

# *British Journal of General Practice*

## 12 month follow-up of a randomised open label trial of nasal sprays and a behavioural intervention for respiratory tract infections (RTIs) in primary care

Paul; Vennik, Jane; Rumsby, Kate; Stuart, Beth; Becque, Taeko;  
Moore, Michael; Francis, Nick; Hay, Alastair; Verheij, Theo;  
Bradbury, Katherine; Greenwell, Kate; Dennison, Laura; Holt, Sian;  
Denison-Day, James; Ainsworth, Ben; Raftery, James; Thomas, Tammy;  
Butler, Christopher; Richards-Hall, Samantha; Smith, Debs; Patel, Hazel;  
Williams, Samantha ; Barnett, Jane; Middleton, Karen; Miller, Sascha;  
Johnson, Sophie; Nuttall, Jacqui; Webley, Fran; Sach, Tracey; Yardley, Lucy;  
Geraghty, Adam

DOI: <https://doi.org/10.3399/BJGP.2025.0269>

To access the most recent version of this article, please click the DOI URL in the line above.

Received 01 May 2025

Revised 15 September 2025

Accepted 03 October 2025

© 2025 The Author(s). This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by/4.0/>). Published by British Journal of General Practice. For editorial process and policies, see: <https://bjgp.org/authors/bjgp-editorial-process-and-policies>

When citing this article please include the DOI provided above.

### **Author Accepted Manuscript**

This is an 'author accepted manuscript': a manuscript that has been accepted for publication in British Journal of General Practice, but which has not yet undergone subediting, typesetting, or correction. Errors discovered and corrected during this process may materially alter the content of this manuscript, and the latest published version (the Version of Record) should be used in preference to any preceding versions

**12 month follow-up of a randomised open label trial of nasal sprays and a behavioural intervention for respiratory tract infections (RTIs) in primary care**

Professor Paul Little FMedSci<sup>1</sup>, Dr Jane Vennik PhD<sup>1</sup>, Ms Kate Rumsby MSc<sup>1</sup>, Professor Beth Stuart PhD<sup>9</sup>, Dr Taeko Becque PhD<sup>1</sup>, Professor Michael Moore BMedSci<sup>1</sup>, Professor Nick Francis PhD<sup>1</sup>, Professor Alastair D Hay FRCGP<sup>4</sup>, Professor Theo Verheij PhD<sup>6</sup>, Dr Katherine Bradbury PhD<sup>3</sup>, Dr Kate Greenwell PhD<sup>3</sup>, Dr Laura Dennison PhD<sup>3</sup>, Dr Sian Holt PhD<sup>3</sup>, Dr James Denison-Day PhD PhD<sup>3</sup>, Dr Ben Ainsworth PhD<sup>3</sup>, Professor James Raftery PhD<sup>7</sup>, Ms Tammy Thomas<sup>1</sup>, Professor Christopher C. Butler FMedSci<sup>5</sup>, Mrs Samantha Richards-Hall BSc<sup>1</sup>, Ms Deb Smith<sup>1</sup>, Ms Hazel Patel<sup>1</sup>, Ms Samantha Williams MRes<sup>1</sup>, Ms Jane Barnett BSc<sup>1</sup>, Ms Karen Middleton<sup>1</sup>, Dr Sascha Miller PhD<sup>1</sup>, Ms Sophie Johnson BSc<sup>1</sup>, Dr Jacqui Nuttall PhD<sup>8</sup>, Ms Fran Webley BSc<sup>8</sup>, Professor Tracey Sach PhD<sup>1</sup>, Professor Lucy Yardley PhD<sup>2,3</sup>, Dr Adam W A Geraghty PhD<sup>1</sup>.

<sup>1</sup>Primary Care Research Centre, University of Southampton, Southampton, UK,

<sup>2</sup>School of Psychological Science, University of Bristol, Bristol, UK

<sup>3</sup>School of Psychology, University of Southampton, Southampton, UK,

<sup>4</sup>Centre for Academic Primary Care, Bristol Medical School: Population Health Sciences, University of Bristol

<sup>5</sup>Nuffield Department of Primary Care Health Sciences, University of Oxford

<sup>6</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Netherlands.

<sup>7</sup>Health Economics Analysis Team, University of Southampton, Southampton, UK.

<sup>8</sup>Southampton Clinical Trials Unit Southampton University

<sup>9</sup> Wolfson Institute of Population Health, Faculty of Medicine and Dentistry, Queen Mary University, London

Correspondence to Professor Little [p.little@soton.ac.uk](mailto:p.little@soton.ac.uk) Tel +44 2380 241050;

University of Southampton Aldermoor Health Centre, Aldermoor close, Southampton UK

SO16 5ST

Word count 2957

**Funding:** This study is funded by the NIHR Programme Grants for Applied Research (RP-PG-0218-20005). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. LY and ADH are NIHR Senior Investigator and LY's research programme is partly supported by NIHR Applied Research Collaboration (ARC)-West and NIHR Health Protection Research Unit (HPRU) for Behavioural Science and Evaluation.

**Competing interests:** The authors have declared no competing interests

**Data availability:** Data is available on request from AG or PL with a proposal for further analysis

## **Abstract (250/250)**

**Background.** The Immune defence trial documented short term impacts on RTIs for nasal sprays, and a stress-management and physical activity website.

**Aim:** To estimate the impact of sprays and the website after 12 months.

**Design:** Four arm parallel randomised controlled trial

**Setting.** Participants with co-morbidities and/or  $\geq 3$  self-reported recurrent illnesses recruited by mailed invitation.

**Methods** Participants were randomised by online software (stratified by recurrent illness and comorbidities) to i) usual care (n=3451) ii) Vick's First-Defence (VFD) spray (n=3448) (2 sprays/nostril,  $\leq 6$ x/day) iii) isotonic saline spray (n=3450) (same dosing) or iv) a website promoting physical activity and stress-management (n=3450).

**Primary outcome:** respiratory illness days.

**Findings.** Usual care participants (n=3051) had on average 22 illness days, reduced by VFD ((n=3076; 18 days, adjusted incidence rate ratio (IRR) 0.84, 99% CIs 0.79,0.90;  $p < 0.0001$ ), and saline (n=3142; 18 days, IRR 0.83; 0.78,0.89;  $p < 0.0001$ ), but not the website (n=2811; 20 days, IRR 0.94;0.88,1.01,  $p = 0.03$ )). The website reduced incident infections (0.96,0.93 to 0.99,  $p = 0.006$ ). All interventions reduced symptom severity and work-days lost, both spray groups reported lower intention to consult and fewer falls, and there were fewer antibiotic courses and practice visits with saline. Among those with recurrent illness saline had the most impact on both recurrence and symptom days (respectively 0.93 (0.87,0.99), 0.70 (0.60,0.82)). Headache were higher for VFD and lower for saline (7.8%, 3.4% respectively; 4.7% usual care).

**Conclusion.** Widely available, inexpensive sprays and a website promoting self-care reduce the incidence, duration and/ or severity of RTIs and impact work-days lost and healthcare use.

**Prospective registration:** ISRCTN (17936080; 30/10/2020)

### Panel: How this fits in Research in context

- Limited prior evidence suggested that anti-viral nasal sprays, or supporting physical activity and stress-management, could lessen the impact of respiratory tract infections (RTIs) which drive the regular winter health crises.
- This evidence was supported by the short term (6 month) results of the Immune Defence trial - of a 'free-standing' website supporting physical activity and stress management, Vicks First Defence (VFD) nasal spray and a nasal saline spray, but longer term impacts are unknown.
- After 12 months, the website reduced incident infections by 4%. Both sprays resulted in 4 fewer illness days, fewer falls and reported lower intention to consult. All interventions reduced symptom severity and work days lost. The saline group reported fewer practice visits, and was most effective for those suffering recurrent illnesses.
- There are range of important longer term impacts on RTIs for widely available, well tolerated, and inexpensive nasal sprays and a website supporting physical activity and stress management

### Summary

- Widely available nasal sprays reduce RTI duration. An exercise/stress-management website reduces RTI incidence, and all interventions reduce illness severity and work days lost.

