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2   **Title page**

3   Full title: Identifying Human Encounters that Shape the Transmission of *Streptococcus*

4   *Pneumoniae* and Other Respiratory Infections

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22 **Abstract**

23 Although patterns of social contacts are believed to be an important determinant of

24 infectious disease transmission, there is little empirical evidence to back this up. Indeed, no

25 previous study has linked individuals' risk of respiratory infection with their current pattern

26 of social contacts. We explored whether the frequency of different types of social

27 encounters were associated with current pneumococcal carriage and self-reported acute

28 respiratory symptoms (ARS), though a survey in Uganda in 2014. In total 566 participants

29 were asked about their daily social encounters and about symptoms of ARS in the last two

30 weeks. A nasopharyngeal specimen was also taken from each participant. We found that the

31 frequency of physical (i.e. skin-to-skin), long (≥1h) and household contacts – which capture

32 some measure of *close* (i.e. relatively intimate) contact –, was higher among pneumococcal

33 carriers than non-carriers, and among people with ARS compared to those without,

34 irrespective of their age. With each additional physical encounter the age-adjusted risk of

35 carriage and ARS increased by 6% (95%CI 2-9%) and 9% (1-18%) respectively. In contrast, the

36 number of *casual* contacts (<5 minutes long) was not associated with either pneumococcal

37 carriage or ARS. A detailed analysis by age of contacts showed that the number of close

38 contacts with young children (<5 years) was particularly higher among older children and

39 adult carriers than non-carriers, while the higher number of contacts among people with

40 ARS was more homogeneous across contacts of all ages. Our findings provide key evidence

41 that the frequency of *close* interpersonal contact is important for transmission of respiratory

42 infections, but not that of *casual* contacts. Such results strengthen the evidence for public

43 health measures based upon assumptions of what contacts are important for transmission,

44   and are important to improve disease prevention and control efforts, as well as inform

45   research on infectious disease dynamics.

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62 **Author summary**

63 Although social contacts are an important determinant for the transmission of many

64 infectious diseases it is not clear how the nature and frequency of contacts shape individual

65 infection risk. We explored whether frequency, duration and type of social encounters were

66 associated with someone's risk of respiratory infection, using nasopharyngeal carriage (NP)

67 of *Streptococcus pneumoniae* and acute respiratory symptoms as endpoints. To do so, we

68 conducted a survey in South-West Uganda collecting information on people's social

69 encounters, respiratory symptoms, and pneumococcal carriage status. Our results show

70 that both pneumococcal carriage and respiratory symptoms are independently associated

71 with a higher number of social encounters, irrespective of a person's age. More specifically,

72 our findings strongly suggest that the frequency of *close* contacts is important for

73 transmission of respiratory infections, particularly pneumococcal carriage. In contrast, our

74 study showed no association with the frequency of short *casual* contacts. Those results are

75 essential for both improving disease prevention and control efforts as well as informing

76 research on infectious disease dynamics and transmission models.

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83   **Introduction**

84   The transmission of respiratory infections is likely to depend on the frequency and age

85   structure of human social contacts, as well as other factors including pre-existing immunity

86   from prior infection or vaccination [1-3]. To understand the dynamics of such infections,

87   studies to quantify social mixing patterns have been conducted in various settings, under

88   the assumption that self-reported encounters reflect transmission probabilities of

89   pathogens transmitted through close contact [2, 4-11]. Combined with disease transmission

90   models, these data are increasingly being used to inform infection control policies [12, 13].

91   There is evidence from population-based models that self-reported social mixing patterns

92   can reproduce observed aggregated seroprevalence data for chickenpox [14], mumps [4],

93   parvovirus [15], influenza [4, 16, 17]) and whooping cough [18]. Moreover, it has been

94   suggested that age-stratified social mixing patterns can capture individual influenza risk, as

95   measured by a four-fold rise in neutralization titres over the course of an epidemic (17, 18).

96   However, it remains unclear precisely how risk of infection is related to the frequency and

97   nature of an individual's social encounters around the time of infection.

98   To establish how social behaviour shapes individual-level infection, we explored whether

99   the frequency and duration of different types of social encounters were associated with an

100   individual's risk of respiratory infection, using nasopharyngeal (NP) carriage of *Streptococcus*

101   *pneumoniae* (the pneumococcus) and self-reported acute respiratory symptoms (ARS) as

102   endpoints.   *S.pneumoniae* is one of the main causes of pneumonia and sepsis globally [19],

103   disproportionally so in low-income settings [19-21]. Colonization of the nasopharynx is a

104   precondition to disease, and the main source of human-to-human transmission. Given that

105   most episodes of carriage remain asymptomatic, social behaviour is unlikely to change as a

106   result of carriage, making pneumococcal carriage a more suitable endpoint than

107   symptomatic illness to explore the association between social behaviour and infection risk,

108   given that people tend to limit their contacts during symptomatic illness [22]. In addition, as

109   natural immunity to carriage is weak [23], pre-existing immunity is less likely to confound

110   associations between disease and social contact patterns than in studies using immunizing

111   infections as biological endpoint [16, 17].

112   We analysed data from a social contact study nested within a survey of NP carriage of

113   *S.pneumoniae* conducted across a rural South-West Uganda in 2014, before the introduction

114   of the pneumococcal conjugate vaccine (PCV). Participants across age groups were

115   randomly selected from 56 villages and one small town. Participants were asked to name all

116   individuals with whom they had a conversational encounter lasting ≥ 5 minutes between

117   wake-up on the day prior to the survey day to wake-up on the survey day (~ 24 hours).

118   Those encounters are further referred to as *'ordinary'* contacts. For very short contacts (i.e.

119   <5 minutes), which we here define as *'casual'* contacts, an estimate of the number of

120   contacts was asked (<10, 10-19, 20-29, ≥30) without further details. ARS were defined as

121   any of the following symptoms in the previous two weeks: sore throat, sneezing, difficulty

122   breathing, and runny nose. A nasopharyngeal specimen was taken from each survey

123   participant and was processed and analysed as per WHO guidelines [24]. Using these

124   individually-matched data, we examined whether the type and frequency of social contacts

125   differed by carriage status and between individuals with and without ARS.

