Aerosolised medicines may reduce the high risk of coronavirus infection

Rapid development of vaccines and other preventative measures has been vital in the response to the COVID-19 pandemic. Dr Michael Dubina, full member of the Russian Academy of Sciences, explores a novel method to reduce coronavirus infection risk. His pilot study explored the effects of an aerosolised combination medication in healthcare workers who had not previously been infected with the virus. The findings show that use of aerosolised medicines may offer an effective pre-exposure prophylaxis treatment.

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To date, almost 3.5 million deaths have been caused by the worldwide COVID-19 pandemic and this figure continues to rise.

COVID-19 is the name given to the disease caused following infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Disease presentation varies from no symptoms (asymptomatic) to the development of pneumonia, acute respiratory distress syndrome or multi-organ failure.

Multiple vaccines against SARS-CoV-2 infection have been approved for use around the world, and there are many more vaccines still in development. One of the most important populations to vaccinate is healthcare workers, who are exposed to the virus daily and are at increased risk of developing COVID-19.

HOW DOES SARS-COV-2 INFECT CELLS?

Like other coronaviruses, SARS-CoV-2 binds to receptors on cell surfaces once it enters the human body. This cell-surface binding allows the virus to initiate the infection process by entering the cell and hijacking its replication machinery to produce more virus particles. Each virus recognises a specific receptor, and this means that the number and distribution of these receptors regulates viral tropism – their ability to productively infect a cell.

To infect cells, SARS-CoV-2 uses a cellular receptor called angiotensin-converting enzyme 2 (ACE2) allowing it to gain entry to the cell. ACE2 receptors are found on a variety of cell types, including cells in the upper and lower airways. This allows the virus to migrate down the respiratory tract and trigger an immune response that can lead to severe respiratory problems and low oxygen levels (hypoxia). ACE2 plays an important role in regulating blood pressure through the production of a hormone called angiotensin II. Angiotensin II normally causes blood vessels, including those in the lung, to constrict – subsequently causing an increase in blood pressure. If SARS-CoV-2 reduces ACE2 activity during cell entry, this may increase angiotensin II activity in the lungs.

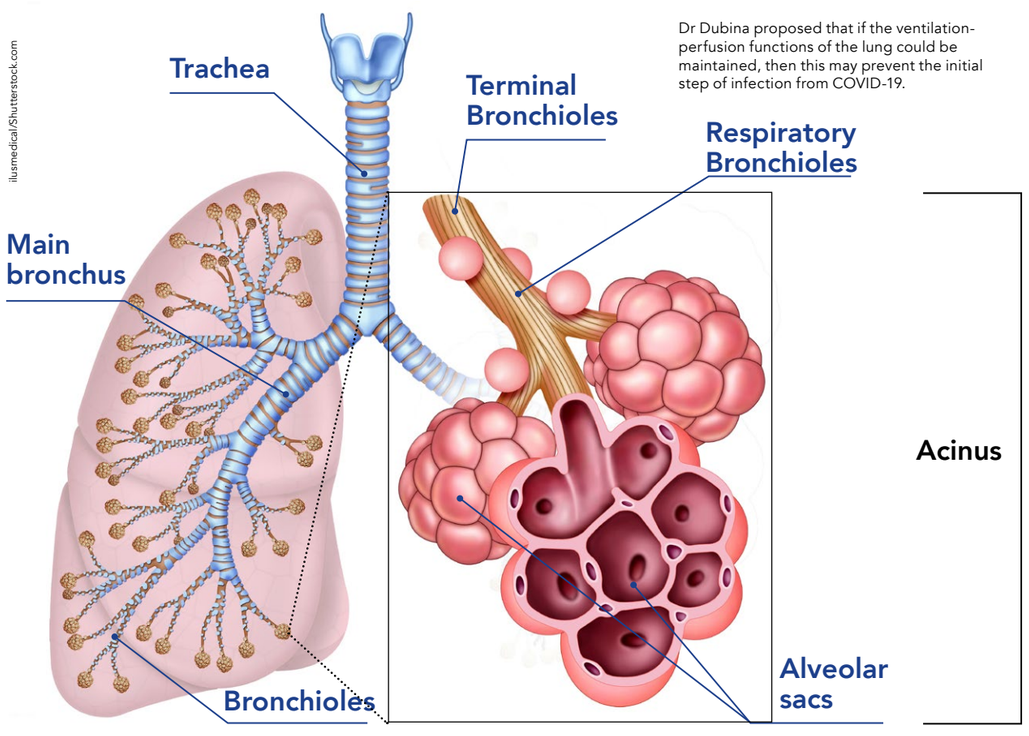
The interactions between SARS-CoV-2 and ACE2 are also crucial in determining tissue tropism, defined as the types of tissues the virus can infect, and progression to COVID-19 disease.

