DELVE Report on Face Masks for the General Public

Summary

Face masks offer an important tool for managing community transmission of Covid19 within the general population. Evidence supporting their effectiveness comes from analysis of: (1) the incidence of asymptomatic and pre-symptomatic transmission; (2) the role of respiratory droplets in transmission, which can travel as far as 1-2 meters; and (3) studies of the use of homemade and surgical masks to reduce droplet spread. Our analysis suggests that their use could reduce onward transmission by asymptomatic and pre-symptomatic wearers if widely used, contrasting to the standard use of masks for the protection of wearers. If used widely and correctly, face masks, including homemade cloth masks, can reduce viral transmission.

Key points

- 1. Asymptomatic (including presymptomatic) infected individuals are infectious. Without mitigation, the current estimate is that 40%-80% of infections occur from individuals without symptoms [He, Nat Med 2020; Ferretti, Science 2020; Ganyani, medrXiv 2020; Li, Science 2020]. Universal screening of SARS-COV2 in women admitted for delivery in New York City shows that the prevalence of asymptomatic infected individuals was 88% [Sutton, NEJM 2020]. Of individuals who do become symptomatic, viral loads are the highest in the presymptomatic and early symptomatic phase, decreasing thereafter [Pan et al., Lancet Inf Dis. 2020; Zu et al., NEJM, 2020; Bai et al., JAMA 2020; Hodroft et al., Swiss Med Weekly, 2020; He, Nature Medicine 2020; Tan, MedRxiv, 2020; Wölfel, Nature 2020].
- 2. **Droplets from infected individuals are a major mode of transmission** [WHO]. This understanding is the basis of the recommendations for physical distancing, and for surgical masks to be adequate protection for HCWs in most settings [PHE]. Droplets do not only come from coughing or sneezing: in a-/pre-symptomatic individuals, droplets are generated via talking and breathing [Anfinrud, NEJM, 2020]
- 3. Face masks reduce droplet dispersal. Cloth-based face masks reduce emission of particles by variable amounts, for example [Anfinrud, NEJM 2020] showed that they are almost completely eliminated. [Davies, Dis Med Pub Pre 2013] showed that they filtered viral particles during coughing at about 50 to 100% of the filtration efficiency of surgical masks, depending on fabric, with absolute filtration efficiencies of 50-70%, and about 70-80% for oral bacteria. [van der Sande, Plos One 2008] showed 50% filtering efficiency for airborne particles.

This evidence supports the conclusion that more widespread risk based face mask adoption can help to control the Covid-19 epidemic by reducing the shedding of droplets into the environment from asymptomatic individuals. Preliminary calculations indicate that it may lead to significant reductions in the reproductive number. It is also consistent with the experiences of countries that have adopted it.

Our analysis focuses on the effect of face masks on onward virus transmission, or source control [Howard, Preprints 2020], of infected but symptom-free wearers. This is to be distinguished from the use of face masks as *personal* protection against virus acquisition. We have found only two randomised control trials in the primary literature on the use of face masks to reduce onward transmission; one [Canini, PLoS One 2010] was underpowered, and the other [MacIntyre et al, Emerg Infect Dis 2009] showed significant reduction. [Greenhalgh, BMJ 2020, Javid BMJ 2020] argue that "absence of evidence" should not be misinterpreted as "evidence of absence", and in support of face mask usage by the public based on the precautionary principle.

Policy implications

- Strategies to transition out of lockdown need to take into account the role of both symptomatic and asymptomatic individuals in spreading Covid-19. Face masks can reduce viral transmissions from such individuals. Both commercially available and homemade cloth masks and surgical masks can play a role.
- Face masks may play an important role in situations where social distancing is not
 possible or unpredictable. These situations include public transport, stores and shopping
 areas, work places, within households, clinics, hospitals, care-homes, social care and
 busy pavements.
- Public health interventions that involve cost to the public and access to reliable
 information tend to be taken up faster, more widely or more effectively by higher socioeconomic status groups. If the use of face masks in public is made mandatory or highly
 recommended, interventions may be necessary to ensure that all members of the public
 have access to these masks and information about proper use.
- While there is anecdotal evidence of individual risk compensation behaviour, at a
 population level the introduction of safety measures like HIV prevention measures,
 seatbelts and helmets have led to increased safety and even increased safety oriented
 behaviour [Howard, Preprint 2020]. There is no evidence for individual risk
 compensation amongst the public during epidemics.
- Clear instructions, that they should be worn in addition to other government measures like physical distancing and handwashing, and that they primarily protect others rather than the wearer, will be necessary to support correct use and avoid risk compensation behaviour. The establishment of standards for homemade face masks, as has been done for other areas of public health, is one approach to achieving this.
- In parallel with any policy recommending the use of homemade face masks for the general public, it will be necessary to take all steps to ensure sufficient supply of surgical masks as well as PPE for frontline NHS workers.

This summary represents the main conclusion of the DELVE Initiative on the wearing of face masks in public, based on a review of the primary literature, and new data-enabled analyses. This evidence base supports the conclusion that widespread use of surgical and homemade face masks among the public can have a significant mitigating effect on the spread of Covid-19.

Technical annexes to this document provide detailed analyses, review additional considerations, and highlight particular practical issues of importance.

Areas where further investigation is needed

- While there is good indirect supporting evidence that suggests droplets are a main transmission route, the relative contribution of droplet transmission has not yet been directly established empirically.
- Evidence on the extent of asymptomatic as opposed to presymptomatic transmissions is evolving. Further work on population testing or prevalence studies is needed to address these gaps.
- Since risk exposure varies (from 0 to 1), it follows that advice on mask wearing is most
 useful if it is risk based. Further work is recommended to evaluate & categorise risk
 exposure, in order to give the public practical advice on when mask use is most and
 least necessary. Until such studies are definitive, it may be useful to consider whether
 simple and universal guidelines could be a constructive interim measure.
- Mask efficacy depends on material, fit, and other factors. It follows that guidance on risk
 exposure would be useful (when is a cloth or homemade mask adequate, what activity
 would merit a well-fitted higher-grade mask?).

Evidence Base

Current Understanding of Transmission Mechanism and Public Mask Wearing

What proportion of transmissions are asymptomatic/presymptomatic?

