Nasal sprays and behavioural interventions compared with usual care for acute respiratory illness in primary care: a randomised, controlled, open-label, parallel-group trial

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Summary

Background A small amount of evidence suggests that nasal sprays, or physical activity and stress management, could shorten the duration of respiratory infections. This study aimed to assess the effect of nasal sprays or a behavioural intervention promoting physical activity and stress management on respiratory illnesses, compared with usual care.

Methods This randomised, controlled, open-label, parallel-group trial was done at 332 general practitioner practices in the UK. Eligible adults (aged ≥18 years) had at least one comorbidity or risk factor increasing their risk of adverse outcomes due to respiratory illness (eg, immune compromise due to serious illness or medication; heart disease; asthma or lung disease; diabetes; mild hepatic impairment; stroke or severe neurological problem; obesity [BMI ≥30 kg/m²]; or age ≥65 years) or at least three self-reported respiratory tract infections in a normal year (ie, any year before the COVID-19 pandemic). Participants were randomly assigned (1:1:1:1) using a computerised system to: usual care (brief advice about managing illness); gel-based spray (two sprays per nostril at the first sign of an infection or after potential exposure to infection, up to 6 times per day); saline spray (two sprays per nostril at the first sign of an infection or after potential exposure to infection, up to 6 times per day); or a brief behavioural intervention in which participants were given access to a website promoting physical activity and stress management. The study was partially masked: neither investigators nor medical staff were aware of treatment allocation, and investigators who did the statistical analysis were unaware of treatment allocation. The sprays were relabelled to maintain participant masking. Outcomes were assessed using data from participants' completed monthly surveys and a survey at 6 months. The primary outcome was total number of days of illness due to self-reported respiratory tract illnesses (coughs, colds, sore throat, sinus or ear infections, influenza, or COVID-19) in the previous 6 months, assessed in the modified intention-to-treat population, which included all randomly assigned participants who had primary outcome data available. Key secondary outcomes were possible harms, including headache or facial pain, and antibiotic use, assessed in all randomly assigned participants. This trial was registered with ISRCTN, 17936080, and is closed to recruitment.

Findings Between Dec 12, 2020, and April 7, 2023, of 19 475 individuals screened for eligibility, 13 799 participants were randomly assigned to usual care (n=3451), gel-based nasal spray (n=3448), saline nasal spray (n=3450), or the digital intervention promoting physical activity and stress management (n=3450). 11 612 participants had complete data for the primary outcome and were included in the primary outcome analysis (usual care group, n=2983; gel-based spray group, n=2935; saline spray group, n=2967; behavioural website group, n=2727). Compared with participants in the usual care group, who had a mean of 8·2 (SD 16·1) days of illness, the number of days of illness was significantly lower in the gel-based spray group (mean 6·5 days [SD 12·8]; adjusted incidence rate ratio [IRR] 0·82 [99% CI 0·76–0·90]; p<0·0001) and the saline spray group (6·4 days [12·4]; 0·81 [0·74–0·88]; p<0·0001), but not in the group allocated to the behavioural website (7·4 days [14·7]; 0·97 [0·89–1·06]; p=0·46). The most common adverse event was headache or sinus pain in the gel-based group: 123 (4·8%) of 2556 participants in the usual care group; 199 (7·8%) of 2498 participants in the gel-based group (risk ratio 1·61 [95% CI 1·30–1·99]; p<0·0001); 101 (4·5%) of 2377 participants in the saline group (0·81 [0·63–1·05]; p=0·11); and 101 (4·5%) of 2091 participants in the behavioural intervention group (0·95 [0·74–1·22]; p=0·69). Compared with usual care, antibiotic use was lower for all interventions: IRR 0·65 (95% CI 0·50–0·84; p=0·001) for the gel-based spray group; 0·69 (0·45–0·88; p=0·003) for the saline spray group; and 0·74 (0·57–0·94; p=0·02) for the behavioural website group.

Interpretation Advice to use either nasal spray reduced illness duration and both sprays and the behavioural website reduced antibiotic use. Future research should aim to address the impact of the widespread implementation of these simple interventions.

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Introduction

Most people have a respiratory illness each year, commonly resulting in sickness absence;[1] severe illness, antibiotic use, and work absence are more common in people with recurrent illness or comorbidities.[2–4] Most people who attend a general practitioner (GP) practice for respiratory illness are prescribed antibiotics,[5,6] and antibiotic use in primary care is strongly associated with antibiotic resistance.[7] Effective, low-cost, non-prescription interventions are needed to reduce symptom burden and antibiotic use.

Modifying the nasal environment is a strategy to shorten duration of acute respiratory infections or to reduce symptom severity. Low pH has been shown to inactivate a range of respiratory viruses in-vivo and in-vitro studies,[8–12] and could potentially reduce the viral inoculum, hence reducing the incidence and severity of illness.[11,13,14] A trial of a buffered-pH antiviral nasal spray in 441 individuals found that median illness duration was 2·5 days shorter in the antiviral nasal spray group (5·3 days) than the saline group (7·8 days), but individuals in the nasal spray group had side-effects (local irritation), therefore the net effect on symptom severity is unclear.[12,15] A systematic review of carrageenan sprays documented reduced symptom severity in respiratory illness, and in some trials shorter illness duration compared with placebo.[16] Furthermore, saline alone might reduce nasopharyngeal viral load by mechanically washing out virus.[15]

Improving immune function has also been suggested as a method to reduce duration of acute respiratory infections. A Cochrane review and other similar observational data suggested that physical activity was associated with a 2-day reduction in symptom days, although the trials included had small sample sizes and studies were of low quality.[17,18] Perceived stress,[19] negative emotions,[20] and poor social support[21] increase susceptibility to subsequent illness and inhibit activity of the immune defence against viruses (eg, increased viral shedding, reduced cytokine activity, and adverse mucosal defence and pathogenicity);[22,23] to counter this, mindfulness can reduce stress and negative emotions.[24] A small trial of a mindfulness intervention documented 3–4 fewer illness days when compared with no mindfulness intervention,[25] and a randomised controlled trial[26] reported a 1-day reduction in illness days.

Based on the accessibility and efficiencies of digital platforms, we developed a brief behavioural intervention

For more on the **Immune Defence behavioural intervention** see https://immunedefence.lifeguide.site/

Research in context

Evidence before this study

A previous systematic review documented four small trials of nasal sprays using the polymer carrageenan, but not buffering of pH. The Cochrane Database, PubMed, ScienceDirect, SpringerLink, Oxford Journals, Elsevier, Clinical Key, Wiley Online Library, and Embase databases were searched from inception to May 31, 2020, for studies published in English, using the search terms: "iota-carrageenan", "carrageenan", "nasal spray", "common cold", "placebo", and "clinical trial". There was mixed evidence to support the use of nasal sprays containing carrageenan, with some evidence of a reduction in symptom severity, and in some trials, a reduction in illness duration by 1 day. A trial of a buffered-pH antiviral nasal spray compared with saline found that illness duration of naturally acquired colds was 3 days shorter. A Cochrane review documented the effect of physical activity on reducing illness duration and indicated a significant effect on symptom days during follow-up, and on the severity of symptoms; however, many trials had a small sample size (14 trials involving 1377 participants), studies were generally of low quality, and they involved intensive supervision of exercise. Two trials of exercise included in the review also assessed the effect of an 8-week supervised course of mindfulness (each session lasting 2·5 h), which documented 1–4 fewer illness days compared with controls.