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128   **Results**

129   <u>Study population</u>

130   Of the 687 individuals initially targeted for inclusion, 568 (83%) individuals from unique

131   households responded to the survey, with data on both social contacts and carriage or ARS

132   available from 566 participants. Participant's age spanned across age groups and the sex

133   distribution was reasonably balanced (58% female). The majority (98%) of children aged 6 –

134   15 years attended school or college. More than a third of all adults (36%) worked in

135   agriculture and 22% were homemakers/housewife.

136   On average, people made seven *'ordinary'* contacts (defined as contacts ≥5 minutes long),

137   ranging from 0 to 25, the majority of which were physical (i.e. 'skin-to-skin' contact or

138   indirect physical contact through utensils passed from mouth-to-mouth). There was no

139   evidence that the average number of contacts differed by weekday or between weekdays

140   and weekends (P=0.623). Children aged 5-9 years reported most contacts and children <5

141   years the fewest (Figure 1). The majority of contacts made by children were physical.

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143   **Figure 1:** Number of reported contacts by age group and type of contact. <u>Legend</u>: Boxplots

144   showing the median (horizontal line), interquartile range (boxes) and 95% confidence

145   interval around the mean (whiskers). The outliers are shown as bubbles above or under the

146   whiskers

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148   The most intense mixing tended to be between individuals of the same age group (i.e.

149   assortative mixing), but there was also substantial mixing between age groups. Contact from

150   and with children aged <10 years involved proportionally more physical touch than contacts

151   between older children and adults (Figure 2A and 2B). The proportion of non-physical

152   contacts, contacts outside the household and contacts of short (<1h) duration was higher

153   among teenagers and adults than among younger children and infants.

154   There was no difference in contact patterns by sex, for all types of contacts considered.

155   Four hundred and ninety (87%) participants estimated how many casual contacts (i.e. <5

156   minutes in duration) they had the day before the survey. Over a third (36%) of these

157   reported 10 or more casual contacts, and 11% reported more than 20 casual contacts.

158   Among the 13% who could not estimate how many casual contacts they had, there were

159   proportionally more children with over half (56%) under 10 years.   The mean number of

160   reported 'ordinary' contacts was higher among individuals reporting ≥10 casual contacts

161   than those reporting fewer than 10 contacts (mean 8.9 vs 5.9, P<0.001), as well as among

162   the 78 individuals who did not know how many casual contacts they had (mean 8.8,

163   P<0.001).

164   The prevalence of pneumococcal carriage was strongly age dependent, decreasing from 75%

165   in children <5 years to 46% among 5 – 9 year olds, 17% in 10 – 19 year olds, and further

166   decreasing to 8% and 7% among 20-39 years and ≥40 years old respectively (Figure 2C).

167   Overall, 72 (13%) people reported having suffered from ARS in the two weeks prior to the

168   survey. The prevalence of ARS varied much less with age than that of carriage (Figure 2D),

169   ranging from 20% among 5 to 9 year olds to 8% among ≥40 years old. There was no sex

170   difference in the prevalence of carriage (age-adjusted RR for males 0.97, P=0.814) or ARS

171   (age-adjusted RR for males 1.40, P=0.134).   Carriage and ARS were poorly correlated

172   (Pearson's correlation coefficient R=0.09, ranging from -0.08 to 0.29 by age group), and

173   there was no evidence that the risk of ARS was higher among carriers compared to non-

174   carriers (age-adjusted relative risk (RR) 1.06 (95%CI 0.85 – 1.33)).

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176   **Figure 2:** Contact matrices and prevalence of *S.pneumoniae* carriage and Acute Respiratory

177   Symptoms (ARS), by age. Legend: Contact matrices and prevalence of *S.pneumoniae*

178   carriage (Panel A) and Acute Respiratory Symptoms (Panel B). In panels C and D, the height

179   of each bar corresponds to the point prevalence and the error bar represents the 95%

180   Confidence Interval (CI).

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182   <u>Social contacts as a risk for pneumococcal carriage or ARS</u>

183   Overall, the mean number of contacts among carriers was significantly higher than non-

184   carriers, and this observation was consistent across age groups, although most differences

185   were not statistically significant due to small numbers (Figure 3). In particular, carriers had

186   more physical contacts (Fig 3A). This pattern was also consistent for ARS, with the exception

187   of 5 – 9 year olds in whom the mean number of contacts among individuals with ARS was

188   lower for physical contacts (Fig 3B).

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190　**Figure 3:** Mean number of contacts by age group and nasopharyngeal carriage status (Panel

191　A) or ARS status (Panel B). Legend: The graph shows the mean number of contacts among

192　carriers (red, panel A), non-carriers (blue, panel A), individuals reporting ARS (red, panel B),

193　and individuals without ARS (blue, panel B). This is shown by age group and for all contacts,

194　physical contacts, household contacts and contacts lasting over 1 hour.

195　In univariable analysis, the risk of carriage increased with all contacts, household contacts,

196　contacts ≥1 hour long and physical contacts. The latter had the largest effect size, with a

197　13% increased risk for each additional contact reported by participants (Table 1). Physical

198　contacts and contacts ≥1 hour were strongly correlated (R = 0.76), particularly among

199　children <5 years (R=0.85) and children aged 5 – 9 years (R=0.87), hence their effect could

200　not be disentangled, whereas the correlation between physical contacts and household

201　contacts was moderate (R=0.61, ranging from 0.47 to 0.70 between age groups). After age

202　adjustment, physical contacts or contacts ≥1 hour remained most significantly associated

203　with carriage, with a 6% increased risk (95%CI 2 – 10%) for each unit increase in the number

204　of reported contacts (Table 1). We found good evidence that the number of household

205　contacts increased the risk as well (Table 1). There was no confounding effect by other

206　covariates and models were therefore only adjusted for age (Supporting Information S1).

