An internet-delivered handwashing intervention to modify influenza-like illness and respiratory infection transmission (PRIMIT): a primary care randomised trial

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Summary

Background Handwashing to prevent transmission of respiratory tract infections (RTIs) has been widely advocated, especially during the H1N1 pandemic. However, the role of handwashing is debated, and no good randomised evidence exists among adults in non-deprived settings. We aimed to assess whether an internet-delivered intervention to modify handwashing would reduce the number of RTIs among adults and their household members.

Methods We recruited individuals sharing a household by mailed invitation through general practices in England. After consent, participants were randomised online by an automated computer-generated random number programme to receive either no access or access to a bespoke automated web-based intervention that maximised handwashing intention, monitored handwashing behaviour, provided tailored feedback, reinforced helpful attitudes and norms, and addressed negative beliefs. We enrolled participants into an additional cohort (randomised to receive intervention or no intervention) to assess whether the baseline questionnaire on handwashing would affect handwashing behaviour. Participants were not masked to intervention allocation, but statistical analysis commands were constructed masked to group. The primary outcome was number of episodes of RTIs in index participants in a modified intention-to-treat population of randomly assigned participants who completed follow-up at 16 weeks. This trial is registered with the ISRCTN registry, number ISRCTN75058295.

Findings Across three winters between Jan 17, 2011, and March 31, 2013, we enrolled 20 066 participants and randomly assigned them to receive intervention (n=10 040) or no intervention (n=10 026). 16 908 (84%) participants were followed up with the 16 week questionnaire (8241 index participants in intervention group and 8667 in control group). After 16 weeks, 4242 individuals (51%) in the intervention group reported one or more episodes of RTI compared with 5135 (59%) in the control group (multivariate risk ratio 0·86, 95% CI 0·83–0·89; p<0·0001). The intervention reduced transmission of RTIs (reported within 1 week of another household member) both to and from the index person. We noted a slight increase in minor self-reported skin irritation (231 [4%] of 5429 in intervention group *vs* 79 [1%] of 6087 in control group) and no reported serious adverse events.

Interpretation In non-pandemic years, an effective internet intervention designed to increase handwashing could have an important effect in reduction of infection transmission. In view of the heightened concern during a pandemic and the likely role of the internet in access to advice, the intervention also has potential for effective implementation during a pandemic.

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Introduction

Patient presentations with respiratory tract infections (RTIs) result in overstretched primary care services and hospital bed shortages as a result of complications,[1–7] particularly during an influenza pandemic.

The routes through which influenza and other RTIs spread are debated, but probably involve close contact (via droplets) and hand-to-face contact.[8] Handwashing was recommended by WHO during the H1N1 pandemic, but a systematic review identified only two high-quality trials[9] that were face-to-face training programmes in handwashing among children (daycare centres in Australia[10] and highly deprived areas of a low-income country[11]). There is no good randomised evidence in broader settings, or among adults, and most previous interventions have involved substantial input from experienced trainers, which restricts implementation.

Rapidly available, low-cost interventions are needed because most of the population contract RTIs and because of the increased risk in a pandemic.[12] The internet is an ideal format; it is widely accessed (according to the UK Office for National Statistics, 22 million UK households [84% of the total] had internet access in 2014), and the internet has been shown to be the first source of information accessed by members of the public in a pandemic.[13] Findings from study of a small web-based intervention to reduce transmission of influenza[14] showed trends in behaviour change, but no effect on hand hygiene.

Previously, we developed and piloted an internet-based intervention to modify handwashing requiring no

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face-to-face training,[15–17] which was shown to increase handwashing.[16] Here, we report the full trial to assess the effect of the intervention on infections in households.

Methods

Study design and participants

In an open-label, primary care, randomised trial, we enrolled adult patients (aged 18 years or older) identified from computerised lists in general practitioner (GP) practices in England, for whom there was at least one other individual living in the household who was willing to report illness to the index person. Exclusion criteria were patients with severe mental problems (eg, major uncontrolled depression or schizophrenia, dementia, or severe mental impairment) or who were terminally ill, and those reporting a skin complaint that would restrict handwashing. Any GP practice was eligible, and widespread practice recruitment continued until recruitment targets were reached. We only sent only one questionnaire per household and excluded new participants from households that had already joined the study.

Postal invitations were sent to people aged over 18 randomly sampled from the lists of GP 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 one in ten randomly chosen practices sent out forms.

Because the aim of the study was to capture the infective period for respiratory infections in autumn, winter, and spring, we limited follow-up to 4 months, and stopped recruiting participants after the March of each winter.

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. The study was approved by a multicentre research ethics committee (number 08/H0502/14).

See Online for appendix

For the **web-based intervention** see https://www.lifeguideonline.org/player/play/primitdemo

Randomisation and masking

Participants were automatically randomly assigned by the intervention software when they registered for the trial online. The unit of randomisation was the index person within each household. Participants were randomly assigned at the point of consent in a 1:1 ratio to receive access to the web-based intervention (with a baseline questionnaire about handwashing practices), or no access to the web-based intervention (with no baseline questionnaire about handwashing practices).