Added value of this study

Most previous studies of nasal sprays and behavioural interventions were small, and both the physical activity or stress reduction interventions were intensive with supervised sessions, and would be difficult to implement in primary care where resources are limited. This is the only large, pragmatic trial of readily implementable interventions that could be widely used. The current study found that the incidence, but not the duration, of illness was significantly reduced among people who were advised to use a behavioural physical activity and stress management website compared with usual care; although the reduction was modest (a 5% relative reduction), this could have an important impact in population terms considering the highly scalable nature of the intervention, and the effect was greater among people at higher risk from respiratory illness (with both comorbidities and recurrent illnesses). Both nasal sprays reduced overall illness duration by around 20%, and resulted in a 20–30% reduction in lost days of work or normal activities compared with usual care. All of the interventions reduced antibiotic use (relative risk reduction of >25%) and also the number of days with more severe symptoms. Adherence to the interventions was moderate, therefore improving adherence could plausibly result in a larger effect. Further research should address strategies to improve adherence in implementing these interventions.

Implications of all the available evidence

If widely advocated, these simple, scalable interventions could potentially have an important role in antimicrobial stewardship and in reducing the impact of respiratory viruses.

requiring no support. The intervention aims to both increase physical activity, based on the evidence-based modules of our POWeR+[27] and CLASP[28] Getting Active interventions, underpinned by self-determination theory,[29–31] and improve stress management via modules of our Healthy Paths intervention.[32] We also developed web-based modules to support use of the nasal sprays.

In this trial, we aimed to determine the effect of low-cost approaches to support people with respiratory tract infections (nasal sprays or a digital intervention for physical activity and stress) compared with usual care on days of illness, and on the possible harms of more severe symptoms, antibiotic use, and workdays lost.

Methods

Study design and participants

The Immune Defence study was a randomised, controlled, open-label, parallel-group trial that took place in UK primary care comprising urban and rural settings, large and small GP practices, and high and low deprivation. Participants were invited by 332 GP practices in three winter seasons: the first season started on Dec 1, 2020, with the next two seasons commencing recruitment in September of each year. For each winter season, recruitment ended in March or April of the subsequent year, and recruitment for season three ended on April 7, 2023. An automated search identified lists of potentially eligible patients that were checked by GP practice staff to ensure suitability to receive an invitation and provide consent online (more details on the invitation process are in the appendix [p 1]).

Eligible individuals were aged 18 years or older and had at least one comorbidity or risk factor for adverse outcomes from respiratory infections (eg, immune compromise due to serious illness or medication; heart disease; asthma or lung disease; diabetes; mild hepatic impairment; stroke or severe neurological problem; obesity [BMI ≥30 kg/m²]; or age ≥65 years) or had a history of at least three respiratory tract infections in a normal year (ie, before the COVID-19 pandemic).

Individuals who had a terminal illness or were receiving palliative care, had dementia, were living in residential care, or had pituitary adenoma, and individuals who were pregnant or breastfeeding, regularly used nasal sprays to prevent illness, had an allergy to nasal sprays, were living in the same household as another participant, were involved in the trial development phase, or were unable to access the internet were excluded from participating in the study.

Full details of the study methods are available in the protocol.[33] Protocol amendments, including those due to the COVID-19 pandemic, are included in the appendix (p 2). This study was approved by the South East Scotland Research Ethics Committee 01 (20/SS/0102) on Oct 23, 2020, and the Health Research Authority on Oct 29, 2020. All participants provided written informed consent.

Randomisation and masking

Randomisation was fully automated: the Immune Defence website software (Global Initiative, Oxford, UK) generated a randomisation sequence and a computer algorithm to block randomise participants to the four trial groups (1:1:1:1). Individuals were randomly assigned to one of four intervention groups: usual care, gel-based nasal spray, saline nasal spray, or a digital intervention comprising access to a behavioural website promoting physical activity and stress management. The randomisation sequence was concealed from the trial team. Patients were stratified to three strata on the basis of whether they were in a higher-risk group (aged >65 years or comorbidity) and whether or not they had recurrent respiratory tract infections (≥3 in the previous year): stratum 1 (recurrence, no risk factors); stratum 2 (risk factors, no recurrence); stratum 3 (risk factors plus recurrence).

The study was partially masked: neither investigators nor medical staff were aware of treatment allocation, and investigators who did the statistical analysis were unaware of treatment allocation. Participants were not aware of the precise nature of their sprays: to reduce possible intervention contamination, considering the availability of nasal sprays in pharmacies and supermarkets, details of both the nasal sprays were concealed by removing the manufacturer labels and adding generic study labels (ie, saline was labelled as liquid-based and Vicks First Defence spray as gel-based).

Procedures

See Online for appendix

Participants assigned to usual care were provided with brief advice about managing illness, which included an advice page about managing respiratory illnesses based on National Health Service (NHS) current advice (rest, keeping warm, fluids, over-the-counter medications for symptom relief). Participants were asked not to use any over-the-counter nasal sprays during the study period.

Participants assigned to the gel-based spray or saline spray groups were provided with two bottles of spray initially (further available on request). The gel-based spray was Vicks First Defence spray (Proctor and Gamble, Harrogate, UK), which contains a polymer and buffers pH (appendix p 2). The saline spray was Sterinase (Earol, Glasgow, UK), which was selected because the method of delivery (a pump-action spray) was identical to that of the gel-based spray without potential active excipients (eg, zinc or copper; appendix p 2). One spray of each spray (gel-based or saline) delivered approximately 0·1 mL of fluid. Both sprays were classed as medical devices. The nasal spray groups were given the same online instructions, supported by paper booklets, developed iteratively using the person-based approach[34,35] (appendix p 2), to use the nasal spray in three ways: (1) at the first signs of an illness (up to six times daily [two sprays in each nostril] until symptom free for 2 days; (2) after potential exposure to infection

(eg, using public transport, supermarkets, cafes, or pubs; two sprays in each nostril immediately after exposures, 1 h later, and last thing at night); (3) after prolonged exposure (eg, close contact with or living with someone who has an illness; up to six times daily [two sprays in each nostril] until the close contact has recovered).

Participants assigned to the behavioural website promoting physical activity and stress management (developed iteratively using the person-based approach[36]) were given access to brief content on the impact of respiratory tract infections, how physical activity and stress management can prevent respiratory tract infections, and subsequently two online modules to support physical activity (Getting Active) and stress reduction (Healthy Paths through Stress; appendix p 2). Participants were also sent inexpensive pedometers to help to monitor their activity, but use was optional with no information collected. More information about the person-based advice developed for all active treatment groups is available online.

Participants were asked to complete a monthly survey about the previous month and a survey at 6 months about the previous 6 months (appendix p 6). At each timepoint, participants were asked if they had developed any acute respiratory illnesses and, if so, how many days of illness they had experienced.

Unless otherwise specified, data were collected using the trial website designed by Global Initiative by investigators who were masked to treatment group, with up to two email reminders for participants, followed by a mailed questionnaire, and a final telephone call as necessary for non-completers of the primary outcome, which was made by members of the study team who were masked to group allocation. Data from paper questionnaires and telephone interviews were entered into a secure access database by the trial team.

Outcomes

The primary outcome was the total number of days of illness due to self-reported respiratory tract illnesses (coughs, colds, sore throat, sinus or ear infections, influenza, or COVID-19) since randomisation, reported at the 6-month questionnaire. We anticipated that the interventions could reduce both the incidence and duration of illness, which would be captured in the total number of days of illness. Based on previous studies, this reduction would be of the order of 1–3 days,[17,25,26] which could be important both for patients and at a population level, considering the brevity of the interventions. Furthermore, patients can remember the incidence and duration of illness over several weeks,[14,36,37] and in the previous PRIMIT trial,[14] estimates from self-report after several months were similar to estimates from monthly reports.

