**A PRImary care randomised trial of an internet intervention to Modify Influenza-like illness and respiratory infection Transmission (PRIMIT trial.)**

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**Abstract.**

**Background.** Hand-washing to prevent transmission of respiratory tract infections (RTIs) has been widely advocated, especially during the H1N1 pandemic, but the role of hand-washing is debated, and no good randomised evidence exists among adults in non-deprived settings.This study aimed to demonstrate whether an intervention to modify hand-washing reduces RTIs among adults.

**Methods.** Individuals sharing a household were recruited by mailed invitation through their general practice. Following consent, participants were randomised on-line by an automated computer-generated random number programme either to no access, or to access a bespoke automated web-based intervention which maximised hand-washing intention, monitored hand-washing behaviour, provided tailored feedback, reinforced helpful attitudes and norms and addressed negative beliefs. Participants could not be blinded, but the analysis syntax was constructed blind to group.

**Results.** 20,066/16,908 (84%) participants were followed up. An intention-to-treat analysis documented fewer RTIs reported after 16 weeks (intervention 51% (4242/8241); controls 59% (5135/8667); multivariate risk ratio 0.86; 95% confidence intervals 0.83 to 0.89). The intervention reduced transmission of RTIs (reported within one week of another household member) both to and from the index person. There was a modest increase in minor self-reported skin irritation (4.3% (231/5429) versus 1.3% (79/6087)) and no serious adverse events.

**Interpretation.** In non-pandemic years an effective internet intervention designed to increase hand-washing could have an important impact in reducing infection transmission. Given the heightened concern during a pandemic and the likelihood of accessing the internet for advice, the intervention also has potential for effective implementation during a pandemic.

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**Background.**

Patient presentations with respiratory tract infections (RTIs) result in overstretched primary care services and hospital bed shortages due to complications 1-4 5-7, particularly during an influenza pandemic.

The routes whereby influenza and other RTIs spread are debated but are probably involve close contact (droplets) and hand-to-face contact8. Hand-washing was recommended by the WHO during the H1N1 pandemic, but a systematic review identified only two high quality trials9 which were face-to-face training programmes in hand-washing among children (day-care centres in Australia10; highly deprived areas of a low income country11). There is no good randomised evidence in broader settings, nor among adults, and most previous interventions involve significant input from experienced trainers, which limits implementation.

Rapidly available, low-cost interventions are needed given that most of the population contract RTIs, and with greater risks in a pandemic12. The internet is an ideal format: it is widely accessed - in 2014 22 million UK households (84%) had internet access (<http://www.ons.gov.uk)>, and the internet is the first source of information in a pandemic13. A small web-based intervention study to reduce transmission of influenza 14 found trends in behaviour change but did not affect hand hygiene.

We developed and piloted an internet-based intervention to modify hand-washing which requires no face-to-face training, 15-17 and which increased hand-washing16. We report here the full trial to assess the impact on infections in households.

**Methods.**

**Approvals.** The study was approved by a Multicentre Research Ethics Committee (number 08/H0502/14)

**Inclusion criteria.** Adult patients (aged 18+) identified from physicians’ computerised lists; at least one other individual living in the household and willing to report illness to the index person.

**Exclusion criteria.** Patients with severe mental problems (e.g. major uncontrolled depression/schizophrenia; dementia; severe mental impairment) or terminally ill; those reporting a skin complaint that would limit hand washing.

**Invitation.** Any GP practice was eligible, and widespread practice recruitment continued until recruitment targets were reached. Postal invitations were sent to people aged over 18 randomly sampled from the lists of general practitioner physicians’ offices in England to take part in ‘a study of methods of reducing the spread of infection from colds and seasonal and pandemic flu’. During the first two winters all those who declined were invited to return a feedback form giving brief reasons; to limit the number in winter 3 only 1:10 randomly chosen practices sent out forms.

**Consent.** Patients agreeing to take part were provided with a link to the website. They could log in directly to the website where they were asked to provide online consent before being randomised and assigned to a group.

**Randomisation.** Participants were automatically randomised by the intervention software when they registered for the trial online. The original intention was to stratify randomisation (by age >65; influenza vaccination status; size of family, children under aged 16 living at home; the willingness of other members of the family to use the website; and attendance in the previous year with respiratory infections). However, it was decided to use simple randomisation, both because the size of the trial rendered stratification unnecessary and to minimise the logistic difficulty of randomisation.

**Intervention.** Blinding of intervention participants was not possible in an open trial.There were four weekly web-based sessions, each with new content to encourage participant interest, and to maximise retention. The intervention provided information about the importance of flu, the role of hand-washing, developed a plan to maximise intention formation for hand-washing, reinforced helpful attitudes and norms and addressed negative beliefs and used tailored feedback. Automated emails were used to prompt participants - to use sessions and also to complete the monthly questionnaires, and in the intervention group questions on a monthly basis to maintain hand-washing – and so were an integral part of the intervention. (see Appendix 1 for more details of the intervention, and the link: <https://www.lifeguideonline.org/player/play/primitdemo>).

**Control (normal care).** The control group did not have access to the intervention webpages and were not asked questions about hand-washing at baseline so as not to provide a prompt to change behaviour. As in the intervention group, the control group had access to the physician/practice in the normal way for respiratory illnesses.

**Modifications: sub-study**. Following the pilot study the independent trial steering committee agreed that the baseline measures could modify handwashing. Randomisation at the point of consent was modified to create separate strata with two additional randomised groups: c) control with questions and d) intervention without questions. We estimated a minimum of 540 patients in each of the additional groups) c) and d) above would enable the impact of the baseline questions on intentions and behaviour to be explored.