There is evidence of transmissions from both infected asymptomatic individuals, as well as from presymptomatic individuals, i.e., infectious individuals who will go on to display symptoms but are asymptomatic at the time of transmission [Rothe, NEJM 2020; Kimball, MMWR 2020]. Mechanistically, this is related to the high viral load typical of SARS-CoV-2 at the time of symptom onset, as well as evidence of viral shedding occurring prior to the appearance of symptoms [He, Nat Med 2020; Zou, NEJM 2020]. One recent paper estimated contributions to the overall reproduction number R0 arising from asymptomatic (Ra), presymptomatic (Rp), symptomatic (Rs), and environmental transmission (Re), i.e. R0=Ra+Rp+Rs+Re, and found ratios of Ra:Rp:Rs:Re = 1:9:8:2 [Ferretti, Science 2020]. Note that in this paper, environmental transmission is defined as transmission via contamination; in other words in a way that would not be attributable to contact with the infected source [Ferretti, Science 2020]. This is broadly consistent with estimates of 46%-55% presymptomatic transmission in (He, Nature Medicine 2020) as well as estimates of 48% and 62% in data from Singapore and Tianjin [Ganyani, MedrXiv 2020]. We note that one report estimated that prior to the implementation of travel restrictions on January 23, 2020, in China, up to 79% of documented cases arose from undocumented infections, many of whom were likely not severely symptomatic [Li, Science 2020].

What proportion of transmissions are from droplets vs aerosols?

It is currently believed that droplets are the main route of transmission. Whilst there is indirect evidence that supports this, the relative contribution of droplet/aerosol transmission has not been estimated.

Aerosols refer to suspensions in gas of small particles (typically < 5-10 µm) and can travel relatively long distances. Droplets refer to large particles (> 20 µm) and can only travel short distances as they will fall to ground due to gravity (Tellier et al. 2019). While the possibility of aerosol transmission of COVID-19 has been clearly demonstrated through experiments (van Doremalen et al. 2020) and outbreak reports (e.g., Washington state choir), it remains unclear what proportion of infection can be attributed to aerosol transmission. Some studies provide indirect evidence that droplets may be the main routes of transmission. For example, a recent report by Lu et al. (2020) describes an outbreak in a restaurant in Guanzhou, China, in which customers were likely to have been infected through droplets that travelled through air conditioning airflow; they conclude that the patterns of outbreak is consistent with droplet transmission, rather than aerosol transmission. Anfinrud et al. (2020) demonstrates that droplets, smaller than those generated through coughing or sneezing, can be generated via

speech, providing further evidence that droplet transmission may play important roles. <u>Public Health England</u> also suggests that droplets and contacts are main routes of transmission. It is currently unknown what proportion of infected cases can be attributed to aerosol vs droplet transmission. The proportion of droplets vs aerosol transmission is unknown.

What proportion of transmissions occur indoors vs outdoors?

Recent analysis from China suggests that a large proportion of transmission occurs indoors, particularly within homes and on transport.

Many outbreak reports describe indoor transmission, including transmission within homes, churches (Wei et al., 2020), hospitals (Bai et al., 2020), gyms, and restaurants (Lu et al., 2020). However, there may be selection bias as indoor transmission is easier to trace and identify. Qian et al. (2020) analyzed 318 outbreaks, involving 3 or more cases, between January 4 and February 11, from China, outside of Hubei province, and found that 80% of the outbreaks are home outbreaks and 34% are transport outbreaks (some outbreaks belong to more than one category); they identified one outbreak in the outdoor setting.

What are the effects of homemade masks relative to surgical masks on droplet/aerosol spread and on viral load?

In addition to events such as coughs and sneezes producing respiratory emissions, speech has also been found to produce substantial numbers of droplets capable of containing respiratory pathogens (Anfinrud, NEJM 2020). To this effect, several studies have assessed the usefulness of masks in mitigating emissions from an individual to the environment. Masks made from household materials have been found to filter pathogens less effectively than surgical masks, with efficiency estimates relative to surgical masks ranging from approximately 70% in a study using bacteria and bacteriophage (Davies, Dis Med Pub Pre 2013) to approximately 50% in a study of airborne particles (van der Sande, Plos One 2008).

In terms of viral load, in a study of influenza, viral RNA was detected in coarse (greater than 5 micron) particles from 11% of the volunteers when they wore surgical masks, and from 43% of the volunteers when they did not. In fine particles (less than 5 micron in size), viral RNA was detected from 78% of individuals when wearing surgical masks and from 92% of individuals when they did not (Milton, Plos Pathogens 2013). This study concluded that the surgical masks produced a 3.4 fold (95% CI 1.8 to 6.3) reduction in viral copies in exhaled breath. Another recent study found that for coronaviruses, surgical face masks reduced virus shedding in respiratory droplets (greater than 5 micron) and aerosols (less than 5 micron) emitted by symptomatic individuals (Leung, Nature Medicine 2020). Specifically, coronaviruses were detected in 30% and 40% of droplet and aerosol samples, respectively, from symptomatic individuals not wearing masks, and in no samples for both droplets and aerosols for symptomatic individuals wearing surgical masks (Leung, Nature Medicine 2020).

There is one study which showed some evidence that wearing cloth masks could increase viral infection rates [MacIntyre et al 2015]. However, the result was not replicated in a different, study but with a different experimental design. (very extended wear of PPE for hospital staff in Vietnam). As such, this is a negligible risk to the public.

How does effectiveness vary with length of mask usage?

A few studies (e.g., Mills et al. 2018, American Journal of Infection Control; Lore et al. 2012, Annals of Work Exposures and Health) have demonstrated that surgical masks can be reused if properly decontaminated (e.g., by using Ultraviolet irradiation). While Lore et al. (2012) showed that the decontamination process did not significantly reduce filtration efficiency, they only tested changes in filtration after one decontamination cycle. A recent study by Kumar et al. (medRxiv 2020) showed that decontamination of SARS-CoV-2 on N95 masks can be done without impairing their filtration efficiency for up to 10 cycles depending on the decontamination method. Optimal decontamination procedures for cloth masks need to be determined urgently.

Observational and RCT Studies of Community Mask Wearing

Is there direct evidence on mask wearing in the community for decreasing onward transmission?