## Introduction

Respiratory tract infections (RTIs) are one of the commonest reasons to attend primary care annually, and most attending GPs still get antibiotics<sup>1,2</sup> which drives antibiotic resistance<sup>3</sup>. Effective non-prescription interventions are needed to improve self management of RTIs and limit the impact of the regular winter crises for the health service.

Some prior evidence suggested that sprays that used lower pH and a polymer<sup>4-8</sup> could potentially reduce the viral load, and hence reduce the number and severity of illnesses<sup>9,10,7</sup><sup>11</sup>. A systematic review of carrageenan sprays found impact on symptom severity and possibly illness duration<sup>12</sup>. There was also some evidence that saline alone might be effective<sup>11</sup>; this was supported by observational evidence, evidence from a trial in children, and more recently both in vitro work (documenting the antiviral properties of saline) and a pilot study<sup>13-15</sup><sup>16</sup>.

Prior evidence also suggested an impact on symptom days with exercise and/or management of stress<sup>17,18-21,22-26</sup>, but with relatively intensive interventions. Based on the accessibility and efficiencies of digital platforms, we developed a brief behavioural intervention (hosted on the 'Immune Defence' study website) based on modules of prior studies, and requiring no support, aiming to both a) increase physical activity<sup>27,28,29-31</sup> ('Getting Active') b) and improve stress<sup>32</sup>. We also developed modules to support using nasal sprays.

The primary analysis of the Immune Defence trial (n=13799) at 6 months demonstrated that the behavioural website reduced infection incidence (a relative reduction of 5%), and that both Vick Frist Defence nasal sprays and an isotonic saline spray reduced days of illness (a relative reduction of 20%). The longer term impact of the interventions is unknown, hence we report here the 12 month follow-up data from the trial.

## Methods

Full details of the study methods are available in the 6 month published data<sup>33</sup>.

### Design summary.

**Invitation.** Participants were invited from GP practices, starting December 2020-2021, for three seasons. Automated searches were used to identify potentially eligible patients<sup>33</sup>.

**Inclusion criteria:**  $\geq 18$  years old; one or more co-morbidity/risk factor, and (e.g. heart disease; asthma/lung disease; diabetes) and/or  $>3$  RTIs in a normal year<sup>33</sup>.

**Exclusion criteria.** Terminal illness or palliative care, residential care, dementia; pregnancy or breast-feeding; regularly using nasal sprays to prevent infections; no internet access<sup>33</sup>.

**Automated Randomisation.** the Immune Defence website software (designed by the Global Initiative company) randomised participants to the 4 trial groups, stratified by a) being in a higher risk group (over 65 and/or having comorbid condition) and/or b) recurrent illness: having had  $\geq 3$  RTIs in the last year<sup>33</sup>.

### Intervention groups<sup>33</sup>

- 1) **Usual care:** brief advice for illness management based on current NHS advice
- 2) **Vicks First-Defence nasal spray** (which contains a polymer and buffers pH).
- 3) **Isotonic buffered saline (Sterinase) nasal spray<sup>11</sup>.**

In both spray groups participants were asked to use the spray:

- i) **At first signs of an illness:** 2 sprays in each nostril up to 6 times daily until symptom-free.
- ii) **After potential exposure to infection** (e.g. supermarkets, public transport): 2 sprays immediately after exposure in each nostril, an hour later and at the end of the evening.
- iii) **After prolonged exposure** (e.g. living with a person who has an infection): up to 6 times daily until recovery of the close contact.

Both sprays were classed as medical devices. To reduce possible intervention contamination, both the nasal sprays were masked by over-labelling with generic study

labels (Vicks: 'Gel-based nasal spray'; Saline: 'Liquid-based nasal spray'). Sprays were resupplied upon request.

Participants were given online motivational information (brief content on the impact of RTIs and how nasal sprays can prevent RTIs) and instructions, supported by paper booklets, developed iteratively using the Person Based Approach<sup>34 35</sup>.

#### 4) **Behavioural website promoting physical activity and stress management**

This was also developed using the Person Based Approach<sup>34</sup>. Participants had access to information on the impact of RTIs, how physical activity and/or stress management could prevent RTIs, and then two online modules supporting physical activity and stress reduction. Participants were also sent optional pedometers, to help personally monitor activity.

**Outcomes.** Unless specified these were measured using a repeated questionnaire, every 28 days for 12 months, and also at 6 and 12 months to recall infections since the start of the trial.

**Primary outcome.** Days of illness from self reported respiratory tract infections (coughs, colds, sore throat, sinus or ear infections, flu and including COVID19). People can remember the incidence and duration of illness over a few months<sup>10 36 37</sup>, and in the previous PRIMIT trial<sup>10</sup> and in the primary analysis of the Immune Defence trial<sup>33</sup> estimates from self-report after several months were very similar to estimates from monthly reports.

- **Secondary outcomes:** incidence of illness (in both contemporaneous monthly questionnaires and retrospectively at 6 months)<sup>10</sup>; possible harms; days with symptoms moderately bad or worse<sup>37 38</sup>; days where work/normal activities were impaired; use of antibiotics<sup>36</sup>; health service contacts<sup>38</sup>; number of days of respiratory illness over 12 months<sup>10</sup>; at 6 and 12 months: belief in antibiotics, intention to consult for future episodes; mental health (using the Perceived Stress Scale<sup>39</sup>, PHQ-8<sup>40</sup> and GAD-7<sup>41</sup>).

#### **Other secondary outcomes to be reported subsequently:**

- NHS contacts through participant self-report and retrospective notes review.
- Health-related quality of life elicited using the EQ-5D-5L
- engagement with the trial interventions, evaluated through participant self-report, and usage data from the trial website

#### **Data collection.**

Unless specified, data was collected using the trial website designed by Global Initiative blind to group, with up to two email reminders, then a mailed questionnaire, and finally a telephone call as necessary by blinded members of the study team for non-completers of the primary outcome. Data from paper questionnaires and telephone interviews were entered into a secure Access database by the trial team.

**Sample size calculations based on data of the incidence of illness (blind to group) from the first two seasons (2020/21; 2021/22):**

- 1) Stratum 1 (recurrence, no risk factors): 71% (not 15%) had an illness. Using the lower limit of the 95% confidence interval of this estimate we assumed at least 65% would get an illness. Based on the original 147 per group (i.e changing no other assumptions), we estimated 226 per group were needed, and 1130 total (with 80% follow-up).
- 2) Stratum 2 (risk factors, no recurrence): 40% had illness (not 15%), requiring  $147/0.4=368$  per group 1472 in total.
- 3) Stratum 3 (risk factors plus recurrence): 62% had illness, requiring 245 per group, and 1225 in total.

**Data analysis**

A detailed statistical analysis plan (SAP) was finalised prior to data analysis and data lock, and superseded the brief protocol description. Count outcomes, including the number of days of illness, were analysed using zero-inflated negative binomial regression models given the large number of zeros due to no illness. Logistic regression was used for dichotomous outcomes and linear regression for continuous outcomes. Skewed outcomes were either transformed before linear regression or analysed using Poisson regression with robust standard errors. All models adjusted for baseline days of illness and stratification variables. Multiple imputation with chained equations was used for the incidence of illness, using 100 imputations<sup>42</sup>. The imputation model included all variables in the analysis model (i.e., outcome, baseline days, strata) and variables which predicted missingness (age, sex, IMD decile, baseline belief in antibiotics and baseline intention to consult). For the primary outcome, we assumed the data were missing completely at random (MCAR), but sensitivity analyses to MNAR<sup>43</sup> were given where missing data were imputed as either 0 or 30 days.