**Outcomes.** Episodes of infection and their duration were documented by self-report since they can be remembered reasonably reliably over several weeks18;19. Since the aim was to capture the autumn, winter and spring infective period for respiratory infections, follow-up was limited to four months, and we stopped recruiting participants after the February of each winter. All participants were sent invitations to complete the on line outcome assessment measures monthly (at 4, 8, 12 and 16 weeks after initial login) regardless of progress through the sessions. Two follow-up emails were sent for each assessment, and then a mailed questionnaire and structured phone follow-up for non-responders at 16 weeks.

**Primary outcome: Episodes of respiratory tract infections reported after 16 weeks.** We hypothesized that the intervention would reduce the number of episodes (by reducing transmission) and hence the number of days with symptoms, and also the severity of symptoms by reducing the viral load.

For each monthly questionnaire and the final questionnaire the index person documented the nature and duration of the infection. An illness was classified as an RTI based on consensus definitions developed in previous studies 20;21 - defined as 2 symptoms of an RTI for at least 1 day or 1 symptom for 2 consecutivedays. For reported Influenza like illness (ILI) WHO or CDC definitions, which require measured temperature, were not appropriate, and the international Influenzanet collaboration note that the ECDC definition (one systemic, one respiratory symptom) does not necessarily differentiate ILI from a cold (<https://www.influenzanet.eu>) and suggest making high temperature a separate element. Our pragmatic definition therefore required a high temperature (feeling very hot/very cold; or measured temperature >37.5 degrees C); a respiratory symptom (sore throat;cough;runny nose) and a systemic symptom (headache;severe fatigue;severe muscle aches;severe malaise).

The original MRC protocol left some ambiguity about whether the final follow-up or the monthly questionnaires would provide the primary outcome. The logistic difficulty of obtaining high follow-up rates for each of the monthly questionnaires led the study team with the agreement of the trial steering committee to specify the primary outcome as respiratory infections reported at final follow-up (i.e. infections since study commencement reported at 16 weeks).Maximal follow-up for the primary outcome was achieved by an additional brief questionnaire and then telephone calls for non-responders.

**Secondary outcomes.**

**Duration of symptoms.** In the monthly and final questionnaires participants documentedthe duration of symptoms rated moderately bad (which we have shown is the most likely to be sensitive to change19 and can be remembered reliably over a period of a few weeks18 19); and the number of days where work/normal activities were impaired19.

**Transmission of respiratory infections.**For the monthly questionnaire the index person was asked to document whether household members had had a similar infection within a week before the index person (i.e. probable transmission from a family member) or after the index person (i.e. probable transmission from the index person).

**Gastrointestinal infections.** Both the monthly questionnaire and the final questionnaire asked participants to document episodes of ‘watery, loose bowel movements or vomiting lasting at least 24 hours’.

**Attendance at the practice, and use of health service resources.** We hypothesized that the intervention would reduce the number of health service contacts by reducing the number of episodes of acute respiratory infection*.* At 12 months post randomisation all patients’ notes were reviewed to document resource use, admission to hospital for respiratory or cardiovascular complications, whether patients attended the physician for their ILI or other respiratory tract infections22. Assessment of the notes was made blind to group, and has been shown to be reliable and unbiased 23.

**Sample size.** We estimated that a minimum of 15908 participants would be needed to detect a 10% reduction in respiratory infections (18% versus 20%, OR 0.88) for 80% power, an alpha of 0.05, and 20% loss to follow-up. A very small difference for a low-cost intervention could be highly cost-effective, but we judged that individual participants would be unlikely to be motivated to change behaviour unless there was of the order of a 10% reduction.

**Main trial analysis.** We performed no interim analyses.The primary analysis was an intention to treat analysis with no imputation of missing data, but a secondary analysis used multiple imputation (50 imputations) by chained equations, imputing all variables simultaneously. Analysis of the 16 week binary outcome data was performed using a logistic model, and for count outcomes a negative binomial model. Odds ratios were converted to risk ratios using the formula of Zhang and Yu24. For the monthly data (serial panel data) the analysis was based on repeated measures logistic regression. 95% confidence intervals are reported. The analysis syntax was done blind to group, but the statistician had to be unblinded at the stage of combining groups from the sub-study. We explored possible effects in pre-specified subgroups (estimating the interaction term for the intervention) : age >65; influenza vaccination status; family size; children under age 16; prior attendance with respiratory infections; and skin complaints. The full economic analysis will be reported elsewhere, but we report the high level findings, which take an NHS perspective.

The study was funded by the Medical Research Council (study number **09/800/22**). Neither the funder nor the sponsor (the University of Southampton) has any part in the study design, the collection, analysis, or interpretation of the data, nor in the writing of the report. BLS, JJ, MM, LYao and LYar had access to the raw data; PL had full access to all of the data and the final responsibility to submit for publication.

**Results.**

344 physician offices were recruited over a wide area of England, and 20066 participants were randomised between 17/01/2011 and 31/03/13 (winter 1: 17/1/11 to 23/3/11, n=427; winter 2 10/11/11 to 30/4/12 (n=3,553, only 25 participants recruited in April and March); winter 3 19/10/12 to 31/3/13, n=16,086) of whom 16,908 participants (84%) were followed-up by 16 weeks (see figure 1 the CONSORT diagram). Medical notes reviews were completed among 19,117 (95%) participants. Table 1 shows the baseline characteristics of the intervention and control groups which are well balanced. Most participants in the intervention group completed at least part of all 4 of the sessions (median 4 sessions; mean 2.9; range 1 to 4).

