

COVID-19 Update

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Jorge Mera, MD

Whitney Essex APRN

The Pathophysiology of COVID-19 and SARS-CoV-2 Infection: Understanding the age divide in COVID-19: why are children overwhelmingly spared?

- Among the first 149,082 US cases (through April 2, 2020), only 2,572 (~1.7%) were infants, children, and adolescents 18 yr old (children)
- 18 yr old make up 22% of the US population
- Children accounted for 1–5% of diagnosed cases
- In 2015 alone, 291.8 million episodes of LRI occurred worldwide, of which more than one-third occurred among children 5 yr old .
 - An estimated 704,000 deaths occurred among children 5 yr old.
 - Approximately 6.6% of these pediatric deaths (more than 46,000) were attributed to respiratory syncytial virus (RSV) or influenza.

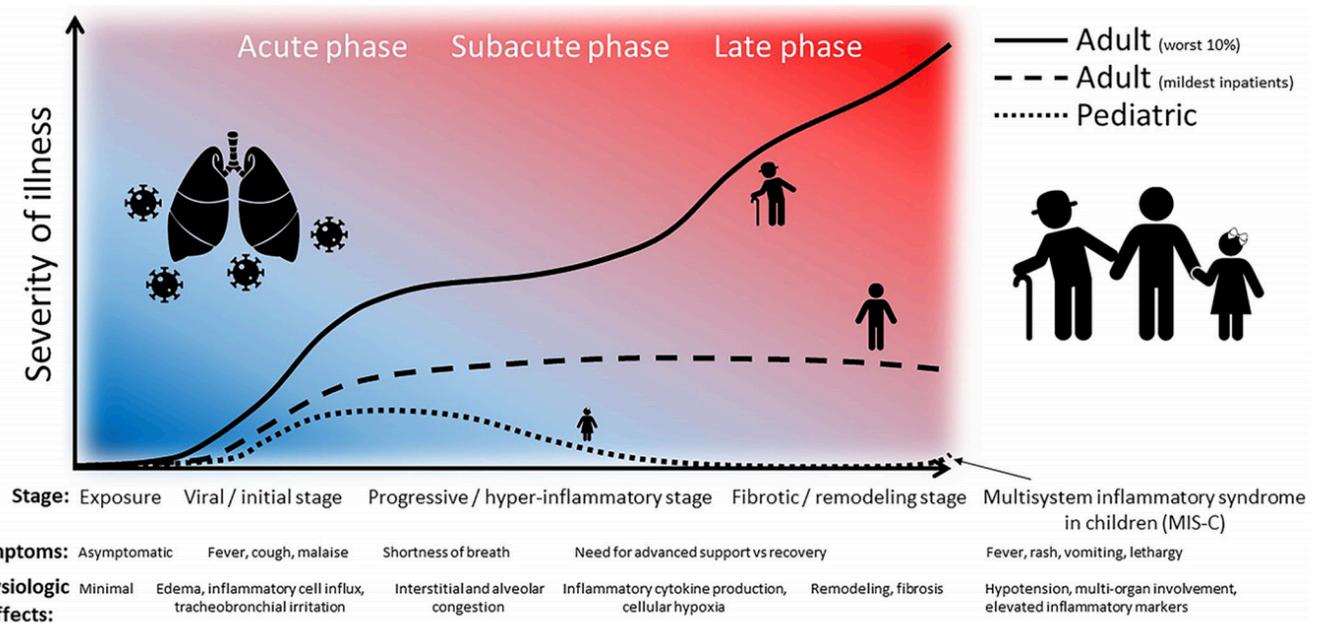


Fig. 1. Differences in the clinical course in children and adults with SARS-CoV-2 infection: depiction of the general progression of disease and overarching severity of illness among symptomatic adult and pediatric patients. Although the most severe adults progress through the inflammatory phase to profound clinical severity, mild/moderate adults seem to stabilize and recover over a protracted course. Pediatric patients rarely require hospitalization for symptoms and, when more symptomatic early, generally recover quickly. Some children develop a multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. [Adapted in part from Siddiqui et al. (32a), with permission from Elsevier.]