Additionally, we enrolled a cohort of patients who were randomly assigned in a 1:1 ratio to receive control (no web-based intervention) with the baseline questionnaire about handwashing practices, or intervention (access to web-based intervention) without the baseline questionnaire. This modification was made after findings from the pilot study[16] were reported and the independent trial steering committee agreed that the baseline measures (ie, administration of the baseline questionnaire about handwashing) might modify handwashing behaviours by providing a prompt to change behavoiur. The modification was made after the trial started enrolment.

The original intention was to stratify randomisation (by age >65 years; influenza vaccination status; size of family, children younger than 16 years living at home; willingness of other members of the family to use the website; and attendance in the previous year with respiratory infections). However, we decided to use simple randomisation, both because the size of the trial rendered stratification unnecessary and to minimise the logistic difficulty of randomisation.

Blinding of participants to treatment allocation was not possible in an open trial. The statistical analysis commands were done masked to treatment allocation, but the statistician was unmasked at the stage of combining groups from the additional enrolled cohort (ie, those assigned to control with the baseline questionnaire, or intervention without the baseline questionnaire).

Procedures

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 influenza and the role of handwashing, developed a plan to maximise intention formation for handwashing, reinforced helpful attitudes and norms, and addressed negative beliefs and used tailored feedback. Automated emails were used to prompt participants (to use sessions, to complete the monthly questionnaires, and in the intervention group questions on a monthly basis to maintain handwashing) and so were an integral part of the intervention (appendix). A demonstration version of the web-based intervention is available online.

The control group did not have access to the intervention webpages. Similar to the intervention group, the control group had access to the GP practice in the normal way for respiratory illnesses. We sent feedback forms to non-participants requesting information about why they did not enrol in the study.

Outcomes

The primary outcome was the number of index individuals that reported one or more RTIs at 16 weeks. We postulated 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. Prespecified secondary outcomes were duration of

symptoms, transmission of respiratory infections, gastrointestinal infections, attendance at the practice, and use of health service resources.

The original study 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 (ie, infections since study commencement reported at 16 weeks). Maximum follow-up for the primary outcome was achieved by an additional brief questionnaire and then telephone calls for non-responders.

We documented episodes of infection and their duration by self-report, because these outcomes can be remembered reasonably reliably over several weeks.[18,19] All participants were sent invitations to complete the online outcome assessment measures monthly (at 4, 8, 12, and 16 weeks after initial login) irrespective of progress through the sessions. Participants received two follow-up emails for each assessment, then a mailed questionnaire and structured phone follow-up for non-responders at 16 weeks.

For each monthly questionnaire and the final questionnaire, the index person documented the nature and duration of the infection. We classified illnesses as RTIs on the basis of consensus definitions developed in previous studies,[20,21] defined as two symptoms of an RTI for at least 1 day or one symptom for two consecutive days. For reported influenza-like illness, we did not use definitions from WHO or the Centers for Disease Control and Prevention because these definitions require measured temperature, and thus were not appropriate (participants were not included after a clinical examination) and we did not use the European Centre for Disease Prevention and Control definition (one systemic and one respiratory symptom) because, according to the international Influenzanet collaboration, this definition does not necessarily differentiate influenza-like illness from a common cold. Influenzanet suggests making high temperature a separate element. Our pragmatic definition of influenza-like illness therefore required a high temperature (feeling very hot or very cold; or measured temperature >37·5°C), a respiratory symptom (sore throat, cough, or runny nose), and a systemic symptom (headache, severe fatigue, severe muscle aches, or severe malaise).