Virtually all studies on mask usage are focused on their use for the protection of the wearer. These include the studies that are the subject of current meta-analyses and reviews [e.g. Brainard, MedrXiv 2020.04.01.20049528]. Such studies are irrelevant to the question of whether mask use will provide source control.

To our knowledge, only two studies have been performed that studied the effectiveness of mask use by the source patient with a viral respiratory infection (mostly influenza) and tracking the development of viral infection symptoms in others. Both studies used medical masks and monitored transmission to household members. Both studies have flaws, the most serious of which were sample sizes that were too low or an expectedly mild respiratory virus season.

The study by [Canini, PLoS One 2010] was stopped early because of poor enrollment; the study had only a 38% chance of detecting a 40% additional protection by masking. Not unexpectedly, the study found no masking effectiveness.

[McIntyre, Emerg Infect Dis 2009] studied the effectiveness of the use of a medical mask placed on a subject with a viral respiratory infection living in a household of two or more people. They found that 15% of subjects not assigned to mask wearing wore them, while 2% of subjects assigned to wear them did not. Also, probably owing to a mild flu season, only 1 to 2% of household contacts developed illness versus the expected 20%. This resulted in only a 9% chance of detecting a 50% decrease in illnesses in mask-wearing households. However, after adjustments for mask wearing in the index cases, the study found that wearing a mask by the

infected person reduced the frequency of viral respiratory infection in household members by 77% (95% CI 11 to 94% reduction).

It is important to note in both studies that mask wearing by the source subjects was still infrequent, around 4 hours a day in both studies. Because of the infrequent use of masks by the source patients, any effect measured can be considered a minimal estimate when considering a recommendation that masks be worn 100% of the time when physical distancing is not possible or predictable in public. Medical and not cloth masks were used in these studies, limiting extrapolation.

An additional point is that a fundamental rule of statistics is that absence of a "statistically significant" difference must not be used to conclude that the effect sizes for compared groups are in fact equivalent unless the power to detect that difference is high. Ignoring this is a fundamental error which should never be used for scientific conclusions or policy decisions.

Behavioural Considerations of Public Mask Wearing

Does wearing masks lead to more risky behaviour by the public?

There is anecdotal evidence that masks can encourage negative behaviours in professional settings (for instance industry). This is attributable to desensitisation from extended wear and familiarity with the hazardous material. However, there is no direct evidence that this is the case in public settings where there is less chance for desensitisation. Further, at a population level past introductions of safety measures like HIV prevention measures, seatbelts and helmets have led to increased safety and even increased safety oriented behaviour [Howard, Preprint 2020].

Will universal use of face masks be accepted by the public?

Survey data shows a high uptake of masks in Italy (81%), a country with no history/culture of widespread mask wearing (<u>Ipsos</u>). An April 15th survey of 1,500 Britons found that 41% of respondents believed that the public should be asked to wear masks, compared to 33% who disagreed (<u>Survey for Telegraph</u>) so there is already public support for this.

Insights from behavioural science suggest:

- Because people view an action as correct in a given situation to the degree that they see others performing it [e.g., Farrow, Eco Econ 2017; Frank, 2020], there is an advantage to encouraging universal application in public science, with the aim of developing a critical mass of adherence and setting new norms around mask use.
- Because such norms act to inform observers that normative behaviour is both pragmatically prudent and morally proper [Nolan, 2020], information campaigns should

- convey that others are undertaking proper conduct for both practical and moral reasons, as that combination produces the greatest adherence [Jacobson, J Business Ethics 2020, Cialdini, 2020].
- Because, especially in the case of new norms, adherence to a specific form of normative conduct can spur adherence to related forms of normative conduct [Mortensen, Soc Psy Pers Sci 2017], the visibility of masks can be expected to act as a reminder of the need for physical distance, increased hand washing, reduced face touching, and group solidarity.
- Because newly installed norms are unfamiliar and potentially unclear, explicit instructions about mask use (e.g., how to wear for adequate coverage and when to end mask use) may be necessary.

International Response and Impact of Public Mask Wearing

What do we know about policy and impact of mask wearing in other countries?

The general consensus among countries with policies in place for mask use is to encourage a variety of material as face masks. Countries that have implemented widespread use of masks early in their national outbreak tend to have flatter curves than those that do not and several officials cite implementing mask policies due to asymptomatic transmission. Though many other control variations complicate this picture, it is consistent with a beneficial effect of mask use.

1. Policies and Mask Types

In Europe, policy recommendations are mostly geared towards encouraging use of makeshift facial masks for the general population for readily-available protection, which can also reduce the potential of limited medical mask supply becoming unavailable for the healthcare professionals (See Appendix). Mask policies range from recommendations of home-made masks, cloths, scarves and bandanas in Germany and the Czech Republic - with fines administered for non-compliance - to government-controlled surgical mask distribution in local pharmacies, such as KF94 masks in South Korea and N95 masks in Taiwan (Wong, 2020). More information on country policies are attached in the Appendices.

2. Impact

The difference in total cases after the 100th confirmed case in European countries with little or no mask wearing practices such as Spain and Italy, and Asian countries such as Taiwan and Hong Kong with stringent mask policies is notable (see figure below). However, it should be noted that New Zealand's approach - which relies heavily on

aggressive testing, tracing and quarantining of virus carriers, with lockdown measures in place - does not include universal mask policies (Hollingsworth, 2020).

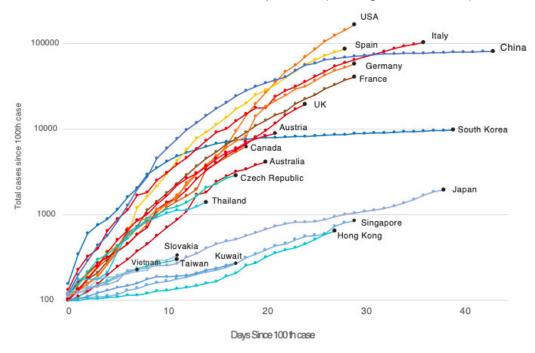


Fig. 1: Retrieved from Longrich and Sheppard (2020).

Korea's government has also witnessed an uptake in mask use due to ease of access: the number of pharmacies that sold all of their mask supplies increased from 67.9% to 86.4% in 11 days (Government of Korea, 2020).