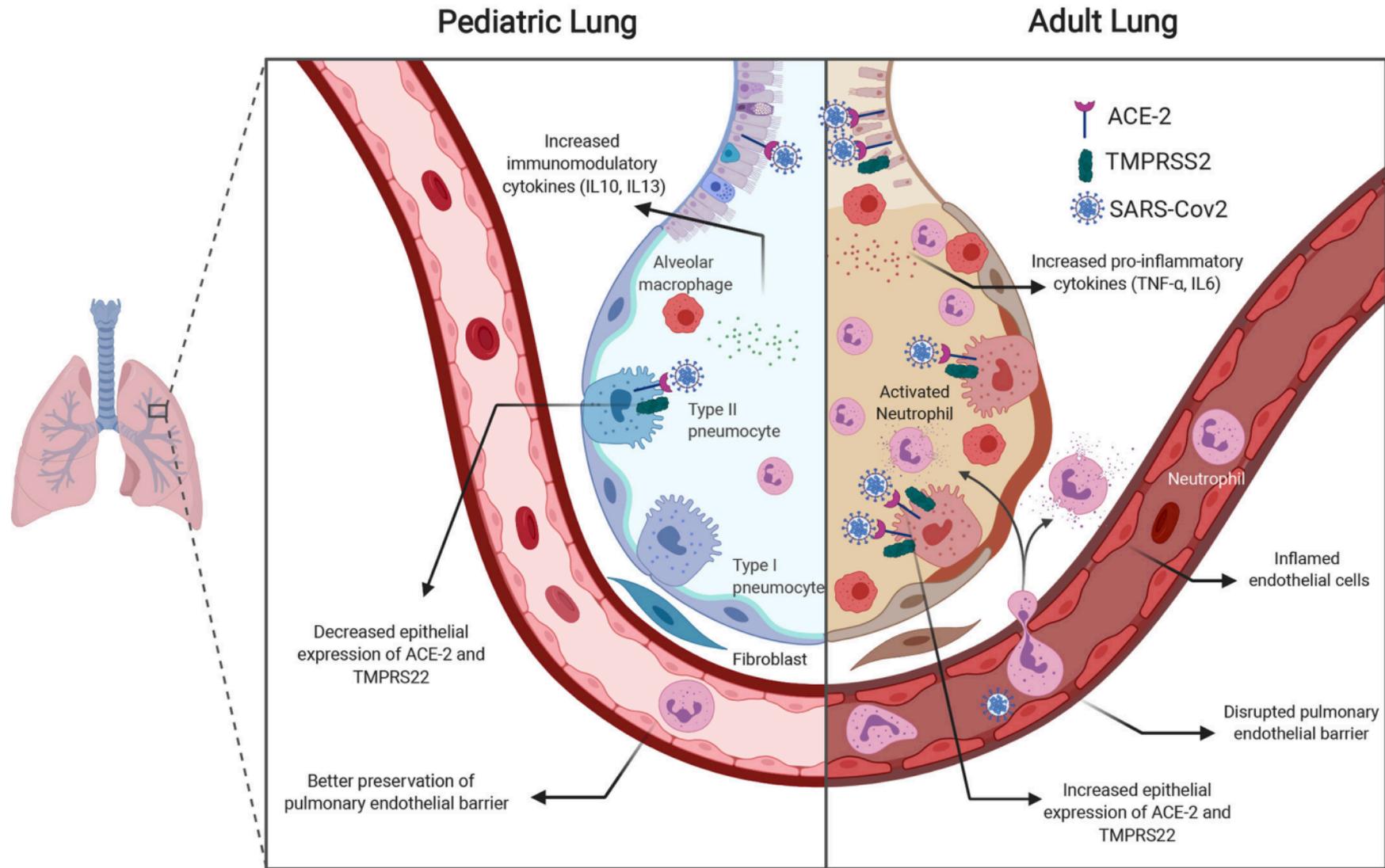


Fig. 2. Mechanisms mediating differential susceptibility of adults and children to COVID-19. Increased expression of mediators essential for viral entry into airway epithelial cells (ACE-2 and TMPRSS2) in adults combined with the proinflammatory milieu in adults may predispose the adult lung to serious pulmonary injury and progression to acute respiratory distress syndrome (ARDS). The pediatric lung has greater expression of immunomodulatory cytokines and possibly a decreased expression of viral entry mediators.

Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: A systematic review and meta-analysis

- There is **conflicting advice** about physical or social distancing.
- Face masks with or without eye protection is **debated** in the mainstream media and by public health authorities
 - Optimum use of face masks in HC settings, is facing challenges amid PPE shortages
- Any recommendations about social or physical distancing, and the use of face masks, should be based on the **best available evidence**
- Evidence has been reviewed for other respiratory viral infections, mainly seasonal influenza, but **no comprehensive review is available** of information on SARS-CoV-2 or related betacoronaviruses

METHODS

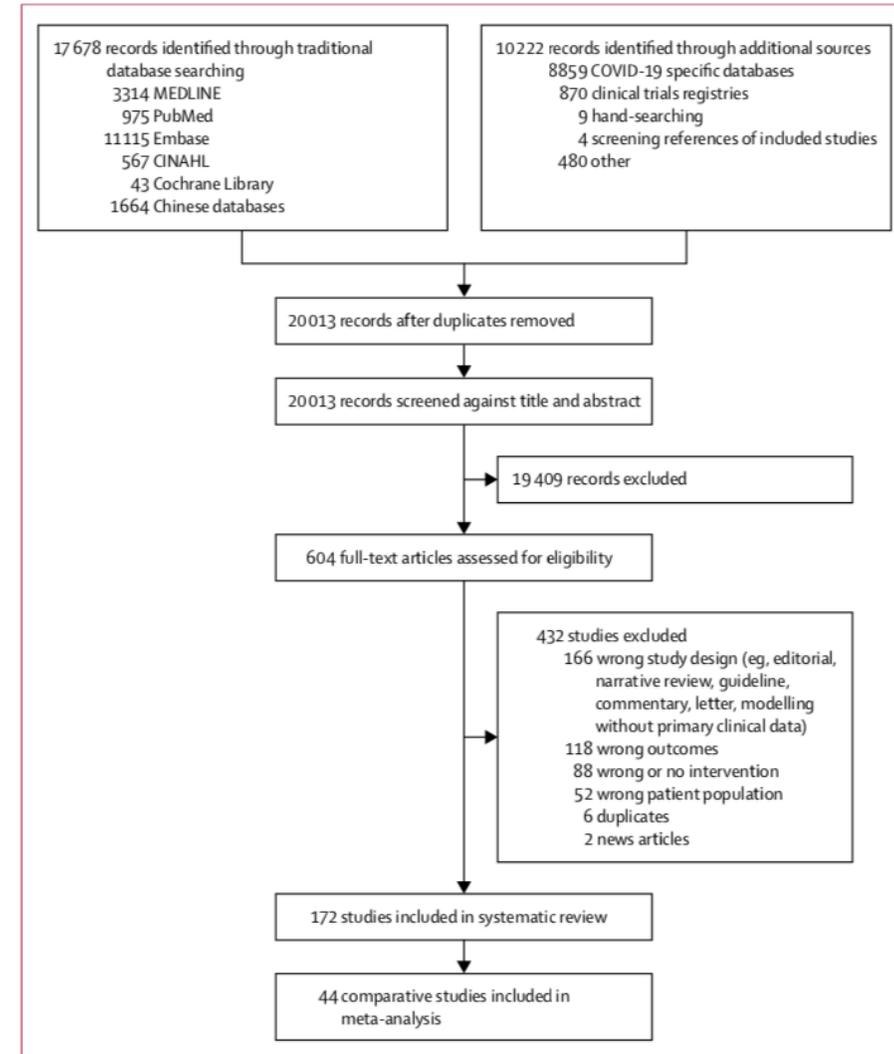
- Studies of any design and in any setting that included patients with
 - WHO-defined confirmed or probable COVID-19, SARS, or MERS, and
 - People in close contact with them
 - Comparing distances between people and COVID-19 infected patients of 1 m or larger with smaller distances, with or without a face mask on the patient, or with or without a face mask, eye protection, or both on the exposed individual.
- The aim of our systematic review was for quantitative assessment to ascertain the physical distance associated with reduced risk of acquiring infection when caring for an individual infected with SARS-CoV-2, SARS-CoV, or MERS-CoV.
- Our definition of face masks included surgical masks and N95 respirators, **among others**; eye protection included visors, faceshields, and goggles, **among others**

Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis

AIMS and Methods

- To investigate the effects of physical distance, face masks, and eye protection on virus transmission in health-care and non-health-care settings.
- Systematic review and meta-analysis of data for
 - SARS-CoV-2
 - SARS
 - MERS