**Main result**s **(Table 2): 16 week data**. There was no evidence of any practice level effects and the intra-cluster correlation ( ICC) values were very small (ICC for the primary outcome measure = 0.009 (0.005, 0.016)), so the estimates have been generated without taking into account clustering by practice. Among index participants in the intervention group there were fewer respiratory infections (intervention 51% (4242/8241), controls 59% (5135/8667); p<0.0001) , including fewer episodes of influenza like illness. There were similar reductions for household members (44% (3545/8075), 49% (4193/8551); p<0.001). There were also slightly less severe infections for those who experienced infections, and because the intervention group had fewer infections, they had half a day fewer moderately bad symptoms overall (2.1 versus 2.6 days). There were also fewer total number of days of infections (not shown in table 2: 5.2 versus 6.5 days, multivariate incident rate ratio 0.91 (95% confidence intervals 0.87 to 0.95, p<0.0001)) and among those who reported infections shorter duration of illness (9.8 vs 10.6 days; 0.91, 0.87 to 0.95; p<0.0001). The intervention group also reported fewer gastrointestinal infections. There were no differential effects of the intervention for the main outcome in for any of the subgroups identified in advance.

**Monthly data (Table 3) reconsultations, antibiotic use (Table 4).** The monthly data suggests that transmission of infection was reduced both to the index person (7.8% (2157/27800), 9% (2757/30,803); p<0.0001) and from the index person (6.8% (1606/23,670), 8.8% (2274/25780); p<0.0001). The estimate for month 1 for the index person (0,.84 (0.81 to 0.88) was similar to the overall effect, as is the household data (0.84, 0.80 to 0.88), which suggests consistent reliable recall over the 16 week period. The notes data (Table 4) documented fewer consultations over 16 weeks period (10.0% versus 10.7% ) and 1 year (16.0% versus 17.3%). Similarly there were fewer antibiotic prescriptions over 16 weeks (5.6% versus 6.4% ) and 1 year (9.3% versus 10.5%). The economic analysis will be reported elsewhere

**Impact of baseline questions (Table 5)**. Due to the smaller numbers, the estimates are imprecise but suggest a trend towards fewer infections in the control group when they were asked baseline questions about handwashing.

**Missing data (Appendix 3:Tables 6 and 7).** As expected most variables at baseline or from the chart review had few items missing (mostly less than 5%, see Table 6) which was similar for randomisation groups and multiple imputation provided very similar results to the complete case analysis for the primary outcome (see Table 7). Questions about performing work/daily tasks were poorly answered (n=9350); for those answering there was no difference between groups (risk ratio1.01; 0.91 to 1.12; p=0.824)

**Non-participants (Appendix 3:Table 8).**

Participants were slightly more likely to be female, older and less deprived (See Table 8). There was no evidence of interaction/effect modification with intervention group for these variables, and including them in the analysis did not modify the estimates. 235,810 feedback forms were sent out in total to non-participants and 18,266 (8%) forms were returned citing reasons for non-participation (see Appendix 2). Of these 4943 (25%) reported not participating because they lived alone and 7910 (43%) because they did not have easy access to the internet.

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**Harms.** There were 4 infection related hospitalisations (2 control; 2 intervention). Minor self-reported skin irritation increased among those who responded to the question (231/5,429 (4.3%) vs 79/6,087 (1.3%), p<0.0001) for those who did not report problems at baseline, but no impact on consultations for skin complaints. Amongst those who had a skin complaint at baseline, reported skin complaints did not increase (423/ 803 (52.7%) intervention, 539/ 986 (54.7%) control, p=0.402).

**Discussion.**

This study demonstrates that a self-accessed internet intervention to increase hand-washing reduces the number and severity of infections among both index patients and their households.

**Potential limitations.**  A free-standing website would be expected to attract those more interested in preventing infections – but this was the intended sample. Having demonstrated effectiveness, the intervention would be expected to attract a wider sample. Although the intervention content is complex, implementation requires minimal resources since all the content, tailoring and email reminders are automated. Participants were less deprived, older and had more females compared to non-participants, but controlling for these features made little difference to the estimates. The very large sample made self-report the only feasible method of determining whether infections occurred. Monthly reporting will not capture detailed data for each illness, but daily diaries over months also suffer reporting bias, and infections are well remembered over weeks18. Both groups were asked questions about infections, and any non-differential measurement error will have underestimated effectiveness. The monthly questionnaires, including the first month, provided similar results to fourth months, and the intervention affected gastrointestinal infections, consultations and antibiotic prescribing (measured independently of self-report), so it is unlikely that reporting bias explains the results. Self-reported gastrointestinal infections were not defined very precisely, being a secondary outcome, and so measurement error will have reduced the precision of the estimates. Self-report for mild skin irritation was low (under 2/3 responded), so we may have overestimated the incidence or harm. Groups were well balanced and controlling for potential confounders did not materially alter the estimates which suggests confounding is unlikely to explain the results; the number of highly significant results suggest type I error is unlikely; and multiple imputation confirms that missing data probably has limited impact. We showed a relatively short term effect over months so it is unclear whether there is a longer term effect on behaviour, but even if the effect is only short term it is likely to be highly cost-effective.

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

This study informs the debate about the relevance of hand-to-face contact in infection transmission8 16, documenting that both transmission to and from household members is prevented. A 15%-25% relative reduction in infections and 10% for household members, and a 10% reduction in consultations and antibiotic prescriptions are important given the population burden of RTI and the dangers of antibiotic resistance. The impact on individuals outside the home was not measured, so the impact is probably larger than we report, and the potential reach will increase given the ongoing growth in internet access. In the context of seriously heightened risk of infection or its consequences, motivation to undertake preventive behaviour increases, but may not be translated into protective behaviour without specific advice and support, so a significantly greater effect of the intervention on hand-washing and hence infection transmission might be expected in a serious pandemic 25;26. Even if the motivation in a pandemic were sufficient by itself the results still provide convincing evidence that hand-washing reduces viral transmission, and the internet is likely to be a key source of advice in a pandemic13.