207　An increase in physical, household and long (≥ 1h) contacts, were also associated with an

208　increased risk of ARS in univariable analysis. There was little or no evidence of a

209　confounding effect of age, given the more constant prevalence of ARS across age groups

210　(Table 1). Unlike pneumococcal carriage, however, the relative risk was more constant

211　across types of contacts, and household contacts rather than physical contacts were most

212   strongly associated with a risk for ARS, with a risk increase of 9% (1 – 18%) for each

213   additional reported contact.

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215   **Table 1:** Relative risk of **_S.pneumoniae_ carriage and ARS** by frequency of contact

Contact types	Mean contacts		Crude RR (95%CI)	Adjusted RR (95%CI)
NP carriage	NP+	NP-		
All contacts	8.09	7.53	1.04 (1.00; 1.07)*	1.03 (1.00; 1.07)*
Physical contacts	6.83	6.09	1.13 (1.09; 1.17)*	1.06 (1.02; 1.09)*
Non-physical contacts	1.25	1.43	0.78 (0.72; 0.86)*	0.97 (0.91; 1.05)
Household contacts	5.64	5.31	1.09 (1.03; 1.14)*	1.04 (0.99 ; 1.10)
Non-household	2.22	2.45	0.98 (0.93; 1.04)	1.03 (0.98; 1.09)
Contacts≥ 1hour	7.50	6.56	1.08 (1.05; 1.12)*	1.06 (1.02; 1.10)*
Contacts <1h	2.38	2.62	0.81 (0.73; 0.92)*	0.94 (0.85; 1.03)
ARS	ARS+	ARS-		
All contacts	8.18	7.63	1.07 (1.02; 1.12)*	1.07 (1.02; 1.13)*
Physical contacts	6.10	6.26	1.09 (1.03; 1.15)*	1.07 (1.00; 1.14)*
Non-physical contacts	2.07	1.36	1.00 (0.89; 1.10)	1.06 (0.95; 1.18)
Household contacts	5.70	5.31	1.10 (1.02; 1.19)*	1.09 (1.01; 1.18)*
Non-household	2.47	2.31	1.04 (0.98; 1.11)	1.05 (0.98; 1.13)
Contacts ≥ 1hour	7.33	6.74	1.07 (1.01; 1.13)*	1.07 (1.00; 1.14)*
Contacts <1 hour	3.14	2.58	1.05 (0.96; 1.15)	1.08 0.99; 1.18)

216   Legend: *=associations significant at P<0.05. RR= Risk Ratio. CI= Confidence Interval. NP+=

217   pneumococcal carrier, NP - = non-carrier, ARS+ = with ARS, ARS- = without ARS

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219   Next, we analysed whether the number of casual contacts (i.e. contacts lasting < 5 minutes)

220   was associated with either pneumococcal carriage or ARS. We found no evidence that the

221   prevalence of pneumococcal carriage or the risk of ARS were associated with reporting

222   higher levels of casual contacts, as shown in Table 2. Given the small numbers of individuals

223   reporting ≥30 casual contacts, we pooled the 56 individuals reporting ≥20 casual contacts

224   into one category.

225   In univariable analysis the risk of pneumococcal carriage was higher in the group of 78

226   participants who did not know how many casual contacts they may have had. This was due

227   to the higher proportion of children <5 years and aged 5 – 9 years in that group, however,

228   after age-adjustment, there was no evidence that the risk of pneumococcal carriage was

229   higher in that group. Similarly, a higher number of casual contacts was associated with

230   increased risk of ARS, and with no confounding effect of age or other variables on the

231   estimates.

232   We found no confounding effect on casual contacts on the relative risk of carriage or ARS as

233   a function of the frequency of reported 'ordinary' contacts.

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238   Table 2: Relative risk (RR) of pneumococcal carriage and ARS by level of reported number of

239   daily casual contacts

Number of casual contacts	Number of individuals	Pneumococcal carriage		Acute Respiratory Symptoms (ARS)	
		Crude RR (95%CI)	Age-adjusted RR (95%CI)	Crude RR (95%CI)	Age-adjusted RR (95%CI)
0 – 9	315	ref	ref	ref	ref
10 – 19	119	0.82 (0.52; 1.27)	0.80 (0.55; 1.75)	1.02 (0.65; 1.49)	1.00 (0.65; 1.54)
≥20	56	0.81 (0.44; 1.49)	1.19 (0.70; 2.04)	0.51 (0.21; 1.27)	0.56 (0.22; 1.39)
Not known	76	1.52 (1.00; 2.31)*	1.07 (0.77; 1.49)	1.01 (0.45; 2.28)	0.88 (0.38; 2.00)

240   Legend: * = associations significant at P<0.05. RR= Risk Ratio. CI= Confidence Interval

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242   Finally, we explored the characteristics of age-specific mixing patterns by ARS or carriage

243   status in greater detail, with a focus on physical contacts and household contacts. We

244   computed the ratio of the mean number of contacts within and between age groups among

245   carriers compared to non-carriers, and among individuals with ARS compared to those

246   without. The average number of physical encounters within and between age groups

247   tended to be higher for carriers than non-carriers in most instances, albeit with substantial

248   uncertainty owing to small numbers (Figure 4). Carriers reported more contacts with

249   children < 5 years, and particularly adult carriers who reported on average more than twice

250   as many physical contacts with children under five than non-carriers (Figure 4). Given that

251   most of such contacts occurred within the household, the effect of physical and household

252   contacts with children <5 years was indistinguishable, whereas for older age groups, the

253   association with physical contact was stronger than that with household contacts (Figure 4).

254   Similar findings were seen for ARS, however, unlike for pneumococcal carriage,

255   symptomatic adults did not have more contacts with young children than asymptomatic

256   ones. Results based on absolute differences in the mean number of contacts rather than

257   relative means are displayed in Figure S1 (Supporting Information), showing the similar

258   associations than the reported ratios, but providing a quantified difference in mean number

259   of contacts instead.

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261   Figure 4: Ratio of the mean reported number of *physical* contacts between pneumococcal

262   carriers and non-carries (panel A) and individuals with ARS compared to those without ARS

263   (Panel B). Legend: Matrices of the ratio of the mean number of contacts among

264   pneumococcal carriers compared to non-carriers (Panel A) and individuals with ARS

265   compared to non-ARS (panel B). The numbers represent the point estimate of the ratio and

266   in brackets the 95% confidence bounds. Blue are cells with a point estimate <1 and in red

267   with point estimates >1.