Dr Michael Dubina, Russian Academy of Sciences, hypothesised that the excessive constriction ability of angiotensin II could also affect tens of thousands of smallest bronchi and blood vessels in the lungs, ultimately causing damage to the small air sacs (alveoli) in the lungs.

He proposed that if the ventilation-perfusion functions of the lung periphery could be maintained, then this may prevent the initial step of COVID-19. This is because prolonged constriction changes may make the lung extremely vulnerable to alveoli destruction and inflammation. Therefore early intervention may reduce SARS-CoV-2 infectivity and progression to COVID-19.

PRE-EXPOSURE PROPHYLAXIS

To achieve this, aerosolised medications known to be beneficial for lung function



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were considered for pre-exposure prophylaxis. In other words, these medications may reduce the risk of infection with SARS-CoV-2 for people who have not yet been infected with the virus as well as prevent the spread of disease in people who have not yet been exposed to SARS-CoV-2.

Pre-exposure prophylaxis is a prevention method most commonly known for reducing the risk of getting HIV. A daily pill can be prescribed to HIV-negative adults and adolescents who are at high risk of getting HIV through sex or drug use, and reduces the risk of getting HIV by more than 90%.

At present, there is no known agent that can be administered before exposure to SARS-CoV-2 that prevents infection, although several clinical trials are looking at possible therapies. One example of this is hydroxychloroquine, more commonly used as an anti-malarial drug, which was considered earlier in the pandemic as a possible pre-exposure prophylaxis candidate. However, multiple research studies showed that it had no effect on coronavirus infection.

AEROSOLISED COMBINATION MEDICATION

Dr Dubina was interested to know if aerosolised medicines with proven health benefits could provide pre-exposure prophylaxis against COVID-19 in healthy adults who are at highest risk of SARS-CoV-2 infection due to delivering care to patients with confirmed COVID-19.

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An aerosolised combination medication (ACM) was used in the trial. This is made up of a low dose of glutathione, inosine and potassium chloride.

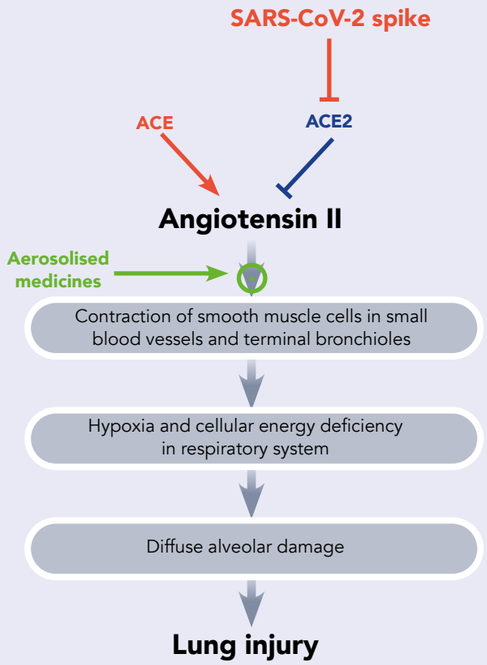
Previous studies have shown that these medications with greater doses are tolerated well in their inhaled form with no adverse effects reported. Each component of the medication was selected due to its ability to protect the lungs and maintain lung function.

