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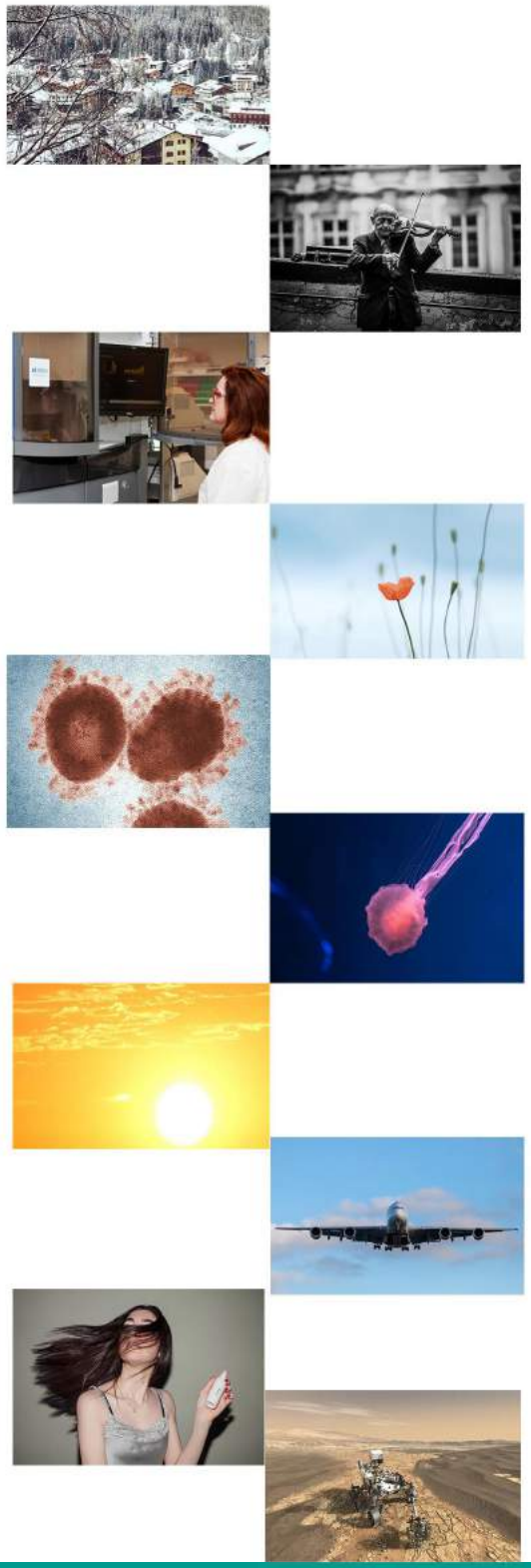

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Nasal Spray Vaccine for COVID-19

All approved COVID-19 vaccines so far are administered in the form of injections. What if the vaccines could be conveniently delivered as spray in the nose? If you do not like shots, here may be the good news! Intranasal administration of COVID-19 vaccine through spray could soon be a reality. Currently, many companies are researching on exploiting the nasal route of administration for COVID-19 vaccines, some of which are undergoing clinical trials. This article discusses the progress made in this regard with particular emphasis on the use of attenuated viruses in a nasal spray formulation against COVID-19.

The emergence of COVID-19 as a pandemic triggered frantic research all over the world to combat this pandemic by developing vaccines in a race against time in order to help countries all over the world to return to normalcy as soon as possible. A number of pharmaceutical and biotech companies have been engaged in vaccine development and till date over 300 vaccine projects have been initiated and more than 40 projects are in clinical evaluation while at least 5 of them have been approved as an emergency use authorization in different countries. Vaccines have been made using different approaches such as live attenuate vaccine, mRNA-based vaccine that expresses the Spike protein of the virus as well as Adenovirus based vaccine that expresses several proteins of the virus. All these proteins are expressed by the host and in turn mount an

antibody response to the viral proteins thereby providing protection.