The prior systematic review concluded that hand-washing interventions are effective in children, particularly younger children in low income settings, but questioned the evidence for older children and adults9. This study clarifies that both adults and the members of their household are likely to benefit from hand-washing in developed country settings, but the effect is smaller than in resource poor settings - probably due to several factors (e.g. affluence; public health infrastructure; baseline hand-washing frequency and infection rates). The web-based intervention was cost-effective, with reduced costs and improved outcomes.

Approximately 1 in 33 individuals will get minor skin irritation, probably due to drying the skin; we suggested advice to use emollients in week 3 but could do so earlier for those reporting irritation. Notably, no problem was found among those who already had skin problems. The intervention was designed for adults in a household setting, but the applications could be developed for schools and nurseries where transmission is common.

**Conclusions**

An internet intervention to increase hand-washing reduces respiratory and gastrointestinal infections among index patients and household members. Given the heightened concern and access to the internet in a pandemic the intervention also has potential for effective implementation during a pandemic.

**Research in Context:**

Systematic Review.

The routes whereby influenza and other respiratory infections spread are still debated. Simple preventive measures, particularly hand-washing, were recommended by the WHO and in national campaigns during the H1N1 pandemic, but there is a paucity of good randomised evidence. A systematic review of handwashing published in *The Cochrane Library* identified eight cluster-randomised studies tested educational programmes to promote handwashing, on the incidence of respiratory infections. The search included the Acute Respiratory Infections (ARI) Group’s Specialised Register, MEDLINE (1966 to October 2010), OLDMEDLINE (1950 to 1965),EMBASE (1990 to October 2010), CINAHL (1982 to October 2010), LILACS (2008 to October 2010), Indian MEDLARS (2008 to October 2010) and IMSEAR (2008 to October 2010). Because of different definitions, comparisons, lack of reporting of cluster coefficients and (in two cases) missing participant data the authors judged it improper to meta-analyse the data. Two trials reported a lack of effect with risk ratios (RR) for the prevention of acute respiratory illness of 0.94 and 0.97, but two high quality trials reported a significant decrease in respiratory illness in children up to 24 months (RR 0.9010, although not significant in older children: RR 0.9510), and a 50% lower incidence of pneumonia in children aged less than five years of age11. The latter trials were of face-to-face training programmes in hand-washing in very particular settings (day care centres in Australia10; highly deprived areas of a low income country11), and only among young children. There is no good randomised evidence that hand-washing prevents of respiratory infection transmission in broader settings, nor among adults, and most previous interventions involve significant input from experienced trainers.

Interpretation

This randomised trial, by estimating the impact of a hand-washing intervention, helps clarify that hand to mouth transmission is likely to be important, both for respiratory infections overall and for influenza like illness. Among more than 20 thousand adults the study demonstrates that a simple free-standing internet based behavioural intervention to increase hand-washing behaviour among adults effectively reduces ARIs (RR 0.86, 95% CI 0.83, 0.89; p<0.0001) i.e. a 14% reduction - slightly more effective than the more intensive face-to-face behavioural intervention among children in day centres in Australia which found a 10% reduction. The study also demonstrated reduced transmission of ARIs to other family members, reduced gastro-intestinal infections, reduced consultations, and reduced antibiotic prescription. Given the heightened concern during a pandemic and the likelihood of accessing the internet for advice, the intervention also has potential for effective implementation during a pandemic.

All authors have completed the Unified Competing Interest form at <http://www.icmje.org/coi_disclosure.pdf> (available on request from the corresponding author) and declare: no support from any organisation for the submitted work ; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years , no other relationships or activities that could appear to have influenced the submitted work. We are grateful to PZ Cussons for supplying handgel. Data sharing: there is no further data available.

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Contributorship:.

F.D.R. Hobbs (GP and Professor of Primary Care, University of Oxford) developed the protocol for funding, contributed to management of the study, supervised the Birmingham study centre and contributed to the drafting of the paper

Jane Barnett and Jo Kelly (senior trial managers, University of Southampton) developed the protocol, provided day to day overall management of the study, coordinated recruitment in the lead study centre and coordination of other centre, commented on drafts of the paper.

Paul Little (GP and Professor of Primary Care Research, University of Southampton) had the original idea for the protocol, led protocol development and the funding application, supervised the running of the lead study centre and coordination of centres, contributed to the analysis, led the drafting of the paper

Karen Middleton (data manager University of Southampton). Provided administrative support, developed data management protocols, coordinated data entry, and commented on drafts of the paper

Guiqing Yao (Health Economist) with JR developed the protocol for analysis of the notes review data and contributed to the drafting of the paper

Sascha Miller (Health Psychologist, University of Southampton), contributed to protocol development, was responsible for the day to day development and piloting of the intervention, and commented on drafts of the paper.

Judith Joseph (research fellow, University of Southampton) provided expert input to the website development and implementation, and the export and analysis of the online data-set.

