COMMENTS ON "AN EVIDENCE REVIEW OF FACE MASKS AGAINST COVID-19" BY HOWARD ET AL. (2021)

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Howard et al. (2021) is a recently published perspective article about the effects of facemask use on infection from viruses. The authors argue in favor of the general use of facemasks in the context of the current COVID-19 pandemics. This study relies heavily on indirect evidence, ignores quantitative evidence going against the widespread use of facemasks, and most importantly misrepresents direct evidence about the benefits of facemasks in community settings. Overall, this yields a very weak case for the use of facemasks in everyday community settings. Thus, the authors' conclusions do not seem to follow from the existing literature. In this manuscript, I examine critically this review.

I start by mentioning two recent studies that they ignored. First, Xiao et al. (2020) is a meta-analysis of 14 studies of facemask use and hand hygiene in various contexts. This meta-analysis considered 10 randomized controlled trials (RCTs) on facemask use, and found no effect of facemask use on influenza transmission. Second, a survey by the American Center for Disease Control (CDC) on 314 participants failed to show any difference in the proportion of time masks were reported to be worn by positive cases to SARS-CoV-2 vs. controls (Fisher et al., 2020). These two studies are not cited by Howard et al. (2021), and it is very well possible that my search was not thorough enough, so that there could be other important studies that have also been ignored by the authors.

Direct evidence

I now focus on the direct evidence reviewed in the section "Direct Evidence of the Efficacy of Public Mask Wearing" that relates to the community use of facemasks. I agree with the authors that the evidence on facemask use in the household seems to indicate a benefit, especially when one family member is symptomatic. Several studies indicate this, for example their ref. (21), thus I will not come back on this evidence in this document. I also agree with them that evidence seems to show a benefit of masks as source control, i.e., when an infected symptomatic person wears a mask. In this document, I will not come back on this either. I will also ignore the evidence on the use of facemasks in health care, which is an established and accepted norm that is well supported by existing science.

Taking the references about facemask use in community settings in the order in which they are cited, reference (11) supposedly shows that facemasks reduce infections in community settings. However, the meta-analysis does not include many of the studies considered in the meta-analysis of Xiao et al. (2020), indicating a potential selection bias. I was unable to find a convincing explanation as to why those studies were not included in this meta-analysis. Moreover, most of the studies examined in ref. (15) are either in health care settings or are in a mix of health care and community settings, which is fairly pointed out by Howard et al. (2021).

Reference (13) is the only convincing evidence that facemasks are beneficial as a personal protective measure against infection from viruses in community settings. It is a Chinese study on 94 case-patients and 281 matched controls assessing the effectiveness of various personal protective measures, including facemasks. They found that people who declared to have worn a mask "sometimes" had an odds ratio of getting infected of 0.4 compared to people who never wore a mask; people declaring to have worn a mask "always" had an odds ratio of getting infected of

0.2 compared to people who never wore a mask. However convincing, this is the only unequivocal direct piece of evidence that facemasks protect against infection from viruses in community settings (note that it was not on SARS-CoV-2, but on SARS). This study was not included in the meta-analysis by Xiao et al. (2020) because it was not a randomized controlled trial.

Starting from ref. (15), Howard et al. (2021) begin to misrepresent evidence in a way that is very much below any acceptable scientific or even journalistic standard. References (15–16) are actually one and only reference. Indeed, ref. (15) is a 2011 Cochrane systematic review on physical interventions to reduce the spread of viruses. The Cochrane systematic reviews are regularly updated to include the most recent evidence. This is exactly what ref. (16) is about, i.e., this is the 2020 updated version of ref. (15) [ref. (16) is the preprint version, but the update has been published, see Jefferson et al., 2020]. Thus, ref. (15) is irrelevant and superseded by ref. (16). Howard et al. (2021) nevertheless ignore the irrelevance of ref. (15) and claim that it says: "overall masks were the best performing intervention across populations, settings and threats." This quote is nowhere to be found in the updated version of the Cochrane review (Jefferson et al., 2020). To the contrary, the updated Cochrane review states in the summary of the results that "[c]ompared with wearing no mask, wearing a mask may make little to no difference in how many people caught a flu-like illness (9 studies; 3507 people); and probably makes no difference in how many people have flu confirmed by a laboratory test (6 studies; 3005 people). Unwanted effects were rarely reported, but included discomfort." (Jefferson et al., 2020). By ignoring the irrelevance of ref. (15), Howard et al. (2021) thus completely twisted the conclusions of this reference, which warrants a correction at the very least. Finally Howard et al. (2021) incorrectly treat ref. (16) as "a preprint with the same lead author [as ref. (15)]" while it was published on Cochrane Library website on November, 20, 2020 (Jefferson et al., 2020).

