Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Plea for multitargeted interventions for severe COVID-19

Severe coronavirus disease 2019 (COVID-19) is not just a serious respiratory viral disease, as influenza is, but rather a systemic multiorgan viral invasion. It is frequently complicated by overwhelming immunological reactions, with overactivation of T cells, leading to acute respiratory distress syndrome and multiorgan failure, secondary to immunopathological processes. The viral load of severe acute respiratory syndrome coronavirus 2 is not correlated with worsening symptoms, but it is the host inflammatory response that is a major cause of lung damage and subsequent mortality.[1,2] Hyper-inflammatory responses in patients with COVID-19 are associated with a cytokine storm that is characterised by an increase in proinflammatory cytokines, including tumour necrosis factor, interleukin (IL)-1β, IL-6, and other chemokines in serum.[3,4] Overwhelming secretion of cytokines causes severe lung damage, which manifests as extensive damage to pulmonary vascular endothelial cells and alveolar epithelial cells, as well as increased pulmonary vascular permeability, leading to pulmonary oedema and hyaline membrane formation.[2–4]

Most clinical trials to date have evaluated various strategies of antivirals, immunomodulators, host-targeted drugs, immune-based therapies, or immunosuppressive drugs, including steroids, IL-6 or IL-1 antagonists, and selinexor; all have assessed single drugs with a clinical endpoint using the WHO seven-point ordinal scale.[5] Although some of these drugs might have clinically meaningful effects on viral burden or some of the immune-related signs, it is highly improbable that a single drug will be enough to control and improve the most severe forms of COVID-19. It is likely that both antivirals and blockage of inflammatory pathways are needed to optimise responses. For example, it would be relevant to understand the role of steroids in combination with or sequential to antiviral treatments. Without studying combinations, and their potential synergies or additive effects, potentially useful agents could be disregarded. Furthermore, in the absence of synergistic combinations, single drugs might cause more harm—for example, mass killing of the virus might enhance inflammatory responses. Because of the urgency of the current situation and, so far, an absence of clear evidence of a clinically meaningful effect of any monotherapy strategy, investigators should join their efforts in proposing, rather than adaptive or sequential studies of a single strategy, combined approaches through multifactorial designs. This approach will enable determination of the risks and benefits of combinations versus monotherapies. Such trials with multifactorial designs (eg, with randomisation first to antivirals and then to adjunctive immune-based therapy) are urgently needed and could provide more rapidly clinically meaningful results.

Furthermore, with improving knowledge of the various clinical presentations of COVID-19, better definitions of patient populations at highest risk of poor outcomes, based not only on clinical status but also on biomarkers (eg, C-reactive protein, D-dimer, ferritin, and IL-6), should be incorporated into inclusion criteria and stratifications.[6] Finally, the optimal timing or sequence of administration of the components of therapy during a worsening COVID-19 disease course need to be explored. We call for collaboration between pharmaceutical companies, institutions, and policy makers to either allow individuals to be enrolled simultaneously in trials of different investigational drugs with distinct targets or to collaborate on trials that include study arms that investigate combination therapy.

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Protecting workers aged 60–69 years from COVID-19

The initial estimates of the case fatality rate of coronavirus disease 2019 (COVID-19) from China and the published modelled estimates both show a very strong age-dependence.[1,2] In the UK, this pattern has been interpreted in public health terms as advice to cocoon (ie, isolate) those older than 70 years and those with underlying health conditions—but is this the right age cutoff?

Applying the infection fatality rate ratios from new estimates (which assume a constant attack rate by age) to the age structure of the population of the UK,[3] we can see how many deaths we would expect in each age group if there were 1 million infections (table). This shows that 70% of all deaths are in the over-70-years age group, so it is important that they are protected. However, nearly two thirds (64%) of the remaining deaths occur in the 60–69 years age group. This age group is not being particularly protected and includes many who are working on the frontline. Indeed, health-care workers have even been encouraged to come out of retirement to assist.

Based on the Chinese data,[1] each death corresponds to about two critical cases (needing intensive care) and six people who require hospitalisation. Both for humanitarian reasons and to prevent overload of the health service, shouldn't we be protecting people older than 60 years and ensuring that those in that age group who are currently not working from home are moved to jobs with minimal person contact, whether it is in the health service, schools, government, or the private sector?

	Proportion of UK population (%)	Infection fatality ratio (%)	Number of deaths if 1 million population infected	Proportion of deaths	Proportion of deaths if over 70s successfully cocooned
0–9	12%	0·00161%	2	<1%	<1%
10–19	11%	0·00695%	8	<1%	<1%
20–29	13%	0·0309%	41	<1%	1%
30–39	13%	0·0844%	112	1%	3%
40–49	13%	0·161%	206	2%	6%
50–59	13%	0·595%	803	8%	25%
60–69	11%	1·93%	2054	19%	64%
70–79	8%	4·28%	3535	33%	..
80+	5%	7·80%	3853	36%	..

Age group given in years. Infection fatality rates from Verity et al,[2] and the population structure of the UK in 2018 from the Office for National Statistics.[3] SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Table: **Estimated deaths by age group if 1 million people in the UK population are infected with SARS-CoV-2**

My partner is older than 60 years and works in the health service. I declare no other competing interests.

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Projecting the demand for ventilators at the peak of the COVID-19 outbreak in the USA

The coronavirus disease 2019 (COVID-19) pandemic has been straining health-care systems worldwide. For countries still in the early phase of an outbreak, there is concern regarding insufficient supply of intensive care unit (ICU) beds and ventilators to handle the impending surge in critically ill patients. To inform pandemic preparations, we projected the number of ventilators that will be required in the USA at the peak of the COVID-19 outbreak.

Our estimates combine recent evaluations of COVID-19 hospitalisations[1] and data on the proportion of patients with COVID-19 in the ICU requiring ventilation (appendix p 2). At a basic reproduction number of 2·5,[1] 115 001 (IQR 101 006–131 770) invasive ventilators and 89 788 (78 861–102 880) non-invasive ventilators would be needed, on average, at outbreak peak (figure).

Considering that 29·0% of the existing 97 776 ICU beds in the USA are routinely occupied by patients without COVID-19 requiring invasive mechanical ventilation,[2,3] we calculated that 69 660 of the 98 015 invasive ventilators in the USA before outbreak start would be available for the COVID-19 response.[4,5] These available ventilators include additional units in stockpile or storage. Consequently, at least 45 341 (IQR 31 346–62 110) additional units would be needed for the surge at the peak. Of the

See **Online** for appendix

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