For the **Influenzanet collaboration** see https://www.influenzanet.eu

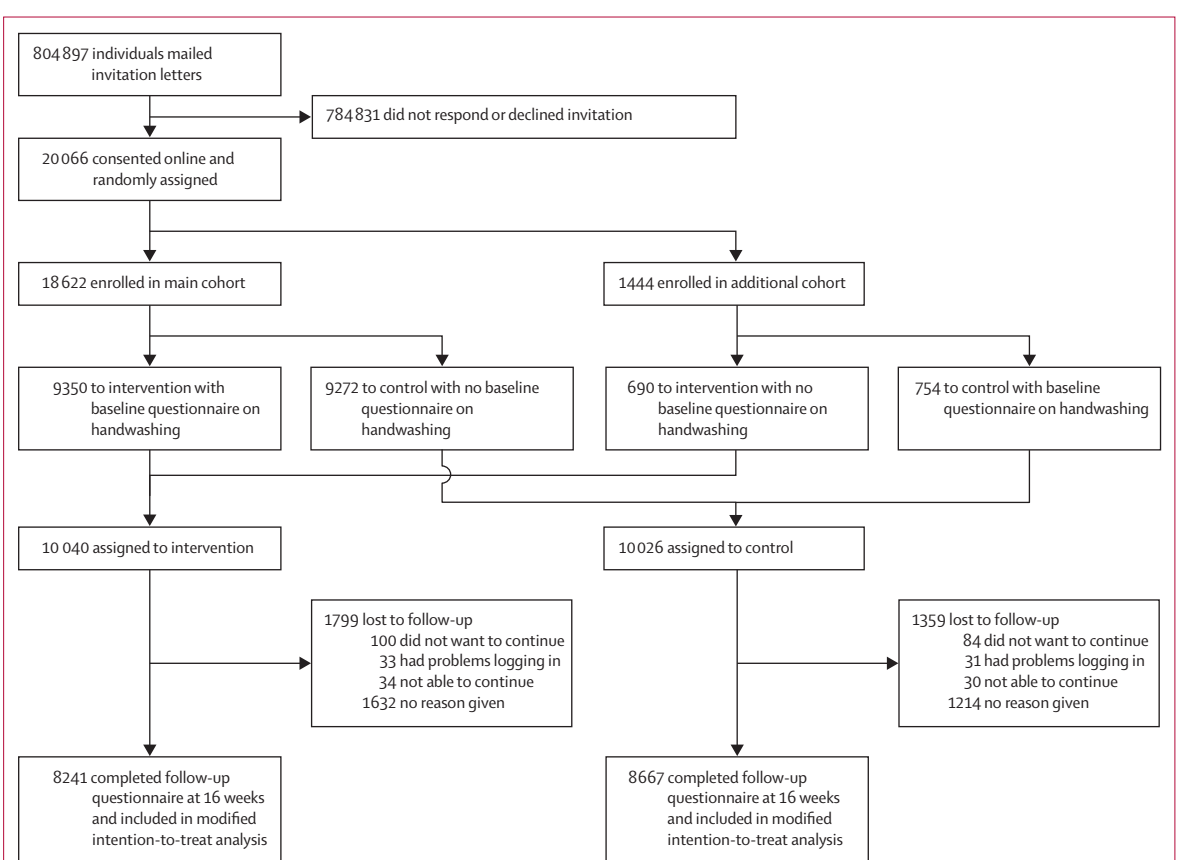

Figure: **Study profile**

In the monthly and final questionnaires participants documented the duration of symptoms rated moderately bad (which are the most likely to be sensitive to change[19] and can be remembered reliably over a period of a few weeks[18,19]); and the number of days where work or normal activities were impaired.[19] 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 (ie, probable transmission from a family member) or after the index person (ie, probable transmission from the index person). Both the monthly questionnaire and the final questionnaire asked participants to document episodes of "watery, loose bowel movements or vomiting lasting at least 24 h".

We postulated that the intervention would reduce the number of health service contacts by reducing the number of episodes of acute respiratory infection. At 12 months after 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 influenza-like illness or other respiratory tract infections.[22] Assessment of the notes was made blind to the group, and has been shown to be reliable and unbiased.[23]

	Control	Intervention
Gender		
Men	4397/9981 (44%)	4383/9967 (44%)
Women	5584/9981 (56%)	5584/9967 (56%)
Age	56·5 (13·6)	56·7 (13·6)
Years in education	8·68 (3·2)	8·7 (3·2)
Number of individuals in household	2·6 (1·0)	2·6 (0·9)
Children younger than 16 years in household	1725/9802 (18%)	1696/9798 (17%)
No ongoing health problems	6760/9578 (71%)	6648/9539 (70%)
Skin condition that could affect handwashing	1012/7325 (14%)	814/6490 (13%)
Had an influenza vaccination in the current season	2979/8224 (36%)	2610/8035 (32%)
Number of times hands washed per day*		
0–2	22/653 (3%)	340/9039 (4%)
3–4	67/653 (10%)	898/9039 (10%)
5–6	150/653 (23%)	2013/9039 (22%)
7–9	155/653 (24%)	2321/9039 (26%)
≥10	259/653 (40%)	3467/9039 (38%)
Any respiratory infections in the past year	7615/9728 (78%)	7827/9634 (81%)
Number of respiratory infections in the past year		
None	1974/9728 (20%)	1672/9635 (17%)
1–2	5351/9728 (55%)	5216/9635 (54%)
3–5	2108/9728 (22%)	2373/9635 (25%)
≥6	295/9728 (3%)	374/9635 (4%)
Number of days with moderate or bad symptoms of respiratory tract infections in past year	4·9 (5·6)	4·9 (5·8)
Visits to the doctor for respiratory infections in the past year	0·6 (1·2)	0·6 (1·2)
Number of respiratory infections in household members in the past year		
None	2694/9722 (28%)	2286/9631 (24%)
1–2	4107/9722 (42%)	4077/9631 (42%)
3–5	2138/9722 (22%)	2346/9631 (24%)
≥6	783/9722 (8%)	922/9631 (10%)
Number of gastrointestinal infections in the past year		
None	5282/9574 (55%)	5014/9511 (53%)
1–2	3046/9574 (32%)	3164/9511 (33%)
3–5	951/9574 (10%)	991/9511 (10%)
≥6	295/9574 (3%)	342/9511 (4%)

Data are n/N (%) or mean (SD). Denominators vary due to missing values. *Only a subset of individuals in the control group asked the question.

