THE VALUE OF MIXED VACCINES IN THE PREVENTION OF THE COMMON COLD.

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(With 3 Figures and 1 Chart.)

Although the common cold may appear to form a relatively trivial constituent of the mass of acute respiratory disease, which presents the student of preventive medicine with one of his most difficult and pressing problems, the total sickness and incapacity to which it gives rise is by no means small; and there are adequate reasons for regarding it as the occasional precursor of far more serious troubles. It is, therefore, not without interest to enquire, whether or no those procedures, which are commonly recommended as possessing prophylactic value, can make good their claim when submitted to an adequate test. The enquiry here recorded suffers from the fact that the total number of individuals at risk was relatively small; but the answer to the main question posed is so unambiguous, and accords so well with the results obtained in the only other adequate tests of which we have knowledge, that it seems desirable that it should be briefly recorded. It is possible, also, that some little interest attaches to the figures of frequency, duration and severity of common colds within a particular community.

The enquiry to be described was carried out in the University of Manchester during the winter of 1924–5. Volunteers were asked for from among the students and departmental staffs, and it was explained that we were desirous, so far as possible, of ourselves determining who should receive inoculations and who should act as controls. Since it was realised that it might be impossible to obtain sufficient volunteers for inoculation, especially as the time at our disposal for the preliminary arrangements was short, we also asked for the names of those who would be willing to act as controls, without receiving inoculation. Each person who was invited to take part in the enquiry was handed Card A, the face and reverse of which is shown in Fig. 1, and was asked to fill it in and return it to this Department. It became clear, when the replies were received, that the number of those who were willing either to receive inoculation or to act as controls, at the discretion of those who were carrying out the test, was too small to provide a satisfactory population for study. We therefore divided our test population into two parts. Of those who had volunteered for either vaccination, or observation without vaccina-

tion, we took the first 144, and divided them into two equal groups by sorting the cards first according to the sex of the volunteers, and then according to the dates on which the last cold was recorded. Thus the two groups were approximately alike with regard to sex-distribution and with regard to the period which had elapsed since the last cold, in all other respects the distribution was entirely random. The information given, concerning the previous

A

No.

Name *Age*

Address

Do you have frequent colds .....

When did you last have a cold .....

Have you ever been inoculated against colds .....

If so, when .....

Have you recently received any other form of inoculation .....

.....

Have you anything wrong with your nose or throat .....

.....

.....

.....

[P.T.O.

Do you travel to the University by:—

(*a*) *Train* .....

(*b*) *Tram or 'Bus* .....

(*c*) *Walking or Cycling* .....

Are you willing:—

(*a*) *To receive inoculation against colds, and keep a record of any colds you may subsequently have* .....

(*b*) *To keep a record without receiving the inoculation* .....

Fig. 1. (White Card.)

frequency of colds, was not sufficiently definite to render possible any accurate equalisation between the two groups; but a survey of the cards after the preliminary sorting did not suggest that there was a preponderance of susceptible individuals in either group. Those who had received any prophylactic against colds during the previous two years, and those who stated that they were suffering from any persistent abnormality of the nose or throat, were rejected. As a matter of fact, it was found that very few of those who volunteered had ever received inoculations of this kind.

There remained some 80 volunteers who were willing to receive inoculation. As a control group to these we obtained a similar number of volunteers who were unwilling to be inoculated, but were willing to keep the necessary records. During the course of the enquiry a certain number of the test population dropped out, because the complete course of inoculations was not administered, or because we did not obtain satisfactory records, or for some other reason. At the close of the enquiry we were left with a total test-population of 286 individuals, distributed as follows.

The group, in which separation into inoculated and uninoculated was determined in the random manner described above, included 68 inoculated, and 72 controls. A second group, in which separation into inoculated and uninoculated was carried out in accordance with the expressed wish of the volunteers, included 70 inoculated and 76 controls.

It may be stated at once that there was no evidence that the difference between voluntary and involuntary assignment to the inoculated or control group had any influence on the subsequent course of events, but the actual figures in the two samples will be considered when discussing the relation of our findings to those of previous observers. For the moment we will regard the test population as homogeneous, apart from inoculation, and as divided into 138 inoculated individuals, and 148 controls.

The vaccine employed was of a type which has been widely used in this country. It contained per c.c.:

M. Catarrhalis	200 M.
B. Septus	200 M.
B. Hofmanni	200 M.
B. Friedlanderi	200 M.
Staph. mixed	200 M.
Pneumo.	40 M.
Strep. Polyv.	40 M.
B. Pfeiffer	120 M.

