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# Signs and symptoms in common colds

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## SUMMARY

The patterns of disease caused by five common viruses which infect the respiratory tract are described. The viruses were strains of rhinovirus types 2, 9, and 14, a strain of coronavirus type 229E and of respiratory syncytial virus. Volunteers were given nasal drops containing a low infectious dose of one of the viruses, quarantined from 2 days before to 5 days after inoculation, and examined daily by a clinician using a standard checklist of respiratory signs and symptoms. Only subjects who developed clinical illness accompanied by viral shedding and/or specific antibody production were analysed [$n = 116$]. The results confirm indication from earlier studies that the main difference between colds induced by different viruses is in duration of the incubation period. Patterns of symptom development were not substantially different with different viruses. Analyses of signs and symptoms in different categories, e.g. nasal symptoms *v.* coughing, justify treatment with different drugs either successively or simultaneously.

## INTRODUCTION

Substantial numbers of volunteers have been inoculated intranasally with viruses that cause common colds and it is well documented that typical illnesses occur within a few days, with symptoms such as nasal blockage and discharge and sometimes lower respiratory symptoms. Studies of human volunteers suggest that both characterized and uncharacterized agents caused illnesses with slightly different clinical patterns [e.g. 1–4]. It is unclear, however, that careful examination of clinical records of infected persons could allow identification of the causative virus. Therefore it is desirable to examine in detail the nature, frequency and severity of the signs and symptoms induced and the time course of their occurrence using the viruses which most frequently cause common colds.

The data we report were collected during a series of trials in which volunteers were exposed to one of five relatively common viruses infecting the respiratory

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tract [5]. Each volunteer received nasal drops containing a low infectious dose of virus, because this is generally how infection occurs under natural conditions. Because we are interested in the patterns of disease produced by different viruses, the analyses were limited to those volunteers who developed clinical illness. Here we consider whether that are differences in the patterns of disease produced by three rhinovirus serotypes [RV types 2, 9, and 14], respiratory syncytial virus [RSV] and a coronavirus [CV type 229E] and describe the time course of various signs and symptoms.

We also analyse the combinations of signs and symptoms that may occur. These may help to resolve differences on whether it is appropriate to provide a mixture of drugs that can treat all complaints seen during a cold or whether to aim to relieve single symptoms or subgroups of symptoms to avoid giving medication unnecessarily. We therefore group symptoms by their likely responsiveness to categories of drugs and assess the extent to which symptoms from different 'drug sensitive' groups occur simultaneously.

## MATERIALS AND METHODS

### *Sample population*

The subjects were participants in trials at the Medical Research Council's Common Cold Unit [CCU] in Salisbury between June 1986 and July 1989. Although the trials were designed to assess possible antiviral drugs and treatment measures, only those volunteers not receiving drugs or treatment are included here. They comprised 41 men and 75 women; 14 receiving rhinovirus [RV] type 2, 32 RV type 9, 25 RV type 14, 11 respiratory syncytial virus [RSV], and 34 coronavirus [CV] 229E. All were between 18 and 53 years old, reported no chronic or acute illness or regular medication regimen, and were judged in good health following clinical and laboratory examination on arrival at the Unit. Pregnant women were excluded. Informed consent was obtained from each subject.

### *Inoculation and clinical procedures*

CV and RV strains were passaged serially in volunteers. Nasal washings were collected at the height of a cold, pooled, titrated in tissue culture, and tested for contamination. They were stored at −70 °C and thawed and diluted in saline just before use as an inoculum. They were usually diluted $10^{-2}$ which gave a titre of about 100 $TCD_{50}$ per ml. The RSV was the eleventh tissue culture passage of strain RSS-2 diluted to give $10^{5\cdot5}$ $TCID_{50}$ per ml, which is equivalent to less than 10 human infectious doses.

During their first 2 days at the CCU, subjects underwent a general medical examination. Subsequently, they were given nasal drops containing one of the five viruses. From 2 days before to 5 days after the viral inoculation, the subjects were quarantined. During this time each subject was examined daily by a clinician using a standard checklist of respiratory signs and symptoms [6]. All these observations were 'double blinded'. Nasal washes to assess viral shedding were also conducted daily. Approximately 28 days after inoculation a second serum sample was collected by the subject's own physician for serological testing.