268

269   **Discussion**

270   Our study provided a unique opportunity to explore whether and how social contact

271   patterns are associated with someone's risk of acute respiratory infection in a mostly rural

272   East African setting. Our results show that people who tend to have more frequent close

273   contacts are more likely to be pneumococcal carriers or to report acute respiratory

274   symptoms, irrespective of their age. In contrast, we found that less intimate or short casual

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275 contacts were not associated with someone's infection risk, suggesting that social contacts

276 important for transmission are close interpersonal encounters.

277 Existing evidence on the association between contact patterns and risk of infection is

278 mostly 'ecological', with very few studies based on individual-level data. Using data of

279 influenza A/H1N1 seroconversion in Hong Kong coupled to social contact data in the same

280 population, Kwok et al. [16] showed that age rather than social contact patterns were the

281 main driver of the individual risk of infection in that setting, and further work by Kucharski

282 et al. [17] on the same data further supported the finding that someone's risk of infection is

283 related to the average mixing pattern within their age group rather than their reported

284 number of contacts. However, the validation of the 'social contact hypothesis' with such

285 data remains difficult, due to challenges in accounting for acquired immunity in the

286 population, assumptions around stability of behaviour over relatively long time periods as

287 well as challenges in capturing influenza infection events based on serological data only [16,

288 17].

289 Studying nasopharyngeal carriage of *S.pneumoniae* as the main biological endpoint enabled

290 us to address many of these issues, for several reasons. First, the high prevalence of carriage

291 provided the statistical power required to study individually-matched acquisition risk in our

292 study. Second, a person's individual behaviour is unlikely to be affected by carriage given

293 that the vast majority of episodes remain asymptomatic, in contrast to symptomatic

294 respiratory infections during which social behaviour might change as a result of illness [22].

295 Most carriage episodes in our study were asymptomatic, and our decision to assess the risk

296 for ARS and NP carriage separately stemmed from that observation. In addition, given that

297 duration of carriage is relatively short – at most 3 months in young children and no longer

298   than a few weeks in adults [25] – , and as no difference in our survey was observed in the

299   mean number of contacts between days of the weeks and between survey weeks, it is

300   reasonable to assume that contact patterns measured on a given day reflect contact

301   patterns around the time of pneumococcal acquisition.   Finally, as colonisation results in

302   weak protective immune responses and limited reduction in serotype-specific reacquisition

303   risk [23, 26], and with over 90 circulating serotypes, natural acquired immunity is unlikely to

304   distort the association between carriage and social contact patterns, unlike immunizing

305   infection for which individuals with more frequent risk of infection due to their social

306   contact patterns are also more likely to be immune.

307   In contrast, self-reported respiratory symptoms may be influenced by factors such as

308   behaviour change in illness [22] or immunity. The definition itself also presents limitations;

309   although respiratory viruses such as the Respiratory Syncytial Virus (RSV), adenovirus,

310   parainfluenza and influenza viruses are likely to account for a large proportion of ARS cases

311   [27], the definition was used as a non-specific proxy for acute respiratory infection and may

312   have captured other infectious and non-infectious conditions. Notwithstanding such

313   caveats, results for ARS were similar to those for nasopharyngeal carriage, but also showed

314   a more consistent association with all types of non-casual contacts, rather than physical or

315   contacts of long duration only. This suggests that the definition may have mostly captured

316   acute infections, and also provides further evidence that the number of close interpersonal

317   contacts, and particularly household contacts, plays a role in the transmission of acute

318   respiratory pathogens.

319   One of the striking features of our analysis of the relative number of mean contacts

320   between age groups is that adults colonised with *S.pneumoniae* reported more than twice

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321   as many close contacts with children under five than non-carriers. This is in agreement with

322   observational and modelling studies showing that pneumococcal carriage risk increases with

323   household size and with the number of children <5 years in the household [28]. It also

324   supports the finding that carriage acquisition in adults occurs mostly within the household

325   as a result of contact with young children who are drivers of infection [29]. In contrast,

326   however, we found that adults with ARS reported an equal or lower number of contacts

327   with children <5 years than asymptomatic adults. This likely reflects the epidemiological

328   differences between carriage and ARS, given the very high prevalence of carriage among <5

329   year olds and the much less marked difference in age-specific prevalence of ARS across age

330   groups, in addition to other potential factors such as acquired immunity among adults more

331   frequently exposed to very young children. Some of the specific details of the contact

332   patterns and differences between *S.pneumoniae* and ARS are harder to interpret, due in

333   part to wide statistical uncertainty, particularly among adults in whom the number of

334   carriers or symptomatic individuals is small. However, overall the results from our analysis

335   support the general finding that increased close contacts are associated with higher risk of

336   ARS or pneumococcal carriage.

337   There is still much debate about how respiratory pathogens are transmitted from person to

338   person; whether through close direct or indirect physical contact, through large droplet

339   transmission at close range (<1 meter), or through aerosolized particles floating over longer

340   distances, particularly in poorly ventilated indoor settings [30, 31]. It is likely that many

341   pathogens can be transmitted through a combination of these routes. Yet the contribution

342   of each mechanism remains uncertain [30, 31]. It is generally assumed that the main

343   transmission route of *S.pneumoniae* is through direct contact [32], as well as indirectly

344   through shared glasses or bottles [33]. Analogously, for other colonising bacteria such as

345   *N.meningitidis*, close contact and intimate kissing are known risk factors among teenagers

346   and young adults [34]. Similarly, it is believed that influenza and other respiratory viruses

347   are primarily transmitted through direct contact or contact with large droplet transmission

348   at close range rather than aerosolized particles [30].

349   Although our objective was not to demonstrate transmission, our findings strongly support

350   that direct close interpersonal contact is an important mode of transmission for pathogenic

351   bacteria of the nasopharynx as well as respiratory viruses, and strengthens the scientific

352   evidence for public health measures based upon these assumptions, such as hand washing

353   campaigns or chemoprophylaxis of close contacts of cases of meningococcal meningitis to

354   name a few. The strong association of ARS with household and other close contacts,

355   independently from physical touch, might suggest that other mechanisms such as indirect

356   transmission through fomites or aerosol transmission may play a role. Elucidating the

357   contribution of such factors in this context would be an important question for future

358   research.