SARS: Severe acute respiratory syndrome, MERS: Middle East respiratory syndrome



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	n	Country	Setting	Disease caused by virus	Case definition (WHO)	Adjusted estimates	Risk of bias*
(Continued from previous page)							
Wang et al (2020) ⁷⁰	5442	China	Health care	COVID-19	Confirmed	No	*****
Wiboonchutikul et al (2016) ⁷¹	38	Thailand	Health care	MERS	Confirmed	No	*****
Wilder-Smith et al (2005) ⁷²	80	Singapore	Health care	SARS	Confirmed	No	*****
Wong et al (2004) ⁷³	66	China	Health care	SARS	Confirmed	No	*****
Wu et al (2004) ⁷⁴	375	China	Non-health care (community)	SARS	Confirmed	Yes	*****
Yin et al (2004) ⁷⁵	257	China	Health care	SARS	Confirmed	Yes	*****
Yu et al (2005) ⁷⁶	74	China	Health care	SARS	Confirmed	No	*****
Yu et al (2007) ⁷⁷	124 wards	China	Health care	SARS	Confirmed	Yes	*****

Across studies, mean age was 30–60 years. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. *The Newcastle-Ottawa Scale was used for the risk of bias assessment, with more stars equalling lower risk.

Table 1: Characteristics of included comparative studies

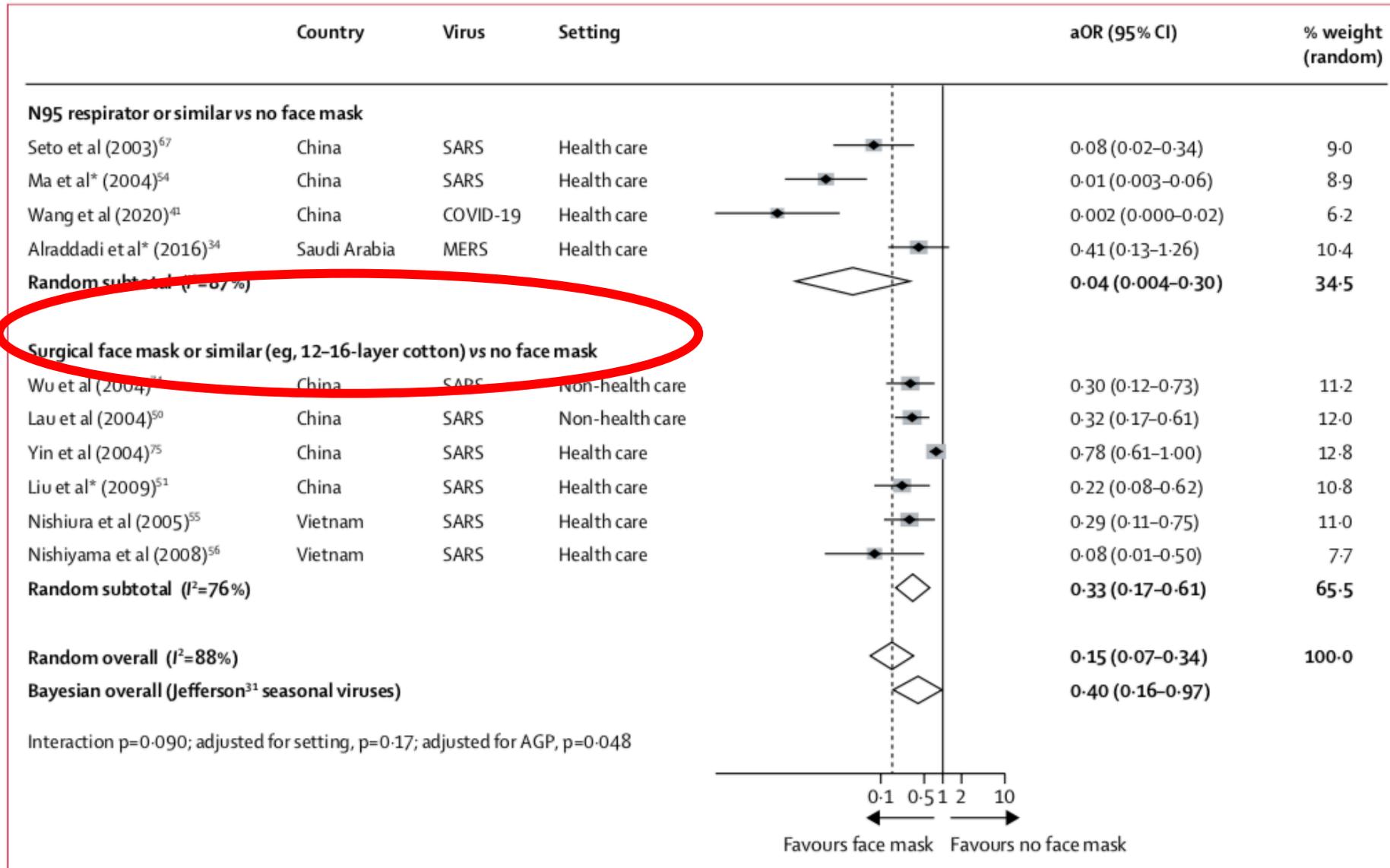


Figure 5: Forest plot showing adjusted estimates for the association of face mask use with viral infection causing COVID-19, SARS, or MERS
 SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. AGP=aerosol-generating procedures.
 *Studies clearly reporting AGP.

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	Studies and participants	Relative effect (95% CI)	Anticipated absolute effect (95% CI), eg, chance of viral infection or transmission		Difference (95% CI)	Certainty*	What happens (standardised GRADE terminology) ²⁹
			Comparison group	Intervention group			
Physical distance ≥1 m vs <1 m	Nine adjusted studies (n=7782); 29 unadjusted studies (n=10 736)	aOR 0·18 (0·09 to 0·38); unadjusted RR 0·30 (95% CI 0·20 to 0·44)	Shorter distance, 12·8%	Further distance, 2·6% (1·3 to 5·3)	-10·2% (-11·5 to -7·5)	Moderate†	A physical distance of more than 1 m probably results in a large reduction in virus infection; for every 1 m further away in distancing, the relative effect might increase 2·02 times
Face mask vs no face mask	Ten adjusted studies (n=2647); 29 unadjusted studies (n=10 170)	aOR 0·15 (0·07 to 0·34); unadjusted RR 0·34 (95% CI 0·26 to 0·45)	No face mask, 17·4%	Face mask, 3·1% (1·5 to 6·7)	-14·3% (-15·9 to -10·7)	Low‡	Medical or surgical face masks might result in a large reduction in virus infection; N95 respirators might be associated with a larger reduction in risk compared with surgical or similar masks§