Michael Moore (GP and Reader in Primary Care, University of Southampton), developed the protocol for funding, contributed to the management of the study, contributed to the analysis and to the drafting of the paper

Mark Mullee (Lead Study Statistician, Director Research Design Service, University of Southampton) developed the protocol for funding, contributed to study management, supervised data management and the quantitative analysis and contributed to the drafting of the paper

Deborah Popoola (senior trial manager), day to day coordination of the Birmingham study centre, and commented on drafts of the papers

Helen Stokes-Lampard supervised the Birmingham study centre, and commented on drafts of the papers

James Raftery (Professor of Health Economics, University of Southampton), developed the protocol for funding, contributed to the management of the study, supervised the analysis of resource use data, contributed to the drafting of the paper

Beth Stuart. (Study Statistician, University of Southampton) developed the analysis protocol, performed the quantitative analysis, and contributed to drafting of the paper

Helen Stokes-Lampard from part way through the study overall coordination of the Birmingham study centre, and commented on drafts of the papers

Ian Williamson (GP and Senior Lecturer in Primary Care, University of Southampton), developed the protocol for funding, contributed to the management of the study and drafting of the paper

Lucy Yardley (Professor of Health Psychology) developed the protocol and funding application with PL, supervised the development of the intervention, contributed to daily supervision of website issues, contributed to broader study management, and contributed to drafting the paper.

Bill Carman (Professor of Virology) and Douglas Fleming (Director of RCGP Research and Surveillance Centre) developed the protocol for funding, contributed to management of the study, and contributed to the drafting of the paper

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**Table1 Baseline characteristics1**

|  |  |  |
| --- | --- | --- |
|  | **Control** | **Intervention** |
| Female | 5,584/9,981 (55.95%) | 5,584/9,967 (56.02%) |
| Age | 56.50 (13.64) | 56.66 (13.62) |
| Years in education | 8.68 (3.20) | 8.71 (3.19) |
| Size of household | 2.56 (0.95) | 2.55 (0.92) |
| Children under 16 in household | 1,725/9,802 (17.60%) | 1,696/9,798 (17.31%) |
| No ongoing health problems | 6,760/9,578 (70.58%) | 6,648/9,539 (69.69%) |
| Skin condition that may affect handwashing | 1,012/7,325 (13.82%) | 814/6,490 (12.54%) |
| Had an influenza vaccination in the current season | 2,979/8,224 (36.22%) | 2,610/8,035 (32.48%) |
| \*Number of times hands are washed per day\* |  |  |
| 0-2 | 22/653 (3.37%) | 340/9,039 (3.76%) |
| 3-4 | 67/653 (10.26%) | 898/9,039 (9.93%) |
| 5-6 | 150/653 (22.97%) | 2,013/9,039 (22.27%) |
| 7-9 | 155/653 (23.74%) | 2,321/9,039 (25.68%) |
| 10+ | 259/653 (39.66%) | 3,467/9,039 (38.36%) |
| Any respiratory infections in the last year | 7,615/9,728 (78.28%) | 7,827/9,634 (81.24%) |
| Number of respiratory infections in the last year |  |  |
| None | 1,974/9,728 (20.29%) | 1,672/9,635 (17.35%) |
| 1-2 | 5,351/9,728 (55.01%) | 5,216/9,635 (54.15%) |
| 3-5 | 2,108/9,728 (21.67%) | 2,373/9,635 (24.63%) |
| 6+ | 295/9,728 (3.03%) | 374/9,635 (3.88%) |
| Number of days moderate/bad symptoms of respiratory tract infections in last year | 4.90 (5.60) | 4.94 (5.81) |
| Visits to the doctor regarding respiratory infections in the last year | 0.57 (1.22) | 0.56 (1.23) |
| Number of respiratory infections in household members in the last year |  |  |
| None | 2,694/9,722 (27.71%) | 2,286/9,631 (23.74%) |
| 1-2 | 4,107/9,722 (42.24%) | 4,077/9,631 (42.33%) |
| 3-5 | 2,138/9,722 (21.99%) | 2,346/9,631 (24.36%) |
| 6+ | 783/9,722 (8.05%) | 922/9,631 (9.57%) |
| Number of gastrointestinal infections in the last year |  |  |
| None | 5,282/9,574 (55.17%) | 5,014/9,511 (52.72%) |
| 1-2 | 3,046/9,574 (31.82%) | 3,164/9,511 (33.27%) |
| 3-5 | 951/9,574 (9.93%) | 991/9,511 (10.42%) |
| 6+ | 295/9,574 (3.08%) | 342/9,511 (3.60%) |

Data are means (SD) or numbers (%)

**1**Denominators vary due to missing values

\*for Controls it was only a sub-set that was asked the question

**Table 2 Results based on questionnaire at 16 weeks**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Control**  **Number (%)** | **Intervention**  **Number (%)** | **Univariate risk ratio**  **(95% confidence**  **Intervals)** | **Multivariate risk ratio\***  **(95% confidence**  **Intervals)** |
| Any respiratory infections in last 4 months | 5,135/8,667 (59.25%) | 4,242/8,241 (51.41%) | 0.87 (0.84, 0.89; p<0.0001) | 0.86 (0.83, 0.89; p<0.0001) |
| Any respiratory infections in a household member in last 4 months | 4,193/8,551 (49.04%) | 3,545/8,075 (43.90%) | 0.90 (0.86, 0.93; p<0.0001) | 0.88 (0.85, 0.92; p<0.0001) |
| Any gastrointestinal infection in last 4 months | 1,821/7,229 (25.19%) | 1,376/6,410 (21.47%) | 0.85 (0.80, 0.91; p<0.0001) | 0.82 (0.76, 0.88; p<0.0001) |
| Any influenza-like illness in the last 4 months | 613/ 8,244 (7.44%) | 449/8,047 (5.58%) | 0.75 (0.67, 0.84; p<0.0001) | 0.80 (0.72, 0.92; p=0.001) |
|  | Control  Mean(sd)  Median (IQR) | Intervention  Mean(sd)  Median (IQR) | Univariate incident rate ratio | Multivariate incident rate ratio\* |
| Number of respiratory infections in last 4 months | 1.09 (1.36)  1 (0,2) | 0.84 (1.13)  1 (0,1) | 0.77 (0.74, 0.80; p<0.0001) | 0.75 (0.72, 0.79; p<0.0001) |
| Number of respiratory infections in household member in last 4 months | 1.17 (2.07)  1 (0,2) | 0.93 (1.48)  0 (0,1) | 0.80 (0.76, 0.84; p<0.0001) | 0.79 (0.74, 0.83; p<0.0001) |
| Number of days moderate/bad symptoms in all study participants (no infection = 0 days) | 2.60 (4.44)  1 (0,3) | 2.08 (4.00)  0 (0,3) | 0.95 (0.90, 1.00; p=0.043) | 0.92 (0.87, 0.98; p=0.009) |
| Number of days of moderate/bad symptoms in those who had an infection | 4.25 (5.29)  3 (1,5) | 3.92 (4.78)  2 (1,5) | 0.94 (0.88, 1.00; p=0.035) | 0.92 (0.86, 0.98; p=0.007) |