**Patient and Public involvement.** Three public contributors helped develop the protocol and all materials (e.g. patient information, topic guides), contributed to management regarding development/operationalising the study, and with outputs (e.g. lay summaries, publications).

**Role of funder.** The funder, NIHR, had no role in data collection, analysis, interpretation, writing of the manuscript nor the decision to submit.

**Ethical approval.** This study was approved by the South East Scotland Research Ethics Committee 01 (20/SS/0102) on 23<sup>rd</sup> October 2020 and the HRA on 29<sup>th</sup> October 2020.

Accepted Manuscript—BJGP—BJGP.2025.0269

## Results

### Recruitment and follow-up

13,799 participants were recruited in three winter seasons (September-April) from 12/12/2020 to 7/4/2023 (see Figure 1). Groups were well balanced (see Table 1), and follow-up was good based on monthly data (usual care 3051/3449 (88.5%); Vicks 3076/3447 (89.2%); Saline 3142/3449 (91.1%); behavioural website 2811/3445 (81.6%)). The monthly reports of days of illness were spread throughout the 12 month period.

10 participants asked for their data to be removed, and 679 withdrew but allowed data use, leaving 13,789 participants: stratum 1 (*recurrence, no risk factors*) n=1,217 (9%); stratum 2 (*risk factors, no recurrence*) n=8,652 (63%); stratum 3 (*risk factors plus recurrence*) n=3,920 (28%).

Reasons for withdrawal provided were: unable to engage with intervention (n=116; Behavioural website n=53 (46%), VFD=27 (23%), Saline n=27 (23%), Usual care=9 (8%)); too unwell/change in medical condition (n= 109); trial processes/too busy (n=107); personal circumstances (n=45); deceased (n=42); study not relevant/does not get RTIs (n=28); other (n=14); pregnancy/breastfeeding (n=3); no reason given (215)).

### Days with illness (Table 2)

Asking about infections since the beginning of the trial (12 months) was apparently interpreted by some participants for the last 6 months (probably because they were asked about infections for the first 6 months, and assumed the same time period applied at the 12 month follow-up) - with participants reporting much lower rate of infections than was plausible (e.g. the saline group, where reported days of illness (a mean of 6 days) was lower than at the 6 month time point). We therefore used the monthly data as providing the more reliable data for the primary outcome, supported by the estimates for complete 12 month data which were very similar to those where at least 1 month was recorded were very similar. Using the latter data both sprays reduced the days with illness, with a mean of 22 days in the usual care group, 18 days in both spray groups, and 20 days in the behavioural website group (Table 2).

### Secondary outcomes.

Occurrence of infections was lower in the behavioural website group (Adjusted RR 0.96, 0.93 to 0.99), but not the spray groups (See Table 3). Moderately bad symptoms were significantly reduced in all intervention groups as were days of work lost (Table 4). Participants in the saline group, but not the other intervention groups reported significantly fewer visits to a health care professional for an

RTI (IRR 0.81 0.69 to 0.97), and fewer antibiotic courses (0.84, 0.71 to 1.00) (Table 4). Both spray groups were less likely to intend seeking care for subsequent infections, and had significantly lower scores for perceived stress and depression (PHQ-8) (Table 4). Anxiety (GAD-7 score) was significantly lower in the website group compared to the usual care group (Table 4). The results in each stratum suggest that the impact of nasal saline might be greatest (a 30% reduction in days of illness) among those with recurrent illness, whereas the behavioural website was most effective among those with comorbidities. (Table S1.)

#### **Use of sprays.**

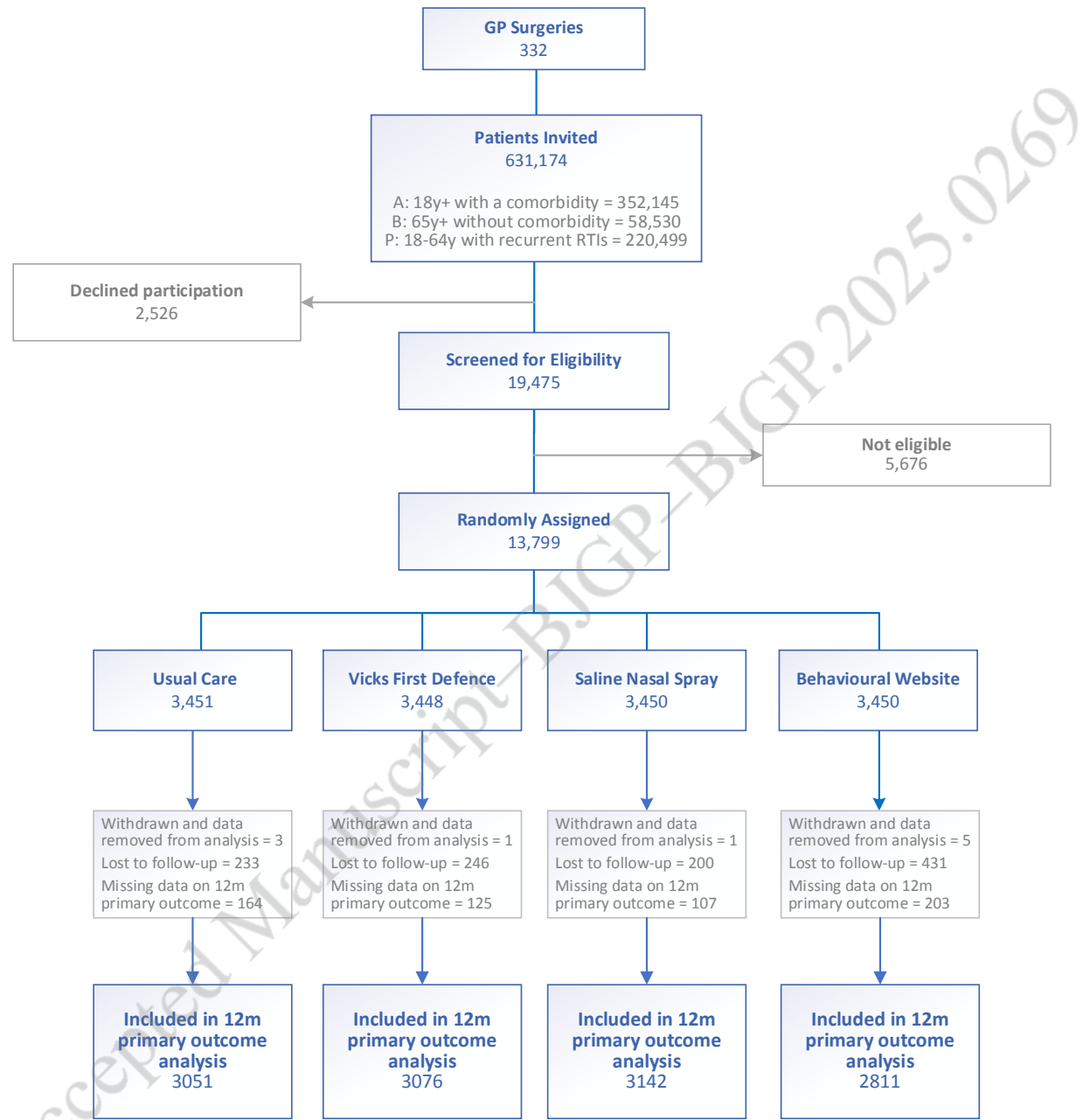
Participants were supplied with 2 bottles of nasal spray by post as soon as possible after randomisation. 1864 people requested additional sprays (Saline 937, VFD 927) during their participation. The mean number of additional bottles supplied per individual were: Saline (1.66, range 1-18, SD 1.273) and VFD (1.69, range 1-15, SD 1.346).