Three doses were given to each individual, at weekly intervals, consisting of 0·25, 0·5 and 1 c.c. respectively. It is unnecessary to describe the reactions in any detail. They were mostly trivial. In a few cases persistent induration at the site of inoculation was noted, lasting for some weeks. In two cases fluctuating swellings occurred, while in one of these cases the necrotic pus, apparently sterile, discharged through the skin leaving a small ulcer, which healed slowly. Constitutional symptoms were in all cases slight. These observations are in agreement with those recorded by others who have employed vaccines of a similar constitution on a large scale.

At the commencement of the trial period, each volunteer was given a copy of Card B, the face and reverse of which are shown in Fig. 2. On the face were entered particulars of the inoculations, or the fact that the person in question was not inoculated. On the back were entered the date of com-

mencement and cessation of all colds contracted by that individual during the trial period. This card was filled up in duplicate, one copy being retained by the volunteer, the other being filed in the laboratory.

B

No.

Name

Address

Inoculations

Date	*Dose*	*Notes*

[P.T.O

Colds	*Date of*		*Notes*
	Commencement	*Cessation*	

Fig. 2. (Blue Card.)

Each volunteer was also given a copy of Card C, the face and reverse of which are shown in Fig. 3. On this, he or she was asked to record particulars of each cold, as it occurred, and to forward the completed card to the laboratory within a few days after the cessation of the cold in question. Immediately

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such a card was received, another copy of Card C was sent to that volunteer, for use in connection with any subsequent cold.

Every effort was made to obtain a complete record from each volunteer. With few exceptions the co-operation of all concerned left little to be desired. On three occasions during the course of the enquiry, at the end of December 1924, at the end of March 1925, and at the end of May 1925, when the enquiry

C

No.

Name

Address

Particulars of any cold which starts after October .....

Date of commencement .....

Date of cessation .....

Chief symptoms .....

.....

.....

.....

[P.T.O.

Record of temperature .....

.....

.....

.....

.....

.....

Did you stay:—

(*a*) *In bed* ..... *How long* .....

(*b*) *Indoors* ..... *How long* .....

(*c*) *Away from work* ..... *How long* .....

Fig. 3. (Pink Card.)

terminated, all records were gone through, and a card was sent to each volunteer from whom we had not heard during the past month or so, asking whether he or she had suffered from any cold since the last date on which our records showed a communication from that individual. In this way we succeeded in keeping in touch with the great majority of the volunteers throughout the course of the enquiry. As stated above, we have rejected from our final records all those with whom touch was lost. We believe that

these records are as complete as can be hoped for, when all members of a test population are not under the constant personal observation of those conducting an enquiry.

The complete series of inoculations took just over a month to complete, from October 24th to November 26th. We dated the commencement of the trial period for each volunteer from the day on which he or she received the third dose of vaccine, the records of the uninoculated being taken over a corresponding period. The trial period for the whole population terminated on May 31st, 1925.

The relevant facts concerning the fate of the inoculated and uninoculated groups are summarised in Tables I to III, and few comments are needed. The

Table I. *Showing frequency of colds among the inoculated and uninoculated during the experimental period.*

	Number of persons at risk	Percentage of persons having One or more colds	Two or more colds	Three or more colds	Four or more colds	Five colds
Inoculated	138	78·3	47·1	17·4	3·6	0·7
Uninoculated	148	70·3	31·1	10·8	1·4	0·0

Table II. *Showing total number of recorded colds, and the mean number of colds per person, among the inoculated and uninoculated.*

	Number of persons at risk	Total recorded colds	Mean number of colds per person
Inoculated	138	203	1·47
Uninoculated	148	168	1·14

Table III. *Showing the results of various methods of estimating the severity of the colds among the inoculated* (203 *colds*), *and among the uninoculated* (168 *colds*).

	Inoculated	Uninoculated
(*a*) Mean duration of colds in days (limited to 30 days) ...	13·0	10·7
(*b*) Percentage of colds associated with a temperature of 99° F. or over, lasting for one or more days	25·1	19·0
(*c*) Percentage of colds in which patient remained in bed for one or more days	19·2	25·0
(*d*) Percentage of colds in which patient remained indoors for one or more days	26·6	27·4
(*e*) Percentage of colds during which patient remained away from work for one or more days	18·2	21·4

frequency of colds was greater among the inoculated than among the uninoculated, and the severity of the colds was greater among the former group than among the latter, as judged by the mean duration of the colds, or by the proportion of the colds associated with fever.

