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.

including the availability of health-care workers, resources, facilities, and preparedness, also affect outcomes. For example, some countries are able to invest resources into contact tracing and containing the spread through quarantine and isolation of infected or suspected cases. In Singapore, where these measures have been implemented, the CFR of 631 cases (as of March 25, 2020) is 0·3%. In other places, testing might not be widely available, and proactive contact tracing and containment might not be employed, resulting in a smaller denominator and skewing to a higher CFR. The CFR can increase in some places if there is a surge of infected patients, which adds to the strain on the health-care system and can overwhelm its medical resources.

A major challenge with accurate calculation of the CFR is the denominator: the number of people who are infected with the virus. Asymptomatic cases of COVID-19, patients with mild symptoms, or individuals who are misdiagnosed could be left out of the denominator, leading to its underestimation and overestimation of the CFR.

A unique situation has arisen for quite an accurate estimate of the CFR of COVID-19. Among individuals onboard the Diamond Princess cruise ship, data on the denominator are fairly robust. The outbreak of COVID-19 led passengers to be quarantined between Jan 20, and Feb 29, 2020. This scenario provided a population living in a defined territory without most other confounders, such as imported cases, defaulters of screening, or lack of testing capability. 3711 passengers and crew were onboard, of whom 705 became sick and tested positive for COVID-19 and seven died,[6] giving a CFR of 0·99%. If the passengers onboard were generally of an older age, the CFR in a healthy, younger population could be lower.[7]

Although highly transmissible, the CFR of COVID-19 appears to be lower than that of SARS (9·5%) and Middle East respiratory syndrome (34·4%),[8] but higher than that of influenza (0·1%).[9,10]

We declare no competing interests.

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COVID-19 and medical education

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The coronavirus disease 2019 (COVID-19) outbreak has rapidly transitioned into a worldwide pandemic. This development has had serious implications for public institutions and raises particular questions for medical schools. Frequent rotations between departments and hospitals make medical students potential vectors for COVID-19. Equally, as trainee doctors we stand to learn a tremendous amount and can contribute to the care of patients. More immediate concerns among medical students centre on the impact of COVID-19 on medical education.

A substantial number of medical students are in the process of preparing for or undertaking assessments that require clinical exposure. The effect of COVID-19 on medical education could therefore be considerable. Several teaching hospitals in the UK have reported cases of COVID-19, with some hospitals suspending medical and observership students from attending clinical attachments. This suspension might extend to more hospitals as the COVID-19 pandemic continues to develop, which could lead to clinical medical students receiving reduced exposure in specific specialties, causing a detrimental effect to exam performance and competency as foundation year 1 doctors.

The situation is more complex for some final year medical students who are in the process of sitting their final assessments. Some medical schools have reduced clinical exposure in the weeks coming up to their final exams to reduce the risk of contracting the virus. Many electives could also be cancelled because of the global prevalence of COVID-19. This situation would not only cause financial losses for students, but also lead to a missed opportunity of working in a health-care system outside of the UK. At this stage, it is difficult to predict what will

happen, and most medical schools are following advice from Public Health England to determine how to proceed.

Despite widespread panic and uncertainty, the medical community must ask itself what history has taught us about medical education during pandemics. To answer this question, we reflect on the effects of severe acute respiratory syndrome (SARS) on medical education in China at the turn of the century.[1] Some Chinese medical schools officially cancelled formal teaching on wards and their exams were delayed, hindering the education of medical students in the face of the newly emerging epidemic.[1] Similarly, in Canada, the impact of the SARS restrictions led to the cessation of clinical clerkships and electives for students for up to 6 weeks.[2] The Canadian national residency match felt the effect of these limitations, particularly because electives are one of the most crucial factors determining allocation.[1]

Despite the challenges posed by the SARS epidemic, several resourceful initiatives were implemented, leading to progress in medical education. In one Chinese medical school, online problem-based learning techniques were implemented to complete the curricula; these methods proved incredibly popular, to the extent that they were applied in subsequent years. These impressive feats illuminate how even in times of distress, solace can always be found. We are waiting to see what ingenuities for medical education will emerge in the face of the COVID-19 pandemic.

See Online for appendix

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See Online for video

The INHALE trial: multiple reasons for a negative result

The INHALE trial, a Bayer-sponsored phase 3 trial in critically ill patients with pneumonia caused by Gram-negative bacteria by Michael Niederman and colleagues,[1] did not find aerosolised amikacin as an adjunctive therapy to intravenous antibiotics to be superior to intravenous antibiotics alone. The study design, the doses of amikacin, and the technique of nebulisation are all likely to explain this negative result.

The main trial inclusion criterion was pneumonia caused by, or showing two risk factors for, a multidrug-resistant, Gram-negative bacteria. The presence (or the risk) of a multidrug-resistant pathogen infecting the lungs was justification for administering two intravenous antibiotics in both the amikacin treatment group and the placebo group.[2] Antimicrobial bitherapy is not superior to monotherapy in ventilator-associated pneumonia caused by non-resistant, Gram-negative bacteria.[3] In the IHNALE trial,[1] 49% of identified pathogens were not multidrug-resistant and a treatment success of 77% in the placebo group reflected the high efficiency of intravenous bitherapy. Therefore, an additional benefit from aerosolised amikacin could not be reasonably expected.

The pulmonary drug delivery system used in the INHALE trial increases the respirable mass[4] but markedly lengthens the time of nebulisation by restricting aerosol generation to the inspiratory phase (appendix). With the pulmonary drug delivery system, the authors previously reported that nebulisation of amikacin at a dose of about 12 mg/kg per day requires two 60 min nebulisations. With a non-synchronised mesh nebuliser, nebulisation of amikacin at 25 mg/kg per day took only 30–45 min thanks to the bolus effect (video).[5] With the pulmonary drug delivery system, nebulisation of amikacin at the high doses recommended to treat multidrug-resistant, ventilator-associated, Gram-negative pneumonia (40 mg/kg/day)[6] would have been unfeasible, requiring two 3·5 h nebulisations per day. Prolonging nebulisation time beyond 60 min should be avoided as heating and humidification of the inspired gas are interrupted during aerosol delivery.[7]

Amikacin is a concentration-dependant antibiotic and the administration of about 6 mg/kg twice daily, as in the INHALE trial, is suboptimal. In 28 patients with ventilator-associated pneumonia treated by nebulised amikacin, amikacin tracheal concentrations were found to be 25 times higher and epithelial lining fluid concentrations were found to be four times higher than the minimum inhibitory concentration of multidrug-resistant, Gram-negative bacteria.[4] These concentrations were interpreted as reflecting high amikacin distal lung deposition and justified the administration of 12 mg/kg per day in the INHALE trial. Interestingly, epithelial lining fluid concentrations of tobramycin in ventilated sheep receiving a single nebulisation were 100 times greater than interstitial space fluid concentrations measured by microdialysis.[8] These data are highly suggestive of a massive bronchial contamination of the fiberscope and the bronchoalveolar lavage; therefore, elevated epithelial lining fluid concentrations of a nebulised drug can be considered an artefact.[9] Finally, the insufficient optimisation of ventilator settings during the nebulisation could have further reduced amikacin distal lung deposition by potentiating the impaction of aerosolised particles on bronchial walls. In the INHALE trial, lung tissue amikacin concentrations were likely to be below the minimal inhibitory concentrations of causative pathogens, explaining the trial failure.

We suggest that future randomised controlled trials exclusively include