\*Controlling for sex, age over 65, ongoing health problem, skin condition before or during study that might affect frequency of handwashing, children under 16 in household, respiratory illness in the last year, number of household members, whether they had a flu vaccine

**Table 3 Results based on monthly questionnaires**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Control**  **Number (%)** | **Intervention Number (%)** | **Univariate risk ratio**  **(95% confidence**  **Intervals)** | **Multivariate risk ratio**  **(95% confidence**  **Intervals)** |
| Any respiratory infection in the last month | 9,091/30,865 (29.45%) | 7,287/27,868 (26.15%) | 0.88 (0.85, 0.91; p<0.0001) | 0.85 (0.83, 0.88; p<0.0001) |
| Influenza-like illness in the last month | 692/32,060 (2.16%) | 521/31,992 (1.63%) | 0.79 (0.71, 0.86; p<0.0001) | 0.85 (0.77, 0.94; p=0.001) |
| Household member with a respiratory infection in the last month | 9,714/30,710 (31.63%) | 7,640/27,668 (27.61%) | 0.87 (0.84, 0.89; p<0.0001) | 0.83 (0.80, 0.86; p<0.0001) |
| Illness occurring in index individual within one week of a household member having a similar illness | 2,757/30,803 (8.95%) | 2,157/27,800 (7.76%) | 0.86 (0.81, 0.91; p<0.0001) | 0.86 (0.81, 0.91; p<0.0001) |
| Another household member gets a similar infection within a week of index individual having it? | 2,274/25,780 (8.82%) | 1,606/23,670 (6.78%) | 0.76 (0.71, 0.81; p<0.0001) | 0.74 (0.69, 0.79; p<0.0001) |

**Table 4 Results based on notes review**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Control**  **Number (%)** | **Intervention Number (%)** | **Univariate risk ratio**  **(95% confidence**  **Intervals)** | **Multivariate risk ratio**  **(95% confidence**  **Intervals)** |
| Antibiotic use in primary case within 4 months | 617/9579  (6.44%) | 535/9540  (5.61%) | 0.87 (0.78, 0.97; p=0.016) | 0.83(0.74, 0.94;p=0.002) |
| Antibiotic use in primary care within 12 months | 1008/9579  (10.52%) | 891/9540  (9.34%) | 0.89 (0.81, 0.96; p=0.006) | 0.85 (0.77, 0.93; p<0.0001) |
| Consultation in primary care or hospitalisation with respiratory infection within 4 months | 1021/9579  (10.66%) | 951/9540  (9.97%) | 0.93 (0.86, 1.02; p=0.117) | 0.90 (0.82, 0.98; p=0.014) |
| Consultation in primary care or hospitalisation with respiratory infection within 12 months | 1653/9579  (17.26%) | 1527/9540  (16.01%) | 0.93 (0.87, 0.99; p=0.020) | 0.90 (0.84, 0.96; p=0.001) |

**Table 5 Results based on questionnaire at 16 weeks – all 4 intervention groups (with 95% confidence**

**intervals)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Any respiratory infections in last 4 months | Any respiratory infections in a household member in last 4 months | Any gastrointestinal infection in last 4 months | Any respiratory infections in last 4 months | Any respiratory infections in a household member in last 4 months | Any gastrointestinal infection in last 4 months |
|  | Univariate risk ratio | | | Multivariate risk ratio | | |
| Control | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Control with baseline handwashing questions | 0.93 (0.87, 1.00; p=0.053) | 0.95 (0.87, 1.04; p=0.242) | 0.88 (0.74, 1.05; p=0.162) | 0.94 (0.89, 1.01; p-0.109) | 0.95 (0.87, 1.03; p=0.208) | 0.91 (0.78, 1.09; p=0.320) |
| Intervention without baseline handwashing questions | 0.94 (0.87, 1.01; p=0.077) | 0.87 (0.79, 0.96; p=0.004) | 0.76 (0.63, 0.91; p=0.002) | 0.93 (0.87, 1.01; p=0.060) | 0.89 (0.82, 0.98; p=0.020) | 0.79 (0.65, 0.95; p=0.013) |
| Intervention  With baseline handwashing questions | 0.86 (0.83, 0.88); p<0.0001) | 0.89 (0.86, 0.92; p<0.0001) | 0.85 (0.80, 0.91; p<0.0001) | 0.87(0.84, 0.89; p<0.0001) | 0.90 (0.87, 0.93; p<0.0001) | 0.84 (0.79, 0.90; p<0.0001) |

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**Appendix 1.**

**Details of the intervention.** The first session provided ‘core’ pages which included information about: the medical team; the importance of preventing seasonal and pandemic flu; the role of hand-washing in interrupting transmission; and instructions for picking up a supply of hand-gel from their physician’s office. Participants entered details of their current hand-washing habits and completed a plan to maximise intention formation for hand-washing. Automated tailored feedback helped users improve their plan (by highlighting situations in which users could increase the frequency of hand-washing), and participants were encouraged to sign the plan and post it up in a prominent place in the household to help involve household members. An automated email was sent to participants after four days to login to Session 2. Invitations to Sessions 3 and 4 followed at weekly intervals, and two follow-up emails were sent to those who didn’t login to any session.