The last three entries in Table III require a word of explanation. It will be noted that the figures for confinement to bed, and confinement to the house, are larger than those for absence from work. Enquiry revealed that this discrepancy arose from the fact that confinement to bed or to the house

during week-ends, or during vacation, was not recorded as absence from work; and it became apparent that the entries under all three heads depended to a large extent on the relation between the period of maximum severity of the cold and the academic or social engagements of the patient. In the absence of other calls upon his time, a person will stay in bed or indoors for a cold which he may disregard in other circumstances. For this reason we are inclined to think that the particulars recorded under these headings afford a less satisfactory basis for comparing the severity of colds in the two groups, than do the figures for duration and fever.

Before proceeding to discuss the significance of these results, it is well to determine, so far as is possible, whether they have been influenced by our method of selecting the groups, or of recording the frequency of colds.

Table IV gives the necessary data for the consideration of the first of these points. It has been argued—and we shall return to this point when considering similar experiments which have been carried out by others—that if

Table IV. *Showing the frequency of colds among the inoculated and uninoculated, and the mean number of colds per person, each group being differentiated into those who were assigned to the inoculated or uninoculated class by random selection, and those assigned in accordance with their own choice.*

	Inoculated			Uninoculated		
	Number at risk	Total colds	Mean colds per person	Number at risk	Total colds	Mean colds per person
Grouped by random selection	68	120	1·76	72	92	1·28
Grouped in accordance with own desire	70	83	1·19	76	76	1·00

all those who volunteer for inoculation are in fact inoculated, while the uninoculated controls consist of those who are unwilling to receive inoculation, it may well be that the inoculated group will contain a disproportionately high percentage of those who are naturally susceptible to colds, and who may hope to receive benefit from the vaccine. The figures recorded in Table IV do not suggest that this possible source of fallacy has been operative in the present enquiry. The disadvantage of the inoculated group is more marked in that part of the test-population which was subject to random grouping, having regard only to sex and to the date of the latest preceding cold, than in that part which was grouped in accordance with the expressed wishes of the volunteers. It will be noted that there is a quite marked difference in the frequency of colds among those subject to random grouping, and those grouped by desire. This is in large part accounted for by the fact that the former group was taken from those volunteers who expressed their willingness to act in either capacity, when the enquiry was started. These were divided into inoculated and uninoculated, as described above, and the inoculations were at once proceeded with. The remainder of these initial volunteers were inoculated as soon as the requisite number of controls, who were unwilling

to receive the vaccine, had been obtained. Thus it happened that the group subject to random selection completed their inoculations earlier than the other group, and were exposed to risk for a longer period, and during a time when colds were very prevalent. It need hardly be added that care was taken that the duration of exposure to risk should be similar for the inoculated and uninoculated in both groups.

As has been noted above, we dated the test period for each volunteer from the day on which he or she received the third and final inoculation. It seemed possible that this arbitrary choice might account for the apparent disadvantage of the inoculated group. Had a disproportionately high percentage of the uninoculated been suffering from colds during the period of inoculation, they might have shown a lower subsequent attack-rate, either in consequence of a transient immunity, or because, during the course of the initial cold, they did not really form part of the population at risk. Although we selected our trial period as described above, we kept a record of all colds during the period of inoculation. Table V records the frequency of colds in the two groups,

Table V. *Showing the total number of colds and the mean number of colds per person among the inoculated and uninoculated, including those colds which were present at the commencement of inoculation, or which developed during the period of inoculation.*

	Number of persons at risk	Total recorded colds	Mean colds per person
Inoculated	138	254	1·84
Uninoculated	148	202	1·36

Table VI. *Showing the total number of colds and the mean number of colds per person recorded as commencing during each month of the trial period, among the inoculated and uninoculated.*

	Inoculated		Uninoculated	
	Total colds	Mean colds per person	Total colds	Mean colds per person
November	27	0·20	17	0·11
December	41	0·30	27	0·18
January	47	0·34	55	0·37
February	31	0·22	24	0·16
March	37	0·27	21	0·14
April	11	0·08	12	0·08
May	9	0·07	12	0·08

when these are included. It is clear that the disadvantage of the inoculated group cannot be ascribed to this possible source of error.

It appeared to be of some interest to determine whether the difference in the frequency of colds among the inoculated and uninoculated was confined to the weeks immediately following inoculation, or was distributed over the whole trial period. Table VI gives the relevant figures. It should be remembered that the figures for November refer to a part of that month only. It will be seen that from November to March, that is during the time when colds

were prevalent, the inoculated appear to be at a disadvantage in each month except January. If this disadvantage be a real one, it does not appear to be confined to the period immediately succeeding inoculation.