Key secondary outcomes were the reported incidence of respiratory tract illnesses (self-reported in both contemporaneous monthly questionnaires and retrospectively at 6 months); possible adverse events (possible poor symptom control secondary to local irritation of sprays) including incidence of headache or facial pain, days with symptoms moderately bad or worse,[37,38] days when work or normal activities were impaired, or use of antibiotics;[36] incidence of COVID-19; number of health service contacts;[38] and number of days of respiratory illness and hospital admissions at 12 months[14] (which will be published elsewhere). Additional secondary outcomes were side-effects of nasal sprays; belief in the effectiveness of antibiotics, intention to consult a doctor with a respiratory infection, mental health measured using the Perceived Stress Scale,[39] Patient Health Questionnaire-8,[40] and Generalised Anxiety Disorder-7.[41] The additional secondary endpoints of adherence to nasal sprays; NHS contacts through retrospective notes review; engagement with the trial interventions, evaluated through participant self-report and usage data from the trial website; physical activity; quality of life; out-of-pocket spending; respiratory infection avoidance behaviours; NHS resource use; and pattern of symptom severity and duration (recorded in optional paper-based daily symptom diary if patients developed a respiratory tract infection during the stud period) will be published elsewhere.

Statistical analysis

A provisional sample size calculation was agreed with the funder after the start of the COVID-19 pandemic. To detect a 1-day difference in illness duration among individuals with a respiratory tract illness (hazard ratio [HR] 1·2) with an α of 0·01 (to allow all between-group comparisons) and 90% power, we originally estimated that 147 individuals would be required per group. Assuming at least 15% of participants contracted illness over a 6-month period (assuming low rates due to COVID-19 restrictions), 980 people would be required per group (4900 total with 80% completing follow-up) and for three strata (recurrent illness alone; risk factors; both combined), with a total of 14700 people. For the secondary outcome of incidence of illness, based on previous publications about the appropriate use of multiplicity corrections for the primary comparisons of interest (each intervention *vs* control[42–44]) and assuming an α of 0·05, the same sample size would provide more than 80% power to estimate a 25% reduction in the incidence of illness from 20% to 15% in each stratum and more than 90% power if the incidence of illness was 15% using all strata combined.

Sample size estimates were revised for the primary outcome on the basis of actual data on the incidence of illness, which differed from the assumption of 15%, from the first two winter seasons in 2020–21 and 2021–22. In stratum 1 (recurrence, no risk factors), 71% of participants had an illness. Therefore, using the lower limit of the 95% CI of this estimate, we assumed that at least 65% of participants would develop an illness. Based on the original sample size of 147 participants per group (ie,

changing no other assumptions), we estimated that 226 individuals per group were needed, and 1130 participants in total (with 80% follow-up). In stratum 2 (risk factors, no recurrence), 40% of participants had illness, thus 368 people were required per group (requiring 147 divided by 0·4), and 1472 in total. In stratum 3 (risk factors plus recurrence), 62% had illness, thus 245 people were required per group, summing to 1225 people in total.

A detailed statistical analysis plan superseded the brief description in the protocol, and was finalised before data analysis and data lock, in discussion with the Programme Steering Committee, with the study team masked to group allocation. The statistical analysis plan proposed harmonising an α of 0·05 for each comparison with control, and 0·01 for comparisons between intervention groups, for all outcomes (whereas the published protocol clarified this only for secondary outcomes). An α of 0·01 was used for the primary outcome to align with the original approved protocol published in 2020 and the published protocol.[33]

Initially, the plan was to assess the primary outcome in the intention-to-treat population, with imputation for missing data (via chained-equations multiple imputation model), with complete cases assessed as a sensitivity analysis, but due to convergence issues with the zero-inflated imputation models, a complete case analysis was needed as the primary analysis. Thus, the primary outcome was assessed in the modified intention-to-treat population, which included all randomly assigned participants who had primary outcome data available (defined as completers). Secondary outcomes were assessed following a similar modelling approach to the primary analyses, including all randomly assigned participants who had secondary outcome data available. Results were reported in line with the CONSORT guidelines.

The primary timepoint for analysis was 6 months. Considering the major pressures in the NHS in the winter of 2022–23, with agreement from the Programme Steering Committee and the funder, here we present an early analysis of the 6-month data, to provide results to inform clinical management as soon as possible. The 12-month data will be reported separately.

The number of days of symptoms was analysed using zero-inflated negative binomial regression models, because of the large number of zeros due to no illness and overdispersion of the outcome. The model provided estimates of the incidence rate ratio (IRR) adjusted for baseline days of symptoms and the stratification variables. Other count outcomes were analysed in the same way. Dichotomous outcomes were analysed using logistic regression, which provided risk ratios (RR), and continuous outcomes were analysed using linear regression. Skewed continuous outcomes were either transformed before linear regression or analysed using a Poisson regression with robust SEs. All analyses were adjusted for baseline outcomes and the same variables as in the primary analysis. We also conducted a sensitivity analysis to include only participants reporting an illness in the previous year. Estimates were provided for key subgroups (people with recurrent illness [≥3 illnesses per year], age >65 years, and the presence and number of serious comorbidities). A complier average causal effect (CACE) model was used to estimate the effects of the intervention assuming compliance with treatment. Multiple imputation with chained equations was undertaken for the occurrence of illness (binary) outcome, using 100 imputations.[45] The imputation model included all variables in the analysis model (ie, outcome, baseline days, strata) and prespecified variables predictive of missingness (age, sex, Index of Multiple Deprivation decile, baseline belief in antibiotics, and baseline intention to consult), and was done separately by randomised group.[46] For the primary outcome, complete case analysis assumed the data were missing completely at random, but sensitivity analyses making the assumption that data might not be missing completely at random[47] were done using extreme assumptions for the primary outcome (missing data being imputed as either 0 or 30 days). A post-hoc analysis was done to assess the impact of smoking status on the estimates of effectiveness. Stata software (version 17.0) was used for statistical analysis.

This trial was registered with ISRCTN, 17936080.

For the **statistical analysis plan** see https://doi.org/10.1186/ISRCTN17936080

Role of funding source

The funder had no role in data collection, analysis, interpretation, writing of the manuscript, or the decision to submit.

Results

Between Dec 12, 2020, and April 7, 2023, 631 174 individuals were invited from 332 GP surgeries to participate across three winter seasons, of whom 19 475 were screened for eligibility and 13 799 were randomly assigned to usual care (n=3451), gel-based nasal spray (n=3448), saline-based nasal spray (n=3450), or the behavioural website intervention (n=3450; figure). Groups were well balanced in terms of baseline characteristics (table 1; appendix pp 14–16) and the number of participants who completed 6-month follow-up was high (2983 [86·4%] of 3451 participants in the usual care group; 2935 [85·1%] of 3448 participants in the gel-based spray group; 2967 [86·0%] of 3450 participants in the saline spray group; 2727 [79·0%] of 3450 participants in the behavioural website group).