An alternative mode of preventing viral entry into the human body and delivering a vaccine candidate is to use the nasal route. Several researchers have used nasal spray1 consisting of sticky substances that coat the nasal mucus lining, thereby preventing the viral entry into the hosts cells. For example, use of nanoconjugate as nasal spray to deliver the shRNA-plasmid to the target site 2. Intranasal route for administration of COVID-19 vaccine has been investigated by many researchers 3. There are several companies in the fore-front in the use of nasal spray technique for administering of vaccines against COVID-19. A few of these companies use the attenuated virus, while others are using the adenovirus based or influenza-based vectors in the form of nasal spray 4.

The companies that are exploiting the adenovirus, influenza-based virus and Newcastle disease virus (NDV)5, 6 based vectors in a nasal spray formulation include Beijing Antai Biol Pharm Enterprise, China, two projects from Acad Mil Sci, China, Bharat Biotech-Washington Univ, India-US, AstraZeneca, Sweden-UK, Altimmune, USA, Univ Hong Kong, Valavax-Abogn, China, Beijin Vantal Biol Pharm, China and Lancaster University, UK. On the other hand, companies that are utilizing attenuated virus in a nasal spray formulation include Codagenix, a New York based company in collaboration with The Serum Inst of India, India, Indian

Immunologicals Ltd, India, in collaboration with the Griffith University, Australia and Mehmet Ali Aydunar Univ, Turkey. Of particular interest are the companies that are using the attenuated whole virus in a nasal spray formulation as the whole virus will retain the capability of mounting an immune response to the varied antigens present in the virus as opposed to only certain proteins being targeted for antibody production as is the case with adenovirus based, influenza-based and Newcastle disease virus-based vaccines. This may potentially take care of the several mutations the virus in undergoing as well. In this article, we will specifically focus on the development and trials for the nasal spray vaccine that use the attenuated virus.

The first group that uses attenuated virus in a nasal spray are researchers at Codagenix, USA whose vaccine is named COVI-VAC. The first patient in the randomised, double-blinded, placebo-controlled trial has been dosed in January 2021. They have entered into collaboration with The Serum Institute of India for the manufacture of this vaccine. The dose-escalation study has been designed to evaluate the safety and tolerability of the vaccine in a total of 48 healthy volunteers. The study will also assess the ability of the vaccine to generate an immune response which will be assessed by measuring neutralising antibodies, mucosal immunity in the airway and cellular immunity. The vaccine can be stored easily in a refrigerator (2-8 C), can be administered easily without the help of skilled personnel and is hopefully available as a single dose that can afford protection. This alleviates the need for storage and transportation at sub-zero temperatures and can be readily given to a large number of people at a time without the need for additional equipment and skilled personnel 7.

Another group at Eureka Therapeutics has developed InvisiMask™ , a Human Antibody Nasal Spray which has been successfully tested in preclinical studies in mice without any significant adverse effects. The human monoclonal antibody binds to the S1 Spike (S) protein of SARS-CoV-2 virus and prevent them from binding to the angiotensin-converting enzyme 2 (ACE2) receptor on cells in the upper respiratory tract. This prevents the virus from entering into human cells and thereby prevents infection. Another key feature of this vaccine is that the human monoclonal antibody used can bind and inhibit more than 20 SARS-CoV-2 variants, including the highly infectious D614G mutation 8,9.

These vaccines based on intra nasal spray route provide an excellent non-invasive way of administering vaccines against SARS-CoV-2 virus and can be of great help in controlling the COVID-19 pandemic. There are several advantages of using the nasal spray route for administering the vaccine. Nasal spray vaccine provides additional local protection at the site of administration (mucosal immunity based on secretory IgA and IgM and as a physical barrier) in addition to the systemic protection, in comparison to injected vaccine that confers only systemic protection. People administered with intra muscular vaccines can still have COVID-19 virus in their nasal cavity and can transmit it to others.

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Ischgl Study: Development of Herd Immunity and Vaccine Strategy against COVID-19

Routine sero-surveillance of the population to estimate presence of antibodies to COVID-19 is required to understand the development of herd immunity in a population. Data from the sero-surveillance study of population in the Ischgl town of Austria throws light on this aspect and have led researchers to develop a prediction model which could help plan an effective vaccine strategy and non-invasive population interventions against the infection.