The authors then cite a review (ref. 17) that focuses on the effect of wearing facemasks on infections in health workers and more generally in communities, as well as source control. This review is not a quantitative meta-analysis and considers 8 studies, all of which are included in the larger 14-study meta-analysis by Xiao et al. (2020) that I cited above. Since ref. (17) examines only a subset of the studies analyzed by Xiao et al. (2020), and does not perform a meta-analysis, the study by Xiao et al. (2020) based on quantitative arguments can be assumed to take precedence over ref. (17) which uses verbal arguments only. Once again, it is surprising that Xiao et al. (2020) is never cited among the 141 references of Howard et al. (2021).

Ref. (18) is another example of flagrant evidence misrepresentation. The authors quote from ref. (18) that "homemade masks worn by sick people can reduce virus transmission by mitigating aerosol dispersal. Homemade masks worn by sick people can also reduce transmission through droplets." This quote is found in ref. (18) but misrepresents its general conclusion. Indeed, this quote was taken out of a list of paragraphs, which head states, about homemade masks: "Overall the quality of the evidence was very low." Evidence misrepresentation by Howard et al. (2021) is even clearer from the opening statement of ref. (18) summary, which reads: "Based on the evidence from three recent systematic reviews and meta-analyses [including our re-analysis focusing on community trials] wearing face masks in the community was not significantly associated with a reduction in episodes of influenza-like illness[ILI]; the overall assessment of the quality was classified as low.". It is noteworthy that Xiao et al. (2020) was one of the 3 meta-analysis considered in ref. (18). Howard et al. (2021) seemed determined to ignore this meta-analysis at all costs.

The use of ref. (19) faces the same problems as ref. (17). Indeed, it is also a verbal review of the evidence on the benefits of facemasks. This review contains various types of evidence, but the evidence that concerns the benefits of facemasks in community settings only consists of one study (all other studies are either about household settings, or theoretical, or mechanical studies). This study by Aiello et al. (2012) [ref. (24) in Howard et al. (2021)] shows a slight benefit of facemasks that does not reach statistical significance. However, Howard et al. (2021) and the authors of ref. (19) summarize the results by saying that "face masks in a general population offered significant benefit in preventing the spread of respiratory viruses especially in the pandemic situation, but its utility is limited by inconsistent adherence to mask usage." This is indeed a statement found in ref. (19) but, as I just explained, both the authors of ref. (19) and Howard et al. (2021) misrepresent the evidence reviewed in ref. (19) since the only study examining the use of facemasks in "the general population" failed to demonstrate the benefits of masks (if by "general

population", they mean in community settings).

The authors of ref. (20) conclude that "[t]he evidence is not sufficiently strong to support widespread use of facemasks as a protective measure against COVID-19. However, there is enough evidence to support the use of facemasks for short periods of time by particularly vulnerable individuals when in transient higher risk situations.". Howard et al. (2021) did a fair job at citing this reference.

The rest of the references cited as direct evidence (refs. 21–24) by Howard et al. (2021) are studies contained in the meta-analysis by Xiao et al. (2020), so I will not spend too much time on these individuals studies. However, I will certainly mention that the authors misrepresent the results of Aiello et al. (2012), which is ref. (24) in their study. In this study, facemasks alone did not have a significant effect on infections, but the combination of facemasks and hand hygiene did have a significant effect, which strongly suggests that this combined effect was mainly due to hand hygiene (there was no group with hand hygiene alone in this study, and the authors did not seem to have tried an inference of the effect of hand hygiene alone on the rate of infections). However, Howard et al. (2021) just say that the combination of facemasks and hand hygiene had an effect, and never mention the existence of a group with facemasks alone, let alone the results obtained for this group. This (intentional?) omission may lead the reader to incorrectly attribute the effect of the mask+hygiene intervention to the masks, while the design and results of the study clearly exclude this possibility.

Ecological evidence

Howard et al. (2021) also review what they call ecological studies, and I should provide at least a quick comment on these seven studies. By "ecological studies", the authors mean studies that measure the effect of mask mandates on the evolution of case counts (or deaths) in a particular country or region. Of the seven studies considered, only one (ref. 29) controlled for possible confounding factors. All other studies only looked at the main effects of facemask use on the evolution of case counts; the studies that only looked at facemask use do not warrant further discussion since the number of pharmaceutical and non-pharmaceutical interventions that can possibly be applied is so large that it is impossible to rule out possible confounding effects. Ref. (29) did control for many factors, but did not control for other important factors including medical guidelines or whether early treatments were in widespread use in the considered countries. Indeed many of the Asian countries that adopted masks very early were also countries that applied strict and rapid quarantines for infected people; some of them are also countries that have used hydroxychloroquine as an early treatment. Moreover, ref. (29) only studied the initial phase of the epidemics, which is biased because the countries that have adopted masks early also adopted the measures I mentioned early. If masks truly reduce the probability of virus transmission, they should do so at all times during a pandemic. Ref. (29) is an impressive effort in the right direction, but we need more studies that take into account all of these factors.