Nine participants requested that their data were removed and 429 withdrew from the trial but allowed data use. Reasons for withdrawal included being unable to engage with the intervention (behavioural website group, n=48; gel-based spray group, n=19; saline spray group, n=18; usual care group, n=8); too unwell or

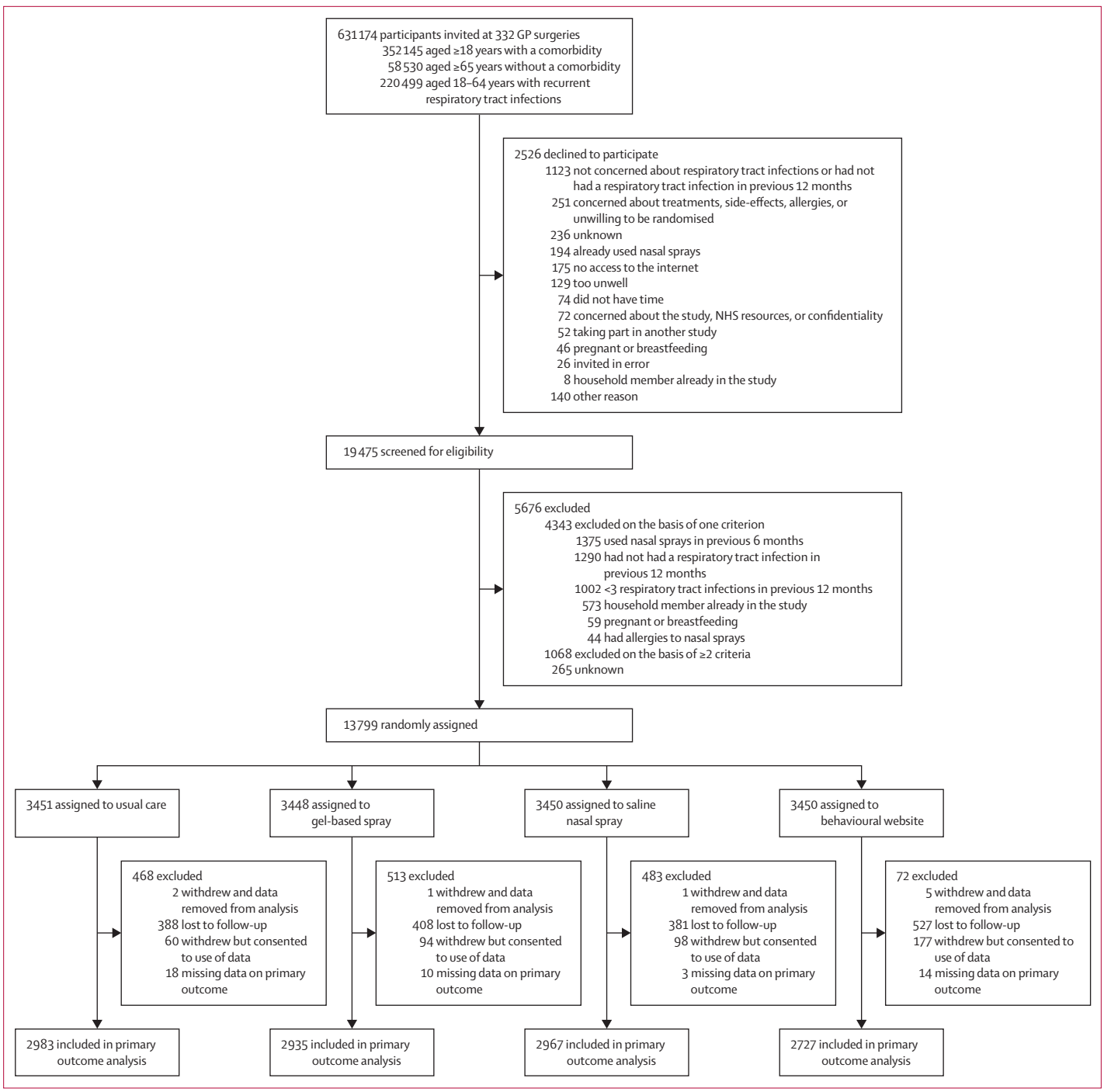

Figure: **Trial profile**
GP=general practitioner. NHS=National Health Service.

a change in medical condition (n=69); trial processes or too busy (n=69); personal circumstances (n=32); death (n=16); participant deemed that the study was not relevant or did not get respiratory tract infection (n=14); other reason (n=7); and being pregnant or breastfeeding (n=3).

Therefore, 13 790 participants could have potentially provided data. Allowing for missing data, data from 12 631 participants were available for the analyses by stratum: 863 (6·8%) participants in stratum 1 (recurrence, no risk factors); 7666 (60·7%) participants in stratum 2 (risk factors, no recurrence); and 3102

	Usual care (n=2983)	Gel-based spray (n=2935)	Saline spray (n=2967)	Behavioural website (n=2727)
Gender				
Male	1388 (46·6%)	1348 (45·9%)	1324 (44·7%)	1244 (45·6%)
Female	1585 (53·2%)	1580 (53·9%)	1637 (55·2%)	1473 (54·0%)
Other	4 (0·1%)	2 (0·1%)	1 (<0·1%)	8 (0·3%)
Prefer not to say	3 (0·1%)	4 (0·1%)	3 (0·1%)	2 (0·1%)
Missing	3 (0·1%)	2 (0·1%)	2 (0·1%)	1 (0·1%)
Age, years				
Mean (SD)	61·6 (14·4)	61·5 (14·3)	61·4 (14·6)	61·7 (14·3)
Median (IQR)	65 (53–72)	65 (54–72)	65 (53–72)	66 (54–72)
Ethnicity				
White	2884 (97·3%)	2837 (97·1%)	2879 (97·5%)	2635 (97·2%)
Mixed	19 (0·6%)	29 (1·0%)	20 (0·7%)	26 (1·0%)
Asian	40 (1·3%)	40 (1·4%)	33 (1·1%)	40 (1·5%)
Black	13 (0·4%)	9 (0·3%)	10 (0·3%)	4 (0·1%)
Other	8 (0·3%)	6 (0·2%)	12 (0·4%)	7 (0·3%)
Missing	20 (0·7%)	19 (0·6%)	15 (0·5%)	17 (0·6%)
Marital status				
Single	295 (9·9%)	297 (10·2%)	307 (10·4%)	274 (10·1%)
Married	2176 (73·2%)	2121 (72·5%)	2139 (72·3%)	1968 (72·3%)
Widowed	198 (6·7%)	204 (7·0%)	209 (7·1%)	184 (6·8%)
Divorced	261 (8·8%)	261 (8·9%)	256 (8·7%)	249 (9·1%)
Separated	44 (1·5%)	42 (1·4%)	47 (1·6%)	48 (1·8%)
Missing	10 (0·3%)	11 (0·4%)	11 (0·4%)	8 (0·3%)
Education				
No qualifications	176 (5·9%)	162 (5·5%)	176 (5·9%)	171 (6·3%)
General Certificate of Secondary Education	590 (19·8%)	619 (21·2%)	609 (20·6%)	534 (19·6%)
Advanced-level	495 (16·6%)	461 (15·8%)	479 (16·2%)	446 (16·4%)
Higher National Diploma or Certificate	259 (8·7%)	254 (8·7%)	249 (8·4%)	278 (10·2%)
Degree	788 (26·5%)	763 (26·1%)	773 (26·1%)	701 (25·7%)
Higher degree	181 (6·1%)	227 (7·8%)	195 (6·6%)	196 (7·2%)
Postgraduate	354 (11·9%)	333 (11·4%)	356 (12·0%)	301 (11·0%)
Other	134 (4·5%)	106 (3·6%)	121 (4·1%)	97 (3·6%)
Missing	9 (0·3%)	10 (0·3%)	9 (0·3%)	3 (0·1%)
Median number of people in household (IQR)	2 (2–2)	2 (2–3)	2 (2–3)	2 (2–3)
Missing	21 (0·7%)	28 (1·0%)	12 (0·4%)	33 (1·2%)
Children younger than 16 years in household	405 (13·7%)	388 (13·4%)	410 (14·0%)	331 (12·3%)
Missing	41 (1·4%)	51 (1·7%)	40 (1·3%)	41 (1·5%)
Mean BMI, kg/m² (SD)	28·4 (6·7)	28·2 (8·2)	28·3 (6·8)	28·2 (6·8)
Missing	78 (2·6%)	81 (2·8%)	55 (1·9%)	66 (2·4%)
Current smoker	128 (4·3%)	130 (4·5%)	129 (4·4%)	109 (4·0%)
Missing	47 (1·6%)	33 (1·1%)	39 (1·3%)	31 (1·1%)
Comorbidity	2385 (80·0%)	2300 (78·4%)	2316 (78·1%)	2134 (78·3%)
Median number of comorbidities (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)
Influenza vaccination in previous 12 months	2578 (86·9%)	2534 (87·3%)	2553 (86·7%)	2362 (87·3%)
Missing	24 (0·8%)	35 (1·2%)	26 (0·9%)	26 (1·0%)
COVID-19 vaccination in previous 12 months	2654 (89·0%)	2584 (88·0%)	2628 (88·6%)	2390 (87·6%)
COVID-19 in previous 12 months				
Yes	848 (28·6%)	862 (29·5%)	843 (28·5%)	765 (28·2%)
No	2028 (68·5%)	1951 (66·8%)	2020 (68·2%)	1873 (69·0%)
Not sure	85 (2·9%)	108 (3·7%)	97 (3·3%)	76 (2·8%)
Missing	25 (0·8%)	18 (0·6%)	9 (0·3%)	13 (0·5%)