The data from Ischgl study demonstrated that approx. 42.4% of the population were sero-positive after 9-10 months of testing since first patients were exposed to the corona virus1,2. However, this requires the use of appropriate antibodies and the right target to ensure that individuals with mild infections are not missed3. This data from the Ischgl study suggests that the antibody response to COVID-19 is not only long lasting but can be a predictor of herd immunity in a population. This, in turn, necessitates the need for a routine sero-surveillance in a population to estimate the number of people who are antibody positive? Although this study may not be representative of the entire population, however, it can still help us in

identifying, not only the sero-positive individuals, but indirectly leads to predicting the estimated population that would require a booster vaccine dose or not. This is of extreme importance at this moment, given the fact that vaccine administration against COVID-19 is in full swing in most countries and the world is waiting anxiously to return to the "normal life" that existed before COVID-19. This will enable the policy makers and administrators to develop guidelines and ensure adequate health care resources are spent towards the population where antibody development is minimal.

In addition, this study has also revealed the development of a non-invasive predictive model based on the self-assessment of three identified symptoms (cough, loss of taste/smell and limb pain) that could accurately predict the sero-positive individuals4 in a population that has been infected by coronavirus. Exploitation of such a non-invasive model can really be beneficial to the entire world to fight against the COVID-19 pandemic by predicting the sero-positiveness in the population.

Combining both these approaches of routine sero-surveillance and predictive modelling using CHES software5 to determine sero-positiveness, countries across the world can efficiently plan sero-surveillance studies that can help in controlling the pandemic by spending the tax-payers money more effectively and bringing normalcy back as soon as possible.

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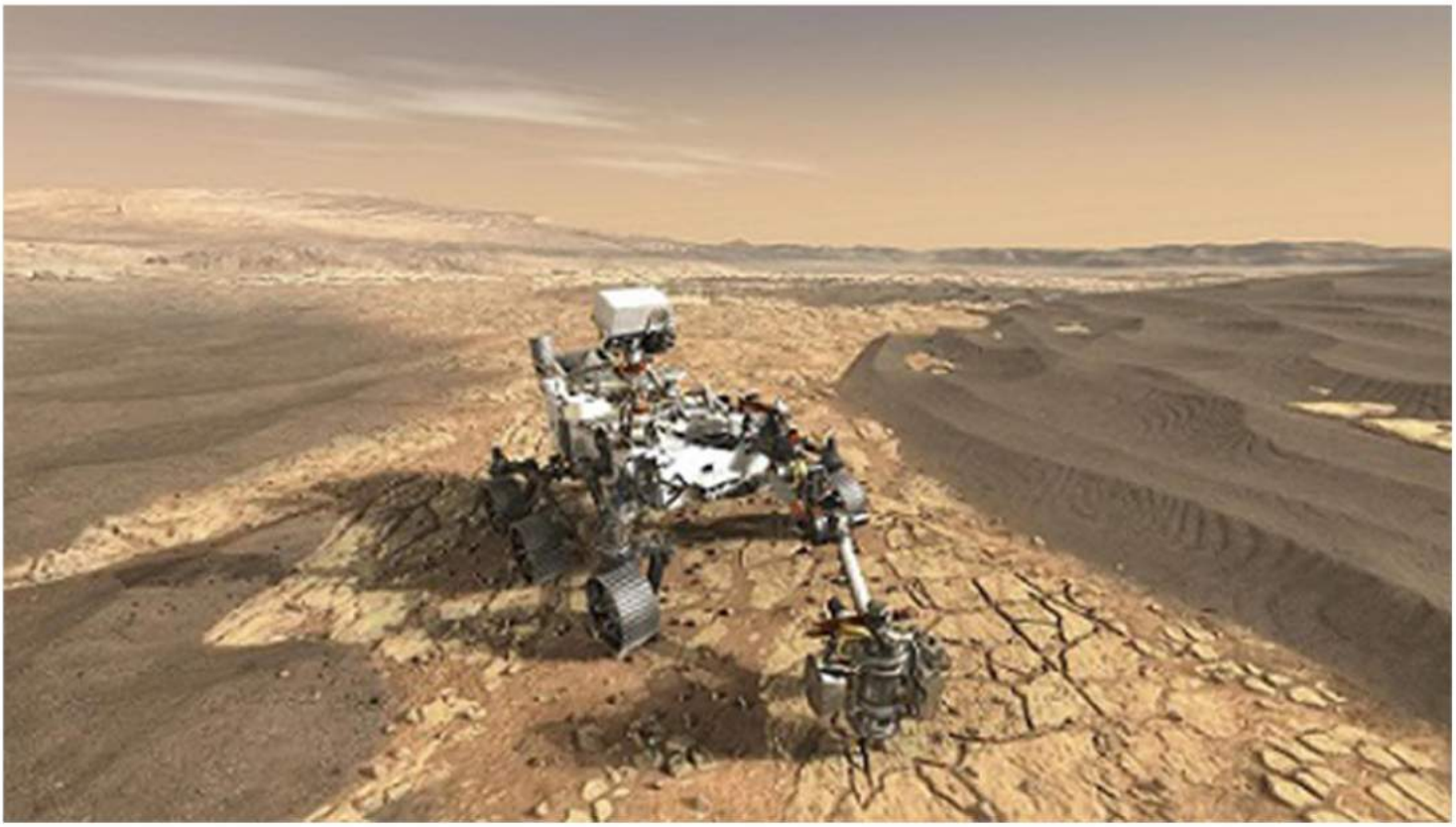
Mars 2020 Mission: Perseverance Rover Successfully Lands on the Mars Surface