#### **Adverse events.**

Headache was more common with VFD and less common for saline, but both spray groups had less nasal dryness and irritation, and fewer reported falls (Table 5).

Figure 1. CONSORT diagram

IMMUNE DEFENCE STUDY:  
12-MONTH FOLLOW-UP



**Table 1. Baseline characteristics of the randomised population**

	Randomised Group			
	Usual care N=3451	Gel-based N=3448	Saline N=3450	Behavioural website N=3450
Gender, n (%)				
Male	1548 (44.9%)	1536 (44.6%)	1488 (43.2%)	1526 (44.3%)
Female	1890 (54.8%)	1900 (55.2%)	1953 (56.7%)	1904 (55.3%)
Other	5 (0.1%)	4 (0.1%)	2 (0.1%)	10 (0.3%)
Prefer not to say	3 (0.1%)	5 (0.1%)	4 (0.1%)	4 (0.1%)
Missing	5	3	3	6
Age, median (Q1-Q3)	64 (51-71)	65(50-71)	64 (50-71)	64 (51-71)
Missing	2	1	1	5
Ethnicity, n (%)				
White	3328 (97.1%)	3324 (97.0%)	3334 (97.1%)	3319 (96.8%)
Mixed	25 (0.7%)	35 (1.0%)	28 (0.8%)	38 (1.1%)
Asian	51 (1.5%)	49 (1.4%)	46 (1.3%)	54 (1.6%)
Black	16 (0.5%)	11 (0.3%)	12 (0.3%)	6 (0.2%)
Other	9 (0.3%)	9 (0.3%)	14 (0.4%)	11 (0.3%)
Missing	22	20	16	22
Marital status, n (%)				
Single	402 (11.7%)	398 (11.6%)	424 (12.3%)	428 (12.5%)
Married	2474 (71.9%)	2439 (71.0%)	2423 (70.5%)	2408 (70.1%)
Widowed	216 (6.3%)	225 (6.5%)	229 (6.7%)	222 (6.5%)
Divorced	292 (8.5%)	320 (9.3%)	303 (8.8%)	308 (9.0%)
Separated	55 (1.6%)	54 (1.6%)	59 (1.7%)	71 (2.1%)
Missing	12	12	12	13
Education, n (%)				
No qualifications	196 (5.7%)	188 (5.5%)	212 (6.2%)	216 (6.3%)
GCSE	711 (20.7%)	749 (21.8%)	730 (21.2%)	694 (20.2%)
A-level	588 (17.1%)	572 (16.6%)	568 (16.5%)	587 (17.1%)
HNC/HND	288 (8.4%)	289 (8.4%)	283 (8.2%)	325 (9.4%)
Degree	898 (26.1%)	891 (25.9%)	893 (26.0%)	872 (25.3%)
Higher degree	204 (5.9%)	247 (7.2%)	216 (6.3%)	239 (6.9%)
Postgraduate	409 (11.9%)	380 (11.1%)	401 (11.7%)	392 (11.4%)
Other	146 (4.2%)	121 (3.5%)	137 (4.0%)	117 (3.4%)
Missing	11	11	10	8
Number in household, median (Q1-Q3)	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)
Missing	23	29	13	38

Children under 16 in household, n (%)	545 (16.0%)	514 (15.1%)	531 (15.6%)	483 (14.2%)
Missing	43	52	41	46
BMI, mean (sd)	28.6 (6.9)	28.5 (8.1)	28.5 (6.9)	28.4 (6.9)
Missing	80	82	56	71
Current smoker, n (%)	178 (5.2%)	192 (5.6%)	177 (5.2%)	157 (4.6%)
Missing	49	34	40	36
Any comorbidity, n (%)	2724 (79.0%)	2706 (78.5%)	2699 (78.3%)	2687 (78.0%)
Missing	2	1	1	5
Number comorbidities, median (Q1-Q3)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)
Flu vaccination in last 12 months, n (%)	2912 (85.0%)	2888 (84.6%)	2882 (84.2%)	2907 (85.0%)
Missing	26	36	27	31
Covid vaccination in last 12 months, n (%)	3045 (88.3%)	3019 (87.6%)	3040 (88.1%)	3000 (87.1%)
Missing	2	1	1	5
Covid illness in last 12 months, n (%)				
Yes	1068 (31.2%)	1070 (31.2%)	1034 (30.1%)	1038 (30.2%)
No	2253 (65.8%)	2236 (65.2%)	2290 (66.6%)	2277 (66.3%)
Not sure	103 (3.0%)	123 (3.6%)	116 (3.4%)	117 (3.4%)
Missing	27	19	10	18
Days of Covid symptoms, n median (Q1-Q3)	1032 8 (5-14)	971 8 (5-14)	1017 7 (5-12)	997 8 (5-14)
Previous use nasal spray, n (%)	2826 (85.3%)	2800 (84.5%)	2811 (84.8%)	2846 (85.9%)
Missing	138	135	137	138
Had RTI in a normal year, n (%)	3093 (89.7%)	3106 (90.1%)	3065 (88.9%)	3114 (90.4%)
Missing	2	1	1	5
Number RTIs in a normal year, n median (Q1-Q3)	3054 2 (1-3)	3073 2 (1-3)	3039 2 (1-3)	3076 2 (1-3)

RTI respiratory tract illness

Table 2. Days of illness using data every 28 days summed over 12 months (i.e. recall period 28 days)

	Usual care (N=3449)	Randomised Group		
		Vicks First Defence (N=3447)	Nasal saline (N=3449)	Behavioural website (N=3445)
Number of days of illness (participants with all 12 months' monthly data)				
n	1548	1531	1564	1269
Median (IQR)	15 (5-32)	13 (4-29)	14 (5-28)	14 (4-29)
Mean (SD)	24.3 (33.6)	20.7 (23.6)	20.9 (24.1)	23.1 (34.9)
Adjusted IRR (99% CI)	REF	<b>0.83 (0.76, 0.91)</b>	<b>0.85 (0.77, 0.92)</b>	0.94 (0.85, 1.03)
Number of days of illness (participants with at least one month of data*)				
n	3051	3076	3142	2811
Median (IQR)	13 (3-29)	10 (2-24)	11 (3-25)	10 (0-25)
Mean (SD)	21.8 (35.2)	17.8 (27.9)	17.7 (22.1)	19.5 (31.2)
Adjusted IRR (99% CI)	REF	<b>0.84 (0.79, 0.90)</b>	<b>0.83 (0.78, 0.89)</b>	0.94 (0.88, 1.01)

\*Assuming missing monthly days of illness are zero

Table 3. Key secondary outcomes – occurrence of infection over the last 12 months