The three subsequent sessions were aimed at reinforcing helpful attitudes and norms and addressed negative beliefs. They included expert recommendations for hand-washing (technique and frequency). Feedback to reinforce hand-washing was tailored to self-reported intended frequency of hand-washing, and the perceived difficulty and efficacy of carrying out the behaviour; those reporting low perceived efficacy were shown information to promote more positive efficacy beliefs, those reporting high perceived difficulty were given advice about overcoming barriers, and those reporting high intended hand-washing adherence were shown pages with additional advice (e.g. on other preventative measures, and involving other family members). Based on a key issue identified in piloting (that demotivation could occur when contracting an infection despite hand-washing), we also included advice on how to reduce infection transmission in other ways (e.g. through social distancing). The demonstration version of the website can be found at <https://www.lifeguideonline.org/player/play/primitdemo>.

|  |  |
| --- | --- |
| Session | Content |
| Session 1 | * Details of the medical team (enhancing credibility). * Information about:   + The importance of preventing seasonal and pandemic flu.   + How viruses are transmitted.   + The role of hand-washing in interrupting transmission. * Questions about the participant’s current hand washing habits in different situations. * Completion of a plan to set hand-washing goals (intention formation). Participants could access and update this plan throughout the intervention. * Automated personalised feedback on the plan. * Provision of a printable version of the plan and encouragement to sign and display this in a prominent place to involve other household members. * Information about collecting a free hand gel from the GP surgery. |
| Session 2 | * Tailored feedback based on participants’ perceived benefits and difficulty of hand-washing, and intended hand-washing (repeated in Sessions 3 and 4). * True or false quiz about cold and flu facts. * Information about cleanliness perceptions (dirt is not always visible). * Evidence of the effectiveness of hand washing. * Expert recommendations for frequency of hand-washing. * Information about specific situations where hand washing is important. * Information about making hand washing a habit. |
| Session 3 | * True or false quiz about hand washing facts (addressing negative beliefs). * Expert recommendations for hand-washing techniques. * Information about transmission caused by touching your face. * Information about where germs are prevalent. * Information about the transmission of viruses from person to person. * Overcoming barriers to hand washing (time, dry hands). |
| Session 4 | * Raising benefit perceptions of hand washing. * Reinforcing hand washing as a social norm. * True or false quiz about cold and flu facts. * Evidence and information about the importance of hand-washing for children. |
| Other information (optional) | * Links to relevant websites, to printable posters and wall charts. * Information about the experts involved in the creation of PRIMIT. * References to scientific evidence about the benefits of hand-washing. * Extra information about flu. * Advice on how to reduce infection transmission using methods other than hand-washing (e.g. through social distancing). |

**Adherence.** Good adherence (defined as our target of handwashing 10+ times per day at 16 weeks) was reported in 36.6% of the control group and 53.1% of the Intervention group (odds ratio 1.96 (1.83, 2.10); p<0.0001) (see table below).

**Supply of materials:** Participants could choose to wash hands with water and soap or with alcohol based handgel. A limited supply of hand gel was provided to practices (up to 4 small bottles of Carex gel (PZCussons) per intervention participant). However only 3660/19,948 (18.35%) participants reported collecting hand gel.

**Handwashing at baseline and follow up**

|  |  |  |
| --- | --- | --- |
|  | **Control** | **Intervention** |
| Number of times hands washed per day at baseline (for those who were asked this question) |  |  |
| 0-2 | 22/653 (3.37%) | 340/9,039 (3.76%) |
| 3-4 | 67/653 (10.26%) | 898/9,039 (9.93%) |
| 5-6 | 150/653 (22.97%) | 2,013/9,039 (22.27%) |
| 7-9 | 155/653 (23.74%) | 2,321/9,039 (25.68%) |
| 10+ | 259/653 (39.66%) | 3,467/9,039 (38.36%) |
| Number of times hands washed per day at 4 month follow-up (for those who were asked this question) |  |  |
| 0-2 | 367/8677 (4.23%) | 119/8270 (1.44%) |
| 3-4 | 874/8677 (10.07%) | 369/8270 (4.46%) |
| 5-6 | 1918/8677 (22.10%) | 1181/8270 (14.28%) |
| 7-9 | 2290/8677 (26.39%) | 2240/8270 (27.09%) |
| 10+ | 3228/8667 (37.20%) | 4361/8270 (52.73%) |

**Appendix 2. Reasons given for non participation**

|  |  |
| --- | --- |
| **NotNot eligible:** | **Total** |
| Not eligible: |  |
| I live in a flat or house with no other people …………………………………………… | **4,943 (27%)** |
| I do not have access to the internet or an email address……………………………... | **7,910 (43%)** |
| Nobody in my household is willing to share information on their illnesses …………. | **592 (3%)** |
| Another member of my household is currently taking part in the study ……………... | **872 (5%)** |
| I am already taking part in another study ………………………………………………. | **326 (2%)** |
|  |  |
| Other reasons |  |
| I am currently suffering from ill health and feel unable to take part …………………. | **981 (5%)** |
| Coughs and colds are generally not a problem to me and I don’t think the study will help me……………………………………………………………………………………. | **3,256 (18%)** |
| I am working abroad and /or out of the country frequently …………………………… | **595 (3%)** |
| I don’t have time to take part ……………………………………………………………... | **1,475 (8%)** |
| I am moving or changing PHYSICIAN …………………………………………………... | **249 (1%)** |
| I do not wish to take part in the study ………………………………………………….. | **5,125 (28%)** |
| **Total number of forms returned\*** | **18,266** |

\*235,383 forms were sent out i.e. a 7.8% return rate. Totals of the reasons do not add to the total number of forms returned as some people gave more than one reason of forms returned.