359   Our findings have also several implications for infectious disease research. Contact

360   structures are central to transmission models, and appropriate assumptions about what

361   type of contact drives infectious disease transmission are essential. Our results suggest that

362   the parameterisation of transmission models of *S.pneumoniae* and similar pathogens using

363   mixing matrices based on physical or another measure of *close* interpersonal contact would

364   more likely capture relevant contact patterns than those based on any type of social

365   encounter.   This has also implications for the design of contact studies, particularly in low-

366   income settings given the scarcity of published data currently available and the need to

367   collect additional data from many more settings [7, 8]. In contrast to diary-based

368   approaches that have been used by many [2, 4, 7, 8], the study design here was relatively

369   simple and only involved a single face-to-face interview. A drawback of such retrospective

370   approach is the lack of detailed information about very short (i.e. 'casual') contacts, as such

371   information was deemed unreliable – and this is further supported by evidence that short

372   contacts tend to be inconsistently recorded even in prospective diary-based approached [1].

373   However, given that very short contacts may not account for much of the transmission, as

374   our study suggests, a more simple retrospective design is a potential attractive option in

375   other settings where contact data are lacking, and in which data collection through more

376   comprehensive diary-based approaches may be difficult to implement.

377

378   There are some additional limitations to our study. We were unable to explore other

379   potential confounding factors, such as bed share, ventilation, indoor smoke or hand washing

380   [35], and the contribution of such factors should be explored further. Moreover, it remains

381   unclear to what extent our results can be generalised to any acute respiratory infection. For

382   example, factors such as ventilation and airflow may be of particular importance for

383   aerosolized transmission of pathogens such as mycobacteria [7], compared to influenza or

384   *S.pneumoniae* [30, 31], and whether household or physical contacts reflect contact patterns

385   important for aerosolized transmission remains uncertain [7]. Finally, while we found a

386   strong association at the individual level, our study does not demonstrate causality.

387   However, in the absence of detailed longitudinal data on acquisition events between all

388   individuals' contacts —which would be challenging and possibly unrealistic to obtain— our

389   findings provide consistent evidence of a 'dose-response' association at the individual level

390   between close social encounters and acquisition risk for respiratory pathogens, and

391   therefore provides robust support both for the social contact hypothesis, and for research

392   and policy work based upon this hypothesis.

393

394   **Materials and Methods**

395   <u>Data collection</u>

396   The study was conducted in Sheema North Sub-District (Sheema district, South-West

397   Uganda) between January and March 2014. Sixty clusters were randomly selected from the

398   215 villages and two small district towns (Kabwohe and Itendero) in the study area,

399   proportionally to the population size of each village and town. In each cluster 11 or 12

400   individuals were randomly sampled from different households to both answer questions

401   about their social contacts and their history of respiratory illness in the last two weeks, as

402   well as having a nasopharyngeal swab taken. A household was defined as the group of

403   individuals living under the same roof and sharing the same kitchen on a daily basis.

404   For the social contact questionnaire, participants were first asked to list all the individuals

405   with whom they had a two-way conversational contact lasting for ≥5 minutes during a

406   period of approximately 24 hours prior to the survey day (from wake up the previous day

407   until wake up on the survey day). Such encounters were defined as 'ordinary contacts'. For

408   each reported ordinary contact, participants (or their parent/guardian) were asked to

409   estimate the contact's age (or estimated age), how long the encounter lasted for and

410   whether it involved skin-to-skin touch or utensils passed from mouth to mouth (either of

411   those defining 'physical contacts'). For very short social encounters (<5 minutes), which

412   were defined as 'casual contacts' (e.g. seeing someone on the way, encounter in a shop

413   etc.), participants were asked to estimate the number of encounters based on pre-defined

414   categories (<10 contacts, 10-19 contacts, 20-29 contacts, ≥30 contacts), but not to provide

415   further details about each contact.

416   Next, participants were asked about respiratory symptoms experienced in the two weeks

417   prior to the survey, including any of the following: cough, runny nose, sneezing, sore throat,

418   difficulty breathing.

419   Finally, after the interview was completed, a nasopharyngeal swab was taken from each

420   participant. NP samples were collected, transported and analysed as per WHO guidelines

421   [24]. NP swabs (flocked nylon swabs, COPAN, Italy) were inoculated in a skim milk tryptone-

422   glucose-glycerol (STGG) medium, transported in cool boxes and frozen at the research

423   laboratory at -20°C within 8 hours of collection. Specimens were inoculated onto a selective

424   agar plate of 5 mg/L gentamicin-Columbia agar with 5% sheep blood and incubated at 37°C

425   in 5% CO_2 atmosphere overnight. Pneumococcal identification was based on optochin

426   susceptibility testing of all alpha-hemolytic colonies and bile solubility testing in case of

427   intermediate susceptibility to optochin.

428   <u>Statistical analysis</u>

429   We first performed descriptive analyses, with age-specific probability weights to account for

430   different inclusion probabilities by age at the design stage, and adjusted for the clustering

431   by village through the use of clustered 'sandwich' variance estimators to account for

432   possible correlation within each of the sixty clusters [36]. We explored social contact

433   patterns within and between age groups through contact matrices. In such matrices we

434   report the mean number of ordinary contacts of participants in age group j with contacts

435   in age group i (m_{ij}), adjusted for reciprocity, as in Melegaro et al. [15].

436   We then analysed whether and how the frequency distribution of contacts was associated

437   with pneumococcal carriage or self-reported ARS.

438   We modelled the effect of 'ordinary' contacts (defined as contacts ≥5 minutes long) on

439   carriage or respiratory symptoms as a function of contact frequency, through a Poisson

440   model with a robust variance estimator, and inclusion probability weights by age group. We

441   treated contacts as continuous variables, but assessed departure from linearity through

442   likely ratio tests and model comparisons of Bayesian Information Criterion (BIC). In

443   multivariable analysis, we considered for inclusion any covariate significantly associated

444   with the outcome at P<0.10 in univariable analysis. Model improvement was considered for

445   any decrease in the BIC. Further details are provided in the Supporting Information S1.