*Viral isolates and virus-specific antibody levels*

Nasal wash samples for viral isolation were collected before inoculation and on days 1–5 thereafter. They were mixed with nutrient broth and stored in aliquots at −70 °C. Rhinoviruses were detected in O-Hela cell, respiratory syncytial virus in Hep2 cells and coronavirus in the C-16 strain of continuous human fibroblast cells [7]. When a characteristic cytopathic effect was observed the tissue culture fluids were passaged into further cultures and identity tests on the virus were performed. Rhinoviruses and coronaviruses were identified by neutralization with specific rabbit immune serum, and respiratory syncytial virus by immunofluorescent staining of tissue culture cells with specific immune serum.

Titres of neutralizing antibodies, and of specific antiviral serum IgA and IgG were determined before and 28 days after inoculation. Neutralizing antibodies, for rhinoviruses only, were determined by neutralization tests with homologous virus [8]. Results were recorded as the highest dilution showing neutralization, and a fourfold rise was regarded as significant. Suitable neutralizing tests were not available for respiratory syncytial virus and coronavirus. Specific IgA and IgG in serum for rhinoviruses [9], coronavirus [10] and respiratory syncytial virus [10] were determined by enzyme-linked immunosorbent assay. These tests detect antibodies which correlate with neutralization titres, are associated with resistance to infection and increase in response to infection.

*Clinical colds*

Subjects were defined as having developed clinical colds if they were both infected and diagnosed by the clinician as having a clinical cold. A subject was deemed infected if virus was isolated after inoculation and/or there was a significant increase in at least one virus-specific serum antibody, i.e. a fourfold increase in neutralizing antibody to rhinoviruses or an increase in IgG or IgA of more than two SD above the mean of uninoculated subjects for all viruses.

At the end of the trial, the clinician judged the severity of each subject's cold on a scale ranging from nil to severe and scored 0–4. Ratings of mild cold [score 2] or greater were considered positive clinical diagnoses. Subjects also judged the severity of their colds on the same scale. The clinician's diagnosis agreed with the self-diagnoses of 94% of subjects.

*Total daily symptom scores*

An upper respiratory sign-symptom protocol was administered daily by a clinician to assess severity of illness [6]. The items in the protocol are shown in Table 1. Signs and symptoms were scored by their severity from 0–3. Zero [0] indicated the symptom's absence and higher scores indicated increased severity. A total symptom score for each day was calculated by summing the scores for individual symptoms.

*Mucus weights*

Mucus weights were determined by collecting the disposable paper tissues used by each subject in sealed plastic bags. These were weighed and the weight of the tissues and bags subtracted. The weights of bags and tissues were found to be very

Table 1. *Signs and symptoms that were monitored daily during the course of a trial*

| | | |
|---|---|---|
| Tissue usage | Hoarseness | Chill |
| Mucopurulent nasal discharge | Cough | Sneezing |
| Nasal obstruction | Sputum | Watering eyes |
| Post-nasal discharge | Headache | Nasal stuffiness |
| Sinus pain | Malaise | Sore throat |
| Cervical adenitis | Myalgia | Pyrexia |
| Mucus weight | Extra bedrest | |

uniform so a standard deduction was made. Pre-inoculation mucus weight was the mean weight for the 2 days before inoculation.

## RESULTS

The response to inoculation was in general as expected. About 20% of the volunteers, mainly those with high titres of neutralizing or other antibodies, resisted infection and remained well (Table 2). The remainder became infected, but about 60% of the volunteers that became infected [mainly those with low levels of antibodies], had dubious or trivial symptoms, or none at all, and could not be distinguished for certain on clinical grounds from normal subjects. Those who had signs of a definite illness, even though it was very mild (for instance an increase of tissue count or nasal secretion weight for a couple of days), were classified as having colds and were used for the subsequent analyses.

### *Total daily symptom scores*

Fig. 1. presents total scores plotted by day of trial. This shows that those infected with a rhinovirus developed illness very quickly and symptoms peaked 2–3 days after inoculation and then began to return to baseline. Those exposed to a CV developed illness more slowly, peaking at 3–4 days and those exposed to RSV developed illness very slowly with symptom scores still climbing on the fifth day after inoculation.

### *Individual signs and symptoms*

For each symptom, we calculated the daily *mean severity* score and the *proportion* of subjects on each day with non-zero severity scores. Both measures showed similar patterns with time and only proportions are presented. Thus Fig. 2 shows the proportion of volunteers with each sign or symptom. We included only those signs or symptoms experienced by at least 15% of the subjects during the 5 days after inoculation. Symptoms not meeting this criterion include mucopurulent nasal discharge, cervical adenitis, sputum, post-nasal discharge, myalgia, and pyrexia. Because the course of symptom development was similar in volunteers given each rhinovirus serotype, Fig. 2 combines the data from all rhinovirus colds.