Launched on 30th July 2020, Perseverance rover has successfully landed on the Mars surface at Jezero Crater on 18th February 2021, after travelling almost seven months from Earth. Designed specially to collect sample of rocks, Perseverance is the biggest and the best rover ever sent to Mars. The sample catching system of the rover is one of most complex robotic system ever made. Mars once had water on its surface, suggesting primitive microbial organisms may have lived there in the past. In view of the detection of methane gas in the atmosphere of Mars in the recent past, there is a possibility of some form of microbial life being present even today. It is thought that the samples collected by the rover may have signs of life. However, this is one way trip of the rover to the Mars and the samples collected will be brought back to the Earth using future missions. The samples will then be analysed for the confirmation of ancient form of life on the Mars. Interestingly, the rover is carrying Ingenuity, a small helicopter that will explore areas like cliffs and craters where the rover cannot go.



Leave Earth before it's too late, Carl Sagan had once warned in view of remote possibility of Earth being hit by an asteroid in future just the way it was 65 million years ago when dinosaurs were eliminated. It may be reasonable to think that the future of humanity lies in becoming space-faring species, in becoming a multi-planet species. And, here is an infinitesimally small step in that direction towards exploration of space for a better understanding of habitable world 1.

The Mars rover Perseverance with its sophisticated robotic system specially designed to collect samples has successfully touched down on the Mars surface at Jezero Crater. This place was once was a water lake that may have nurtured primitive life forms on Mars. The robotic system of the rover will serve as eyes and arms of mankind for exploration on Mars when it is not possible at this juncture to send astronauts. The Mars 2020 Mission will set up a series of missions in future for bringing the collected samples to Earth for analysis 2.

Mars once had a thick atmosphere that retained enough heat for water to remain in liquid state enabling running rivers and lakes on its surface. This suggests that primitive microbial life forms may have existed on Mars. But, unlike Earth, Mars unfortunately does not have a magnetic field to provide protection against powerful solar wind and ionising radiations. As a result, it lost its atmosphere to space in due course and the climate of Mars changed to inhospitable frozen desert with a very thin atmosphere of today 3.

The key brief of this Mars 2020 mission is to search for the signs of ancient microbial life that may have existed on Mars before its climate changed to cold desert. Interestingly, in view of the detection of methane, it is postulated that some primitive life form may be present on Mars even today. However, it requires confirmation because methane may be released from non-living sources as well.

Some of cutting-edge instruments that will play a key role in this are SHERLOC and PIXL. Few others will help the rover to collect data from a distance. It is pertinent to note that the rover has touched down on the Martian surface at Jezero Crater, which was a water lake in the past making it a high potential area to support microbial life forms. The rover is also collecting data about the past climate and geology of Mars.

Not to miss the fact that this Mars mission is not a round trip to Earth. The samples collected by Perseverance will potentially be delivered to a planned lander in future which will bring the samples to the Earth for analysis to condirm the existence of ancient form of life on Mars.