446   Next, we used the same analytical approach to assess whether carriage and ARS were

447   associated with the level of self-reported 'casual' contacts (i.e. <5 minutes long).

448   Finally, we explored differences in the social mixing matrices by status of pneumococcal

449   carriage and ARS. To do so, we computed the ratio of the mean number of reported

450   contacts by participants j with contacts i among carriers compared to non-carriers (R_{ij}^C) or

451   symptomatic compared to asymptomatic individuals (R_{ij}^R) , such that $R_{ij}^C = \dfrac{m_{ij}^C}{m_{ij}^{N-C}}$ and

452    $R_{ij}^R = \dfrac{m_{ij}^R}{m_{ij}^{N-R}}$, where C = carriers, R = participants with ARS and N = the total number of

453   participants. Estimates were not adjusted for reciprocity given that subpopulations were

22

454   not closed (e.g. contacts of carriers may not be carriers), and that our aim was to compare

455   reported number of contacts rather than calculate a contact matrix. The uncertainty in

456   reported values and ratios was obtained through resampling techniques, drawing random

457   samples from each m_{ij}, with the number of draws equal to the study population in each age

458   group j. Ratios and uncertainty around them was obtained from the ratio of bootstrapped

459   matrices.

460   The same approach as described above was used to compute the differences in m_{ij} with

461    $D_{ij}^C = m_{ij}^C - m_{ij}^{N-C}$ and $D_{ij}^C = m_{ij}^R - m_{ij}^{N-R}$.

462   All analyses were performed in STATA 13.1 IC and R version 3.2.

463   Ethics

464   Approval was obtained from the Ethical review boards of the London School of Hygiene and

465   Tropical Medicine, Médecins Sans Frontières, the Faculty of Medicine Research & Ethics

466   Committee of the Mbarara University of Science and Technology, the Institutional Ethical

467   Review Board of the MUST, and the Uganda National Council for Science and Technology.

468

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474   their valuable input in the design and protocol of the field surveys.

475   **Conflict of interest**

476   The authors declare they have no conflict of interest.

477   **Funding**

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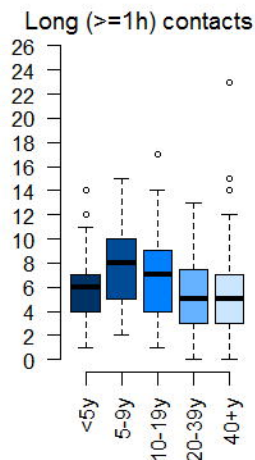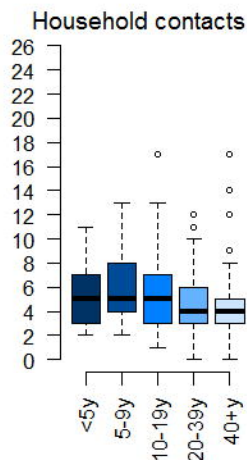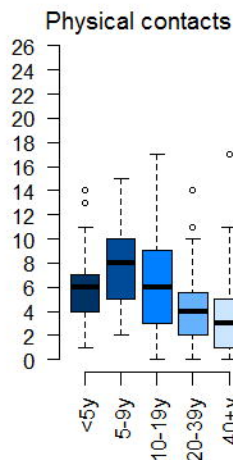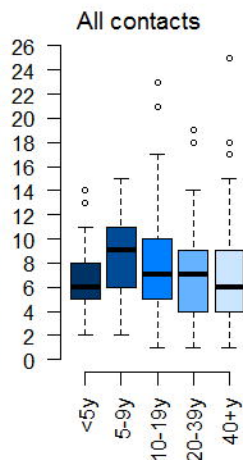614   **Supporting Information Captions**

615   **S1 Text.** Analytical approach and model comparison

616
617   **S1 Figure**: Difference in the mean number of *physical* contact between pneumococcal
618   carriers and non-carriers (Panel A) and between individuals suffering and not suffering from
619   respiratory symptoms (Panel B).Legend: Matrices of the mean difference between the mean
620   number of contacts among pneumococcal carriers and non-carriers (panel A), and
621   individuals with ARS compared to non-ARS (panel B). The numbers represent the point
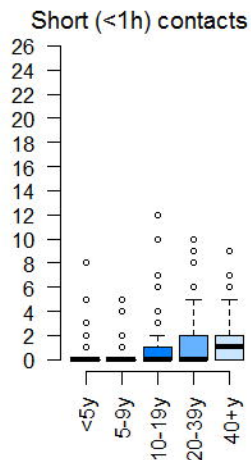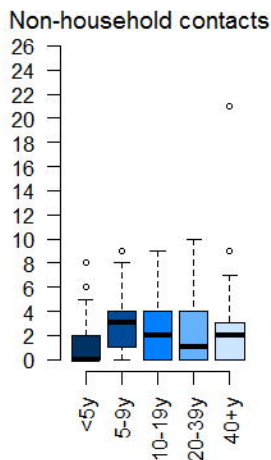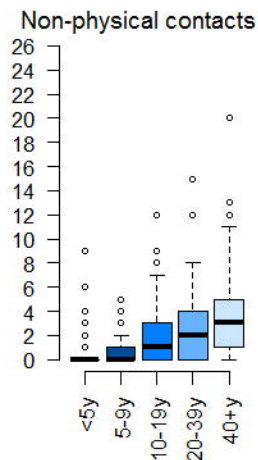622   estimate and the lower and upper bound of the 95% credible interval are shown inside the
623   brackets.
624
625
626   **S2 Text**: Data dictionary
627
628   **S3 Data**: Dataset

A. All contacts

Age of contacts / Age of participants

	<5y	5-9y	10-19y	20-39y	40+y
40+y	0.55	0.68	1.02	1.38	2.41
20-39y	1.36	1.07	1.34	2.91	1.95
10-19y	1.11	1.71	3.20	1.09	1.16
5-9y	1.02	2.46	1.06	0.54	0.48
<5y	0.87	0.94	0.64	0.63	0.36

