Author's response to reviews

Title: The role of facemasks and hand hygiene in the prevention of influenza transmission in households: results from a cluster randomised trial; Berlin, Germany, 2009-2011.

Authors:

Thorsten Suess (SuessT@rki.de)
Cornelius Remschmidt (RemschmidtC@rki.de)
Susanne B. Schink (SchinkS@rki.de)
Brunhilde Schweiger (SchweigerB@rki.de)
Andreas Nitsche (NitscheA@rki.de)
Kati Schroeder (SchroederK@rki.de)
Joerg Doellinger (DoellingerJ@rki.de)
Jeanette Milde (MildeJ@rki.de)
Walter Haas (HaasW@rki.de)
Irina Koehler (IrinaKoehler@gmx.net)
Gérard Krause (KrauseG@rki.de)
Udo Buchholz (BuchholzU@rki.de)

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Author's response to reviews: see over
Dear Madam, dear Sir,

hereby we submit our revised manuscript entitled “The role of facemasks and hand hygiene in the prevention of influenza transmission in households: results from a cluster randomised trial; Berlin, Germany, 2009-2011” for publication as “Research article” in BMC Infectious Diseases. We included our answers to the referee’s comments in this cover letter (see below). Passages corresponding to actual changes made in the manuscript are printed in italics.

Yours faithfully,

Dr. Thorsten Suess

Robert Koch Institute
Department of Infectious Disease Epidemiology
DGZ-Ring 1, 13086 Berlin, Germany
SuessT@rki.de
Telephone: 0049-30-18754-3541, Fax: 0049-18754-3341

Responses to Referee 1

Comment 1. Top of page 9, I wonder whether "subclinical" would be better terminology than "asymptomatic".

Answer 1: This has been changed.

Comment 2. Near top of page 9, please clarify whether EUR150 was paid per participating person (i.e. to each index case and each household member) or per participating household. If per person, this seems like a large amount.

Answer 2: It was paid per participating person. We agree that the reimbursement was large. In our experience, however, this proved necessary in order to make recruitment feasible especially in light of the high number of household visits and specimens we intended to obtain.

“Possible limitations to the interpretation of the study’s results due to reimbursements are discussed near the end of the discussion section: Finally, we cannot rule out the possibility that behaviour of participating households may have been influenced by monetary incentives and frequent household visits. However, they did not differ in all three study arms so we do not expect this to have biased our results. Furthermore, the other clinical trials had a similar design so that it should not endanger comparability of results.”

Comment 3. Near top of page 9 - please consider slightly expanding the description of sample collection, so that this manuscript can be read and the study replicated without reference to [#9].

Answer 3: The “Sample collection and laboratory methods” subsection has been enhanced and now reads like this:

“For the collection of nasal wash, we used 5 mL of isotonic saline, which were instilled into one nostril with participants heads tilted backwards. Participants were asked to remain in this position for 10–15 s while making hard ‘K’ sounds without swallowing. Subsequently, the participants were told to tilt their heads forward and the fluid was collected in a sterile cup [11]. Nasal swabs were collected by using virus transport swabs (Mastaswab™; MAST Diagnostica, Reinfeld, Germany). Samples were stored refrigerated (at a temperature of approximately 5 °C) before analysis [12].”
**Comment 4.** Bottom of page 9, power calculation, please could you add a note on the observed overall effect sizes in the Hong Kong and Bangkok studies, i.e. point estimates ranging from a 43% reduction to a 20% increase in risk.

**Answer 4:** Our reason to consider a 75% reduction of risk as the basis of our sample size calculation was the anticipation of a higher adherence compared to the Hong Kong and Bangkok studies. This was supported by our pilot study which was conducted during the influenza season 2008/09 and which showed high levels of adherence. Accordingly, we were confident to achieve similar good adherence in the main study and thus be able to detect a higher and stronger effect of the interventions.

To reflect this we added the following sentence to the discussion section: “Our sample size calculation was based on a 75% reduction of risk due to the interventions. This may seem questionably high in comparison to other studies, however based on experience from our pilot study we felt that adherence would be better than reported in the Hong Kong [5] and Bangkok [7] studies. We therefore expected a larger effect size in our main study.”

**Comment 5.** Page 10 - "... adjusting for potential confounders." Please note that these variables should not be confounders assuming your randomization was implemented as stated. To be a confounder here, a variable must be associated with the intervention as well as the outcome. Perhaps rephrase as "...variables potentially associated with risk of secondary infection...”

**Answer 5:** This has been changed. The sentence now reads “We used a forced-entry method adjusting for variables potentially associated with risk of secondary infection (including age, sex, timely antiviral therapy of the index, vaccination of household contacts, etc).”