Fig. 2 shows that in most cases the pattern for individual signs or symptoms runs parallel to that for total symptom scores with a rise occurring earliest in rhinovirus infections, then in coronavirus, and last in RSV. The most frequent

Table 2. *Number of volunteers inoculated, and outcome*

| | Virus given | | | | | |
|---|---|---|---|---|---|---|
| | RV2 | RV9 | RV14 | RSV | CV | Total |
| No. inoculated | 80 | 115 | 78 | 36 | 55 | 364* |
| No. infected | 67 | 86 | 65 | 26 | 50 | 294 |
| No. with clinical colds | 14 | 32 | 25 | 11 | 34 | 116 |

* These are drawn from a total study population of 399 volunteers. The 35 others were excluded because they received experimental therapies.

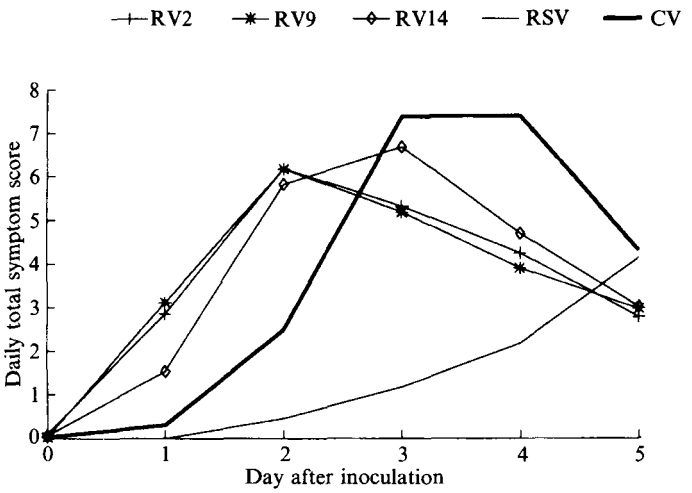


Fig. 1. Mean total symptom scores for each virus by day after inoculation [—+— RV2; —✱— RV9; —◇— RV14; —— RSV; —— CV].

problems were related to the nose, either the sensation of nasal stuffiness, the sign of nasal obstruction, or an increase in the number of paper tissues used or (more objectively) an increase in the weight of nasal secretion mucus. As these were mainly mild illnesses many fewer volunteers had symptoms such as headache, malaise, myalgia, or fever. However a few volunteers had lower respiratory symptoms such as hoarseness or cough, but there was never any clinical sign of pulmonary disease. The patterns of two of the signs, cough and nasal obstruction, varied among rhinoviruses. Fig. 3 presents the results for the three RV serotypes separately for these two parameters. Although all three were associated with a cough developing on about day 3, a much larger proportion [$> 50\%$] of those receiving RV2 developed a cough than those inoculated with the other serotypes [$< 20\%$]. In the case of nasal obstruction, those infected with RV2 were less likely to develop obstructions than those infected with the other two serotypes.

*Relative time course of symptoms*

We chose five representative symptoms [sore throat, sneezing, nasal stuffiness, mucus weight increase, and cough] to provide a picture of the time course of the colds caused by these viruses. As is apparent from Fig. 4, the individual symptoms