(Table 1 continues on next page)

	Usual care (n=2983)	Gel-based spray (n=2935)	Saline spray (n=2967)	Behavioural website (n=2727)
(Continued from previous page)				
Median duration of COVID-19 symptoms, days (IQR)	8 (5–14)	8 (5–14)	7 (5–12)	8 (5–14)
Previous use of nasal spray	424 (14·8%)	428 (15·2%)	438 (15·4%)	357 (13·7%)
Missing	136 (4·6%)	134 (4·6%)	136 (4·6%)	133 (4·9%)
Respiratory tract illness in normal year*	2656 (89·0%)	2628 (89·5%)	2615 (88·1%)	2442 (89·5%)
Number of respiratory tract illnesses in normal year*, n (participants)	2588	2561	2557	2358
Median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Respiratory tract infections in previous 12 months	2195 (73·6%)	2201 (75·0%)	2203 (74·3%)	2023 (74·2%)
Number of respiratory tract infections in previous 12 months				
Mean (SD)	1·7 (1·7)	1·7 (1·8)	1·7 (1·7)	1·6 (1·6)
Median (IQR)	1 (0–2)	1 (0–2)	1 (0–3)	1 (0–2)
Missing	10 (0·3%)	11 (0·4%)	3 (0·1%)	9 (0·3%)
Days with respiratory tract infection symptoms in previous 12 months				
Mean (SD)	13·0 (18·3)	13·0 (17·3)	12·8 (17·7)	12·4 (17·1)
Median (IQR)	7 (0–15)	7 (0–16)	7 (0–15)	7 (0–15)
Days with moderately bad symptoms in previous 12 months				
Mean (SD)	5·6 (10·1)	5·6 (9·9)	5·6 (10·2)	5·3 (9·8)
Median (IQR)	3 (0–6)	3 (0–6)	3 (0–6)	3 (0–6)
Days of work lost in previous 12 months				
Mean (SD)	3·4 (8·8)	3·3 (8·1)	3·2 (8·3)	3·1 (7·6)
Median (IQR)	0 (0–4)	0 (0–4)	0 (0–3)	0 (0–3)
Health-care practitioner contacts in previous 12 months, mean (SD)	0·5 (1·3)	0·5 (1·1)	0·5 (1·2)	0·5 (1·2)
Courses of antibiotics in previous 12 months, mean (SD)	0·4 (1·1)	0·4 (1·0)	0·4 (1·0)	0·4 (1·0)
PHQ-8†				
Mean (SD)	4·2 (4·6)	4·1 (4·4)	4·1 (4·4)	4·0 (4·4)
Median (IQR)	3 (1–6)	3 (1–6)	3 (1–6)	3 (1–6)
Missing	247 (8·3%)	209 (7·1%)	217 (7·3%)	223 (8·2%)
GAD-7 score‡				
Mean (SD)	3·3 (4·0)	3·3 (4·0)	3·2 (3·9)	3·2 (4·0)
Median (IQR)	2 (0–5)	2 (0–5)	2 (0–5)	2 (0–5)
Missing	192 (6·4%)	186 (6·3%)	186 (6·3%)	207 (7·6%)

Data are n (%), unless otherwise stated. PHQ-8=Patient Heath Questionnaire-8. GAD-7=Generalised Anxiety Disorder-7. *Normal year defined as a year before the COVID-19 pandemic. †The PHQ-8 score measures depression on a scale of 0–24, with a score of 10 or higher indicating major depression. ‡The GAD-7 score measures anxiety on a scale of 0–21, with a score of 10 or higher indicating generalised anxiety disorder.

Table 1: **Baseline characteristics of primary analysis population**

(24·6%) participants in stratum 3 (risk factors plus recurrence).

Primary outcome data were missing mainly due to loss to follow-up (1704 [12·3%] of 13799 participants) or withdrawal (429 [3·1%] participants). 11612 [84·2%] of 13799 participants had complete data (ie, submitted the 6-month survey) for the primary outcome. Individuals who did not contribute data for the primary outcome analysis (n=2187) were younger than completers (median age 51 years [IQR 37–66] *vs* 65 years [54–72]), reported a slightly higher number of respiratory tract infections in a normal year (mean 2·5 infections [SD 2·2] *vs* 1·7 infections [1·7]), and were more likely to be smokers (208 [9·5%] of 2187 individuals *vs* 496 [4·3%] of 11612 individuals).

For the primary outcome of total number of days of illness in the previous 6 months, individuals in the usual care group reported a mean of 8·2 (SD 16·1) days of illness (IRR 1 [ref]), which was lower among participants in the gel-based spray group (6·5 days [SD 12·8]; IRR 0·82 [99% CI 0·76–0·90]; p<0·0001) and the saline spray group (6·4 days [12·4]; 0·81 [0·74–0·88]; p<0·0001), but not among individuals assigned to the behavioural website (7·4 days [14·7]; 0·97 [0·89–1·06]; p=0·46; table 2). Among participants who reported an illness, the mean number of days with illness was 15·1 days (SD 19·2) in the usual care

group, 12·0 days (15·3) in the gel-based spray group, 11·8 days (14·9) in the saline spray group, and 14·2 days (17·9) in the behavioural website group. The estimates for total days of illness in the previous 6 months from monthly questionnaires (months 1–6) were similar to the estimates from the 6-month questionnaires (IRR 0·79 [0·74–0·85] for the gel-based spray group; 0·80 [0·75–0·86] for the saline spray group; 0·98 [0·90–1·05] for the behavioural website group). Compared with usual care, participants in all intervention groups had fewer moderately bad symptoms (table 3). The CACE analysis for the use of nasal sprays at the first sign of infections on the primary outcome (appendix p 22) suggested a larger effect on duration of illness with better adherence in both spray groups (IRR 0·78 [95% CI 0·70–0·86] for the gel-based group; 0·75 [0·68–0·83] for the saline spray group). Compared with usual care, a larger proportion of participants in the spray groups had symptoms for 7 days or less (2052 [68·6%] of 2983 participants in the usual care group; 2156 [73·5%] of 2935 participants in the gel-based spray group; 2179 [73·4%] of 2967 participants in the saline spray group; 1981 [72·6%] of 2727 participants in the behavioural website group) and fewer had prolonged illness of 15 days or more (462 [15·5%] of 2983 participants in the usual care group; 345 [11·8%] of 2935 participants in the gel-based spray group; 342 [11·5%] of 2967 participants in the saline spray group; 392 [14·4%] of 2727 participants in the behavioural website group; appendix p 7). The inferences for the primary outcome were not altered when assuming all missing data were in either the 5th percentile or 95th percentile of days of illness in each group (appendix p 20).