Conclusion

In the conclusion of their article, the authors state that "people are most infectious in the initial period postinfection, where it is common to have few or no symptoms", citing references that show that the saliva of presymptomatic patients displays a higher viral load than that of symptomatic patients. However, this does not imply that presymptomatic patients will be more infectious, since one has to take into account the fact the symptomatic people sneeze and cough more often than presymptomatic people (it sounds obvious but this is often overlooked). Indeed, a study not cited by the authors (Buitrago-Garcia et al., 2020) finds that symptomatic cases are on average 3 times more likely to transmit the SARS-CoV-2 virus than asymptomatic cases, as measured by the secondary attack rate (an asymptomatic case is different than a presymptomatic case; it is defined as a person who tested positive for the presence of SARS-CoV-2, but never developed symptoms). However this estimate has a wide confidence interval. To be completely fair, this study reviews modeling work that suggests that presymptomatic transmission is more likely

than asymptomatic transmission. In another very recent study by Qiu et al. (2021), which was probably posted online after the final version of Howard et al. (2021) was written, the authors perform a thorough meta-analysis on the secondary attack rate depending on the symptom status of index cases of SARS-CoV-2. They find that, on average, 1% of the contacts of asymptomatic cases become infected; for presymptomatic, this rate is 6% and for symptomatic 7%. Hence asymptomatic cases are 7 times less likely to infect other people than symptomatic. It is noteworthy that presymptomatic and symptomatic have a very close secondary attack rate. The authors of this meta-analysis note that presymptomatic transmissions mostly occurred within the households in the studies they examined. Moreover they also note, regarding four studies that focus only on family outbreaks, that "these investigations did not test contacts outside the household, and it is challenging to truly differentiate transmission during the pre-symptomatic period from symptomatic transmission in the household setting". Thus it is possible that a proportion of the symptomatic transmissions were misclassified as presymptomatic or *vice versa*.

A Chinese study (Luo et al., 2020) shows that among the 3410 contacts of 391 Covid-19 cases, 3.5% were symptomatic while only 0.2% were asymptomatic. Even though the design of this study makes it difficult to know in which direction the transmission occurred (from the studied cases to their contacts vs. from the contacts to the studied cases), this gives a hint that asymptomatic transmission is much less prevalent than symptomatic transmission. Moreover, in this study 82.7% of infections occurred in the household.

A study on ten million people in Wuhan in the post-lockdown phase (Cao et al., 2020) showed that among close contacts of asymptomatic cases, none (0%) of them tested positive for the presence of SARS-CoV-2. I must remind the reader here that "[c]lose contacts are individuals who have had contact, without effective protection regardless of duration of exposure, with 1 or more persons with suspected or confirmed COVID-19 any time starting 2 days before onset of symptoms in persons with a suspected or confirmed case, or 2 days before sampling for laboratory testing of asymptomatic infected persons" (Luo et al., 2020). Taken together, these results suggest that a typical infection occurs from a symptomatic person in the household. The general use of facemasks defended by Howard et al. (2021) depends a lot on asymptomatic transmission outside, but the evidence shows that asymptomatic transmission is disproportionately less likely than symptomatic transmission and most infections occur in the household. They fail to review this evidence.

I did not examine in detail the rest of the evidence reviewed, but taking it for granted, it is an important scientific question to understand why mechanistic studies with manikins or humans in the laboratory seem to show a benefit of wearing facemasks, but studies in natural community settings do not show such an effect. The compliance argument does not seem to explain everything because studies in households show stronger evidence in favor of wearing facemasks at home. I think the role of ventilation and more generally air flow should be investigated further. Answering these difficult scientific questions will not be made easy if renowned scientists twist evidence in order to advance their own personal opinions.

To conclude, from the evidence I could gather about facemasks in non-medical settings, I think that masks can be useful as source control (i.e., an infected symptomatic person should wear a mask when interacting with others), especially within households and similar contexts (typical example: the workplace). But evidence on the usefulness of facemasks in community settings is too scarce to recommend them. In non-medical settings, there does not seem to be sufficient reason why people who are not sick should wear masks.

References

I list here the references that cannot be found in Howard et al. (2021).

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