Table 1: **Baseline characteristics**

Statistical analysis

We estimated that a minimum of 15 908 participants would be needed to detect a 10% relative reduction in respiratory infections (18% *vs* 20%, odds ratio [OR] 0·88) for 80% power, an α 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 reduction of roughly 10% or greater. In the additional cohort, to detect the effect of administration of the baseline questionnaire, we used the estimated difference in the mean number of handwashes between the control group and the control group with baseline questions in the pilot study (mean difference 0·22; SD 1·15). To detect a similar difference in the main study, and allowing for 20% loss to follow-up, 80% power, and α of 0·05, we estimated we would need 540 people per subgroup.

We did no interim analyses. The primary analysis was a modified intention-to-treat analysis of all participants randomly assigned to receive intervention or control who completed follow-up surveys at 16 weeks with no imputation of missing data. We report multivariate risk ratios; multivariate analysis was specified for the primary endpoint, but controlling factors were specified based on the analysis rather than being prespecified. We did a secondary analysis using multiple imputations (50 imputations) by chained equations, imputing all variables simultaneously. We analysed the binary outcome data after 16 weeks using a logistic model, and count outcomes using a negative binomial model. We converted ORs to risk ratios using the formula of Zhang and Yu.[24] For the monthly data (serial panel data), we based the analysis on repeated measures logistic regression. We report 95% CIs. We explored possible effects in prespecified subgroups (estimating the interaction term for the intervention): age older than 65 years; influenza vaccination status; family size; children younger than 16 years; previous attendance with respiratory infections; and skin complaints. The full economic analysis will be reported elsewhere. We calculated the intracluster coefficients (ICC) for practice

	Control	Intervention	Univariate risk ratio	Multivariate risk ratio*	Univariate incident rate ratio	Multivariate incident rate ratio*
Any respiratory infections in past 4 months	5135/8667 (59%)	4242/8241 (51%)	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 past 4 months	4193/8551 (49%)	3545/8075 (44%)	0·90 (0·86–0·93; p<0·0001)	0·88 (0·85–0·92; p<0·0001)	..	..
Any gastrointestinal infection in past 4 months	1821/7229 (25%)	1376/6410 (21%)	0·85 (0·80–0·91; p<0·0001)	0·82 (0·76–0·88; p<0·0001)	..	..
Any influenza-like illness in the past 4 months	613/8244 (7%)	449/8047 (6%)	0·75 (0·67–0·84; p<0·0001)	0·80 (0·72–0·92; p=0·001)	..	..
Number of respiratory infections in past 4 months	..	..	..	..	0·77 (0·74–0·80; p<0·0001)	0·75 (0·72–0·79; p<0·0001)
Mean (SD)	1·09 (1·36)	0·84 (1·13)	..	..	..	..
Median (IQR)	1 (0–2)	1 (0–1)	..	..	..	..
Number of respiratory infections in household member in past 4 months	..	..	..	..	0·80 (0·76–0·84; p<0·0001)	0·79 (0·74–0·83; p<0·0001)
Mean (SD)	1·17 (2·07)	0·93 (1·48)	..	..	..	..
Median (IQR)	1 (0–2)	0 (0–1)	..	..	..	..
Number of days moderate or bad symptoms in all study participants (no infection is 0 days)	..	..	..	..	0·95 (0·90–1·00; p=0·043)	0·92 (0·87–0·98; p=0·009)
Mean (SD)	2·60 (4·44)	2·08 (4·00)	..	..	..	..
Median (IQR)	1 (0–3)	0 (0–3)	..	..	..	..
Number of days of moderate or bad symptoms in those who had an infection	..	..	..	..	0·94 (0·88–1·00; p=0·035)	0·92 (0·86–0·98; p=0·007)
Mean (SD)	4·25 (5·29)	3·92 (4·78)	..	..	..	..
Median (IQR)	3 (1–5)	2 (1–5)	..	..	..	..

Data are n/N (%) or effect size between control and intervention (95% CI; p value) unless otherwise stated. Table shows data for participants in the modified intention-to-treat population (ie, those who were randomly assigned, who completed the questionnaire at 16 weeks). *Controlling for sex, age older than 65 years, ongoing health problem, skin condition before or during study that might affect frequency of handwashing, children younger than 16 years in household, respiratory illness in the past year, number of household members, and whether participant had received an influenza vaccine.