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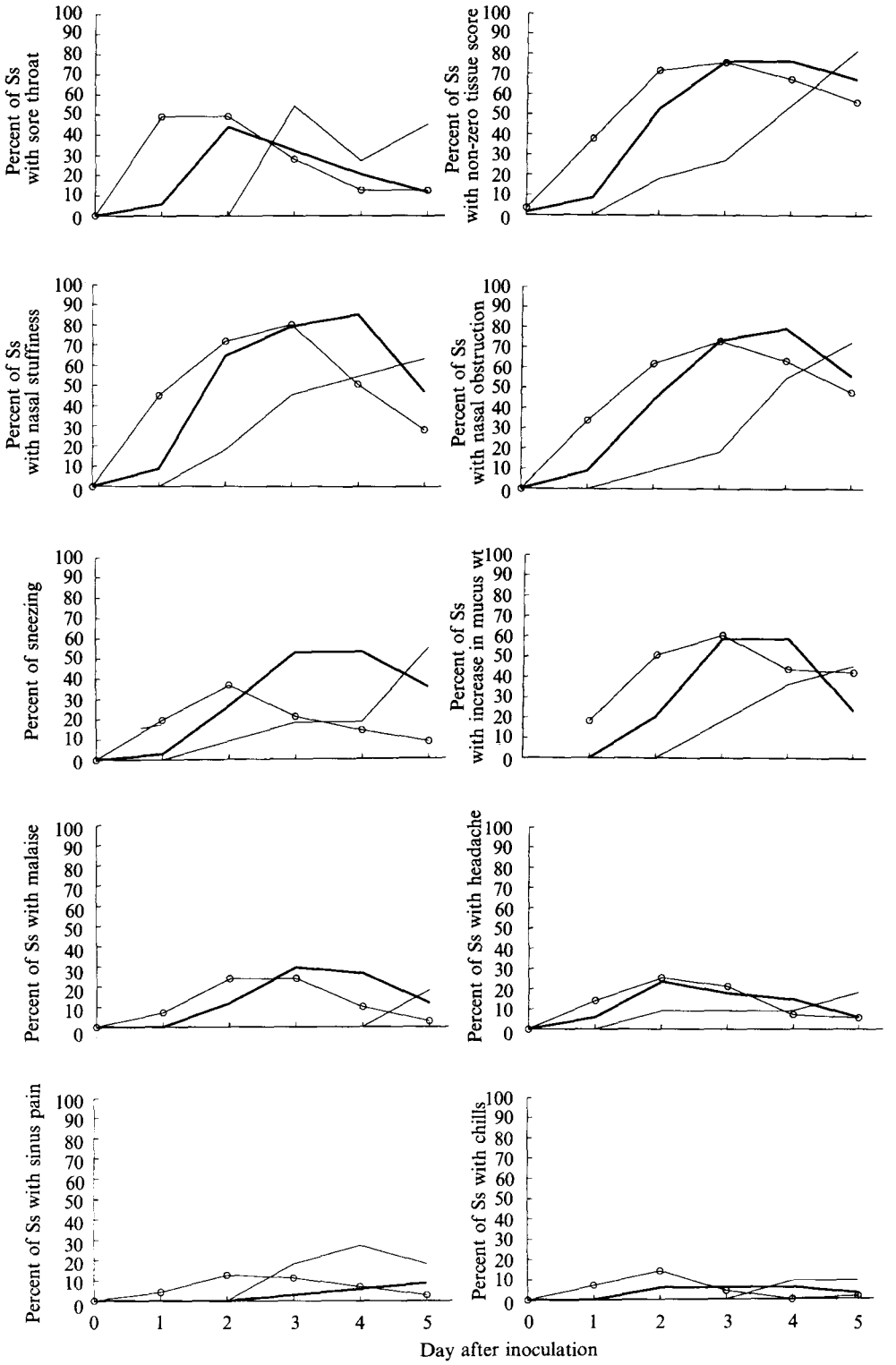


Fig. 2. For legend see opposite.

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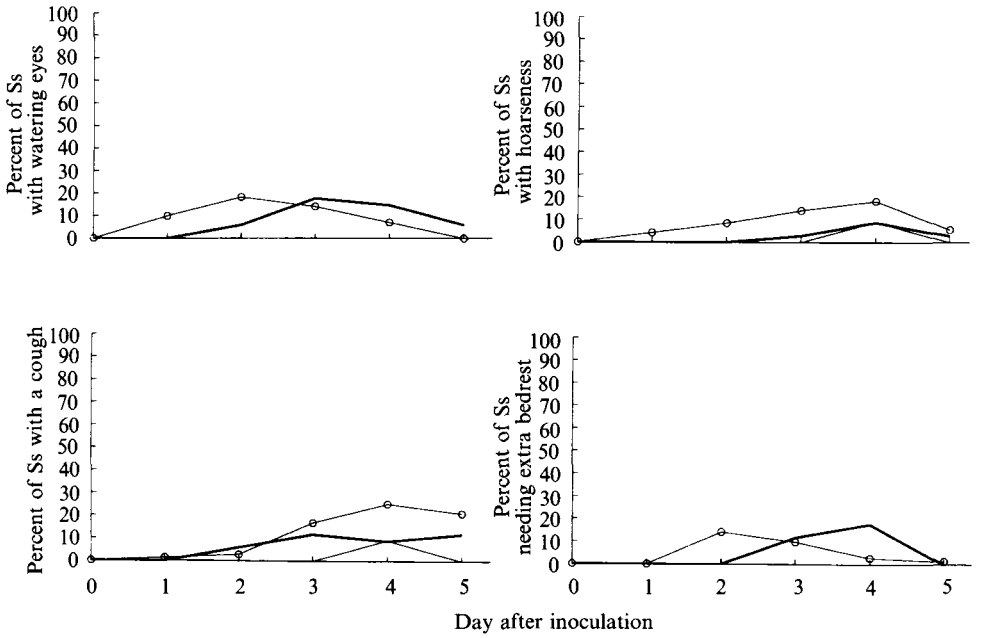