B. Physical contacts

Age of contacts / Age of participants

	<5y	5-9y	10-19y	20-39y	40+y
40+y	0.50	0.55	0.67	0.57	1.09
20-39y	1.26	0.95	0.94	1.42	0.80
10-19y	1.02	1.51	2.64	0.76	0.77
5-9y	1.01	2.39	0.94	0.48	0.39
<5y	0.82	0.94	0.59	0.59	0.32
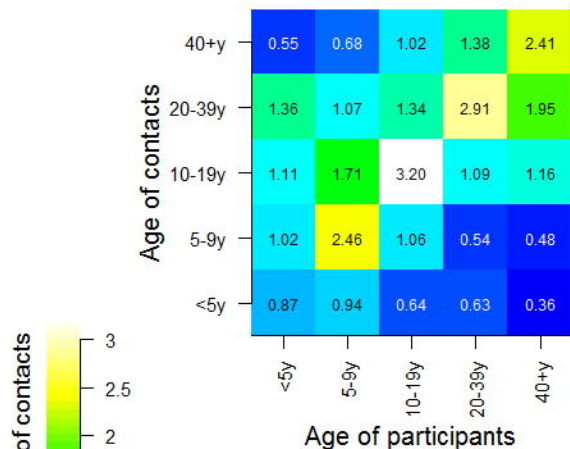
Mean number of contacts
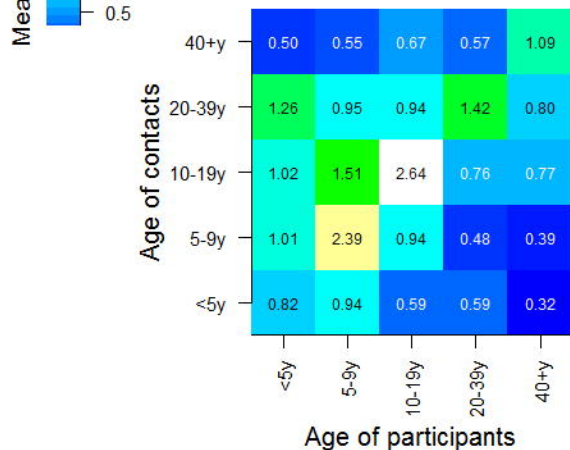
C. Pneumococcal carriage prevalence
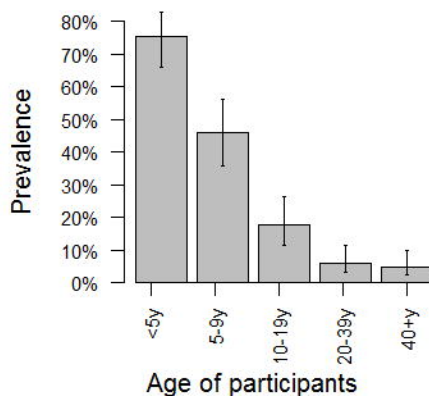
D. Prevalence of respiratory symptoms