Is the disadvantage real or apparent? We doubt whether it is possible to answer this question on the evidence afforded by our own enquiry. In Table VII we have set out the comparisons, which seem to us to yield the best available criteria. It will be noted that while the difference in the probability of suffering from one or more colds during the trial period does not differ significantly in the two groups, the difference in the probability of suffering from two or more colds closely approaches the arbitrary limit of significance. This fact must, we think, be considered in connection with the data concerning the relative severity of the colds in the two groups.

Table VII. *Showing the difference in the percentage of the inoculated and uninoculated who recorded (a) one or more colds, and (b) two or more colds, during the trial period, and the standard deviation of the difference.*

	Percentage among inoculated	Percentage among uninoculated	Percentage difference	Standard deviation of difference
Persons recording one or more colds	78·3	70·3	8·0	±5·18
Persons recording two or more colds	47·1	31·1	16·0	±5·75

Table VIII. *Showing the attack-rate (for ordinary colds) among the inoculated and uninoculated during two American enquiries.*

Authority	Period of enquiry	Number at risk	Inoculated number contracting one or more colds	Percentage attacked	Number at risk	Uninoculated number contracting one or more colds	Percentage attacked
Von Sholly and Park	30. ix. 19 to 3. v. 20	1327	766	57·7	3025	1156	38·2
Jordan and Sharp	Nov. 1919 to June 1920	448	246	54·9	461	238	51·6

We may now compare our results with those recorded in two similar, but more extensive trials of the prophylactic value of a mixed vaccine, which formed part of a general enquiry into the problems of respiratory disease undertaken in several centres in America during recent years (Von Sholly and Park, 1921; Jordan and Sharp, 1921). We are concerned here only with those observations which deal with the frequency of common colds among the inoculated and uninoculated groups. The relevant figures are abstracted in Table VIII. The general agreement with our own results is obvious; moreover, reference to the original reports will show that the apparent disadvantage of the inoculated groups is accentuated when the occurrence of repeated colds in the same individual is made the basis of comparison. In both these enquiries, however, the division into inoculated and uninoculated was made in accordance with the wishes of the volunteers, and the possible source of error to which we have referred above is fully realised and ade-

quately discussed by the authors. Von Sholly and Park, indeed, obtained histories of the incidence of respiratory infections among the test-population during previous winters, and found a definitely higher frequency of such infections among the inoculated group.

We may note that the vaccine employed by the American investigators differed widely from that employed by ourselves. It contained a smaller variety of bacteria, but the dosage of these bacteria common to the two vaccines was markedly greater in the American formula, which was as follows:

B. influenzae	1000 M. per c.c.
Strep. haemolyticus	1000 ,,
Strep. viridans	1000 ,,
Pneumo. Type I	2000 ,,
Pneumo. ,, II	2000 ,,
Pneumo. ,, III	1000 ,,