	Usual care (N=3449)	Vicks First Defence (N=3447)	Nasal saline (N=3449)	Behavioural website (N=3445)
<b>Occurrence of infection in last 12 months</b>				
Reported RTI, n/N (%)	1923/2612 (73.6%)	1887/2503 (75.4%)	1917/2534 (75.7%)	1643/2320 (70.8%)
Missing (n, %)	837 (24.3%)	944 (27.4%)	915 (26.5%)	1125 (32.7%)
Adjusted* RR (95% CI)	REF	1.01 (0.98, 1.03)	1.01 (0.98, 1.03)	<b>0.96 (0.93, 0.99)</b>
<b>Number of infections in last 12 months</b>				
n	2584	2488	2522	2297
Median (IQR)	1 (0-3)	2 (1-3)	2 (1-3)	1 (0-2)
Mean (SD)	1.94 (2.27)	1.87 (1.94)	1.86 (1.94)	1.80 (2.18)
Adjusted* IRR (95% CI)	REF	0.94 (0.89, 1.01)	0.94 (0.88, 1.00)	0.95 (0.88, 1.02)

Complete cases analysis; RR, risk ratio; IRR, incidence rate ratio for intervention vs usual care; \*Adjusted for baseline number of days of RTI symptoms and stratum; Bold indicates statistically significant at 5% level; CI confidence interval

Table 4. Secondary outcomes - 12months

	Usual care N=3449	Vicks First Defence N=3447	Nasal saline N=3449	Behavioural website N=3445
Days of moderately bad symptoms over last 12 months, n	2605	2501	2529	2310
Median (IQR)	2 (0-5)	2 (0-5)	2 (0-5)	2 (0-5)
Mean (SD)	4.9 (10.0)	4.1 (8.7)	3.9 (7.1)	4.1 (7.8)
IRR (95% CI)	REF	<b>0.86 (0.80, 0.94)</b>	<b>0.83 (0.76, 0.90)</b>	<b>0.91 (0.83, 0.99)</b>
Days of work lost over last 12 months, n	2575	2465	2510	2273
Median (IQR)	0 (0-3)	0 (0-2)	0 (0-2)	0 (0-2)
Mean (SD)	3.0 (8.4)	2.3 (6.9)	2.1 (5.3)	2.2 (5.4)
IRR (95% CI)	REF	<b>0.84 (0.74, 0.97)</b>	<b>0.82 (0.72, 0.94)</b>	<b>0.85 (0.74, 0.97)</b>
Number times saw HCP over last 12 months	2609	2500	2531	2314
Median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Mean (SD)	0.44 (1.52)	0.33 (1.08)	0.32 (0.98)	0.37 (1.15)
IRR (95% CI)	REF	0.88 (0.74, 1.06)	<b>0.81 (0.68, 0.97)</b>	1.01 (0.84, 1.21)
Number of courses of antibiotics last 12m, n	2580	2468	2513	2270
Mean (SD)	0.32 (0.96)	0.27 (0.86)	0.27 (0.78)	0.31 (0.99)
IRR (95% CI)	REF	0.90 (0.75, 1.07)	0.84 (0.71, 1.00)	1.09 (0.91, 1.30)
Had Covid over last 12 months, n/N (%)	945/2569 (36.8%)	865/2451 (35.3%)	903/2499 (36.1%)	817/2261 (36.1%)
RR (95% CI)	REF	0.96 (0.89, 1.03)	0.98 (0.91, 1.05)	0.99 (0.92, 1.07)
Belief in antibiotics, n	2492	2379	2448	2199
Mean (SD)	3.5 (1.6)	3.4 (1.5)	3.4 (1.6)	3.5 (1.6)
OR <sup>1</sup> (95% CI)	REF	0.93 (0.83, 1.02)	0.96 (0.87, 1.06)	1.09 (0.98, 1.21)
Likelihood seeing doctor for next infection, n	2509	2404	2452	2211
Mean (SD)	2.9 (1.4)	2.8 (1.3)	2.8 (1.3)	2.9 (1.4)
Mean diff (95% CI)	REF	<b>-0.10 (-0.18, -0.02)</b>	<b>-0.08 (-0.16, -0.003)</b>	-0.04 (-0.12, 0.04)
Total IPAQ score at 12 months, n	2544	2426	2485	2231
Mean (SD)	2675 (2887)	2646 (2672)	2674 (2699)	2783 (2815)
IRR <sup>2</sup> (95% CI)	REF	1.01 (0.96, 1.06)	0.99 (0.94, 1.04)	1.03 (0.98, 1.08)

Sitting hours weekday, n	2355	2283	2324	2032
Mean (SD)	8.7 (5.1)	8.7 (5.0)	8.9 (5.1)	8.6 (5.1)
Mean diff (95% CI)	REF	0.04 (-0.21, 0.29)	0.14 (-0.11, 0.39)	-0.02 (-0.28, 0.24)
Perceived stress scale, n	2301	2202	2246	2035
Mean (SD)	19.9 (8.9)	19.4 (8.7)	19.3 (8.7)	19.4 (9.2)
Mean diff (95% CI)	REF	<b>-0.7 (-1.0, -0.3)</b>	<b>-0.5 (-0.9, -0.1)</b>	-0.3 (-0.7, 0.04)
PHQ-8 at 12 months, n	2393	2280	2312	2090
Mean (SD)	4.4 (4.8)	3.9 (4.4)	3.9 (4.4)	3.9 (4.6)
Mean diff (95% CI)	REF	<b>-0.08 (-0.13, -0.02)</b>	<b>-0.06 (-0.11, -0.00)</b>	<b>-0.07 (-0.12, -0.02)</b>
GAD-7 at 12 months, n	219	159	172	2101
Mean (SD)	4.3 (4.7)	4.8 (5.2)	3.8 (4.2)	3.3 (4.3)
Mean diff (95% CI)	REF	-0.06 (-0.72, 0.60)	-0.27 (-0.92, 0.39)	<b>-0.66 (-1.12, -0.20)</b>

<sup>1</sup> OR odds ratio from ordinal logistic regression; <sup>2</sup> IRR from Poisson with robust standard errors; IRR Incidence Rate Ratio; RR risk ratio; OR odds ratio; \*Adjusted for baseline outcome and stratum; CI confidence interval

Table 5. Adverse events of special interest – 12months

	Usual care	Vicks First Defence	Nasal Saline	Behavioural website
<b>Headache/sinus pain</b>				
Yes	120 (4.7%)	187 (7.8%)	85 (3.4%)	110 (4.9%)
No	2344 (92.4%)	2136 (88.7%)	2330 (94.4%)	2070 (93.1%)
Not sure	73 (2.9%)	85 (3.5%)	53 (2.1%)	43 (1.9%)
RR (95% CI)	REF	<b>1.61 (1.29, 2.00)</b>	<b>0.73 (0.56, 0.95)</b>	1.05 (0.82, 1.35)
<b>Heavy nosebleed</b>				
Yes	72 (2.8%)	85 (3.5%)	77 (3.1%)	83 (3.7%)
No	2449 (96.6%)	2309 (95.9%)	2377 (96.5%)	2126 (95.9%)
Not sure	14 (0.6%)	13 (0.5%)	10 (0.4%)	9 (0.4%)
RR (95% CI)	REF	1.23 (0.91, 1.69)	1.10 (0.81, 1.51)	1.32 (0.97, 1.80)
<b>Nasal dryness/irritation</b>				
Yes	703 (27.7%)	625 (25.9%)	513 (20.8%)	577 (26.0%)
No	1740 (68.6%)	1709 (70.9%)	1875 (75.9%)	1558 (70.1%)
Not sure	95 (3.7%)	75 (3.1%)	81 (3.3%)	88 (4.0%)
RR (95% CI)	REF	<b>0.91 (0.83, 0.99)</b>	<b>0.73 (0.67, 0.81)</b>	0.93 (0.84, 1.02)
<b>Slight nosebleed</b>				
Yes	407 (16.0%)	367 (15.3%)	357 (14.5%)	342 (15.4%)
No	2098 (82.7%)	2008 (83.5%)	2083 (84.4%)	1861 (83.6%)
Not sure	31 (1.2%)	31 (1.3%)	29 (1.2%)	22 (1.0%)
RR (95% CI)	REF	0.95 (0.83, 1.08)	0.90 (0.79, 1.02)	0.96 (0.84, 1.10)
<b>Trips/falls</b>				
Yes	586 (23.1%)	414 (17.2%)	420 (17.0%)	475 (21.3%)
No	1915 (75.5%)	1968 (81.7%)	2014 (81.6%)	1720 (77.3%)
Not sure	36 (1.4%)	26 (1.1%)	34 (1.4%)	31 (1.4%)
RR (95% CI)	REF	<b>0.74 (0.66, 0.83)</b>	<b>0.73 (0.66, 0.82)</b>	0.92 (0.83, 1.02)