At 6 months, 1637 (54·7%) of 2994 individuals in the usual care group had reported an illness, with fewer individuals reporting an illness in the behavioural website group (1424 [52·3%] of 2729 participants; adjusted RR 0·95 [95% CI 0·91–0·99]). Compared with usual care, no significant differences were identified in the number of participants reporting illness in the gel-based spray group (1591 [54·1%] of 2939 participants; adjusted RR 0·98 [0·94–1·03]) or the saline spray group (1615 [54·4%] of 2969 participants; 0·98 [0·94–1·02]; table 4). These findings were robust to multiple imputation of the data (appendix p 7). The number of illnesses was slightly lower in all intervention groups when compared with usual care (IRR 0·94 [95% CI 0·89–1·01] for the gel-based spray group; 0·96 [0·90–1·02] for the saline spray group; 0·93 [0·87–1·00] for the behavioural website group; appendix p 7).

Despite concern regarding possible local upper respiratory irritation with the use of nasal sprays, the number of days with moderately bad symptoms was lower in all intervention groups (IRR 0·82 [95% CI 0·73 to 0·91] for the gel-based spray group; 0·82 [0·74 to 0·92] for the saline spray group; 0·89 [0·80 to 0·99] for the behavioural website group), as was the number of courses of antibiotics (0·65 [0·50 to 0·84] for the gel-based spray group; 0·69 [0·54 to 0·88] for the saline spray group; 0·74 [0·57 to 0·94] for the behavioural website group; table 5). Additionally, the number of lost workdays or lost days of normal activity was lower in the spray groups than the usual care group (0·81 [0·67 to 0·98] for the gel-based spray group; 0·72 [0·59 to 0·87] for the saline spray group). At 6 months, participants in all groups had low scores for anxiety and depression, with no differences identified between intervention groups and the usual care group. In both spray groups, there was less belief in the effectiveness of antibiotics compared with the usual care group (OR 0·90 [95% CI 0·82 to 0·99] in the gel-based spray group; 0·89 [0·81 to 0·99] in the saline spray group) and lower intention to consult a doctor with a future respiratory infection compared with the usual care group (mean between-group difference –0·10 [95% CI –0·18 to –0·02] in the gel-based spray group; –0·11 [–0·19 to –0·03] in the saline spray group; appendix p 22).

12 267 (88·9%) of 13 799 participants accessed the webpages for their allocated intervention and 8967 (86·7%) of 10 348 participants in the active intervention groups completed the key rationales sections (2987 [86·6%] of 3448 participants in the gel-based spray group; 3030 [87·8%] of 3450 participants in the saline spray group; 2950 [85·5%] of 3450 participants in the behavioural website group; appendix p 1). 2670 (77·4%) of 3450 participants in the behavioural website group accessed Getting Active (supporting physical activity), and 1755 (50·9%) accessed Healthy Paths (supporting stress reduction). Most participants used nasal sprays early in an illness (1440 [58·3%] of 2471 participants in the gel-based spray group; 1512 [60·0%] of 2520 participants in the saline spray group), but use was lower after close contact with infected individuals (630 [25·6%] of 2460 participants in the gel-based spray group; 681 [27·2%] of 2502 participants in the saline spray group). 910 (26·4%) of 3448 participants in the gel-based group and 929 (26·9%) of

	Usual care (n=3451)	Gel-based spray (n=3448)	Saline spray (n=3450)	Behavioural website (n=3450)
Number of days of illness due to self-reported respiratory tract illness in previous 6 months				
n	1626	1587	1613	1422
Median (IQR)	10 (5–16)	7 (4–14)	7 (5–14)	8 (5–15)
Mean (SD)	15·1 (19·2)	12·0 (15·3)	11·8 (14·9)	14·2 (17·9)
Number of days of illness among all participants in previous 6 months				
n	2983	2935	2967	2727
Missing, n (%)	468 (13·6%)	513 (14·9%)	483 (14·0%)	723 (21·0%)
Median (IQR)	3 (0–10)	3 (0–8)	3 (0–8)	2 (0–9)
Mean (SD)	8·2 (16·1)	6·5 (12·8)	6·4 (12·4)	7·4 (14·7)
Adjusted IRR*† (99% CI); p value	1 (ref)	0·82 (0·76–0·90); p<0·0001	0·81 (0·74–0·88); p<0·0001	0·97 (0·89–1·06); p=0·46

IRR=incidence rate ratio. *Adjusted for baseline number of days of respiratory tract infection symptoms and stratum. †Complete cases analysis; IRR for intervention vs usual care.

Table 2: **Primary outcome (total days of illness in previous 6 months)**

	Usual care (N=3451)	Gel-based spray (N=3448)	Saline spray (N=3450)	Behavioural website (N=3450)
Days with moderately bad symptoms				
Participants with data available, n	2986	2934	2964	2725
Median (IQR)	0 (0–3)	0 (0–3)	0 (0–3)	0 (0–3)
Mean (SD)	3·0 (7·9)	2·4 (7·0)	2·3 (5·8)	2·6 (6·6)
Adjusted effect estimate* (95% CI); p value	1 (ref)	IRR 0·82 (0·73 to 0·91); p<0·0001	IRR 0·82 (0·74 to 0·92); p<0·0001	IRR 0·89 (0·80 to 0·99); p=0·04
Days of work lost				
Participants with data available, n	2736	2716	2759	2470
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Mean (SD)	1·6 (6·6)	1·2 (4·5)	1·0 (3·3)	1·2 (4·5)
Adjusted effect estimate* (95% CI); p value	1 (ref)	IRR 0·81 (0·67 to 0·98); p=0·03	IRR 0·72 (0·59 to 0·87); p=0·001	IRR 0·87 (0·72 to 1·06); p=0·17
Number of times saw doctor				
Participants with data available, n	2951	2902	2926	2684
Mean (SD)	0·23 (0·81)	0·17 (0·69)	0·18 (0·79)	0·23 (0·98)
Adjusted effect estimate* (95% CI); p value	1 (ref)	IRR 0·80 (0·63 to 1·01); p=0·06	IRR 0·87 (0·69 to 1·10); p=0·24	IRR 1·09 (0·87 to 1·37); p=0·46
Number of courses of antibiotics				
Participants with data available, n	2747	2716	2756	2470
Mean (SD)	0·17 (0·68)	0·12 (0·57)	0·12 (0·52)	0·14 (0·52)
Adjusted effect estimate* (95% CI); p value	1 (ref)	IRR 0·65 (0·50 to 0·84); p=0·001	IRR 0·69 (0·54 to 0·88); p=0·003	IRR 0·74 (0·57 to 0·94); p=0·02
Hospital admission, n/N (%)	22/2537 (0·9%)	17/2499 (0·7%)	17/2519 (0·7%)	21/2360 (0·9%)
Adjusted effect estimate* (95% CI); p value	1 (ref)	RR 0·77 (0·41 to 1·44); p=0·41	RR 0·77 (0·41 to 1·45); p=0·42	RR 1·03 (0·57 to 1·87); p=0·92
COVID-19, n/N (%)	575/2605 (22·1%)	522/2554 (20·4%)	553/2601 (21·3%)	499/2282 (21·9%)
Adjusted effect estimate* (95% CI); p value	1 (ref)	RR 0·92 (0·83 to 1·02); p=0·14	RR 0·97 (0·88 to 1·08); p=0·58	RR 1·01 (0·91 to 1·12); p=0·85
Perceived Stress Scale†				
Participants with data available, n	2353	2306	2349	2051
Mean (SD)	19·7 (8·8)	19·5 (8·7)	19·6 (8·6)	19·4 (9·1)
Adjusted effect estimate* (95% CI); p value	1 (ref)	Mean difference 0·16 (–0·52 to 0·20); p=0·39	Mean difference 0·02 (–0·38 to 0·33); p=0·90	Mean difference 0·01 (–0·35 to 0·38); p=0·95
PHQ-8 score‡				
Participants with data available, n	2427	2340	2421	2110
Mean (SD)	4·1 (4·6)	3·8 (4·3)	3·9 (4·4)	3·9 (4·5)
Adjusted effect estimate* (95% CI); p value	1 (ref)	Mean difference 0·01 (–0·07 to 0·04); p=0·58	Mean difference 0·02 (–0·04 to 0·07); p=0·56	Mean difference 0·00 (–0·05 to 0·05); p=0·94
GAD-7 score§				
Participants with data available, n	2414	2377	2417	2128
Mean (SD)	3·4 (4·2)	3·2 (4·1)	3·3 (4·1)	3·1 (4·0)
Adjusted effect estimate* (95% CI); p value	1 (ref)	Mean difference 0·14 (–0·31 to 0·03); p=0·11	Mean difference 0·08 (–0·25 to 0·09); p=0·37	Mean difference 0·14 (–0·32 to 0·03); p=0·11