Similarly in Hong Kong, a recent survey found that "85% of respondents reported avoiding crowded places and 99% reported wearing face masks when leaving home" (Cowling et al., 2020). Microbiologist Yuen Kwok-yung from Hong Kong, who helped confirm the spread of COVID-19 in humans has stated that apart from population control, mask-wearing, hand-washing, and social distancing are all necessary and must be implemented early to suppress transmission (Li and Zuoyan, 2020). This is indicative that clear guidance on mask use aids mask uptake in the community.

Reasons for implementing public mask policies:

In Singapore, National Development Minister Lawrence Wong cited recent fears of asymptomatic spread as one reason for the country's introduction of mandatory mask wearing: "We updated our advice on masks based on the latest scientific evidence: the finding that people without symptoms or very mild symptoms could be spreading the virus" (CNA, 2020).

The Director General of the Chinese Center for Disease Control and Prevention (CDC) highlights the prevention of virus transmission via droplets expelled during speaking in close contact, particularly from asymptomatic and presymptomatic carriers, in their guidance: "The big mistake in the U.S. and Europe, in my opinion, is that people aren't wearing masks. Many people have asymptomatic or presymptomatic infections. If they are wearing face masks, it can prevent droplets that carry the virus from escaping and infecting others" (Cohen, 2020).

In Germany, the Robert Koch Institute, the national disease control and prevention agency stated that "some infected people do not become ill at all (asymptomatic infection), but could still pass it on to others. Therefore, the wearing of temporary masks by people entering public places where the safety distance cannot be maintained, e.g. public transport, grocery stores or even at the workplace, could help to reduce the spread of SARS-CoV-2" (The Local, 2020).

Inconsistency of WHO and current government recommendations.

The current World Health Organization (WHO)'s recommendation is to wear a mask to prevent onward transmission only if the wearer is symptomatic or is treating someone suspected to have been infected by COVID (World Health Organization, 2020). However, this inevitably leads to discrepancies as a significant fraction of transmissions are from those exhibiting no symptoms or are in the pre-symptomatic phase (He et al., 2020). Therefore, by not wearing masks we are enabling a significant number of transmissions. Further to this, previous studies conducted on the effect of hand hygiene, facemask use and influenza transmission found that hand hygiene alone was insufficient, but when coupled with facemask use, there was reduced transmission (Wong et al., 2014). WHO are considering changing their advice in light of the growing evidence (Devlin and Campbell, 2020).

Is there evidence that early adoption of public mask wearing in Czech Republic as compared to Austria mitigated epidemic spread?

There is anecdotal (<u>Greenhalgh & Howard, 2020</u>) but no conclusive evidence. Government policies of these neighbouring countries largely overlap, with lockdown occurring on the same day. From lockdown, their relative growths in cumulative infection counts match for 2½ weeks, when Austria follows the Czech Republic and also introduces public mask-wearing. At that point new Austrian cases *slow down* compared to the Czech Republic.

It is plausible that Austria's comparative slow-down 2½ weeks after lockdown should instead be attributed to **more comprehensive testing**, which started 1½ weeks after lockdown. Austria broadened their testing criteria *one week* before enforcing mask-wearing, testing anyone who

shows COVID-19 symptoms, as opposed to only those who also fill narrower criteria (e.g. key workers only). The Czech Republic didn't broaden their testing criteria like Austria did in that period.

Is there international evidence that public mask wearing reduces R?

On 17th April, the DELVE action team started a propensity score-matched analysis to empirically estimate the causal connection between public mask-wearing and infection rate and mortality (link). Analysis takes data from 77 countries, including other government policies, population density, average age, and stage of the epidemic in each country. Initial results suggest a reduction in new cases and mortality rates. It is too early to interpret the results, as other factors (e.g. compliance, existing norms) are not accounted for in the data.

Appendices

Findings on microorganism reduction and compliance of mask wearing

Davies, A. et al. Disaster Medicine and Public Health Prepardeness (2013)

Homemade masks various household materials

Tested 2 microorganisms (they say comparable to influenza: 60-100nm):

- -Bacillus atrophaeus is a rod-shaped spore-forming bacterium (0.95-1.25 micron)
- -Bacteriophage MS2 is a nonenveloped single-stranded RNA coliphage (23 nm)

Filtration ability of bacteriophage 10% lower than B atrophaeus in general All materials show filtration ability

Filtration efficiency:

Surgical masks: 96% (B atropheus), 90% (Bacteriophage)

Average of all household materials: 70% (B atropheus), 63% (Bacteriophage)

Their data on reduction in colony-forming units from mask use much harder to interpret

Leung, N. H. L.. et al. Nature Medicine (2020)

	Droplet	particles>5 µm	Aerosol particles ≤5 μm					
Virus type	Without surgical face mask	With surgical face mask	P	Without surgical face mask	With surgical face mask	P		
	Detection of virus							
	No. positive/no. total (%)	No. positive/no. total (%)		No. positive/no. total (%)	No. positive/no. total (%)			
Coronavirus	3 of 10 (30)	0 of 11 (0)	0.09	4 of 10 (40)	0 of 11 (0)	0.04		
Influenza virus	6 of 23 (26)	1 of 27 (4)	0.04	8 of 23 (35)	6 of 27 (22)	0.36		
Rhinovirus	9 of 32 (28)	6 of 27 (22)	0.77	19 of 34 (56)	12 of 32 (38)	0.15		
	Viral load (log ₁₀ virus copies per sample)							
	Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)			
Coronavirus	0.3 (0.3, 1.2)	0.3 (0.3, 0.3)	0.07	0.3 (0.3, 3.3)	0.3 (0.3, 0.3)	0.02		
Influenza virus	0.3 (0.3, 1.1)	0.3 (0.3, 0.3)	0.01	0.3 (0.3, 3.0)	0.3 (0.3, 0.3)	0.26		
Rhinovirus	0.3 (0.3, 1.3)	0.3 (0.3, 0.3)	0.44	1.8 (0.3, 2.8)	0.3 (0.3, 2.4)	0.12		

MacIntyre, C. R. et al. BMJ Open (2015)

RCT of healthcare workers in Vietnam assigned either cloth or medical masks.

