a virus did not signifi-

cantly affect the duration or severity of reported episodes of lower respiratory tract symptoms or falls in peak expiratory flow.

The samples from asymptomatic children were analysed by polymerase chain reaction for only picornavirus. The number of samples giving positive signals (8 (12%)) was significantly lower than that for samples from symptomatic children ($P<0.001$, McNemar's test). In five of the eight positive samples the signal was weak compared with that in samples from symptomatic children,[21] and the three children whose samples gave a strong polymerase chain reaction signal all tested negative three weeks later.

TABLE III—*Rate of detection of viruses according to number and type of reported episodes of respiratory symptoms and fall in peak expiratory flow*

Characteristics of episode	No of episodes	No (%) with virus detected
Lower respiratory tract	200	162 (81)
Peak flow fall	157	126 (80)
Lower respiratory tract and peak flow	130	105 (81)
Peak flow and upper respiratory tract	141	116 (82)
Lower and upper respiratory tract	184	155 (84)
Cough	192	156 (81)
Cough and peak flow	126	102 (81)
Cough and upper respiratory tract	177	145 (82)
Cough, peak flow, and upper respiratory tract	113	94 (83)
Wheeze	82	66 (80)
Wheeze and peak flow	58	48 (83)
Wheeze and upper respiratory tract	73	61 (84)
Wheeze, peak flow, and upper respiratory tract	51	43 (84)
Wheeze, cough, peak flow, and upper respiratory tract	48	41 (85)

PATTERNS OF ILLNESS

The median fall in peak expiratory flow for coronavirus infections was 56 (35-88) l/min, significantly less than the 85·5 (55-108) l/min observed for the other viruses ($P=0.005$). Similarly coronaviruses caused less severe lower respiratory tract symptoms than other viruses (median maximum lower respiratory symptom scores 3 (2-5) and 5 (3-7) respectively, $P<0.05$). No other significant differences in the patterns of illness caused by the different viruses were observed, though the number of detections was too small to assess these patterns properly.

Discussion

We detected upper respiratory viral infections in 80-85% of exacerbations of asthma in school age children. Picornaviruses (mostly rhinoviruses) accounted for two thirds of the viral infections. Coronavirus was the next commonest but caused less severe asthma exacerbations than other respiratory viruses. Continuous monitoring identified many less severe episodes that were not reported to the investigators. These findings emphasise the importance of viral infections as a cause of lower respiratory tract morbidity in children.

The community setting and the intensive monitoring carried out by the children and their parents enabled early sampling, which probably increased our detection rate of viruses. Without the polymerase chain reaction, however, our virus detection rate would have been similar to that in previous studies—around 40%.[4]

ACCURACY OF DATA

Previous studies of upper respiratory infections have suggested that detection with cell cultures missed many infections.[20] These were thought to be mainly rhinoviruses or undiscovered agents, and our results suggest that most are indeed rhinoviruses or coronaviruses. Many of the samples that had initially been culture negative but had given positive results with the picornavirus polymerase chain reaction later grew rhinoviruses on repeat culture for longer periods (several of these rhinoviruses were slow growing).[21] The detection rate in samples from asymptomatic children and that of multiple pathogens in the same sample agreed with previous data.[4] The seasonal distribution of viral detections was similar to that in previous studies (data not shown here). A semiquantitative analysis of the positive signals in the picornavirus positive polymerase chain reaction[21,29] showed that the signal increased with the duration of upper respiratory symptoms (Kruskal-Wallis one way analysis of variance, $P<0.05$) and correlated with the severity of peak expiratory flow reductions (Spearman's rank correlation $r=0.29$, $P<0.01$).[21,28] These observations suggest that our results are valid, as do the findings of Nicholson *et al* in adults.[29] Their study had lower detection rates but used less intensive surveillance and detection methods and took nasal and throat swabs instead of nasal aspirates.