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

	Control	Intervention	Univariate risk ratio	Multivariate risk ratio
Any respiratory infection in the past month	9091/30 865 (29·5%)	7287/27 868 (26·1%)	0·88 (0·85–0·91; p<0·0001)	0·85 (0·83–0·88; p<0·0001)
Influenza-like illness in the past month	692/32 060 (2·2%)	521/31 992 (1·6%)	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 past month	9714/30 710 (31·6%)	7640/27 668 (27·6%)	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	2757/30 803 (9·0%)	2157/27 800 (7·8%)	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?	2274/25 780 (8·8%)	1606/23 670 (6·8%)	0·76 (0·71–0·81; p<0·0001)	0·74 (0·69–0·79; p<0·0001)

Data are n/N (%) or risk ratio (95% CI; p value). Table shows sum of responses from all monthly questionnaires.

Table 3: **Results based on monthly questionnaires**

in Stata by assuming that practice is a random effect in a mixed model and then used post-estimation commands to give the ICC and its confidence interval. We used StataSE version 13 for all statistical analyses.

This trial is registered with the ISRCTN registry, number ISRCTN75058295.

Role of the funding source

The study was funded by the Medical Research Council (study number 09/800/22). Neither the funder nor the sponsor (the University of Southampton) had any part in the study design, the collection, analysis, or interpretation of the data, or in the writing of the report. BS, JJ, MMu,

	Control	Intervention	Univariate risk ratio	Multivariate risk ratio
Antibiotic use in primary case within 4 months	617/9579 (6%)	535/9540 (6%)	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 (11%)	891/9540 (9%)	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 (11%)	951/9540 (10%)	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%)	1527/9540 (16%)	0·93 (0·87–0·99; p=0·020)	0·90 (0·84–0·96; p=0·001)

Data are n/N (%) or risk ratio (95% CI; p value).

Table 4: **Results based on notes review**

	Control	Control with baseline handwashing questions	Intervention without baseline handwashing questions	Intervention with baseline handwashing questions
Any respiratory infections in past 4 months				
n	8015	652	7640	601
Univariate risk ratio	1·00	0·93 (0·87–1·00; p=0·053)	0·94 (0·87–1·01; p=0·077)	0·86 (0·83–0·88; p<0·0001)
Multivariate risk ratio	1·00	0·94 (0·89–1·01; p-0·109)	0·93 (0·87–1·01; p=0·060)	0·87(0·84–0·89; p<0·0001)
Any respiratory infections in a household member in past 4 months				
n	7918	647	7489	593
Univariate risk ratio	1·00	0·95 (0·87–1·04; p=0·242)	0·87 (0·79–0·96; p=0·004)	0·89 (0·86–0·92; p<0·0001)
Multivariate risk ratio	1·00	0·95 (0·87–1·03; p=0·208)	0·89 (0·82–0·98; p=0·020)	0·90 (0·87–0·93; p<0·0001)
Any gastrointestinal infection in past 4 months				
n	486	6750	5915	499
Univariate risk ratio	1·00	0·88 (0·74–1·05; p=0·162)	0·76 (0·63–0·91; p=0·002)	0·85 (0·80–0·91; p<0·0001)
Multivariate risk ratio	1·00	0·91 (0·78–1·09; p=0·320)	0·79 (0·65–0·95; p=0·013)	0·84 (0·79–0·90; p<0·0001)

Data are risk ratio (95% CI; p value).

Table 5: **Results based on questionnaire at 16 weeks, by baseline questionnaire on handwashing**

GY, and LY had access to the raw data; PL had full access to all of the data and the final responsibility for the decision to submit for publication.

Results

344 physician offices were recruited over a wide area of England, and 20 066 participants were enrolled and randomly assigned between Jan 17, 2011, and March 31, 2013 (winter 1 [Jan 17, 2011, to March 23, 2011], n=427; winter 2 [Nov 10, 2011, to April 30, 2012], n=3553, with only 25 participants recruited in April and March; and winter 3 [Oct 19, 2012, to March 31, 2013], n=16 086). 10 040 index participants were assigned to intervention and 10 026 were assigned to control (figure).

Medical notes reviews were completed among 19 117 (95%) participants. Table 1 shows the baseline characteristics of participants in the intervention and control groups. Most participants in the intervention group completed at least part of all four of the sessions (median 4 [IQR 1–4] sessions; mean 2·9 [SD 1·3]). We noted no evidence of any practice-level effects and the ICC values were very small (ICC for the primary outcome measure 0·009, 95% CI 0·005–0.016), so estimates were generated without taking into account clustering by practice.