Relative risk of Influenza-Like-Illness (ILI) 13x higher in cloth mask group than medical mask group

ILI (RR 6.64 95% CI 1.45 to 28.65) and lab confirmed virus (RR=1.72, 95% CI 1.01 to 2.94) significantly higher in cloth mask group than medical mask.

They find high penetration of masks by particles (97% for cloth masks, 44% for medical masks) although I'm not entirely sure how this was determined or what particles are referred to...

MacIntyre, C. R. et al. EID (2009)

Approached parents of children seeking treatment at pediatric health services and monitored family's use of masks.

Relative reduction in daily risk of acquiring a respiratory infection associated with adherent mask (P2 or surgical) use was 60-80%

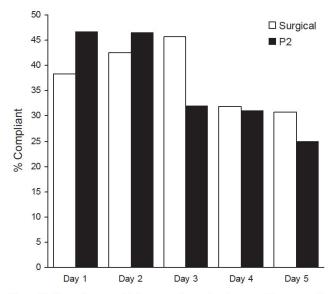


Figure 2. Compliance with face mask use by day over 5 consecutive days during the study, Sydney, New South Wales, Australia, 2006 and 2007 winter influenza seasons.

They cite 76% of population in Hong Kong wearing a mask during SARS as high adherence

Milton, D.K. et al. *Plos Pathogens* (2013)

Detect influenza RNA in coarse (greater than 5 micron) particles from 11% of volunteers wearing surgical mask and from 43% when not wearing masks. Detect viral RNA in fine particles from 78% of individuals wearing masks and from 92% of individuals when not wearing masks.

Fine particles contained 8.8x more viral copies than coarse particles.

van der Sande, M. K. et al. Plos One (2008)

Inward protection: protect you from environment

Outward protection: protect environment / others from you

Surgical masks provided about twice as much protection as homemade masks, the difference a bit more marked among adults. FFP2 masks provided adults with about 50 times as much protection as home made masks, and 25 times as much protection as surgical masks.

Table 1. Median (IQR) protection factor by mask, by activity, by age category.

		no activity	nodding	shaking	reading	walking
Tea cloth	Adults	2.5 (2.1-2.9)	2.2 (1.9-2.5)	2.2 (1.9–2.7)	3.2 (2.5-3.9)	2.4 (2.1-3.3)
	children	2.2 (1.5-2.2)	1.9 (1.5-2.3)	1.9 (1.4-2.3)	2.2 (1.8-3.7)	2.2 (1.8-2.4)
Surgical mask	Adults	4.1 (3.1-7.2)	4.7 (3.4–7.3)	5.1 (3.2-7.6)	5.3 (4.3-8.0)	4.2 (3.1-5.7)
	children	3.2 (2.2-4.1)	3.4 (2.7-5.2)	3.6 (2.7-4.3)	4.9 (4.0-5.3)	3.6 (2.4-4.2)
FFP2 mask	Adults	113 (26–210)	82 (45–179)	91 (23–187)	66 (29–107)	99 (19–169)
	children	18 (6.1-165)	13 (3.8-41)	18 (4.0-54)	35 (8.6-91)	15 (5.1-176)

IQR = interquartile range doi:10.1371/journal.pone.0002618.t001

They do some assessments of these protection factors over time

Protection factors for all type of masks were considerably lower for outward protection than those observed for inward protection. The home-made masks only provided marginal protection, while protection offered by a surgical mask and an FFP2 mask did not differ.

Mask Policies in Various Countries

Country	At what point in the spread of disease were masks introduced?	What form of mask is used?	Who is required to wear a mask? In what circumstances?	How is this enforced?
Germany	31st March 2020: Mask use introduced in city of Jena, 2 weeks after school closures and ban of public gatherings. 15th April 2020: Announcement from Chancellor Merkel that mask-wearing should extend nationwide, following concern of spread via potential asymptomatic carriers. Germany's first reported case was on 27th January and it is beginning to relax current lockdown measures.	General public encouraged to use home-sewn masks or wear protective cloth, rather than medical masks to prevent shortage of supply for medical professionals and essential workers.	For those going outside into public spaces i.e. shoppers, those using public transport.	Certain cities such as Jena have made mask use mandatory, whereas nationwide these measures are rather recommended.
Czech Republic	19th March 2020: 18 days after the first confirmed case. This occurred at the same time commuting became restricted to essential grocery shopping.	If surgical masks are unavailable for public use, any form of cotton material such as folded bandanas and scarves.	Anyone moving outside their home for any reason. People are required to wear protective medical masks and keep a distance of 2m everywhere.	Initially encouraged through a social media campaign that promoted mask use. Now compulsory by law Fines for non-compliance.

South Korea	Mid-January 2020: Mask use, particularly for healthcare professionals and those showing respiratory symptoms already in place due to societal practices. 9th March 2020: Mask distribution policy introduced. This is a 5-day rotation system that restricts the number of masks someone can buy, to ensure more equitable distribution and to minimise price-hiking from panic buying. Government bought masks from manufacturers to then distribute to the public to control supply. South Korea's first reported case was announced on 20th January and infection control seems to be stable.	General population advised to wear KF80 (i.e. FFP1)-type masks. Those required to wear more protective masks (i.e. KF94): 1. Those showing respiratory symptoms (coughing, sneezing, runny/blocked nose, sore throat, producing sputum). 2. Those taking care of COVID-19 patients. 3. People who visit hospitals or clinics. 4. Those working in areas which require them to contact many people (e.g. bus drivers, salesperson, postman, janitor etc.).	Everyone in public, especially showing respiratory symptoms. Those in their personal space (e.g. indoors) and non-crowded areas do not need to wear masks.	Regulated and monitored via social security number. Members of the public can go to a pharmacy on an assigned day of the week, allocated by birth year, and can buy only 2 masks per week. ID required to track purchases to prevent multiple purchases from different pharmacies. Mask availability for every pharmacy can be found via a mobile app.
China	December 2019: Mask use, particularly for healthcare professionals and those showing respiratory symptoms already in place due to societal practices. 26th January 2020: China's State Council approved subsidies worth USD \$1.63bn for COVID19 efforts to procure more masks. By 27th January, there were nearly 4,500 confirmed cases and 106 deaths The first reported case was in December 2019, whilst the lockdown in Wuhan occurred on 23rd January 2020. 19th March 2020: national guidelines introduced for the general population.	Surgical or disposable masks for those at moderate risk of infection: 1. Those working in crowded areas (e.g. hospitals, train stations). 2. Those in contact with someone in quarantine. 3. Those likely to come into contact with COVID19-infected people (e.g. police). Low-risk people should wear disposable masks e.g. those visiting hospitals. A mask should not be used for more than 8 hours in total.	Those in public areas likely come across other members of the public.	Some provincial differences in enforcement/penalties but it is generally mandatory.