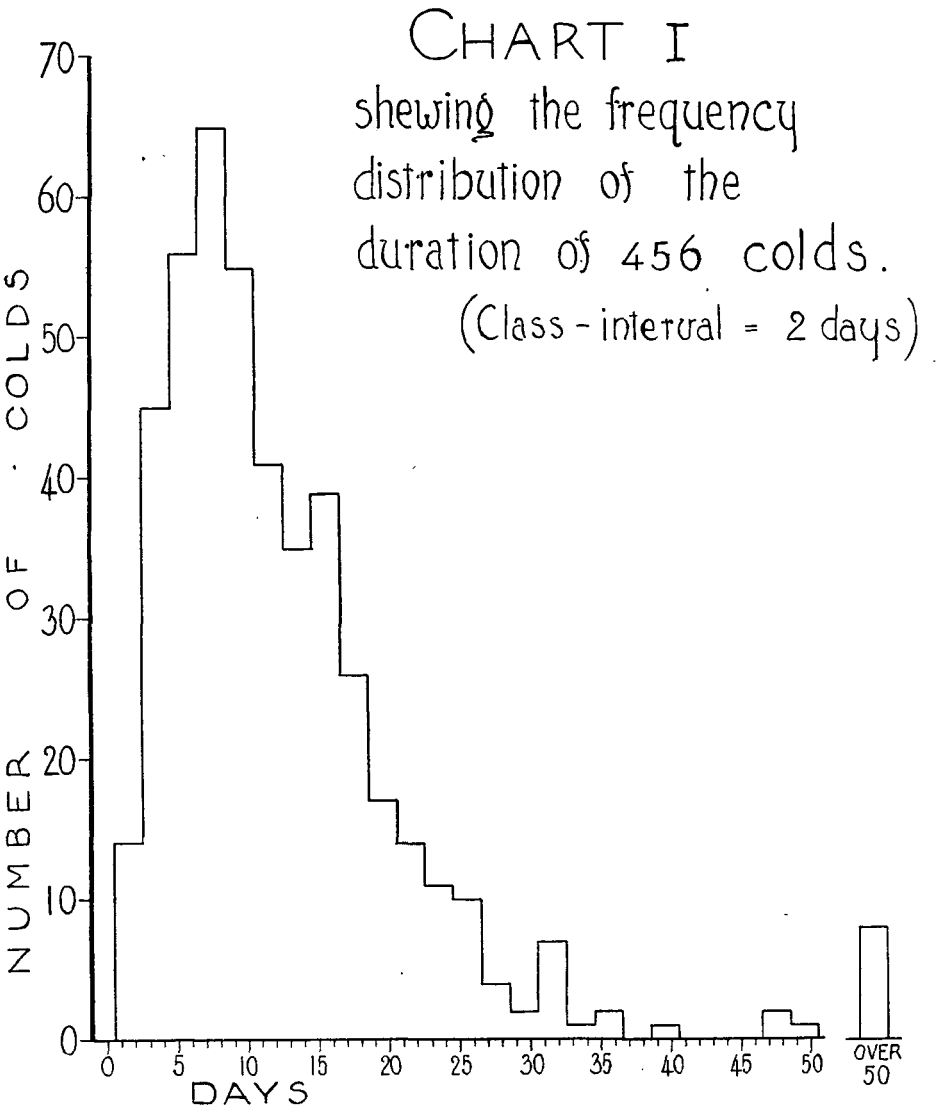
Three doses of this vaccine were given at weekly intervals consisting of 0·5, 1 and 1 c.c. respectively. As already explained, we selected the particular vaccine employed in the present enquiry because it is of a type very commonly used in this country. Had the American results been more favourable than our own, it might, we think, have been argued with justice, that the doses we employed were too small to be effectual. The concordance of the results suggests that the absence of effective immunisation is not due to the failure to employ optimal dosage, or to the selection of unsuitable bacterial types, within the limits which are necessarily imposed on stock vaccines of this kind.

It appears to us that the available evidence suggests very strongly that it is futile to hope for a reduction in the incidence of common colds among the population at large, as the result of the prophylactic inoculation of any of the stock vaccines now available. We doubt whether the evidence justifies the conclusion that such inoculations do harm.

We would add a word of warning with regard to the utter uselessness of the reports of individual patients as evidence of efficient prophylaxis. Among any large population, some persons will experience fewer colds during any particular winter, than they have experienced in previous years. In no department of human reasoning does the argument, *post hoc propter hoc* hold more absolute sway, than in the lay evaluation of medical procedures. Several of the volunteers in the present enquiry were quite convinced that they had received definite benefit from the inoculations. Jordan and Sharp record similar happenings, and we would echo their comment "'Satisfied patient' conclusions differ widely from those of controlled statistics."

If we are to conclude, as we think we must, that there is no justification for the prophylactic use of such stock vaccines as are available in the hope of lessening the frequency of the common cold, it clearly does not follow either that such vaccines are devoid of immunising power against other respiratory infections—there is indeed some evidence that pneumococcal

vaccines have definite prophylactic value against lobar pneumonia—or that we should cease from our endeavours to find some more effective immunising agent against the common cold. Our lack of alternative methods of attack suggests rather the urgent need for a more intensive study of these infections



of the upper respiratory tract, and of the variations of the normal bacterial flora in this situation, in the reasonable hope that *ignoramus* does not imply *ignorabimus*.

We add, in Chart I, the available data on the duration of the 456 colds recorded during the present enquiry. We do not know that such information

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is available elsewhere, and it completes the picture, so far as we can present it, of the incidence and inconvenience of this type of infection, in a particular community and over a particular period of time.

In conclusion, we would express our indebtedness to many who have helped us in this investigation. To Prof. J. H. Dible and Dr G. S. Wilson, who helped us with the inoculations, to Miss E. C. Iliff whose assistance with the record-keeping has been invaluable, and by no means least to those who volunteered as subjects for the test.

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