Importantly, Perseverance is carrying several instruments and technologies whose successful use in data collection and exploration on this mission, will pave the way for future missions to the Moon and the Mars 4.

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microRNAs: New Understanding of Mechanism of Action in Viral Infections and its Significance

MicroRNAs or in short miRNAs (not to be confused with mRNA or messenger RNA) were discovered in 1993 and have been extensively studied in the past two decades or so for their role in regulating gene expression. miRNAs are expressed differentially in various body cells and tissues. Recent research by the scientists at the Queen's University, Belfast have unraveled the mechanistic role of miRNAs in immune system regulation when body cells are challenged by viruses. These findings will lead to an enhanced understanding of the disease and their exploitation as targets for novel therapeutic development.

MicroRNAs or miRNAs have gained popularity over the past two decades for their role in post-transcriptional processes such as differentiation, metabolic homeostasis, proliferation and apoptosis (1-5). miRNAs are small single-stranded RNA sequences that do not encode for any proteins. They are derived from larger precursors, which are double-stranded RNAs. The biogenesis of miRNA starts in the nucleus of the cell and involves generation of primary miRNA transcripts by RNA polymerase II followed by trimming of the primary transcript to release the pre-miRNA hairpin by an enzyme complex. The primary miRNA is then exported to the cytoplasm where it is acted upon by DICER (a protein complex that further cleaves the pre-miRNA), thereby producing the mature single-stranded miRNA. The mature miRNA integrates itself as part of the RNA induced silencing complex (RISC) and induces post-transcriptional gene silencing by fastening RISC to the complementary regions, found within the 3' untranslated regions (UTRs), in the target mRNAs.

The story began in 1993 with the discovery of miRNAs in C. elegans by Lee and his colleagues (6). It was observed that the LIN-14 protein was downregulated by another transcribed gene called lin-4 and this downregulation was necessary for the larval development in C. elegans in progressing from stage L1 to L2. The transcribed lin-4 resulted in downregulating LIN-14 expression via complementary binding to the 3'UTR region of lin-4 mRNA, with little changes to mRNA levels of lin-4. This phenomenon was initially thought to be exclusive and specific to C. elegans, until about 2000, when they were discovered in other animal species (7). Since then, there has been a deluge of research articles describing the discovery and existence of miRNAs in both plants and animals. Over 25000 miRNAs have been discovered so far and for many, the exact role they play in the biology of the organism still remains elusive.

miRNAs exert their effects by post-transcriptionally repressing the mRNAs by binding to complementary sites in the 3' UTRs of the mRNA they control. A strong complementarity earmarks the mRNA for degradation while a weak complementarity does not cause any changes in mRNA levels but causes inhibition of translation. Although the major role of miRNA is in transcriptional repression, they also act as activators in rare cases (8). miRNAs are play an indispensable role in the organism's development by regulating the genes and gene products right from the embryonic state to the development of organ and organ systems (9-11). In addition to their role in maintaining cellular homeostasis, miRNAs have also been implicated in various diseases such as cancer (miRNAs acting as both activators and repressor of genes), neurodegenerative disorders and cardiovascular diseases. Understanding and elucidating their role in various diseases can lead to new biomarker discovery with concomitant new therapeutic approaches for disease prevention. miRNAs also play a critical role in the development and pathogenesis of infections caused by micro-organisms such as bacteria and viruses by regulating the genes of the immune system to mount an effective response to the disease. In case of viral infections, Type I interferons (IFN alpha and IFN beta) are released as anti-viral cytokines which in turn modulates the immune system to mount a combative response (12). The production of interferons is tightly regulated both at the level of transcription and translation and play a pivotal role in determining the anti-viral response by the host. However, viruses have evolved sufficiently to deceive the host cells into suppressing this immune response, providing advantage to the virus for its replication and thereby aggravating the disease symptoms (12, 13). The tight c trol of interplay between IFN production by the host upon viral infection and its suppression by the infecting virus determines the extent and duration of the disease caused by the said virus in question. Although the transcriptional control of IFN production and related IFN stimulated genes (ISGs) is well established (14), the mechanism of translational control has still remained elusive (15).