Eye protection (faceshield, goggles) vs no eye protection	13 unadjusted studies (n=3713)	Unadjusted RR 0·34 (0·22 to 0·52)¶	No eye protection, 16·0%	Eye protection, 5·5% (3·6 to 8·5)	-10·6% (-12·5 to -7·7)	Low	Eye protection might result in a large reduction in virus infection

Implications of all the available evidence

- In view of inconsistent guidelines by various organizations based on limited information, **our findings provide some clarification** and have implications for multiple stakeholders.
- **The risk for infection is highly dependent on distance** to the individual infected and the type of face mask and eye protection
 - Current policies of at least 1 m physical distancing seem to be strongly associated with a large protective effect, and distances of 2 m could be more effective.
- **For health-care workers and administrators:**
 - N95 respirators might be more strongly associated with protection from viral transmission than surgical masks
 - Both N95 and surgical masks have a stronger association with protection compared with single-layer masks
 - Eye protection might also add substantial protection

Implications of all the available evidence

- **For the general public:**
 - Evidence shows that physical distancing of more than 1 m is highly effective and that face masks are associated with protection, even in non-health-care settings, with either disposable surgical masks or **reusable 12–16-layer cotton ones**
 - Eye protection is typically under considered and can be effective in community settings.
- However, no intervention, even when properly used, was associated with complete protection from infection. Other basic measures (eg, hand hygiene) are still needed in addition to physical distancing and use of face masks and eye protection.

Interpretation

- **The findings of this systematic review and meta-analysis support physical distancing of 1 m or more and provide quantitative estimates for models and contact tracing to inform policy.**
- **Optimum use of face masks, respirators, and eye protection in public and health-care settings should be informed by these findings and contextual factors.**
- **Robust randomized trials are needed to better inform the evidence for these interventions, but this systematic appraisal of currently best available evidence might inform interim guidance.**