U.S.A.: State of New York	15th April 2020: Governor Cuomo of New York in the process of issuing an executive order to make face coverings obligatory for residents, to take effect on 17th April. The state's first confirmed case was reported on 1st March; schools and non-business were closed as restrictive measures were put in place from 15th March The spread of infection is showing very early signs of potentially stagnating but this remains to be seen. New York, New Jersey and Maryland are so far the only states to have issued broad orders mandating face coverings in most public settings in the US.	Any form of face covering that masks the mouth and nose; examples include protective masks, scarves and bandanas	Anyone not able to maintain social distancing measures in public and/or crowded areas e.g. on public transport, sidewalks and shops. This is in line with non-binding guidelines from the Centers for Disease Control and Prevention	Cuomo stated that these rules enforced by local governments but no one would be forcibly removed from public transport for noncompliance. Consideration of issuing civil, not criminal, penalties.
------------------------------	--	--	--	--

References

Anderson, E. 2020. First case of coronavirus confirmed in Germany. 28 January. POLITICO. Available at: https://www.politico.eu/article/first-case-of-coronavirus-confirmed-in-germany/

Anfinrud, P., Stadnytskyi, V., Bax, C. E., & Bax, A. (2020). Visualizing Speech-Generated Oral Fluid Droplets with Laser Light Scattering. New England Journal of Medicine. Available at: https://www.nejm.org/doi/full/10.1056/NEJMc2007800

Bai Y, Yao L, Wei T, et al. (2020). Presumed Asymptomatic Carrier Transmission of COVID-19. JAMA. https://jamanetwork.com/journals/jama/fullarticle/2762028

Brainard, J. S., Jones, N., Lake, I., Hooper, L., & Hunter, P. (2020). Facemasks and similar barriers to prevent respiratory illness such as COVID-19: A rapid systematic review. medRxiv. Available at: https://www.medrxiv.org/content/10.1101/2020.04.01.20049528v1

Canini, L., Andreoletti, L., Ferrari, P., Angelo, D. R., Blanchon, T., Lemaitre, M., Filleul, L., Ferry, J. P., Desmaizieres, M., Smadja, S., Valleron, A. J. & Carrat, F. 2010. Surgical mask to prevent influenza transmission in households: A cluster randomized trial. PLoS One. Available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0013998

Chan, E. 2020. Coronavirus: China's surgical mask shortage ripples through global supply chain as health crisis continues. 16 February. South China Morning Post. Available at: https://www.scmp.com/economy/china-economy/article/3050717/coronavirus-chinas-surgical-mask-shortage-ripples-through

Cialdini, R. 2020. Advice for Reducing Undesirable COVID-19 Behaviors. Available at: https://www.influenceatwork.com/inside-influence-report/advice-for-reducing-undesirable-covid-19-behaviors/

CNA. 2020. COVID-19: Why Singapore changed its guidance on masks and made it mandatory. 14 April. Youtube. Available at: https://www.youtube.com/watch?v=dWxfZjH2kf8

Cohen, J. 2020. Not wearing masks to protect against coronavirus is a 'big mistake,' top Chinese scientist says. 27 March. ScienceMag. Available at: https://www.sciencemag.org/news/2020/03/not-wearing-masks-protect-against-coronavirus-big-mistake-top-chinese-scientist-says

Cowling, B., Ali, S. et al. 2020. Impact assessment of non-pharmaceutical interventions against coronavirus disease 2019 and influenza in Hong Kong: an observational study. 17 April. Lancet Public Health. Available at: https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30090-6/fulltext

Davies, A., Thompson, K. A., Giri, K., Kafatos, G., Walker, J., & Bennett, A. (2013). Testing the efficacy of homemade masks: would they protect in an influenza pandemic?. Disaster medicine and public health preparedness, 7(4), 413-418. Available at:

https://www.cambridge.org/core/journals/disaster-medicine-and-public-health-preparedness/article/testing-the-efficacy-of-homemade-masks-would-they-protect-in-an-influenza-pandemic/0921A05A69A9419C862FA2F35F819D55

Devlin, H. and Campbell, D. 2020. WHO considers changing guidance on wearing face masks. 1 April. The Guardian. Available at: https://www.theguardian.com/world/2020/apr/01/all-uk-hospital-staff-and-patients-should-wear-masks-says-doctors-group#maincontent

Eikenberry, S. Mancuso, M. Iboi, E. Phan, T. Eikenberry, K. Kuang, Y. Kostelich, E. and Gumel, A. To mask or not to mask: Modeling the potential for face mask use by the general public to curtail the COVID-19 pandemic, ArXiv. Available at: https://arxiv.org/pdf/2004.03251.pdf

Farrow, K., Grolleau, G., & Ibanez, L. (2017). Social norms and pro-environmental behavior: A review of the evidence. Ecological Economics, 140, 1-13.

Feng, S., Shen, C., Xia, N., Song, W., Fan, M. and Cowling, B. 2020. Rational use of face masks in the COVID-19 pandemic. 20 March. The Lancet Respiratory Medicine. Available at: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30134-X/fulltext#box1

Ferré-Sadurní, L. and Cramer, M. 2020. New York Orders Residents to Wear Masks in Public. 15 April. NY Times. Available at: https://www.nytimes.com/2020/04/15/nyregion/coronavirus-face-masks-andrew-cuomo.html

Ferretti, L., Wymant, C., Kendall, M., Zhao, L., Nurtay, A., Abeler-Dörner, L., ... & Fraser, C. (2020). Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. Science.