The recent study by researchers at the McGill University, Canada and the Queens University, Belfast provides a mechanistic understanding of the translational control of IFN production that highlights the role of 4EHP protein in suppressing IFN-beta production and involvement of miRNA, miR-34a. 4EHP downregulates IFN production by modulating the miR-34a-induced translational silencing of Ifnb1 mRNA. Infection with RNA viruses and IFN beta induction increase the levels of miR-34a miRNA, triggering a negative feedback regulatory loop that represses IFN beta expression via 4EHP (16). This study is of great signifi cance in the wake of the current pandemic caused COVID-19 (an infection caused by an RNA virus) as it will help in further understanding of the disease and lead to novel ways to deal with the infection by modulating the levels of miR-34a miRNA using designer activators/inhibitors and testing them in clinical trials for its effects on IFN response. There have been reports of clinical trials utilising IFN beta therapy (17) and this study will help unravel the molecular mechanisms by highlighting the role of miRNA in intrinsically regulating the host translational machinery for maintaining a homeostatic environment.

Future investigations and research on such and other known and emerging miRNAs coupled with integration of these findings with genomic, transcriptomic, and/or proteomic data, will not only enhance our mechanistic understanding of the cellular interactions and disease, but would also lead to novel miRNA based therapies by exploiting miRNA as actimirs (utilizing miRNAs as activators for replacement of miRNAs that have been mutated or deleted) and antagomirs (utilizing miRNAs as antagonists where there is abnormal upregulation of the said mRNA) for prevalent and emerging human and animal diseases.

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Interferon-β for Treatment of COVID-19: Subcutaneous Administration more Effective

Results from the phase2 trial support the view that subcutaneous administration of IFN- β for treatment of COVID-19 enhances speed of recovery and reduces mortality

The extraordinary situation presented by the COVID-19 pandemic has warranted exploring different possible avenues for the treatment of severe COVID-19 cases. Several new drugs are being tried and existing drugs being repurposed. Corticosteroids have already been found to be useful. Interferon therapy is already in use for viral infections like hepatitis. Can IFN be used against SARS CoV-2 in COVID-19?

In preclinical trials earlier, IFN had proved to be effective against SARS CoV and MERS viruses. In July 2020, administration of Interferon-β through nebulisation (viz. pulmonary inhalation) route was reported to show promising results in treating severe COVID-19 cases based on data from phase 2 clinical trial 1,2.

Now, the latest report based on data from phase 2 clinical trial conducted on 112 patients with COVID-19 hospitalized at Pitié-Salpêtrière in Paris, France suggests that administration of IFN- β through subcutaneous route enhances recovery rate and decreases mortality in COVID-19 cases 3.

Interferons (IFN) are proteins secreted by the host cells in response to viral infections to signal the other cells for the presence of virus. The exaggerated inflammatory response in some of the COVID-19 patients is found to be associated with impaired IFN-1 response and blockade IFN-β secretion. It is used in China to treat viral pneumonia due to SARS CoV however its use is not standardised 4.

The phase 3 clinical trial for use of Interferons (IFN) in treatment of severe COVID-19 patients is currently in progress. Approval will depend on whether the final results are within the acceptable range stipulated by the regulators.

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Space Weather, Solar Wind Disturbances and Radio Bursts

Solar wind, the stream of electrically charged particles emanating from the outer atmospheric layer corona of Sun, poses threat to life form and electrical technology based modern human society. Earth's magnetic field provide protection against the incoming solar wind by deflecting them away. Drastic solar events like mass ejection of electrically charged plasma from the corona of Sun creates disturbances in the solar wind. Therefore, study of disturbances in the conditions of solar wind (called Space weather) is an imperative. Coronal Mass Ejection (CMEs), also called 'solar storms' or 'space storms' is associated with the solar radio bursts. Study of solar radio bursts in the radio observatories can give an idea about CMEs and solar wind conditions. The first statistical study (published recently) of 446 recorded type IV radio bursts observed in the last solar cycle 24 (each cycle refers to the change in Sun's magnetic field every 11 years), have found that the majority of Long Duration Type IV Radio Solar Bursts were accompanied by Coronal Mass Ejection (CMEs) and disturbances in the solar wind conditions.