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

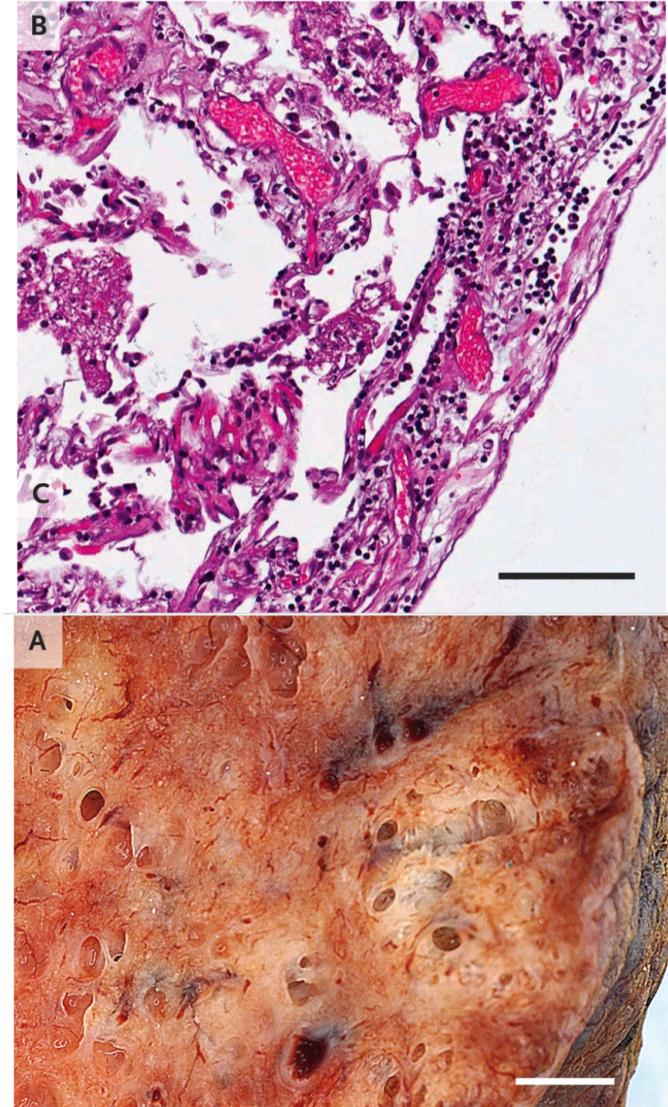
- **Autopsy examination and comparison of:**
 - 7 lungs from patients who died from Covid-19
 - 7 lungs obtained from patients who died from acute respiratory distress syndrome (ARDS) secondary to influenza A(H1N1)
 - 10 age-matched, uninfected control lungs
- **The lungs were studied with the use of:**
 - Seven-color immunohistochemical analysis
 - Micro-computed tomographic imaging
 - Scanning electron microscopy
 - Corrosion casting
 - Direct multiplexed measurement of gene expression.

Results

- **Both Covid-19 and influenza-associated respiratory failure**, had diffuse alveolar damage with perivascular T-cell infiltration.
- **The lungs from patients with Covid-19** also showed distinctive vascular features, consisting of:
 - *Severe endothelial injury* associated with intracellular virus and disrupted cell membranes.
 - *Widespread thrombosis* with microangiopathy.
 - *Alveolar capillary microthrombi* were 9 times as prevalent compared to patient with influenza (P<0.001).
 - *New vessel growth* was 2.7 times as high as that in the lungs from patients with influenza (P<0.001).
- **CONCLUSIONS**
 - Vascular angiogenesis distinguished the pulmonary pathobiology of Covid-19 from that of equally severe influenza virus infection.