Fig. 2. Percent of subjects with individual symptoms on each day after inoculation [—— RSV; —— CV; —⊖— RVs combined].

peaked at different times after inoculation: sore throat followed by nasal symptoms and sneezing, and then cough. This sequence was seen following infection with all five viruses (with the possible exception of RSV infections). The time of occurrence was similar with all three rhinoviruses, but was seen later with coronaviruses and so late with RSV that for the most part the later symptoms were not observed at the Unit. This longer incubation period for coronavirus and RSV illnesses was anticipated from earlier studies [e.g. 11]. The incidence of symptoms declined at a similar rate in all infections though in many cases some symptoms were still present when volunteers left the Unit and so the end of the disease could not be defined.

*Proportion of persons experiencing individual symptoms*

Having studied the proportions of persons experiencing symptoms on each day of the trial, we then analysed the proportion experiencing a symptom *on any day* after inoculation. These data are reported in Table 3. Because RSV illnesses were still developing after 5 days, the proportions reported for RSV *underestimate* the incidence of these symptoms. Other than RSV, most symptoms occurred with similar frequencies for all the other viruses. However there were differences in the frequencies of certain symptoms in infections with the closely related rhinoviruses, i.e. RV2 seemed more prone to produce hoarseness and cough than the other serotypes, and at the same time RV2 seemed less prone to induce nasal obstruction, sneezing, and sinus pain. None of the illnesses showed much systemic involvement, as indicated by the low frequency of fever, myalgia, and need for extra bedrest.

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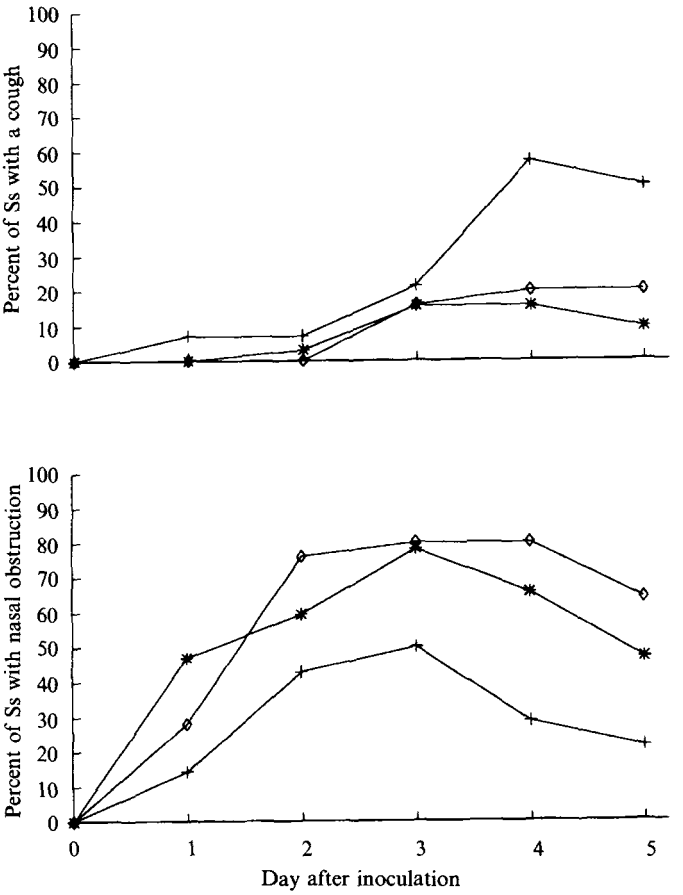


Fig. 3. Percentage of subjects with (*a*) cough and (*b*) nasal obstruction on each day for all rhinoviruses [—+— RV2; —✱— RV9; —◇— RV14].

*Timing and frequency of therapeutic targets*

The symptoms of colds may need treatment, but there are differing views on whether it is appropriate to provide a mixture of drugs, which can treat all the complaints seen during a cold, or whether to be selective and try to relieve single symptoms or subgroups of symptoms and so avoid giving medication unnecessarily. We therefore examined our databases to obtain evidence of how often limited or comprehensive medication might be needed.

*Proportions of persons experiencing symptoms in each symptom group.* For these analyses signs and symptoms were grouped as shown in Table 4 to represent symptoms that may respond to different types of drug intervention such as nasal decongestants and antihistamines, systemic analgesics and antipyretics, and antitussives.