Appendix 3.

**Table 6. Missing data analysis**

|  |  |
| --- | --- |
| **Variable** | **Percent missing data** |
| Sex | 0.6% |
| Age | 0.6% |
| Number of household members | 5.8% |
| Children under 16 | 2.3% |
| Skin condition at baseline that may affect handwashing | 31.2% |
| Skin condition during the study that may affect handwashing | 33.1% |
| Influenza vaccination in the current season | 30.0% |
| Ongoing health problem | 4.7% |
| Any respiratory infection in the last 4 months | 17.7% |
| Number of respiratory infections in the last 4 months | 17.8% |
| Any respiratory infections in household members in the last 4 months | 19.1% |
| Any gastrointestinal infection in the last 4 months | 32.0% |
| Complication of illness (otitis media, quinsy, cellulitis, sinusitis) | 4.7% |
| Complication of illness (any) | 4.7% |
| Reconsultation/hospitalisation | 4.7% |
| Complication of treatment | 4.7% |
| Monthly panel data for primary outcome:  Month 1 | 23.6% |
| Month 2 | 25.1% |
| Month 3 | 28.9% |
| Month 4 | 30.0% |

**Table 7. Multiple imputation analysis (with 95% confidence intervals)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Imputed data (50 imputations)** | | **Complete cases** | |
|  | Univariate risk ratio | Multivariate risk ratio | Univariate risk ratio | Multivariate risk ratio |
| Any respiratory infections in last 4 months | 0.86 (0.84, 0.89; p<0.0001) | 0.85 (0.83, 0.88; p<0.0001) | 0.87 (0.84, 0.89; p<0.0001) | 0.86 (0.83, 0.89; p<0.0001) |
| Any respiratory infections in a household member in last 4 months | 0.91 (0.88, 0.93; p<0.0001) | 0.88 (0.85, 0.91; p<0.0001) | 0.90 (0.86, 0.93; p<0.0001) | 0.88 (0.85, 0.91; p<0.0001) |
| Any gastrointestinal infection in last 4 months | 0.86 (0.81, 0.91; p<0.0001) | 0.85 (0.80, 0.90; p<0.0001) | 0.85 (0.80, 0.91; p<0.0001) | 0.82 (0.76, 0.88; p<0.0001) |

**Table 8. Comparison or non-participants and participants\***

|  |  |  |
| --- | --- | --- |
|  | **Non-participants** | **Participants** |
| Female | 300,269/601,721 (49.90%) | 11,242 /20,061 (56.04%) |
| Age | 46.99 (17.89) | 56.58 (13.61) |
| Index of Multiple Deprivation (IMD) Rank | 18485.61 (8779.38) | 21824.17 (7533.38) |

\*We had data from 285 practices on the age, sex of the patients that they contacted, regardless of whether those patients went

on to participate in the study. Only 179 practices were able to supply postal codes which enabled allocation of deprivation rating.

**TRIAL CHECKLIST based on CONSORT statement:**

**Reported? If Y: Page no**

1a.TITLE Identify the study as RCT Y 1

1b. Abstract: Use structured format Y 2

Introduction 2a. Back ground and rationale Y 3

2b. Specific trial objectives Y 3

Protocol: 3a. Trial design Y 4

3b Changes to methods after trial commencement Y 4

.

4a Study population eligibility criteria Y 4

4b Settings and location where data was collected Y 4

5. Intervention and timing Y 4-5

5. Objectives Y 3

6a Outcome measures: pre-specified 1y/2y outcomes Y 5-6

6a Outcome measures: any changes Y 5

7a Sample size Y 6

7b Interim analysis/stopping rules Y 6

Randomisation: 8a methods used Y 5

8b type of randomization Y 4

9 mechanism used to implement (e.g. sequential pots) Y 4

10 who generated allocation sequence, who assigned Y 4

Blinding 11a Who blinded after assignment Y 4-5

11b Description of the similarity of interventions Y 4-5

Stats methods 12a Methods used to compare groups Y 6

12b Other analyses (subgroups, adjusted) Y 6

Results 13a Provide trial flow diagram (assigned,treated,analysed) Y Fig 1

13b Losses, exclusions, reasons Y 7 and Fig 1

Recruitment 14a Periods and follow-up Y 5

14b Why trial ended or stopped Y 6

15. Baseline data for outcomes Y table 1

16. State numbers analysed and intention to treat Y 6 and table 2

Outcomes: 17a) Estimated effect sizes and precision Y tables 2 to 8

17b For Binary absolute and relative effect sizes Y tables 2 to 8

18. Ancillary analyses subgroup/adjusted/pre-specified) Y 6

19. Harms/adverse events Y 8

20. Trial limitations Y 9

21 Generaliseability Y 9

22 Interpretation Y 9-10

Other: 23 Registration Y 2

24 Site of full trial protocol This can be provided

25. Funding Y 1