A: Pneumococcal carriage

B: ARS

A. Pneumococcal carriage

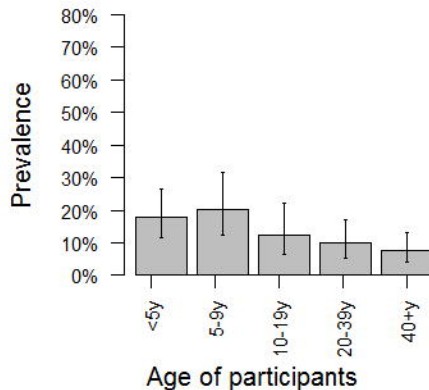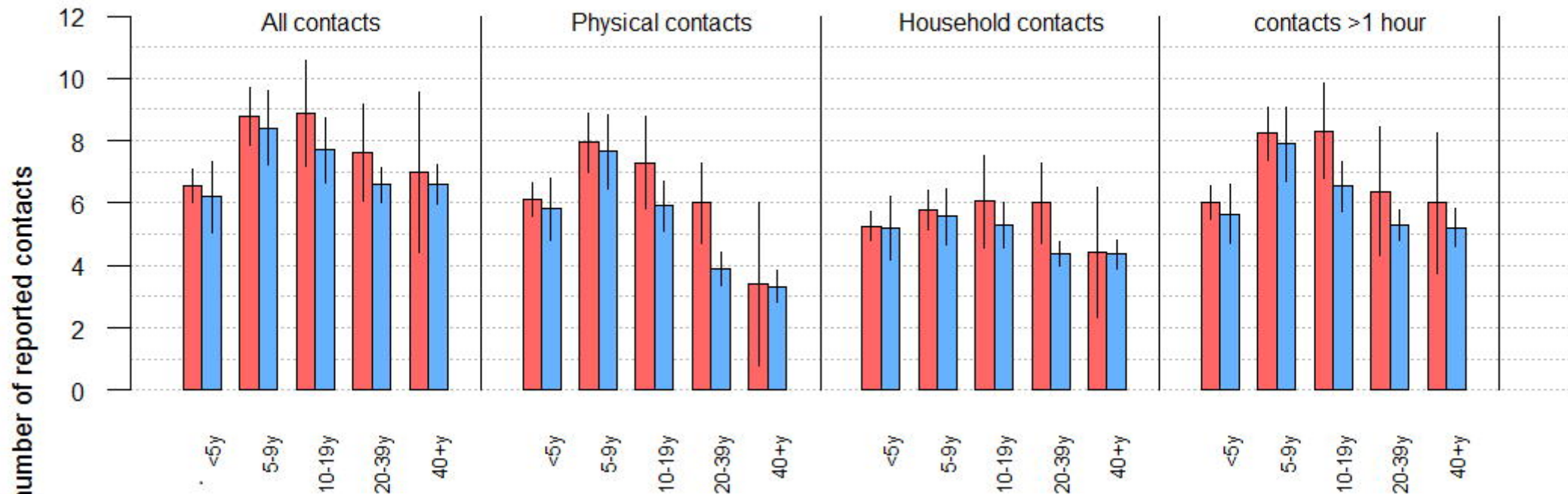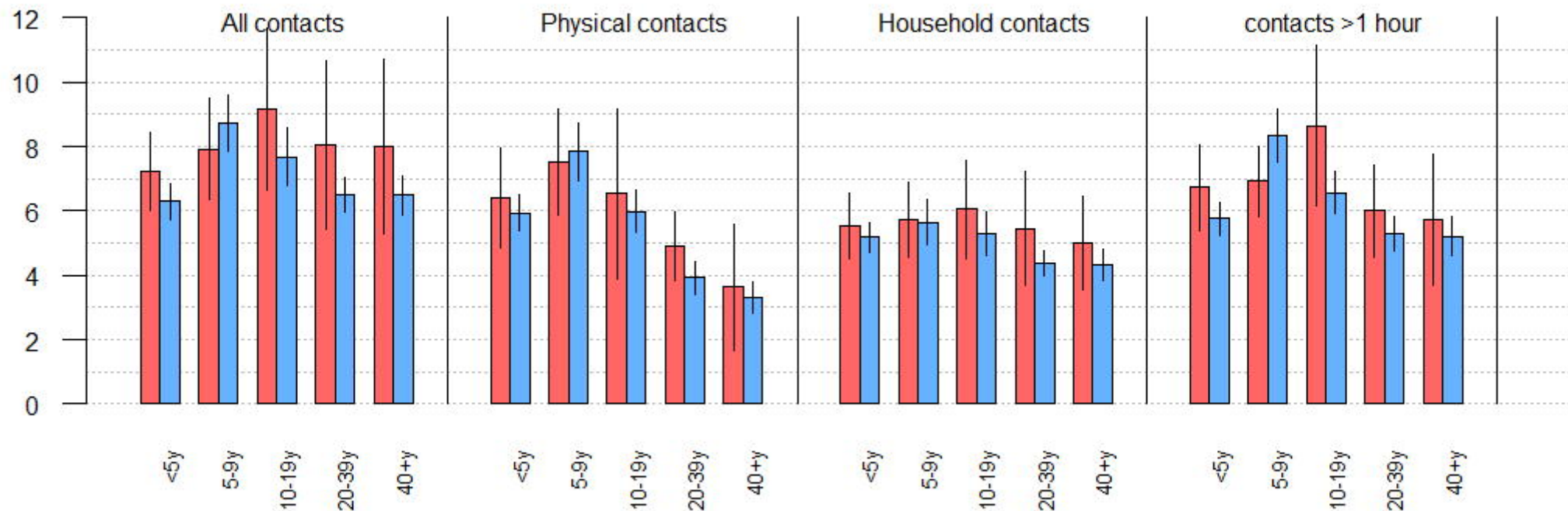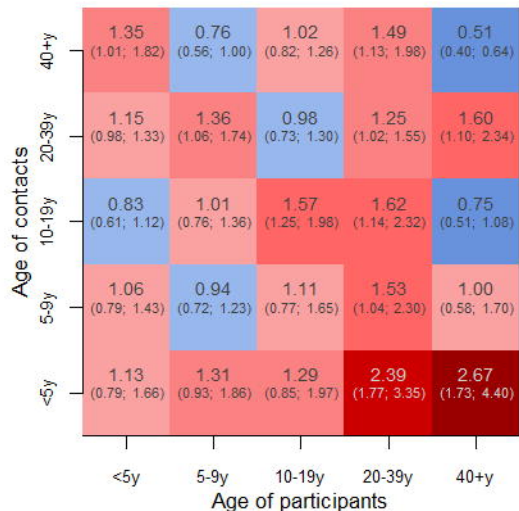| Age of contacts	<5y	5-9y	10-19y	20-39y	40+y
40+y	1.35 (1.01; 1.82)	0.76 (0.56; 1.00)	1.02 (0.82; 1.26)	1.49 (1.13; 1.98)	0.51 (0.40; 0.64)
20-39y	1.15 (0.98; 1.33)	1.36 (1.06; 1.74)	0.98 (0.73; 1.30)	1.25 (1.02; 1.55)	1.60 (1.10; 2.34)
10-19y	0.83 (0.61; 1.12)	1.01 (0.76; 1.36)	1.57 (1.25; 1.98)	1.62 (1.14; 2.32)	0.75 (0.51; 1.08)
5-9y	1.06 (0.79; 1.43)	0.94 (0.72; 1.23)	1.11 (0.77; 1.65)	1.53 (1.04; 2.30)	1.00 (0.58; 1.70)
<5y	1.13 (0.79; 1.66)	1.31 (0.93; 1.86)	1.29 (0.85; 1.97)	2.39 (1.77; 3.35)	2.67 (1.73; 4.40)

Age of participants

B. Respiratory symptoms

Age of contacts	<5y	5-9y	10-19y	20-39y	40+y
40+y	1.19 (0.89; 1.57)	0.54 (0.39; 0.74)	1.14 (0.92; 1.42)	1.01 (0.76; 1.37)	0.48 (0.36; 0.62)
20-39y	1.35 (1.14; 1.59)	1.60 (1.28; 2.03)	0.91 (0.67; 1.24)	1.22 (0.98; 1.52)	1.36 (0.92; 1.99)
10-19y	0.84 (0.63; 1.12)	0.89 (0.63; 1.21)	1.08 (0.83; 1.41)	1.72 (1.27; 2.39)	1.94 (1.38; 2.79)
5-9y	0.76 (0.57; 1.00)	0.77 (0.61; 0.98)	2.06 (1.47; 3.04)	1.36 (0.95; 2.03)	1.08 (0.71; 1.71)
<5y	1.75 (1.28; 2.43)	1.31 (0.95; 1.85)	1.26 (0.83; 1.91)	0.65 (0.44; 0.95)	0.77 (0.44; 1.35)

Age of participants

Ratio of mean reported contacts

2.50 / 2.25 / 2.00 / 1.75 / 1.50 / 1.25 / 1.00 / 0.75 / 0.50 / 0.25 / 0.00