16 908 (84%) participants completed the questionnaire at 16 weeks (8241 in intervention group and 8667 in control group) and were included in our modified intention-to-treat analysis. After 16 weeks, 4242 individuals (51%) in the intervention group reported one or more episodes of RTI compared with 5135 (59%) in the control group (multivariate risk ratio 0·86; 95% CI 0·83–0·89; p<0·0001; table 2). There were also fewer episodes of influenza-like illness in the intervention group than in the control group. We noted similar reductions for household members. We noted slightly less severe infections among individuals who reported infections; because individuals in the intervention group had fewer infections, they had half a day less of moderately bad symptoms overall (mean 2·1 days [SD 4·0] *vs* 2·6 days [4·4]). There were fewer total number of days of infections (5·2 days [SD 8·4] *vs* 6·5 days [9·0]; multivariate incident rate ratio 0·91, 95% CI 0·87 to 0·95, p<0·0001) and, among those who reported infections, shorter duration of illness (9·8 days *vs* 10·6 days; 0·91, 0·87–0·95; p<0·0001). Participants in the intervention group also reported fewer gastrointestinal infections. We noted no differential effects of the intervention for the main outcome in for any of the subgroups identified in advance (data not shown).

Data from the monthly questionnaires suggested that transmission of infection was reduced both to the index person and from the index person (table 3). The estimate for month 1 for the index person (risk ratio 0·84, 95% CI 0·81–0·88) was similar to the overall effect, as were the household data (0·84, 0·80–0·88), which suggests consistent reliable recall over the 16 week period (data not shown). Review of medical notes suggested fewer consultations over the 16 week period and 1 year (table 4). Similarly, we noted fewer antibiotic prescriptions over 16 weeks and 1 year. Although estimates are imprecise because of small numbers, analysis of participants in the additional cohort suggested a trend towards fewer infections in the

control group when they were asked baseline questions about handwashing (table 5).

As expected, most variables at baseline or from the chart review had few items missing (mostly less than 5%; appendix), which was similar between the randomisation groups; multiple imputation provided very similar results to the complete case analysis for the primary outcome (appendix). Questions about performance of work or daily tasks were poorly answered (n=9350); for those answering we noted no difference between groups (risk ratio 1·01, 95% CI 0·91–1·12, p=0·824).

Compared with individuals who were invited but did not participate in the study, participants were slightly more likely to be women, older (non-participants mean age 47·0 years [SD 17·9], participants mean age 56·6 years [13.6]), and less deprived (appendix). We noted no evidence of interaction or effect modification with intervention group for these variables, and their inclusion in the analysis did not modify the estimates. 235 810 feedback forms were sent out to non-participants, of which 18 266 (8%) were returned citing reasons for non-participation (appendix). Of these individuals returning these forms, 4943 (25%) reported not participating because they lived alone and 7910 (43%) because they did not have easy access to the internet.

Four infection-related hospital admissions occurred during the study (two in the control group and two in the intervention group). Minor self-reported skin irritation increased among those who responded to the question (231 [4%] of 5429 *vs* 79 [1%] of 6087, p<0·0001) for those who did not report problems at baseline, but no effect on consultations for skin complaints. Among individuals who had a skin complaint at baseline, reported skin complaints did not increase (423 [53%] of 803 in intervention group compared with 539 [55%] of 986 in control group; p=0·402).

Discussion

Findings from this large, primary care, open-label randomised study suggest that a self-accessed internet intervention to increase handwashing reduces the number and severity of infections among both index patients and their households (panel).

There are some potential limitations to the study, in particular, a free-standing website would be expected to attract individuals more interested in preventing infections; however, this population was the intended sample for our study. Having demonstrated effectiveness, the intervention would be expected to attract a wider sample. Although the intervention content was complex, implementation required few resources because all the content, tailoring, and email reminders were automated. Participants were less deprived, older, and more likely to be women compared with non-participants, but controlling for these features made little difference to the estimates. The very large sample made self-report the only feasible method to determine whether infections occurred. Monthly reporting would not have captured detailed data for each illness, but daily diaries over months are also affected by reporting bias, and infections are well remembered over weeks.[18] Both groups were asked questions about infections, and any non-differential measurement error would have underestimated effectiveness. The monthly questionnaires, including from the first month, provided similar results to the fourth month. Additionally, the intervention affected gastrointestinal infections, consultations, and antibiotic prescribing (measured independently of self-report), so reporting bias is unlikely to account for the results. Self-reported gastrointestinal infections were not defined very precisely, being a secondary outcome, and so measurement error might have reduced the precision of the estimates.

Panel: Research in context

Systematic review

The routes whereby influenza and other respiratory infections spread are still debated. Simple preventive measures, particularly handwashing, were recommended by the WHO and in national campaigns during the H1N1 pandemic, but there is a paucity of good randomised evidence. A Cochrane review[9] of handwashing identified eight cluster-randomised studies testing the effect of educational programmes to promote handwashing on the incidence of respiratory infections. The search included the Acute Respiratory Infections 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 investigators judged it improper to meta-analyse the data. Findings from two trials showed a lack of effect with risk ratios for the prevention of acute respiratory illness of 0·94 and 0·97, but findings from two high-quality trials showed a significant decrease in respiratory illness in children aged up to 24 months (risk ratio 0·90,[10] although not significant in older children [risk ratio 0·95]), and a 50% decreased incidence of pneumonia in children younger than 5 years.[11] These trials were of face-to-face training programmes in handwashing in very particular settings (day care centres in Australia[10] and highly deprived areas of a low-income country[11]), and only among young children. There is no good randomised evidence that handwashing prevents respiratory infection transmission in broader settings, nor among adults, and most previous interventions involve significant input from experienced trainers.