Fetzer, T., Witte, M., Hensel, L., Jachimowicz, J. M., Haushofer, J., Ivchenko, A., ... Yoeli, E. (2020). Global Behaviors and Perceptions in the COVID-19 Pandemic. *PsyArXiv Preprints*. https://doi.org/10.31234/osf.io/3kfmh

Flaxman, S. et al. 2020. Estimating the number of infections and the impact of non-pharmaceutical interventions on covid-19 in 11 europen countries. Available at: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-13-europe-npi-impact/

Fleming, S. 2020. South Korea's Foreign Minister explains how the country contained COVID-19. 31 March. WEForum. Available at: https://www.weforum.org/agenda/2020/03/south-korea-covid-19-containment-testing/

Frank, R. H. (2020). *Under the Influence: Putting peer pressure to work.* Princeton, NJ: Princeton University Press.

Ganyani, T., Kremer, C., Chen, D., Torneri, A., Faes, C., Wallinga, J., & Hens, N. (2020). Estimating the generation interval for COVID-19 based on symptom onset data. medRxiv. https://www.medrxiv.org/content/10.1101/2020.03.05.20031815v1

GardaWorld. 2020. Czech Republic: First cases of COVID-19 confirmed March 1 /update 1. 1 March. Available at: https://www.garda.com/crisis24/news-alerts/318896/czech-republic-first-cases-of-covid-19-confirmed-march-1-update-1

Government of the Czech Republic. 2020. The government requires the wearing of protective equipment and reserved time for pensioners to do their food shopping. 18 March. Available at: https://www.vlada.cz/en/media-centrum/aktualne/the-government-has-decided-to-require-thewearing-of-protective-equipment-and-reserved-time-for-senior-citizens-to-do-their-food-shopping-180465/

Government of Korea. 2020. Flattening the curve on COVID-19: How Korea responded to a pandemic using ICT. 15 April. Available at:

http://www.korea.kr/common/download.do?fileId=190536078&tblKey=GMN

Greenhalgh T., Schmid MB.,, Czypionka T., Bassler D., Gruer L. 2020. Face masks for the public during the covid-19 crisis BMJ 2020; 369 :m1435 https://www.bmj.com/content/369/bmj.m1435

He, X., Lau, E.H.Y., Wu, P. et al. 2020. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med https://doi.org/10.1038/s41591-020-0869-5

Hollingsworth, J. 2020. New Zealand reported a decline in new coronavirus cases for the fourth consecutive day. The country is still tightening its border restrictions. 9 April. CNN. https://edition.cnn.com/2020/04/09/asia/new-zealand-lessons-intl-hnk/index.html

Howard, J. 2020. To help stop coronavirus, everyone should be wearing face masks. The science is clear. 4 April. The Guardian. Available at: https://www.theguardian.com/commentisfree/2020/apr/04/why-wear-a-mask-may-be-our-best-weapon-to-stop-coronavirus

Ipsos MORI 2020, More people say they're wearing masks to protect themselves from COVID-19 since March, available at: https://www.ipsos.com/en/more-people-say-theyre-wearing-masks-protect-themselves-covid-19-march

Jacobson, R.P., Marchiondo, L.A., Jacobson, K.J.L. et al. (2020). The Synergistic Effect of Descriptive and Injunctive Norm Perceptions on Counterproductive Work Behaviors. Journal of Business Ethics, 162, 191–209 https://doi.org/10.1007/s10551-018-3968-1

Kim, T. How South Korea Solved Its Face Mask Shortage. 2020. 1 April. NY Times. Available at: https://www.nytimes.com/2020/04/01/opinion/covid-face-mask-shortage.html

Kimball, A.; Hatfield, K. M., et al. (2020). Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility — King County, Washington, March 2020. MMWR Morbidity and Mortality Weekly Report. https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e1.htm

Leung, N. H. L.; Chu, D. K. W.; et al. (2020). Respiratory virus shedding in exhaled breath and efficacy of face masks. Nature Medicine. https://www.nature.com/articles/s41591-020-0843-2

Li, R., Pei, S., Chen, B., et al. (2020). Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). Science. https://science.sciencemag.org/content/early/2020/03/24/science.abb3221.long

Li, I. and Zuoyan, Z. 2020. Q&A with HK microbiologist Yuen Kwok-yung who helped confirm coronavirus' human spread. 10 March. The Straits Times. Available at: https://www.straitstimes.com/asia/east-asia/exclusive-qa-with-hong-kong-microbiologist-yuen-kwok-yung-who-helped-confirm

Li R, Pei S, Chen B, Song Y, Zhang T, Yang W, Shaman J (2020). Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). Science

Longrich, N. and Sheppard, S. 2020. Public use of face masks to control the coronavirus (SARS-Cov-2) pandemic: a review of theory and evidence. 12 April. Working Paper. Available at: https://www.preprints.org/manuscript/202004.0021/v2

Lore, M., Heimbuch, B., Brown, T., Wander, J., Hinrichs, S. 2012 Effectiveness of Three Decontamination Treatments against Influenza Virus Applied to Filtering Facepiece Respirators, *The Annals of Occupational Hygiene*, Volume 56, Issue 1, January 2012, Pages 92–101, https://doi.org/10.1093/annhyg/mer054

Ludwig, P. 2020. How to Significantly Slow Coronavirus? 27 March. Youtube. Petr Ludwig / Konec prokrastinace [CZE]. Available at: https://www.youtube.com/watch?v=HhNo IOPOtU

Lu, P.; Gu, J.; Li, K,; Xu, C.; Su, W.; Lai, Z.; Zhou, D.; Yu, C.; Xu, B.; Yang, Z. (2020). COVID-19 Outbreak Associated with Air Conditioning in Restaurant, Guangzhou, China. Emerging Infectious Diseases. https://wwwnc.cdc.gov/eid/article/26/7/20-0764 article

MacIntyre CR, Cauchemez S, Dwyer DE, et al. Face mask use and control of respiratory virus transmission in households. Emerg Infect Dis 2009;15:233-41. 10.3201/eid1502.081166 19193267.