We calculated the proportion of individuals with at least one of the symptoms in each group on successive days of the trial. As can be seen from Fig. 5a, the proportion of subjects with nasal symptoms [Group 1] rose sharply immediately

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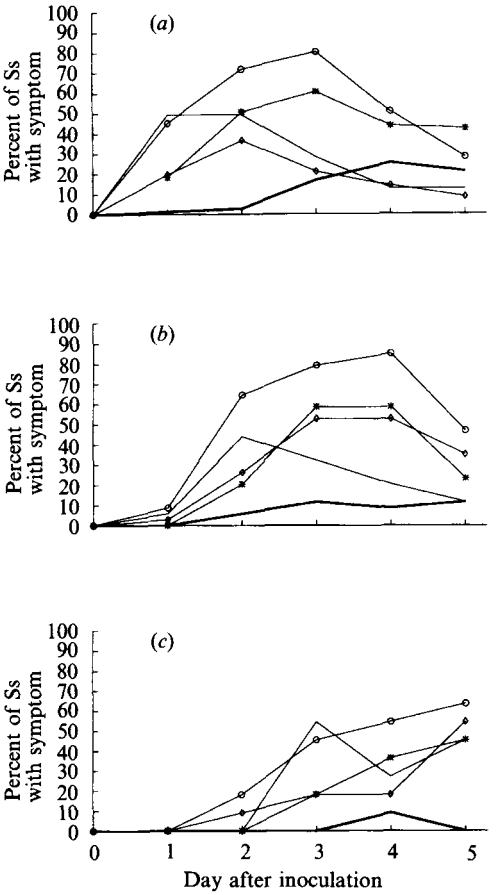


Fig. 4. Percentage of subjects with five representative symptoms for all viruses showing the time course of symptoms [(*a*) rhinoviruses, (*b*) coronavirus, (*c*) RSV; —— sore throat; —⊖— stuffiness; —✱— mucus increase; —◇— sneezing; —— cough].

after inoculation for all five viruses; rhinoviruses were considered together in this figure because all three followed a similar pattern. A large majority of subjects experienced some nasal symptoms regardless of the virus given.

As is apparent in Fig. 5b, Group 2 symptoms were experienced by fewer subjects than were the nasal symptoms of Group 1. The rise in Group 2 symptoms occurred first for RV, then for CV and finally for RSV. Again, rhinovirus groups were combined since all three followed a similar pattern.

Group 3 consists of only one item, cough. Cough reached a peak at the end of the observation period, and presumably continued after this for RSV (Figure 5c). For the most part, coughing occurred among $< 20\%$ of the subjects on any post-inoculation day. However, RV2 was the exception with nearly 60% of the subjects experiencing coughing on the fourth and fifth days after inoculation.

*Different symptoms experiences simultaneously.* Our data so far indicate the independent occurrence of symptoms in the three groups in individual volunteers. However, decisions regarding appropriate combinations of drugs are dependent on

Table 3. *Percentage of subjects that experienced each symptom at any time during the post-inoculation period, by virus**

| | Virus | | | | |
|---|---|---|---|---|---|
| | RV2 [No = 14] | RV9 [No = 32] | RV14 [No = 25] | RSV [No = 11] | CV [No = 34] |
| Cough† | 64 | 22 | 20 | 9 | 21 |
| Hoarseness† | 57 | 28 | 28 | 9 | 12 |
| Sore throat | 93 | 91 | 76 | 82 | 68 |
| Nasal obstruction† | 64 | 94 | 100 | 91 | 94 |
| Sneezing | 50 | 69 | 76 | 64 | 85 |
| Increased tissue usage | 93 | 100 | 100 | 82 | 94 |
| Nasal stuffiness | 93 | 94 | 100 | 82 | 97 |
| Sinus pain | 7 | 25 | 32 | 36 | 9 |
| Post-nasal discharge | 14 | 16 | 12 | 9 | 9 |
| Cervical adenitis | 14 | 0 | 4 | 9 | 0 |
| Sputum | 7 | 3 | 0 | 0 | 3 |
| Chills | 21 | 19 | 20 | 9 | 18 |
| Extra bed rest | 29 | 28 | 12 | 0 | 24 |
| Watering eyes | 43 | 25 | 44 | 0 | 29 |
| Headache | 50 | 47 | 44 | 27 | 32 |
| Malaise | 43 | 31 | 44 | 18 | 47 |
| Myalgia | 21 | 6 | 20 | 18 | 9 |
| Mucopurulent discharge | 0 | 0 | 0 | 0 | 0 |
| Temperature increase (a.m.) | 0 | 6 | 8 | 0 | 9 |
| Temperature increase (p.m.) | 7 | 6 | 12 | 0 | 6 |

* A symptom was present on a day if the volunteer had a non-zero score for the symptom on that day.