Glutathione is an antioxidant molecule that is capable of protecting cells from damage by highly reactive oxygen molecules. These reactive oxygen species are formed as by-products during normal oxygen metabolism but can be harmful if uncontrolled, a scenario that may occur in lung alveoli.

Glutathione is already used successfully in some patients with cystic fibrosis to help their lung function and has already been used in two cases of COVID-19 to improve COVID-19 related pneumonia.

Inosine is indirectly used by cells to make ATP, their main energy source and has already been shown to exert

Schematic diagram of the renin-angiotensin system, proposed SARS-CoV-2 action in acute lung failure, and its prevention with aerosolised medicines



Early intervention may reduce SARS-CoV-2 infectivity and progression to COVID-19 disease. (Modified from Kuba K. *et al. Nature Medicine*, 2005, fig.2a).

Dr Dubina suggests that direct aerosol delivery of appropriate medications may maintain lung function and thus protect from COVID-19.

possible anti-inflammatory properties in the lung.

Finally, potassium chloride was selected due to its basic physiological ability to dilate blood vessels and small bronchi.

PILOT STUDY OF HEALTHCARE WORKERS

The study, recently published in *BMC Infection Diseases*, recruited 99 healthcare workers who had not previously been exposed to SARS-CoV-2. The participants received ACM via a hand help nebuliser for 14 days, involving four, 5 minute inhalation sessions per day. Interestingly the healthcare workers were generally young, with almost 90% of the intervention and non-intervention group being under 40 years old. The number of study participants who tested positive for SARS-CoV-2 was compared to the number of infections in untreated healthcare workers at the same place. Information relating to untreated healthcare workers was collected retrospectively as part of local routine COVID-19 testing.

The study showed a 2% chance of being infected with SARS-CoV-2 after taking ACM, compared to a 9% change in the control group. Mild short-term adverse reactions were observed in five of the ACM participants, including itchy throat or headache.

Dr Dubina concludes that direct aerosol delivery of appropriate medications may maintain lung function and protect from COVID-19. He proposes that this is due to prevention of ventilation-perfusion abnormalities in the peripheral area of lung due to a dysregulated balance between ACE2 and angiotensin II, which is induced by SARS-CoV-2 infection.

CONCLUSIONS

One of the limitations of the study is that it was carried out in a single centre only. Due to ethical issues there was no control group to compare to the intervention group, for example healthcare workers who received an aerosolised intervention that did not contain the medications. (It was decided by local ethics committee that it was not ethical to treat any individuals at high risk for SARS-CoV-2 infection with a placebo during the COVID-19 pandemic). It would also be interesting to collect further data about the participants, for example were they more likely to avoid contact with other people outside work as they were involved in a research study and thus had a reduced risk of infection? [Participants were not requested to avoid contact with other people outside work during their involvement in the study].

The results of the pilot are promising however, and the next steps may involve larger, more detailed studies into the effectiveness of pre-exposure prophylaxis. Dr Dubina aims to do further studies to look at the effect of pre-exposure prophylaxis in different populations at different locations, through a randomised trial, to include a placebo treatment alongside ACM.

The findings from this pilot study suggest that ACM may be used to help reduce the risk of SARS-CoV-2 and to progress other research into more effective treatments for COVID-19. Notably, the results also highlight mechanisms and pathways that could be targeted to reduce SARS-CoV-2 infection rates.

Behind the Research

Dr Michael Dubina

E: michael.dubina@gmail.com

Research Objectives

Michael Dubina is developing an aerosol to prevent the initial step of the infection process from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

Detail

Address
Russian Academy of Sciences, 14 Leninsky Prospect, 119991 Moscow, Russia

Bio

Michael Dubina studied medicine at I.P. Pavlov First State Medical University, St. Petersburg, Russia. He received his PhD there in 1998 and DMSc (pathophysiology) in 2004. He completed his Alma mater; Zh.I. Alferov National Academic University, St. Petersburg, Russia; International Agency for Research on Cancer WHO, Lyon, France. He has been honored for outstanding research achievements with D.W. Lubbers award, UNESCO medal and others. He was elected full member (academician) of Russian Academy of Sciences in 2016.