IRR=incidence rate ratio. RR=risk ratio. PHQ-8=Patient Heath Questionnaire-8. GAD-7=Generalised Anxiety Disorder-7. *Adjusted for baseline outcome and stratum. †The Perceived Stress Scale is scored on a scale of 0–56: scores of 0–18 indicate low stress, 19–37 indicate moderate stress, and 38–56 indicate high stress. ‡The PHQ-8 score measures depression on a scale of 0–24, with a score of 10 or higher indicating major depression. §The GAD-7 score measures anxiety on a scale of 0–21, with a score of 10 or higher indicating generalised anxiety disorder.

Table 3: **Secondary outcomes**

3450 participants in the saline spray group requested additional supplies.

Analyses were performed to document the impact of the interventions in key subgroups (appendix pp 8–12, 17–19, 21). There was some evidence that participants who had risk factors and recurrence gained more preventive effects from the behavioural website (appendix p 8); sprays worked better by season 3 (appendix p 9); the behavioural website had less of an effect on participants who were not vaccinated for COVID-19 (appendix p 10); and gel-based spray was a little more effective among those with no comorbidities, and more effective among ethnic

	Usual care (N=3451)		Gel-based spray (N=3448)		Saline spray (N=3450)		Behavioural website (N=3450)	
	n/N (%)	Adjusted RR†	n/N (%)	Adjusted RR*† (95% CI); p value	n/N (%)	Adjusted RR*† (95% CI); p value	n/N (%)	Adjusted RR*† (95% CI); p value
Reported respiratory tract infection	1637/2994 (54·7%)	1 (ref)	1591/2939 (54·1%)	0·98 (0·94–1·03); p=0·46	1615/2969 (54·4%)	0·98 (0·94–1·02); p=0·31	1424/2729 (52·3%)	0·95 (0·91–0·99); p=0·02
Missing	457 (13·2%)	..	509 (14·8%)	..	481 (13·9%)	..	721 (20·9%)	..

RR=risk ratio. *Complete cases analysis; risk ratio for intervention *vs* usual care. †Adjusted for baseline number of days of respiratory tract infection symptoms and stratum.

Table 4: **Occurrence of illness in previous 6 months among participants with available data**

	Usual care (N=3451)		Gel-based spray (N=3448)		Saline spray (N=3450)		Behavioural website (N=3450)	
	n (%)	Risk difference	n (%)	Risk difference (95% CI)	n (%)	Risk difference (95% CI)	n (%)	Risk difference (95% CI)
Deaths	5 (0·14%)	1 (ref)	1 (0·03%)	−0·0012 (−0·0031 to 0·0040)	11 (0·32%)	0·0017 (−0·007 to 0·0044)	4 (0·1%)	−0·0003 (−0·0024 to 0·0017)
Other serious adverse events	12 (0·35%)	1 (ref)	7 (0·2%)	−0·0014 (−0·0042 to 0·0012)	13 (0·38%)	0·0003 (−0·0027 to 0·0033)	9 (0·3%)	−0·0012 (−0·0041 to 0·0017)
Serious adverse device effects	0 (0·0%)	1 (ref)	0	0 (−0·0011 to 0·00011)	0 (0·0%)	0 (−0·0011 to 0·0011)	2 (0·1%)*	0·0006 (−0·0006 to 0·0021)
Adverse events	5 (0·14%)	1 (ref)	6 (0·2%)	0·0003 (−0·0019 to 0·0025)	5 (0·14%)	0·0000 (−0·0021 to 0·0021)	8 (0·2%)	0·0009 (−0·0014 to 0·0033)
Adverse device effects	0 (0·0%)	1 (ref)	30 (0·9%)†	0·0087 (0·0059 to 0·0124)	15 (0·43%)	0·0043 (0·0023 to 0·0072)	1 (0·03%)‡	0·0003 (−0·0008 to 0·0016)

*Broken hip falling off bike when exercising (n=1) and fractured radius (n=1) of unknown cause. †Headache or facial pain (n=6); rash, urticaria, or dermatitis (n=6); worsening of respiratory tract infection symptoms (n=5); sinusitis, conjunctivitis, or mouth symptoms (n=5); dizziness, fainting, or palpitations (n=5). ‡Back injury prevented participant from exercising.

Table 5: **Adverse events**

minorities (appendix p 12); all interactions were statistically significant, but caution is needed in interpreting these findings since these were secondary analyses. No differential effect of educational status was observed (appendix pp 12, 17–19). Post-hoc analysis suggested that the behavioural website might have had less effect in smokers than non-smokers (appendix p 21).

Of those with data available, the only common side-effect was headache in the gel-based group: 123 (4·8%) of 2556 participants in the usual care group; 199 (7·8%) of 2498 participants in the gel-based group (RR 1·61 [95% CI 1·30–1·99]; p<0·0001); 101 (4·5%) of 2377 participants in the saline group (0·81 [0·63–1·05]; p=0·11); and 101 (4·5%) of 2091 participants in the behavioural intervention group (0·95 [0·74–1·22]; p=0·69). Compared with the usual care group, nasal dryness and irritation were less common among participants in the saline spray and behavioural website groups, and falls were less common among participants in the two spray groups. Adverse device effects reported by patients were uncommon, but were more common in the spray groups (30 [0·87%] of 3448 participants in the gel-based spray group; 15 [0·43%] of 3450 participants in the saline spray group; table 5) than the usual care and behavioural website groups.