RR risk ratio assuming 'not sure' categorised as 'no'; Adjusted for baseline days of illness and stratum; CI confidence interval

## Discussion

This trial provides good evidence for the longer term impact of robustly developed<sup>35 44</sup> accessible, easily scalable interventions for preventative or very early use in order to reduce symptom days of RTIs in primary care. Both nasal sprays reduced the number of days of illness – from 3 weeks of illness over a year, reducing by just over half a week. All three interventions also reduced the severity of symptoms and work days lost. Illness incidence was also reduced by the behavioural website.

## Strengths and Limitations.

The study was open label, but since the mechanisms of action of sprays are complex (probably a mixture of washing out virus and an anti-viral effect<sup>14</sup>) devising a meaningful placebo would be difficult, and nasal sprays were relabelled (retaining some blinding). Placebo effects and resentful demoralisation<sup>45</sup> in open trials could bias results, but for RTIs the estimates from open label trials (e.g. sore throat<sup>36</sup> acute bronchitis<sup>37</sup> and otitis<sup>46</sup> - where placebo effects and resentful demoralisation are possible) are very similar to placebo controlled trials<sup>38 47-49</sup> (where resentful demoralisation is very unlikely) - including trials of medicines in COVID<sup>50 51</sup>. The impact on severity and workdays lost, and the different pattern of impact for the website and the sprays also suggest non-specific 'placebo' effects are less likely. Self reported outcomes are not 'objective', but medical history examination and self report agree moderately well<sup>52</sup>; there is no meaningful alternative to self-report to assess symptom presence and severity, and self-report of normal activities and symptoms are sensitive to change and reliable<sup>36 53</sup>. Reports of symptom duration after several weeks are reliable<sup>36 53</sup>, and the reports over months are also comparable to monthly reports<sup>10</sup> (presumably since relatively few infections makes remembering easier). We found evidence that some participants had misunderstood the time frame of the questions for days of illness at 12 months, so for the days of illness the monthly data had to be used. The results in season 3 (post pandemic) were slightly better than the pandemic period, and since SarsCov2 remains prevalent throughout the year with coinfections common<sup>54</sup> the post pandemic spike in infections makes the current results even more relevant for patients.

Although 'cold calling' mailed invitations provide low uptake rates, the PRIMIT trial (which used similar invitation methods<sup>10</sup>) demonstrated comparable behavioural intentions outside the trial setting<sup>55</sup>, which suggests the results may be generalisable. The novel methodology of recruitment via the internet and central distribution/supply of the sprays was very efficient and convenient for

patients, reducing barriers to participation. There was clear evidence of suboptimal adherence to sprays (which we reported in the first 6 months), particularly for preventive use of sprays<sup>33</sup>. Despite slightly fewer participants from ethnic minorities (3.2% vs 5% 2021 census data for this age group), and more with A level qualification or above (50% vs 40% census data), there was no clear effect of these imbalances on the estimates.

It is likely that we have underestimated the impact of saline or VFD, for several reasons: sprays were only resupplied upon request and we know adherence to the recommended use of sprays was limited (particularly for preventive behaviours). The study also used isotonic saline rather than hypertonic saline – which is likely to be more effective given the mechanism of action of saline almost certainly involves the supply of chloride ions to cells<sup>13 14</sup>.

### **Main findings in the context of previous literature**

All interventions largely retained impact on the primary and secondary outcomes after 12 months to the impact at 6 months despite no routine resupply of sprays, albeit there was perhaps slightly less impact of sprays on days of illness (Hazard ratios of 0.83 vs 0.80 found at 6 months<sup>33</sup>) and antibiotic use. The impact of sprays is supported by smaller studies - by previous invitro, pilot work, a trial of saline in children and observational data<sup>13-15 16</sup> and trials of other nasal sprays<sup>9 10 7 11 56</sup>. The reduction in illness severity and work-days lost for all interventions was consistent with the 6 month findings, as was the small but important population effect of the behavioural website on infection incidence<sup>33</sup>. The results for individual strata suggests that saline was most effective among participants with a history of recurrent illnesses. The VFD had more headache, and the saline group less headache when compared to usual care. An interesting finding was the reduction in self reported falls in both spray groups. Despite concerns about measurement error in recall of falls<sup>57</sup>, measurement error would be expected to make it more difficult to detect a signal. Furthermore these findings are unlikely to be due to chance given the finding was consistent in both spray groups – and if a real effect it is presumably due to lessening the impact of infections on balance: falls are known to be associated with infections in more frail individuals<sup>58 59</sup>, and so the observed reduction in illness duration and severity might be expected to reduce falls. The experience of using the sprays might also reduce fear of falling which is known to be a strong predictor of falls<sup>60 61</sup>.

While the Cochrane review suggested promising effects of physical activity for symptom days<sup>17</sup>, all the trials required intensive input. In the current study the impact on symptom days was close to significance, similar to the estimate (2 days benefit) from the Cochrane review<sup>17</sup>, and consistent with the effect of the intervention on more severe symptoms and workdays lost. To our knowledge,

our brief, unsupervised digital approach website is the first effective robustly developed, pragmatic, scalable intervention to support physical activity and stress management for preventing and managing RTIs<sup>35 44</sup>.

**Conclusion.** Advice to use inexpensive and widely available nasal sprays even when not routinely resupplying them, has moderate but important longer term impacts on a range of outcomes - illness duration, the severity of symptoms, work days lost, intention to consult health professional in future episodes and the incidence of falls. Both sprays were well tolerated, albeit VFD was associated with slightly more headaches, and saline fewer headaches. Providing a physical activity and stress management website also retained significant impacts at 12 months for the incidence of illness, illness severity and work days lost. The potential for sprays to prevent illness has not been tested adequately given the limited adherence to preventive use of sprays. Further research should concentrate on boosting adherence, and using hypertonic rather than isotonic saline

Accepted Manuscript—BJGP—BJGP:2025:0269

## **Contributorship.**

**Conceptualisation:** LY, AG and PL suggested the initial ideas for the study – LY suggested the need for a large study of nasal sprays, and AG and PL developed the initial ideas for the development of the interventions and the structure of the trial.

**Funding acquisition.** PL AG LY KB CB SRH JR MM NF TV BS and AH developed the ideas further and developed the grant application.

**Investigation:** All authors contributed to the development of the protocol, revisions of the protocol, study procedures or study documentation. The development of the interventions was overseen by AG; LY led the development of the nasal spray online support, AG led the development of the behavioural website with KG,LD,SH, KB, JDD,BA, contributing to both aspects, as well as important input from SRH,DS,HP, and PL.

**Project administration.** Supervision of the study at regular study management meetings involved all authors but was coordinated on a day to day basis by JV and KR, but with input from JB,TT,KMi,SJ,SM,SW. JV KR TB and BS had access to the raw data and TB and BS verified the data.