† The proportion of subjects experiencing the symptom was significantly different among the viruses [$P \leqslant 0{\cdot}01$].

Table 4. *Signs and symptoms in each of the three symptoms groups*

| Group 1* | Group 2† | Group 3‡ |
|---|---|---|
| Tissue usage increase | Headache | Cough |
| Nasal secretion increase | Pyrexia | |
| Watering eyes | Sore throat | |
| Post-nasal discharge | Sinus pain | |
| | Myalgia | |

* May respond to nasal decongestants and antihistamines.
† May respond to systemic analgesics and antipyretics.
‡ May respond to antitussives.

the simultaneous occurrence of different symptoms. Fig. 6 shows the proportions of persons experiencing symptoms from various combinations of symptom groups. As can be seen from Fig. 6a, $> 50\%$ of volunteers experienced Group 1 and 2 symptoms simultaneously, irrespective of the virus used. Because of the fairly low proportion of persons developing coughs when inoculated with RV9, RV14, CV, and RSV, very few persons experienced the Group 3 symptom [cough] simultaneously with either of the other two symptom groups [Figures 6b–d]. In the case of RV2, where approximately 60% of volunteers developed coughs, there is substantial overlap with Group 1 and some overlap with Group 2.

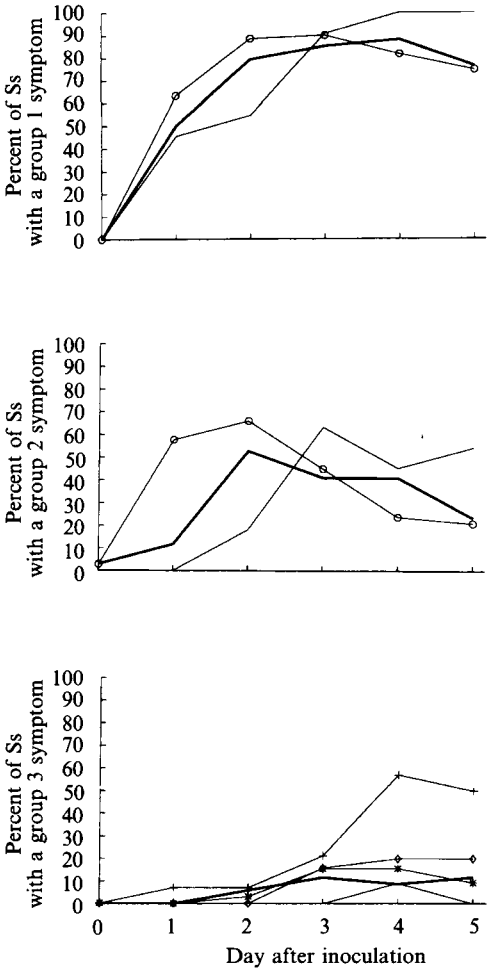


Fig. 5. Occurrence of symptoms in certain possible therapeutic groups: (*a*) percentage of subjects with at least one Group 1 symptom on each day after inoculation; (*b*) as (*a*) for Group 2 symptoms; (*c*) as (*a*) and (*b*) for Group 3 symptoms [+RV2; —✱— RV9; —◇— RV14; —— RSV; —— CV; —⊖— RVs combined].

## DISCUSSION

Although it is a common observation that some symptoms, such as a sore throat or chill, usher in a cold, while others, such as a cough, occur at the end, we know of no systematic quantitative study to document the timing, frequency and severity of these symptoms and signs. Our results are therefore the first to document systematically these clinically impressions and anecdotal reports.

The results also confirm indications from earlier studies [11 and unpublished] that the main difference between the colds induced by different viruses is in the duration of the incubation period. This appeared to be the same for all the rhinoviruses but longer for coronaviruses and much longer for RSV. Parainfluenza viruses, which are related biologically to RSV, also cause colds with long incubation periods when studied in volunteers by similar methods [2]. We were surprised to find an apparent difference in the pattern of disease induced by