Interpretation

Our randomised trial, by estimating the effect of a handwashing 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 20 000 adults, the study findings demonstrate that a simple free-standing internet-based behavioural intervention to increase handwashing behaviour among adults effectively reduces acute respiratory infections (risk ratio 0·86, 95% CI 0·83–0·89; p<0·0001), equivalent to a 14% reduction and slightly more effective than the more intensive face-to-face behavioural intervention among children in daycentres in Australia (10% reduction). The study findings also showed reduced transmission of acute respiratory infections to other family members, reduced gastrointestinal infections, reduced consultations, and reduced antibiotic prescription. In view of 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.

Self-report for mild skin irritation was low (less than two-thirds of participants answered this question), so we might have overestimated the incidence or harm of this effect. Groups were well balanced and controlling for potential confounders did not materially alter the estimates, suggesting that confounding is unlikely to explain our results; the number of highly significant results suggest that type I error is unlikely, and multiple imputation lent support to the notion that missing data probably had little effect on our overall results. We showed a fairly short-term effect over months, so whether there is a longer-term effect on behaviour is unclear.

Our study findings inform the debate about the relevance of hand-to-face contact in infection transmission,[8,16] suggesting that both transmission to and from household members is prevented. A 15–25% relative reduction in infections (10% for household members) and a 10% reduction in consultations and antibiotic prescriptions are important in view of the population burden of RTI and the dangers of antibiotic resistance. We did not measure the effect of our intervention on individuals outside the home, so the overall effect is probably larger than reported here, and its potential reach will probably increase in view of 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 might not be translated into protective behaviour without specific advice and support; a substantially increased effect of the intervention on handwashing and hence infection transmission might therefore 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 handwashing reduces viral transmission, and the internet is likely to be a key source of advice in a pandemic.[13]

A previous systematic review concluded that handwashing interventions are effective in children, particularly younger children in low-income settings, but questioned the evidence for older children and adults.[9] Our study findings clarify that both adults and the members of their household are likely to benefit from handwashing in high-income countries, but the effect is smaller than in resource-poor settings, probably due to several factors (eg, affluence, public health infrastructure, baseline handwashing frequency, and infection rates).

Roughly one in every 33 individuals who received the intervention in our study had minor skin irritation, probably due to drying of the skin; we suggested advice to use emollients in week 3, but could do so earlier for individuals reporting irritation. Notably, we did not note increased problems in individuals 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.

In conclusion, our intervention to increase handwashing reduced respiratory and gastrointestinal infections among index patients and household members. In view of heightened concern in a pandemic and widespread availability of internet access, the intervention also has potential for effective implementation during a pandemic.

Contributors

FDRH developed the protocol for funding application, contributed to management of the study, supervised the Birmingham study centre, and contributed to the drafting of the paper. JB and JK developed the protocol, provided day-to-day overall management of the study, coordinated recruitment in the lead study centre and coordination of other centre, and commented on drafts of the Article. PL 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, and led the drafting of the Article. KM provided administrative support, developed data management protocols, coordinated data entry, and commented on drafts of the Article. GY with JR developed the protocol for analysis of the notes review data and contributed to the drafting of the Article. SM contributed to protocol development, was responsible for the day-to-day development and piloting of the intervention, and commented on drafts of the Article. JJ provided expert input to the website development and implementation, and the export and analysis of the online dataset. MMo developed the protocol for funding, contributed to the management of the study, and contributed to the analysis and to the drafting of the Article. MMu developed the protocol for funding, contributed to study management, supervised data management and the quantitative analysis, and contributed to the drafting of the Article. DP did day-to-day coordination of the Birmingham study centre and commented on drafts of the Article. HS-L supervised the Birmingham study centre, and commented on drafts of the Article. JR developed the protocol for funding, contributed to the management of the study, supervised the analysis of resource use data, and contributed to the drafting of the Article. BS developed the analysis protocol, did the quantitative analysis, and contributed to drafting of the Article. IW developed the protocol for funding and contributed to the management of the study and drafting of the Article. LY 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 Article. WC and DF developed the protocol for funding, contributed to management of the study, and contributed to the drafting of the Article.

Declaration of interests

We declare no competing interests.

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References

1 Zambon M, Stockton J, Clewley J, Fleming DM. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet* 2001; **358:** 1382–83.

2 MacFarlane J, Holmes W, Gard P, et al. Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *Thorax* 2001; **56:** 109–14.