**Comment 6.** Table 1 contains a lot of numbers and some may be redundant. For example in the first Control group column, all the “/13” may be deleted since n=13 is stated at the top of the column, and a footnote added for chronic illness that data were missing for one participant.

**Answer 6:** Thank you for this suggestion. As there are several different missing data especially for household contacts in the intervention groups, a lot of footnotes would be necessary, thus potentially annulling the positive effect from the shortening. However, we would like to ask the editor about her/his preference, which we would be happy to accommodate.

**Comment 7.** Please confirm in the methods whether swabs from household contacts were tested for both A and B regardless of index case influenza type, and if so please mention in the results whether all PCR-confirmed infections in household contacts were of the same type as the index case. More detailed analysis to confirm household transmission could be done by viral sequencing (as reported by Papenburg 2010 Clin Infect Dis, Poon et al. 2011 J Clin Virol) but comparison of types would be an easier way to reassure readers that secondary cases were infected by the corresponding household index case.

**Answer 7:**
Secondary cases were only tested for either influenza A or B depending on the infection of the index patient.

We have included this limitation in the “Discussion” section:
“A further limitation is the fact that laboratory testing of household contacts was only conducted for the virus subtype the index patient was infected with. This could have led to an underestimation of secondary cases.”

Comment 8. In Table 3 please clarify whether the ORs are univariable or multivariable. It seems from the footnote that the ORs come from separate models each only including one variable plus the intervention group.

Answer 8:
The legend for table 3 was enhanced:
“Table 3: Separate models for predictors of secondary infection among included households. Independent variables: (i) intervention group, (ii) intervention group (with pooled data of M and MH group), (iii) one separate model for each individual variable that may influence household transmission of influenza (i.e. age, sex, timely antiviral therapy of the index, vaccination of household contacts) adjusted for intervention group.”

To clarify this aspect further, we also enhanced the methods section which now reads:

The intention-to-treat analysis was conducted in the following order:
1. Comparison of SAR between intervention groups via adjusted chi-square tests [17] (overall and stratified by virus subtype, season and time of implementation of intervention) to account for the cluster design of the study. We used a cluster bootstrapping technique for the calculation of 95% confidence intervals (95% CI) [18].
2. We used the generalized estimating equations (GEE) approach to fit logistic regression models [19] for evaluation and comparison of SAR between intervention groups. First, we calculated Odds Ratios (OR) for the outcome “laboratory confirmed influenza” with the following independent variables: (i) intervention group, (ii) intervention group (with pooled data of M and MH group), (iii) one separate model for each individual variable that may have influenced household transmission of influenza (i.e. age, sex, timely antiviral therapy of the index, vaccination of household contacts, etc) adjusted for intervention group. This corresponds to a univariable analysis with the exception of the adjustment for intervention group.
3. Calculation of ORs for the clinical case definition (otherwise as in 2.).
4. Calculation of ORs for the outcome “laboratory confirmed influenza” to analyse the effect of the interventions while adjusting for variables with possible influence on influenza transmission. In a further model we used the variable intervention group with pooled data of M and MH group.
5. Calculation of ORs for the outcome “laboratory confirmed influenza” adjusting for variables with possible influence on influenza transmission in the following subgroups: (i) only data from season 2009/10, (ii) only data from season 2010/11, (iii) only data from households with full implementation of intervention <36h after symptom onset of the index case, (iv) only influenza A(H1N1)pdm09 cases. We used a forced-entry method adjusting for variables potentially associated with risk of secondary infection. Sample sizes for these subgroups analyses were small and sometimes did not allow the inclusion of the full list of variables.

The per-protocol-analysis was conducted according to the intention-to-treat analysis but only with data from participants who had followed the assigned interventions.”

Comment 9. Discussion, bottom of page 32 could one other reason for greater reported adherence be the greater frequency of home visits compared to the Hong Kong and Bangkok studies? Please consider showing a little more caution in comparing self-reported adherence between studies, since reporting behaviours
may differ for cultural or other reasons. The last sentence may clarify that there was "high overall /reported/ adherence". Certainly the magnitude of the effect observed in this study is consistent with good adherence to the interventions.

**Answer 9:** We included the following sentence at the end of the named paragraph to clarify this limitation: “However, adherence data in all studies were based on self reporting and differences in reporting behaviour may have influenced results.”

**Response to Referee 2**

**Background**

**Comment 1.** It might be worth highlighting that other groups have recently highlighted the need for more research in this area including the Institute of Medicine of the National Academies (Committee on Personal Protective Equipment for Healthcare Workers During an Influenza Pandemic, 2010)

**Answer1:** We incorporated the respective reference into the “Background” section: “Since 2006, the World Health Organisation (WHO) and other organisations have highlighted the need for controlled trials to assist in formulating recommendations on the use of non-pharmaceutical interventions (NPI) - such as facemasks or hand hygiene measures - as options to prevent influenza transmission, particularly in households [1, 2].”