**Analysis and interpretation.** TB and BS and undertook the statistical analysis. All authors contributed to interpretation of the results. Writing PL wrote the first draft of the paper and all authors contributed to serial revisions of the paper and have approved the final text. The decision to submit the manuscript was made by PL and AG but with support from all authors.

## References

1. Gulliford MC, Moore MV, Little P, et al. Safety of reduced antibiotic prescribing for self limiting respiratory tract infections in primary care: cohort study using electronic health records. *BMJ* 2016;354:i3410. doi: 10.1136/bmj.i3410
2. Gulliford MD, A.; Moore, M.; Ashworth, M.; Staa, T.; McCann, G.; Charlton, J.; Yardley, L.; Little, P.; McDermott, L. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. *BMJ Open* 2014;4(10):e006245. doi: 10.1136/bmjopen-2014-45.
3. Goossens H, Ferech M, Vander Stichele R, et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;365:579-87.
4. Hughes JH, Thomas DC, Hamparian VV, et al. Acid liability of rhinovirus type 14: effect of pH, time, and temperature. *Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine (New York, NY)* 1973;144(2):555-60. doi: 10.3181/00379727-144-37634 [published Online First: 1973/11/01]
5. Giranda VL, Heinz BA, Oliveira MA, et al. Acid-induced structural changes in human rhinovirus 14: possible role in uncoating. *Proceedings of the National Academy of Sciences of the United States of America* 1992;89(21):10213-7. doi: 10.1073/pnas.89.21.10213 [published Online First: 1992/11/01]
6. Pratelli A. Canine coronavirus inactivation with physical and chemical agents. *Vet J* 2008;177(1):71-79. doi: 10.1016/j.tvjl.2007.03.019 [published Online First: 05/21]
7. Rennie P, Bowtell P, Hull D, et al. Low pH gel intranasal sprays inactivate influenza viruses in vitro and protect ferrets against influenza infection. *Respir Res* 2007;8:38. doi: 10.1186/1465-9921-8-38 [published Online First: 2007/05/19]

8. Gern JE, Mosser AG, Swenson CA, et al. Inhibition of rhinovirus replication in vitro and in vivo by acid-buffered saline. *J Infect Dis* 2007;195(8):1137-43. doi: 10.1086/512858 [published Online First: 2007/03/16]
9. Little P, Read RC, Amlot R, et al. Reducing risks from coronavirus transmission in the home-the role of viral load. *Bmj* 2020;369:m1728. doi: 10.1136/bmj.m1728 [published Online First: 2020/05/08]
10. Little P, Stuart B, Hobbs FDR, et al. An internet-delivered handwashing intervention to modify influenza-like illness and respiratory infection transmission (PRIMIT): a primary care randomised trial. *Lancet* 2015;DOI: [http://dx.doi.org/10.1016/S0140-6736\(15\)60127-1](http://dx.doi.org/10.1016/S0140-6736(15)60127-1)
11. Hull D, Rennie P, Noronha A, et al. Effects of creating a non-specific, virus-hostile environment in the nasopharynx on symptoms and duration of common cold. *Acta otorhinolaryngologica Italica* 2007;27:73-77.
12. Bichiri D, Rente AR, Jesus Â. Safety and efficacy of iota-carrageenan nasal spray in treatment and prevention of the common cold. *Med Pharm Rep* 2021;94(1):28-34. doi: 10.15386/mpr-1817 [published Online First: 2021/02/26]
13. Ramalingam S, Cai B, Wong J, et al. Antiviral innate immune response in non-myeloid cells is augmented by chloride ions via an increase in intracellular hypochlorous acid levels. *Scientific reports* 2018;8(1):13630. doi: 10.1038/s41598-018-31936-y [published Online First: 2018/09/13]
14. Ramalingam S, Graham C, Dove J, et al. A pilot, open labelled, randomised controlled trial of hypertonic saline nasal irrigation and gargling for the common cold. *Sci Rep* 2019;9(1):1015. doi: 10.1038/s41598-018-37703-3
15. Rabone SJ, Saraswati SB. Acceptance and effects of nasal lavage in volunteer woodworkers. *Occup Med (Lond)* 1999;49(6):365-9. doi: 10.1093/occmed/49.6.365 [published Online First: 2000/01/11]

16. Slapak I, Skoupá J, Strnad P, et al. Efficacy of isotonic nasal wash (seawater) in the treatment and prevention of rhinitis in children. *Arch Otolaryngol Head Neck Surg* 2008;134(1):67-74. doi: 10.1001/archoto.2007.19 [published Online First: 2008/01/23]
17. Grande AJ, Keogh J, Silva V, et al. Exercise versus no exercise for the occurrence, severity, and duration of acute respiratory infections. *Cochrane Database Syst Rev* 2020;4(4):Cd010596. doi: 10.1002/14651858.CD010596.pub3 [published Online First: 2020/04/05]
18. Nieman DC, Henson DA, Austin MD, et al. Upper respiratory tract infection is reduced in physically fit and active adults. *British journal of sports medicine* 2011;45(12):987-92. doi: 10.1136/bjsm.2010.077875 [published Online First: 2010/11/03]
19. Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. *N Engl J Med* 1991;325(9):606-12. doi: 10.1056/nejm199108293250903 [published Online First: 1991/08/29]
20. Doyle WJ, Gentile DA, Cohen S. Emotional style, nasal cytokines, and illness expression after experimental rhinovirus exposure. *Brain, behavior, and immunity* 2006;20(2):175-81. doi: 10.1016/j.bbi.2005.05.005 [published Online First: 2005/07/19]
21. Cohen S, Doyle WJ, Skoner DP, et al. Social ties and susceptibility to the common cold. *Jama* 1997;277(24):1940-4. [published Online First: 1997/06/25]
22. Trueba AF, Ritz T. Stress, asthma, and respiratory infections: pathways involving airway immunology and microbial endocrinology. *Brain Behav Immun* 2013;29:11-27. doi: 10.1016/j.bbi.2012.09.012 [published Online First: 2012/10/09]
23. Stover CM. Mechanisms of Stress-Mediated Modulation of Upper and Lower Respiratory Tract Infections. *Adv Exp Med Biol* 2016;874:215-23.

doi: 10.1007/978-3-319-20215-0\_10 [published Online First: 2015/11/22]

24. Carmody J, Baer RA. Relationships between mindfulness practice and levels of mindfulness, medical and psychological symptoms and well-being in a mindfulness-based stress reduction program. *J Behav Med* 2008;31(1):23-33. doi: 10.1007/s10865-007-9130-7 [published Online First: 2007/09/28]
25. Barrett B, Hayney MS, Muller D, et al. Meditation or exercise for preventing acute respiratory infection: a randomized controlled trial. *Ann Fam Med* 2012;10(4):337-46. doi: 10.1370/afm.1376 [published Online First: 2012/07/11]
26. Barrett B, Hayney MS, Muller D, et al. Meditation or exercise for preventing acute respiratory infection (MEPARI-2): A randomized controlled trial. *PLoS One* 2018;13(6):e0197778. doi: 10.1371/journal.pone.0197778 [published Online First: 2018/06/23]
27. Little P, Stuart B, Hobbs FR, et al. An internet-based intervention with brief nurse support to manage obesity in primary care (POWeR+): a pragmatic, parallel-group, randomised controlled trial. *The lancet Diabetes & endocrinology* 2016;4(10):821-8. doi: 10.1016/S2213-8587(16)30099-7 [published Online First: 2016/07/31]
28. Bradbury K, Steele M, Corbett T, et al. Developing a digital intervention for cancer survivors: an evidence-, theory- and person-based approach. *npj Digital Medicine* 2019;2(1):85. doi: 10.1038/s41746-019-0163-4
29. Anthierens S, Tonkin-Crine S, Cals JW, et al. Clinicians' views and experiences of interventions to enhance the quality of antibiotic prescribing for acute respiratory tract infections. *J Gen Intern Med* 2015;30(4):408-16. doi: 10.1007/s11606-014-3076-6
30. Tonkin-Crine S, Yardley L, Little P. Antibiotic prescribing for acute respiratory tract infections in primary care: a systematic review and