3 Simpson J, MacFarlane J, Watson J, Woodhead J. A national confidential enquiry into community acquired pneumonia deaths in young adults in England and Wales. *Thorax* 2001; **55:** 1040–45.

4 Woodhead MA, MacFarlane J, McCraken JS, Rose D, Finch R. Prospective study of the aetiology and outcome of pneumonia in the community. *Lancet* 1987; **329:** 671–74.

5 Meier C, Jick S, Derby L, Vasilakis C, Jick H. Acute respiratory-tract infections and risk of first-time acute myocardial infarction. *Lancet* 1998; **351:** 1467–1471.

6 Madjid M, Naghavi M, Litovsky S, Casscells S. Review: current perspective influenza and cardiovascular disease: a new opportunity for prevention and the need for further studies. *Circulation* 2003; **108:** 2730.

7 Smeeth L, Thomas S, Hall A, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004; **351:** 2611–18.

8 Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M. Transmission of influenza A in human beings. *Lancet Infect Dis* 2007; **7:** 257–65.

9 Jefferson T, Del Mar C, Dooley L, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. *Cochrane Database Syst Rev* 2011; **7:** CD006207.

10 Roberts L, Smith W, Jorm L, Patel M, Douglas R, McGilchrist C. Effect of infection control measures on the frequency of upper respiratory infection in child care: a randomized, controlled trial. *Pediatrics* 2000; **105:** 738–42.

11 Luby S, Agboatwalla M, Feikin D, et al. Effect of handwashing on child health: a randomised controlled trial. *Lancet* 2005; **366:** 225–33.

12 Brug J, Aro R, Richardus J. Risk perceptions and behaviour: towards pandemic control of emerging infectious diseases: international research on risk perception in the control of emerging infectious diseases. *Int J Behav Med* 2014; **16:** 3–6.

13 Janssen A, Tardif R, Landry S, Warner J. Why tell me now? The public and healthcare providers weigh in on pandemic influenza messages. *J Public Health Manag Pract* 2006; **12:** 388–394.

14 Bourgeois F, Simons W, Olson K, Brownstein J, Mandl K. Evaluation of influenza prevention in the workplace using a personally controlled health record: Randomized controlled trial. *J Med Internet Res* 2008; **10:** e5.

15 Yardley L, Miller S, Teasdale E, Little P, Primit Team. Using mixed methods to design a web-based behavioural intervention to reduce transmission of colds and flu. *J Health Psychol* 2011; **16:** 353–64.

16 Yardley L, Miller S, Scholz W, Little P. Evaluation of a Web-based intervention to promote hand hygiene: exploratory randomized controlled trial. *J Med Internet Res* 2011; **13:** e107.

17 Miller S, Yardley L, Little P. Development of an intervention to reduce transmission of respiratory infections and pandemic flu: measuring and predicting hand-washing intentions. *Psychol Health Med* 2012; **17:** 59.

18 Little PS, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. An open randomised trial of prescribing strategies for sore throat. *BMJ* 1997; **314:** 722–27.

19 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.

20 Lee G, Salomon J, Friedman J, et al. Illness transmission in the home: a possible role for alcohol-based hand gels. *Pediatrics* 2005; **115:** 852–60.

21 Sandora T, Taveras E, Shih M, Resnick E, Lee G, Ross-Degnan R. A randomized, controlled trial of a multifaceted intervention including alcohol-based hand sanitizer and hand-hygiene education to reduce illness transmission in the home. *Pediatrics* 2005; **116:** 587–94.

22 Hay A, Fahey T, Peters T, Wilson A. Predicting complications from acute cough in pre-school children in primary care: a prospective cohort study. *Br J Gen Pract* 2004; **54:** 9–14.

23 Little PS, Gould C, Williamson I, Warner G, Gantley M, Kinmonth AL. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ* 1997; **315:** 350–52.

24 Zhang J, Yu K. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998; **280:** 1690–91.

25 Morrison L, Yardley L. What infection control measures will people carry out to reduce transmission of pandemic influenza? A focus group study. *BMC Public Health* 2009; **9:** 258.

26 Bish A, Yardley L, Nicoll A, Michie S. Factors associated with uptake of vaccination against pandemic influenza: a systematic review. *Vaccine* 2011; **29:** 6472–84.

27 Milne S, Sheeran P, Orbell S. Prediction and intervention in health-related behavior: a meta-analytic review of protection motivation theory. *J Appl Soc Psychol* 2000; **30:** 106–43.

28 Rodgers R. Cognitive and physiological processes in fear appeals and attitude change: a revised theory of protection motivation. In: Cacioppo J, Petty R, Shapiro D, eds. Social Psychophysiology, 1st edn. London: Guildford, 1983: 153–76.

29 Witte K, Allen M. A meta-analysis of fear appeals: implications for effective public health campaigns. *Health Educ Behav* 2006; **27:** 591–615.