**Comment 2.** When referring to the studies conducted to date, I think it is important to include a sentence which outlines that the study designs have been different and that only one study has compared masks/respirators while the other studies have focused on comparing different interventions.

**Answer2:** The introduction was enhanced with this sentence: “Regarding interventions, one study compared facemasks to respirators [6], another evaluated facemasks only [4], while three studies assessed facemasks, and/or hand hygiene measures in various combinations [3, 5, 7].”

**Comment 3.** In regards to the following sentence (‘In all publications, it was hypothesised that the effect...’) could you include some of the data from the observational studies which examine the use of the interventions (especially mask use) during SARs or pandemic H1N1.

**Answer3:** The introduction was enhanced with this sentence: “In all publications, it was hypothesized that the effect of interventions may be more pronounced in the case of an influenza pandemic, due to higher public anxiety with resulting higher rates of adherence. This was supported by observations made in a comparable crisis, namely the SARS epidemic.”

**Methods**

**Comment 4.** How many recruitment sites were included in the study and who was responsible for recruitment?

**Answer4:** There were 20 recruitment sites in season 2009/10 and 12 in 2010/11. Only the physicians at the respective study sites were responsible for recruitment. After recruitment, further study-related tasks were fulfilled by the physician’s assistants.

The methods section was enhanced: “Index patients were recruited by general practitioners or pediatricians. We cooperated with 20 study sites in 2009/10 and 12
study sites in 2010/11 evenly distributed in the city of Berlin. We included index patients if they presented at the study sites within two days of symptom onset...”

**Comment 5.** How were you able to blind the physicians in the randomisation process? Did they not need to distribute the masks/hand rub out to the parents?

**Answer 5:** The methods section was enhanced as follows:

“Intervention material was given to the study sites in closed boxes marked only with the randomisation number. Recruiting physicians were not aware of the allocation of the numbers to the interventions and the boxes for the three intervention arms looked identical. After randomisation, participants were given their box by the physician’s assistants”

All these measures helped to insure that the physicians remained blinded towards the allocated interventions.

**Comment 6.** Who determined the fit of the mask for the child? Was this done at recruitment? Or was it during the follow up visit?

**Answer 6:** The decision on which mask to use for the children was made provisionally during the initial telephone conversation with study personnel based on oral information by the parents. Final assessment of the mask’s fit was done during the first household visit. We clarified this in the methods section: “If masks intended for participants younger than 14 years did not fit properly (as assessed by study personnel during the first household visit), we asked them to wear adult masks instead.”

**Comment 7.** In each of the households, were there a maximum number of people who could participate? If there were not present at the initial recruitment visit, how were they consented?

**Answer 7:** There was no maximum for the number of participating household members. We took care that all participating household members were present during the first household visit when informed consent was obtained and scheduled the visits accordingly.

**Comment 8.** How many masks were participants provided with on a daily basis? When were they instructed to change them?

**Answer 8:** At the start of the study, all households in M or MH arms received 50 facemasks for adults and 50 facemasks for children. When the number of adults or children respectively was greater than three, households received a further 50 facemasks of that size. Households in the MH group received one large bottle (500ml) of alcohol based hand rub for the whole household and one small bottle (100ml) for each individual participant of the household.

During the following household visits, the number of remaining facemasks and hand hygiene material was constantly assessed by study personnel and replenished if necessary.

We did not provide participants with fixed times after which to change facemasks, but rather told them to change them “regularly during the day” (as already stated in the manuscript).

**Comment 9.** Can you please clarify what you mean in the following sentence: ‘When household members developed fever.....they were asked to adopt the same preventative behaviour...’
Answer 9: The sentence was enhanced accordingly for clarification: “When household members developed fever (>38.0°C), cough, or sore-throat they were asked to adopt the same preventive behaviour as the index patient (i.e. use facemasks or hand hygiene measures as required by index patients to protect other healthy household members) until the end of the observation period.”

Comment 10. Can the authors please revise the paragraph at the bottom on page 8. It is currently a series of short sentences. Also, can you please provide further information about the use of antiviral therapy- was this provided to the index case or to the families? If it was provided to the families- information about the impact of its use should be included in the results (beyond the table).

Answer 10: The paragraph on the bottom of page 8 was restructured. The definition of “children” was moved to the beginning of the methods section under the design subheading. The rest of the paragraph with a revised section on antiviral medication now reads as follows:

Antiviral medication was given to index patients and secondary cases by their individual physicians based on their clinical evaluation independent of study procedures. By definition, a “timely” antiviral therapy started within two days of symptom onset.