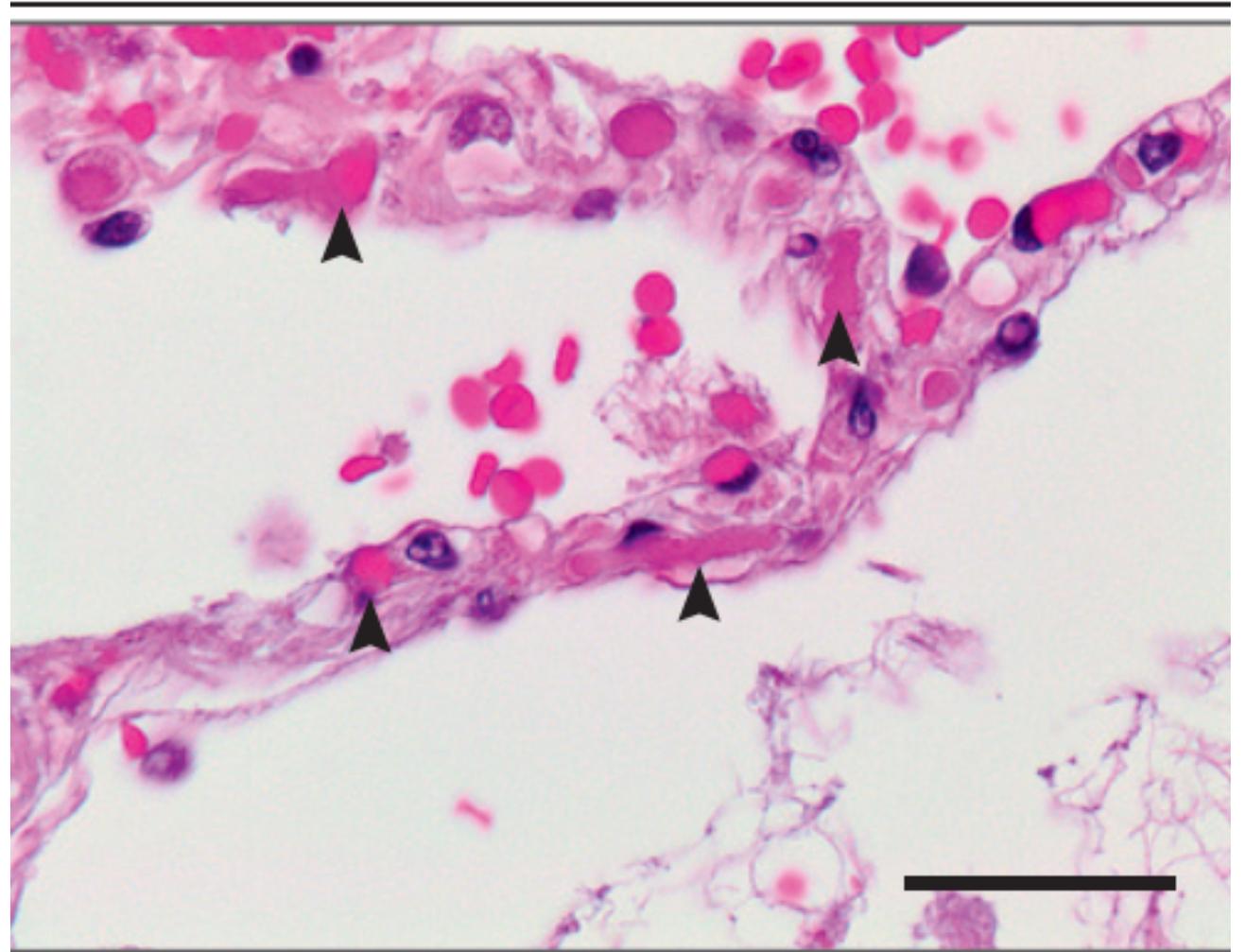
Lymphocytic Inflammation in a Lung from a Patient Who Died from Covid-19.

- The gross appearance of a lung from a patient who died from coronavirus disease 2019 (Covid-19) is shown in Panel A (the scale bar corresponds to 1 cm).
- The histopathological examination, shown in Panel B, revealed
 - Interstitial and perivascular predominantly lymphocytic pneumonia with multifocal endothelialitis (hematoxylin–eosin staining; the scale bar corresponds to 200 μ m).



Microthrombi in the Interalveolar Septa of a Lung from a Patient Who Died from Covid-19

The interalveolar septum of this patient (Patient 4 in Table S1A in the Supplementary Appendix) shows slightly expanded alveolar walls with multiple fibrinous microthrombi (arrowheads) in the alveolar capillaries. Extravasated erythrocytes and a loose network of fibrin can be seen in the intraalveolar space (hematoxylin–eosin staining; the scale bar corresponds to 50 μ m)



Microvascular Alterations in Lungs from Patients Who Died from Covid-19

Panels A and B show scanning electron micrographs of microvascular corrosion casts from the thin-walled alveolar plexus of a healthy lung (Panel A) and the substantial architectural distortion seen in lungs injured by Covid-19 (Panel B). The loss of a clearly visible vessel hierarchy in the alveolar plexus is the result of new blood-vessel formation by intussusceptive angiogenesis. Panel C shows the intussusceptive pillar localizations (arrowheads) at higher magnification. Panel D is a transmission electron micrograph showing ultrastructural features of endothelial cell destruction and SARS-CoV-2 visible within the cell membrane (arrowheads) (the scale bar corresponds to 5 μ m). RC denotes red cell. A RC RC RC RC B C D The New England Journal of Medicine Downloaded from nejm.org