Discussion

This is the largest study to explore the benefit of accessible, easily scalable interventions used preventatively or early in respiratory illness in primary care settings. Compared with usual care, both nasal sprays when used at the first sign of a respiratory tract infection had a clinically significant effect on illness duration and reduced number of workdays lost, and all three interventions reduced antibiotic use. The only intervention to reduce illness incidence was the behavioural website: although the impact was modest, no support is required for this intervention, which could be potentially important at the population level.

The study was an open-label trial, and it would be difficult to devise a meaningful placebo since the delivery mechanism (spraying) is an inherent part of the intervention. However, the nasal sprays were relabelled (to retain some form of masking). Furthermore, for some conditions, there are large placebo effects, but for acute respiratory infections even where belief in medication efficacy is high, the estimates from open-label trials (eg, for sore throat,[36] acute bronchitis,[37] and otitis[48]) suggest no or minimal placebo effect compared with estimates from placebo-controlled trials in the Cochrane reviews,[38,49–51] with similar evidence for trials of medicines in COVID-19.[52,53] Furthermore, the significant impact of all three interventions on antibiotic use, workdays lost, and the differential impact on outcomes for the website and the sprays suggests non-specific placebo effects are unlikely to explain the results.

We could only analyse data for participants who had available data for the primary outcome, but we were able to use imputation for secondary outcomes and results were robust to missing data assumptions. For secondary

outcomes, no allowances were made for multiplicity, but the number and consistent pattern of significant secondary outcomes across intervention groups indicate that chance is an unlikely explanation for our findings. The outcomes were self-reported, but self-report and medical history and examination agree reasonably for acute respiratory illness,[54] for symptoms and symptom severity there is no alternative to self-report, and self-reported symptoms are reliable and sensitive to change.[36,55] Self-report of infection incidence and severity after several months has been shown to be reliable compared with monthly reports,[14] which was also observed in the current study. For the secondary outcome of antibiotic use, self-reported antibiotic use rather than antibiotic prescription is more important since it is use that drives antibiotic resistance and many patients do not use all of their prescribed medication.[56] Similarly, self-report is essential to document the effect of illness on work and activities.

Infectious agents in this study were not confirmed, but the management of illness in primary care is syndromic and, when such syndromes are investigated, the majority have a viral cause, with a minority having a bacterial cause.[57,58]

The data suggest that the results are likely to be generalisable: so-called cold-calling invitations result in similar uptake rates, but the intervention from the PRIMIT trial (which used similar invitation methods[14]), when used outside the trial, demonstrated changes in behavioural intentions similar to those found in the trial;[59] few individuals declined due to lack of internet access (175 [7%] of 2526 people), and although our sample included a smaller proportion of participants from minority ethnic groups than the general UK population (3·2% *vs* 6·4% 2021 census data for this age group), and slightly more with higher than A-level qualifications (50% *vs* 40% census data), no significant differences in effectiveness were identified with regard to minority ethnic status or educational level. In response to COVID-19, in season 1, we included participants aged 65 years and older, who were considered to be at higher risk of infection. From season 2 onwards, at least one report of respiratory tract infection in a normal year (ie, before COVID-19) was an inclusion criterion, and in season 3 (a more normal year), we focused particularly on the smallest strata: people with comorbidities or risk factors. The slightly larger effect estimates observed in season 3 suggest that the likely impact of the interventions outside a pandemic context might be underestimated. One possible route for inclusion could have been psychological and social risk factors, but in pragmatic terms it was easier to use standard biomedical risk factors that are available on GP systems. The novel methodology of recruitment via the internet and central distribution and supply of the sprays was efficient and convenient for participants, reducing barriers to participation by taking the research to the patient.

The complex interventions were developed robustly using the person-based approach.[14,27,60] All interventions are readily scalable, which increases the possibility of an important national impact. Both sprays are available over the counter in many pharmacies, and the behavioural website requires no additional support.

A previous trial of a buffered-pH antiviral nasal spray compared with saline (n=441) found that illness duration among participants in the antiviral spray group with a naturally acquired cold was almost 3 days shorter than amng participants who used saline spray when used early in the illness (mean illness duration 5·3 days for gel-based spray *vs* 7·8 days for saline spray[15,61]). The current trial was more pragmatic and attempted to engage participants over several months and multiple illnesses. We have not been able to confirm the superiority of gel-based spray compared with saline spray. In our study, both sprays had almost identical impact: for participants who had an respiratory tract infection, duration of illness was 3 days shorter with spray than with usual care (IRR 0·8), and the number of individuals with prolonged illness, work absences, and antibiotic use was reduced, which previous trials were underpowered to detect. The reduction in antibiotic use and workdays lost was small in terms of absolute benefit, but considering these are interventions that could be implemented at a population level, this could have a large effect for the population. Considering the brief nature of the interventions in the current study, adherence was reasonable, but better adherence would be expected to have a larger impact, as indicated by the CACE analysis. Engaging spray behaviours to prevent illness proved more difficult, with only 25% of individuals using the sprays when having been in close proximity to someone with illness. Further research is needed to explore better engagement of patients in the use of sprays in prevention. The fact that advice to use a saline spray is as effective as advice to use a gel-based spray suggests that most of the impact in reducing illness duration documented in the current study was due to washing out the nasopharynx, thus reducing viral load.[13]

To our knowledge, this is the only trial that has robustly developed a website to provide a pragmatic, scalable behavioural intervention to address both the encouragement of physical activity and the management of stress or distress for the prevention and the management of illness.[35,62] A Cochrane review suggested that physical activity had significant effects on the severity of acute respiratory infection symptoms and the number of symptom days during follow-up,[17] but the review had important limitations, and all trials involved more intensive interventions than that included in the current study. The behavioural intervention included in our study used a much briefer, unsupervised digital approach. Although a significant reduction in the duration of symptoms overall was not observed with the behavioural website intervention, the duration of symptoms rated

moderately bad or worse was reduced, as was the incidence of illness and antibiotic use. The biggest effect was observed among participants with recurrent illness and risk factors for illness. Further research could investigate both dose-dependency and mechanism of action for both the nasal sprays and the behavioural interventions.

Advice to use nasal sprays at the first sign of an respiratory tract infection had an important effect on illness duration and reduced the number of workdays lost. Advice to use a physical activity and stress management website resulted in a modest reduction in the incidence of illness, and all interventions reduced antibiotic use when compared with usual care. If widely advocated and implemented, these simple scalable interventions could potentially have an important impact on antimicrobial stewardship, and in reducing the impact of respiratory viruses for patients, the health service, and the wider economy.

Contributors

LY, AWAG, and PL conceptualised the study. PL, AWAG, LY, KB, CCB, SRH, JR, MM, NF, TV, BS, and ADH developed the ideas further and developed the grant application. All authors contributed to the development of the protocol, revisions of the protocol, and study procedures or study documentation. The development of the interventions was overseen by AWAG; LY led the development of the nasal spray online support, AWAG led the development of the behavioural website with KG, LD, SH, KB, JDD, and BA, contributing to both aspects, with important input from SRH, DS, HP, and PL. All authors were involved in supervision of the study at regular study management meetings, but supervision was coordinated on a day-to-day basis by JV and KR, with input from JB, TT, KM, SJ, SM, and SW. JV, KR, TB, and BS had access to the raw data, and TB and BS verified the data. TB and BS did the statistical analysis. All authors contributed to interpretation of the results. PL wrote the first draft of the paper and all authors contributed to subsequent revisions of the paper and have approved the final text. The decision to submit the manuscript was made by PL and AWAG with support from all authors.

Declaration of interests

We declare no competing interests.

Data sharing

Data are available on request from AWAG or PL, with a proposal for further analysis.

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