When household members developed fever (>38.0°C), cough, or sore-throat they were asked to adopt the same preventive behaviour as the index patient (i.e. use facemasks or hand hygiene measures as required by index patients to protect other healthy household members) until the end of the observation period. All participants self-recorded symptoms (fever, shivering, measured temperature, cough, sore throat) and daily routines (incl. the time spent at home, and within close range (i.e. <2m) of the index patient) in a daily monitoring questionnaire.

Outcome definitions

The primary outcome measure for secondary cases was qRT-PCR confirmed influenza infection. We defined a symptomatic secondary influenza virus infection as a laboratory confirmed influenza infection in a household member who developed fever (>38.0°C), cough, or sore-throat during the observation period. We termed all other secondary cases as subclinical. A secondary outcome measure was the occurrence of ILI as defined by WHO [11] as fever plus cough or sore throat.”

Comment 11. Did the participants know about the reimbursement at the time of recruitment? Especially as it is quite a large reimbursement.

Answer 11: Potential participants were informed about details of the study (including reimbursement) before recruitment by their physician. We agree that the reimbursement was large. In our experience, however, this proved to be necessary in order to make recruitment feasible especially in light of the high number of household visits and specimens we intended to obtain.

Possible limitations to the interpretation of the study’s results due to reimbursements are discussed on the bottom of the discussion section:

“Finally, we cannot rule out the possibility that behaviour of participating households may have been influenced by monetary incentives and frequent household visits. However, they did not differ in all three study arms so we do not expect this to have biased our results. Furthermore, the other clinical trials had a similar design so that it should not endanger comparability of results.”
Comment 12. Did you specify the times where participants were not required to wear their masks (if any)? Previous studies have stated meal times, when sleeping or when the index case was away from the residence.

Answer 12: Part of this information was already included in the manuscript. This was enhanced and now reads as follows: “Facemasks were to be changed regularly during the day and not to be worn during the night or outside the household.” Index patients were asked to take meals separately from household contacts, thus making it unnecessary to wear masks during these situations.

Comment 13. Have you tested whether there was any differences in quality and efficacy (in lab controlled conditions) between the two brands of masks used in the study? Why did you decide to use two different brands?

Answer 13: We decided to use adult facemasks as provided by LCH Medical Products, France because these were identical to the facemasks used in the study of Canini et al. Children’s masks were chosen out of practical and logistic reasons (in particular availability). We tested neither brand for quality and efficacy.

Comment 14. Can you please provide the reference for the WHO definition of ILI

Answer 14: This has been included in the manuscript. The reference is: WHO global technical consultation: global standards and tools for influenza surveillance. WHO, 2011. [http://whqlibdoc.who.int/hq/2011/WHO_HSE_GIP_2011.1_eng.pdf].

Comment 15. It would be useful if the authors used some more headings in the methods section: objectives, outcomes, randomisation, blinding, statistical methods etc. Also, a table outlining the components of the different arms would also be useful.

Answer 15: The following subheadings have been added to the methods section: Design, Informed consent, Randomisation and Blinding, Follow up, Outcome definitions, Adherence, Reimbursement, Sample collection and laboratory methods, Sample size estimation and statistical analysis, Ethics statement, Trial Registration Concerning the second point, we believe that a table outlining the components of the interventions might only provide redundant information that is already incorporated in the main text. However, we would like to leave the final decision on this question to the editor. We would be happy to provide a table if it is deemed helpful.

Comment 16. It would be better if the information regarding the virus transmission was reported separately and that the first paragraph was dedicated to report the statistically significant differences between the arms.

Answer 16: Although this could be a sensible approach in some cases, we would prefer to leave the structure as it is (thus leading from descriptive analysis of the study population to the overall number of secondary infection to the effect of the interventions in the whole study population and in different subgroups) as we believe this to be more intuitive.

Please note that in response to comment 8 of referee 1 we enhanced the methods section on statistical analysis considerably, thus possibly also addressing this comment.

Comment 17. Can you please comment on symptom onset to randomisation- what was the range in time/median etc.

Answer 17: Information now included in table 1 and the text of the results section: “Finally, in 2009/10 randomisation occurred significantly earlier after symptom onset
compared to 2010/11 (p=0.004) and a higher proportion of households was visited by study personnel within 36 hours (p= 0.04)."

Discussion

Comment 18.
In regards to your statement about influenza B transmission (page 30)- has there been any studies to support this?

Answer 18: To our knowledge, there have not been any studies about this subject. As we agree that it is highly hypothetical, we erased the respective statement from the discussion section.