MacIntyre CR, Seale H, Dung TC, et al. A cluster randomised trial of cloth masks compared with medical masks in healthcare workers. *BMJ Open.* 2015;5(4):e006577. Published 2015 Apr 22. doi:10.1136/bmjopen-2014-006577

Mahbubani, R. and Mosher, D. 2020. 'In search of the apex and the other side of the mountain': The coronavirus has killed more than 4,100 New Yorkers in just over a month, and the worst is still to come. 5 April. Business Insider. Available at: https://www.businessinsider.com/new-york-coronavirus-crisis-1-month-cases-surge-apex-2020-4?r=US&IR=T

Mills, D., Harnish, D., Lawrence, C., Sandoval-Powers, M., Heimbuch, B. 2018 Ultraviolet germicidal irradiation of influenza-contaminated N95 filtering facepiece respirators. American Journal of Infection Control. Vol 46, Issue 7, Pages e49-e55, https://doi.org/10.1016/j.ajic.2018.02.018

Milton, D.K.; Fabian, M. P. et al. (2020). Influenza Virus Aerosols in Human Exhaled Breath: Particle Size, Culturability, and Effect of Surgical Masks. Plos Pathogens. https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1003205

Mortensen, C. H., Neel, R., Cialdini, R. B., Jaeger, C. M., Jacobson, R. P., & Ringel, M. M. (2017). Upward trends: A lever for encouraging behaviors performed by the minority. Social Psychology and Personality Science. https://doi.org/10.1177%2F1948550617734615

National Health Commission of the People's Republic of China. 2020. China issues guideline for wearing masks effectively amid COVID-19 epidemic. 19 March. Available at: http://en.nhc.gov.cn/2020-03/19/c 77956.htm

Nolan, J. M., Schultz, P. W., Cialdini, R. B., & Goldstein, N. J. (2020). The Social Norms Approach: A Wise Intervention for Solving Social and Environmental Problems. In G. Walton and A. Crum (Eds.) *Handbook of Wise Interventions*. Guilford.

Pan X, Chen D, Xia Y, et al. (2020). Asymptomatic cases in a family cluster with SARS-CoV-2 infection. The Lancet Infectious Diseases. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30114-6/fulltext

Public Health England. 2020. Transmission characteristics and principles of infection prevention and control. Available at:

https://www.gov.uk/government/publications/wuhan-novel-coronavirus-infection-prevention-and-control/transmission-characteristics-and-principles-of-infection-prevention-and-control

Qian, H.; Miao, T.; LIU, L.; Zheng, X.; Luo, D.; Li, Y. (2020). Indoor transmission of SARS-CoV-2. MedRxiv.https://www.medrxiv.org/content/10.1101/2020.04.04.20053058v1

Reuters. 2020. German city introduces face masks for shoppers as COVID-19 spreads. 31 March. Available at: https://gulfnews.com/world/europe/german-city-introduces-face-masks-for-shoppers-as-covid-19-spreads-1.70731693

Rothe C., Schunk M., Sothmann P., et al. (2020). Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. NEJM.

https://www.nejm.org/doi/full/10.1056/NEJMc2001468

South China Morning Post. 2020. China allocates US\$1.63 billion for urgently needed medical supplies to fight coronavirus. 27 January. Youtube. Available at: https://www.youtube.com/watch?time_continue=57&v=YguhnBRlshU&feature=emb_logo

Sutton D, Fuchs K, D'Alton M, Goffman D (2020) Universal screening for SARS-COV2 in women admitted for delivery. NEJM

Tan, W. et al. 2020. Viral Kinetics and Antibody Responses in Patients with COVID-19. MedRxiV. https://www.medrxiv.org/content/10.1101/2020.03.24.20042382v1

The Local. 2020. Coronavirus and face masks: How countries have shifted their advice to the public. 5 April. Available at: https://www.thelocal.com/20200405/coronavirus-and-face-masks-how-countries-have-changed-their-advice

The Local. 2020. Germany recommends face masks in shops and public transport. 15 April. Available at: https://www.thelocal.de/20200415/german-government-pushes-to-make-masks-mandatory-in-public-transport-and-retail

The Local. 2020. 'They could reduce the risk': Germany's public health institute updates stance on face masks. 2 April. Available at: https://www.thelocal.de/20200402/latest-face-masks-in-public-could-help-to-reduce-spread-of-coronavirus-says-germanys-robert-koch-institute

The Telegraph 2020 Support for wearing face masks in public outweighs opposition, 18 April 2020, available at: https://www.telegraph.co.uk/news/2020/04/18/public-support-wearing-face-masks-public-outweighs-opposition/

U.S. Embassy in the Czech Republic. 2020. COVID-19 Information. 7 April. Available at: https://cz.usembassy.gov/covid-19-information/

van Doremalen, N., Bushmaker, T., Morris, D., Holbrook, M., Gamble, A., Williamson, B. 2020. 2020 Aerosol and Surface Stability of HCoV-19 (SARS-CoV-2) Compared to SARS-CoV-1. medRxiv https://www.nejm.org/doi/full/10.1056/nejmc2004973

van der Sande, M., Teunis, P., & Sabel, R. (2008). Professional and home-made face masks reduce exposure to respiratory infections among the general population. PLoS One, 3(7). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2440799/

Wei W.E., Li, Z., Chiew C.J., Yong S.E., Toh M.P., Lee V.J. (2020). Presymptomatic Transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020. MMWR Morbidity and Mortality Weekly Report.

https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e1.htm?fbclid=lwAR1b S3wC7pqWsIF5wUhjMqQWXbxA6rc-YLy80so8Vcxx7160WQHHB0wxm4

Wölfel, R. et al. (2020). Virological assessment of hospitalized patients with COVID-2019. Nature. https://www.nature.com/articles/s41586-020-2196-x

Wong, T. 2020. Coronavirus: Why some countries wear face masks and others don't. 31 March. BBC News. Available at: https://www.bbc.co.uk/news/world-52015486

Wong, V., Cowling, B. and Aiello, A. 2014. Hand hygiene and risk of influenza virus infections in the community: A systematic review and meta-analysis. Epidemiol Infect. doi: 10.1017/S095026881400003X

World Health Organization. 2020. Coronavirus disease (COVID-19) advice for the public: When and how to use masks. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/when-and-how-to-use-masks

World Health Organization. 2020. Novel Coronavirus (2019-nCoV) SITUATION REPORT – 1. 21 January. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf?sfvrsn=20a99c10 4

World Health Organization. 2020. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). 16-24 February. Available at: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

World Health Organization. 2020. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations. Available at: https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations

Zou L., Ruan F., Huang M., et al. (2020). SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. NEJM. https://www.nejm.org/doi/full/10.1056/NEJMc2001737