A weakness of this study is the absence of a control group. We thought that asymptomatic children would be difficult to recruit to an intensive and invasive study of this type and that they would not constitute a valid control group since they would have less commitment to the study than symptomatic children. We did, however, take control samples when children were asymptomatic. These samples represent the best controls for non-specific properties of the mucus and other factors known to be important in viral infections such as family structure and socioeconomic status. However, they do not control for seasonal variation.[16]

ASSOCIATION WITH ASTHMA

Many of the respiratory episodes recorded by children were severe, with a median maximal fall in peak expiratory flow of over 50 l/min for all episodes identified and over 80 l/min for the reported episodes. The similarity of the seasonal patterns of the reported and unreported episodes suggests a common cause. Inspection of the charts for each child showed that most had relatively stable baseline peak expiratory flow recordings, with sudden severe falls associated with viral infections, followed by recovery to baseline again over the next two to three weeks (fig 1). Such episodic symptoms fit the syndrome previously described as "wheezy bronchitis."[30,31] Further longitudinal study of this cohort will show whether such children will grow out of their asthma.

In conclusion, this study has shown that upper respiratory, principally rhinoviral infections are associated with 80-85% of reported exacerbations of asthma in a cohort of school age children. These findings have considerable implications for understanding the cause of recurrent wheezing in childhood.

Key messages

- Asthma is an important and increasing problem in school age children
- In this study common cold viruses were found in 80-85% of reported exacerbations of asthma in children
- Rhinoviruses, which cause most common colds, accounted for two thirds of viruses detected
- Analysis of diary cards also showed large numbers of similar but less severe episodes that may also be viral in origin

We thank the children and their parents who contributed to this study, Morag Forsyth for help with the virus culture and

diagnosis, and Jo Clough for help with planning the study and preparing the manuscript and recruiting the original cohort.

The study was supported by grants from Miles, New Haven, CT; Action Research; the National Asthma Campaign; the British Lung Foundation; the British Medical Association; and the Chest Heart and Stroke Association. Clement Clarke International and Allen and Hanburys shared the costs of the peak flow meters. SLJ received the 1990 British Medical Association H C Roscoe Fellowship, PKP was supported by the Medical Research Council of New Zealand, the Asthma Foundation of New Zealand, and Allen and Hanburys (NZ).

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(Accepted 7 March 1995)

Effects of self medication programme on knowledge of drugs and compliance with treatment in elderly patients

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BMJ 1995;310:1229-31

Abstract

***Objective*—To determine whether a programme of self medication for inpatients improves compliance with treatment and knowledge of their drugs after discharge from hospital.**

***Design*—Patients were prospectively recruited from four wards: two with a self medication programme and two acting as controls. Ten days after discharge the patients were visited at home. They were questioned about their drugs, and a tablet count was undertaken.**

***Setting*—The pharmacy department and four medical wards with an interest in elderly patients at a district general hospital, and the patients' homes.**

***Patients*—88 patients discharged to their own homes who were regularly taking one or more drugs.**

***Intervention*—A hospital self medication programme in which patients are educated about their medicines and given increasing responsibility for taking them in hospital.**

***Main outcome measure*—Compliance with and knowledge of the purpose of their medicines 10 days after discharge from hospital.**

***Results*—The mean compliance score in patients taking part in the self medication programme was 95% compared with 83% in the control group (difference 12%, 95% confidence interval 4% to 21%; $P<0{\cdot}02$). Of the patients in the self medication group, 90% (38/42) knew the purpose of their drugs compared with 46% (17/37) in the control group (difference 44%, 26% to 63%; $P<0{\cdot}001$).**

***Conclusion*—A self medication programme is an effective aid for improving compliance with and knowledge of patients' drugs after discharge.**

Introduction

It is widely known that patients, including elderly patients, do not always comply with their drug treatment. Many authors have attempted to measure the extent to which this occurs,[1-3] and in a recent review Wright concluded that compliance was about 50%.[4] This clearly has an effect on morbidity, with many patients receiving suboptimal treatment. The financial cost of non-compliance also needs to be considered. Many strategies have been suggested to improve compliance. These include simplifying medication regimens,[5] providing written and verbal information,[6,7] and more appropriate packaging of drugs.[8] Self medication in hospital has also been suggested as a way of improving compliance on discharge.[9-11] A scheme of self medication allows patients to give themselves their drugs in hospital after education.

There are few data evaluating the benefits of self medication; previous studies have been small and gave conflicting results.[12,13] We report the effect of such a programme on patients' compliance and knowledge of