- meta-ethnography. *J Antimicrob Chemother* 2011;66(10):2215-23. doi: 10.1093/jac/dkr279 [published Online First: 2011/07/19]
31. Yardley L, Williams S, Bradbury K, et al. Integrating user perspectives into the development of a web-based weight management intervention. *Clin Obes* 2012;2(5-6):132-41. doi: 10.1111/cob.12001 [published Online First: 2012/10/01]
32. Geraghty AW, Munoz RF, Yardley L, et al. Developing an Unguided Internet-Delivered Intervention for Emotional Distress in Primary Care Patients: Applying Common Factor and Person-Based Approaches. *JMIR Ment Health* 2016;3(4):e53. doi: 10.2196/mental.5845 [published Online First: 2016/12/22]
33. Little P, Vennik J, Rumsby K, et al. Nasal sprays and behavioural interventions compared with usual care for acute respiratory illness in primary care: a randomised, controlled, open-label, parallel-group trial. *Lancet Respir Med* 2024 doi: 10.1016/S2213-2600(24)00140-1 [published Online First: 20240711]
34. Yardley L, Morrison L, Bradbury K, et al. The person-based approach to intervention development: application to digital health-related behavior change interventions. *Journal of medical Internet research* 2015;17(1):e30. doi: 10.2196/jmir.4055
35. Williamson S, Dennison L, Greenwell K, et al. Using nasal sprays to prevent respiratory tract infections: a qualitative study of online consumer reviews and primary care patient interviews. *BMJ Open* 2022;12(6):e059661. doi: 10.1136/bmjopen-2021-059661 [published Online First: 2022/07/01]
36. Little PS, Williamson I, Warner G, et al. An open randomised trial of prescribing strategies for sore throat. *BMJ* 1997;314:722-27.
37. Little P, Rumsby K, Kelly J, et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomised controlled trial. *JAMA* 2005;293:3029-35.

38. Little P, Stuart B, Moore M, et al. Amoxicillin for acute lower respiratory tract infection where pneumonia is not suspected clinically : a 12 country randomised placebo controlled trial in primary care. *Lancet Infectious Disease* 2013;Feb;13(2):123-9. doi: 10.1016/S1473-3099(12)70300-6.
39. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24(4):385-96. [published Online First: 1983/12/01]
40. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16(9):606-13. [published Online First: 2001/09/15]
41. Ruiz MA, Zamorano E, Garcia-Campayo J, et al. Validity of the GAD-7 scale as an outcome measure of disability in patients with generalized anxiety disorders in primary care. *Journal of affective disorders* 2011;128(3):277-86. doi: 10.1016/j.jad.2010.07.010 [published Online First: 2010/08/10]
42. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;30(4):377-99. doi: 10.1002/sim.4067 [published Online First: 2011/01/13]
43. Jakobsen JC, Gluud C, Wetterslev J, et al. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med Res Methodol* 2017;17(1):162. doi: 10.1186/s12874-017-0442-1 [published Online First: 2017/12/07]
44. Dennison L, Williamson S, Greenwell K, et al. Patient perceptions of vulnerability to recurrent respiratory tract infections and prevention strategies: a qualitative study. *BMJ Open* 2022;12(4):e055565. doi: 10.1136/bmjopen-2021-055565 [published Online First: 2022/04/22]
45. Adamson J, Cockayne S, Puffer S, et al. Review of randomised trials using the post-randomised consent (Zelen's) design. *Contemp Clin*

- Trials* 2006;27(4):305-19. doi: 10.1016/j.cct.2005.11.003 [published Online First: 20060207]
46. Little P, Gould C, Williamson I, et al. A pragmatic randomised controlled trial of two prescribing strategies for acute otitis media. *BMJ* 2001;322:336-42.
47. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for treatment of sore throat in children and adults. *Cochrane Database Syst Rev* 2021;12(12):Cd000023. doi: 10.1002/14651858.CD000023.pub5 [published Online First: 2021/12/10]
48. Smith S, Fahey T, Smucny J, et al. Antibiotics for acute bronchitis. *Cochrane Library* 2014;DOI: 10.1002/14651858.CD000245.pub3
49. Venekamp RP, Sanders SL, Glasziou PP, et al. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev* 2023;11(11):Cd000219. doi: 10.1002/14651858.CD000219.pub5 [published Online First: 2023/11/15]
50. Butler CC, Yu LM, Dorward J, et al. Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet Respir Med* 2021;9(9):1010-20. doi: 10.1016/s2213-2600(21)00310-6 [published Online First: 2021/07/31]
51. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet* 2021;397(10279):1063-74. doi: 10.1016/s0140-6736(21)00461-x [published Online First: 2021/03/08]
52. Xu J, Schwartz K, Monsur J, et al. Patient-clinician agreement on signs and symptoms of 'strep throat': a MetroNet study. *Fam Pract* 2004;21(6):599-604. doi: 10.1093/fampra/cmh604 [published Online First: 2004/11/06]

53. Watson L, Little P, Williamson I, et al. Validation study of a diary for use in acute lower respiratory tract infection. *Family Practice* 2001;18:553-54.
54. Loosen SH, Plendl W, Konrad M, et al. Prevalence of Upper Respiratory Tract Infections Before, During, and After the COVID-19 Pandemic in Germany: A Cross-Sectional Study of 2 167 453 Outpatients. *J Prim Care Community Health* 2023;14:21501319231204436. doi: 10.1177/21501319231204436
55. Ainsworth B, Miller S, Denison-Day J, et al. Infection Control Behavior at Home During the COVID-19 Pandemic: Observational Study of a Web-Based Behavioral Intervention (Germ Defence). *J Med Internet Res* 2021;23(2):e22197. doi: 10.2196/22197 [published Online First: 2021/02/11]
56. Reid G, Bruce A, Cook R, et al. Effect on the urogenital flora of antibiotic treatment for urinary tract infection. *Scand J Infectious Dis* 1990;22:43-47.
57. Hauer K, Lamb SE, Jorstad EC, et al. Systematic review of definitions and methods of measuring falls in randomised controlled fall prevention trials. *Age and Ageing* 2006;35(1):5-10. doi: 10.1093/ageing/afi218
58. Soliman Y, Meyer R, Baum N. Falls in the Elderly Secondary to Urinary Symptoms. *Rev Urol* 2016;18(1):28-32. [published Online First: 2016/05/11]
59. Pigłowska M, Kostka J, Kostka T. Association between respiratory tract infections and incidence of falls in nursing home residents. *Pol Arch Med Wewn* 2013;123(7-8):371-7. doi: 10.20452/pamw.1823 [published Online First: 2013/05/08]
60. Gazibara T, Kurtagic I, Kusic-Tepavcevic D, et al. Falls, risk factors and fear of falling among persons older than 65 years of age. *Psychogeriatrics* 2017;17(4):215-23. doi: 10.1111/psyg.12217 [published Online First: 20170127]

61. Li Q, Mpofu E, Yin C, et al. Perception of Falls and Confidence in Self-Management of Falls among Older Adults. *Int J Environ Res Public Health* 2019;16(24) doi: 10.3390/ijerph16245054

Accepted Manuscript—BJGP—BJGP.2025.0269