Funding
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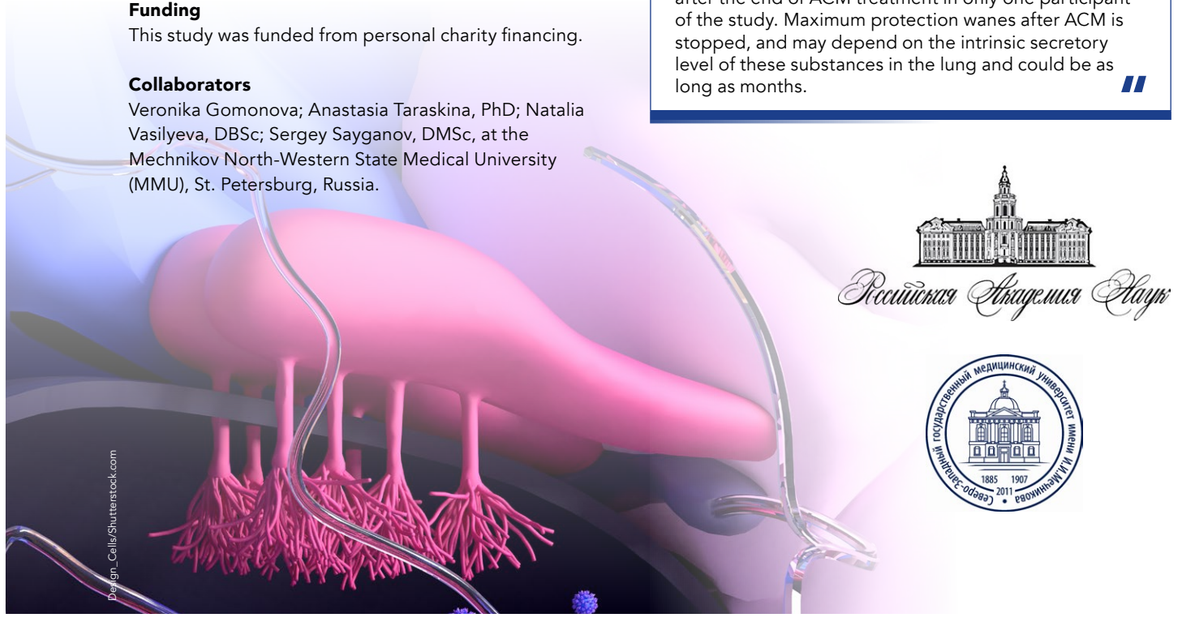
Collaborators

Veronika Gomonova; Anastasia Taraskina, PhD; Natalia Vasilyeva, DBSc; Sergey Sayganov, DMSc, at the Mechnikov North-Western State Medical University (MMU), St. Petersburg, Russia.



References

Dubina, M.A, Gomonova, V.V, Taraskina, A.E., Vasilyeva, N.V. & Sayganov, S.A. (2021). Pathogenesis-based preexposure prophylaxis associated with a low risk of SARS-CoV-2 infection in healthcare workers at a designated COVID-19 hospital: a pilot study. *BMC Infectious Diseases*. 21:536 https://doi.org/10.1186/s12879-021-06241-1

Personal Response

What are the long-term effects of frequent administration of ACMs to reduce SARS-CoV-2 infection and does protection wane when ACM is stopped i.e. how practical and safe is it for people to continue inhaling ACM multiple times a day?

"Each component of the medication is a simple biological substance or ion, produced in the lungs to help maintain normal lung function (like many vitamins for other physiological functions, for example). Thus, they are not harmful at low doses even during long-term inhalation. In accordance with the results of the pilot study, minimal protection wanes when ACM is stopped is about 10 days at high risk of the infection. This time point equates to the term of SARS-CoV-2 detection after the end of ACM treatment in only one participant of the study. Maximum protection wanes after ACM is stopped, and may depend on the intrinsic secretory level of these substances in the lung and could be as long as months."