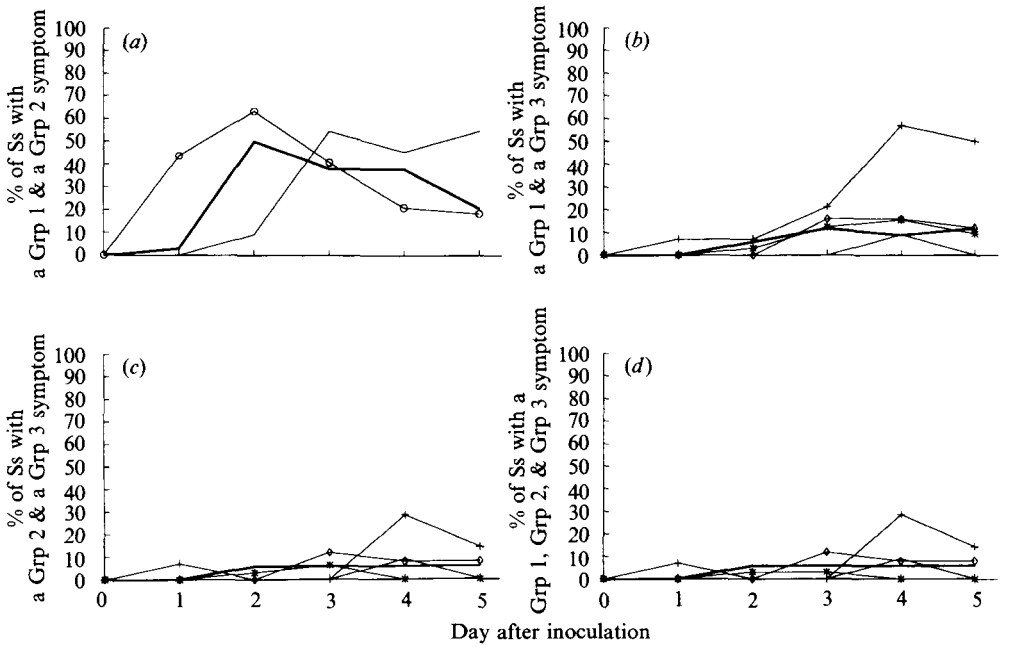


Fig. 6. Occurrence of combinations of symptoms from different groups. (*a*) Percentage of subjects with at least one Group 1 symptom and one Group 2 symptom on each day after inoculation; (*b*) as (*a*) for Group 1 plus Group 3 symptoms; (*c*) as (*a*) for Group 2, plus Group 3 symptoms; (*d*) as (*a*) for Group 1 plus Group 2, plus Group 3 symptoms [+RV2; ✱ RV9; ◇ RV14; —— RSV; —— CV; —○— RVs combined].

different rhinoviruses. Whether this was associated with the serotype or the particular isolates used could not be decided, but certainly the RV2 used here caused more coughs and less nasal obstruction than the other two strains. It has been suggested already that certain serotypes, as a group, are more pathogenic than others, and this has been associated with differences in the sequence of 'deeper' regions of the capsid proteins, which is reflected in their susceptibility to capsid binding drugs [12].

Nevertheless other viruses that affect the upper respiratory tract cause illnesses which are clinically different. For example, adenoviruses and enteroviruses cause sore throats or pharyngitis and often fever and systemic symptomatology. Influenza A and B viruses often cause high fever and prostration though mild infections resemble common colds [e.g. 13]. However, apart from the incubation period, which in clinical practice can rarely be known, we could find no substantial difference in the illnesses caused by the three biologically distinct types of viruses used in this study to produce common colds, even using grouped data, and there was no support for the hope that by careful analysis of clinical records it might be possible to identify the causative virus. We studied typical mild illnesses induced in healthy adults, but in the field, where these viruses can cause more severe illnesses, differences between viruses may be seen. For instance, bronchiolitis in infants is often caused by RSV and almost never by rhinoviruses. All the same, in remote communities the combination of clinical pattern and epidemic behaviour may indicate that different respiratory viruses are circulating [14].

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This is not the place to discuss the pathophysiology and the mediators of the signs and symptoms. These are complex and poorly understood. At present drugs of several different classes would have to be used to alleviate the full range of signs and symptoms. Thus there are arguments on whether one should supply or prescribe drugs singly or in combination. This is partly a matter of therapeutic philosophy. Individual types of symptoms can be relieved with appropriate drugs [15]. However patients and some professionals emphasize the improved compliance and convenience of using a drug mixture, and discount the disadvantages of giving drugs for symptoms that patients do not have. We have documented that patients do quite often have symptoms in both of our groups 1 and 2, but we have to say that they do not have the combination all the time; also some individuals included in this category had symptoms graded as 1 or mild, and for most people these were not really worth treating. Cough usually appears as other symptoms are declining and it is common experience that it may be troublesome when no other symptoms are, but our records show that it is often combined with symptoms in Group 1.

In everyday life patients would probably regard some of these colds as too mild to treat, but our data show the frequency with which symptoms and signs in different categories occur, and can justify treatment with different drugs successively or simultaneously, separately or in combination.

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