Just the way weather on Earth is affected by the disturbances in the wind, space weather' is affected by the disturbances in the 'solar wind'. But the similarity ends here. Unlike wind on Earth which is made of air comprising of atmospheric gases like nitrogen, oxygen etc, the solar wind consists of superheated plasma comprising of electrically charged particles like electrons, protons, alpha particles (helium ions) and heavy ions that continuously emanate from the sun's atmosphere in all directions including in the direction of Earth.

Sun is the ultimate source of energy to life on Earth hence respected in many cultures as giver of life. But there is other side too. The solar wind, the continuous stream of electrically charged particles (viz. plasma) originating from the solar atmosphere poses threat to the life on Earth. Thanks to Earth's magnetic field that deflects most of the ionising solar wind away (from the Earth) and the Earth's atmosphere that absorb most of the remaining radiation thus providing protection from the ionising radiation. But there is more to it – in addition to threat to the biological life forms, solar wind also poses threat to electricity and technology driven modern society. The electronic and computer systems, power grids, oil and gas pipelines, telecom, radio communication including mobile phone networks, GPS, space missions and programmes, satellite communications, internet etc. – all these can potentially be disrupted and brought to standstill by disturbances in solar wind1. Astronauts and the spacecrafts are particularly at risk. There were several instances of this in the past e.g., March 1989 'Quebec Blackout' in Canada caused due to massive solar flare had badly damaged power grid. Some satellites too had suffered damages. Therefore, the imperative to keep a watch on conditions of the solar wind in the vicinity of the Earth – how its characteristics like speed and density, magnetic field strength and orientation, and energetic particle levels (i.e., space weather) will have an impact on life forms and modern human society.

Like 'weather prediction', can 'space weather' too be predicted? What determines the solar wind and its conditions in the vicinity of Earth? Can any serious changes in space weather be known in advance to take pre-emptive actions to minimise damaging impact on Earth? And, why at all does the solar wind form?

Sun is a ball of hot electrically charged gas and therefore, it does not have a definite surface. The photosphere layer is treated as surface of the sun because this is what we can observe with light. Layers below the photosphere inwards towards the core are opaque to us. Solar atmosphere is made of layers above the photosphere surface of the sun. It is the transparent gaseous halo surrounding the Sun. Better seen from the Earth during the total solar eclipse, solar atmosphere has four layers: chromosphere, solar transition region, corona and heliosphere.

Solar wind is formed in corona, the second layer (from outside) of the solar atmosphere. Corona is a layer of very hot plasma. While the temperature of the surface of the Sun is about 6000K, the average temperature of corona is about 1-2 million K. Called 'Coronal Heating Paradox', the mechanism and the processes of heating of corona and acceleration of the solar wind to very high speed and expansion into interplanetary space is not well understood yet, 2 though in a recent paper, researchers have sought to solve this by way of axion (the hypothetical dark matter elementary particle) origin photons 3.

Occasionally, huge amount of hot plasma is ejected from corona into the outermost layer of solar atmosphere (heliosphere). Called Coronal Mass Ejections (CMEs), the mass ejections of plasma from corona are found to generate large disturbances in solar wind temperature, velocity, density and interplanetary magnetic field. These create strong magnetic storms in the geomagnetic field of the Earth 4. Eruption of plasma from corona involves acceleration of electrons and acceleration of charged particles generates radio waves. As a result, Coronal Mass Ejections (CMEs) is also associated with bursts of radio sig nals from the Sun 5. Therefore, space weather studies would involve study of timing and intensity of mass ejections of plasma from the corona in conjunction with the associated solar bursts which is a Type IV radio burst lasting for long-duration (greater than 10 min.).

The occurrence of radio bursts in the earlier solar cycles (the periodic cycle of Sun's magnetic field every 11 years) in relation to Coronal Mass Ejections (CMEs) has been studied in the past.

One recent long-term statistical study by Anshu Kumari et al. of University of Helsinki on radio bursts observed in the solar cycle 24, sheds further light on association of long-duration, wider frequency radio bursts (called type IV bursts) with CMEs. The team found that about 81% of the type IV bursts were followed by coronal mass ejections (CMEs). About 19% of type IV bursts were not accompanied by CMEs. In addition, only 2.2% of the CMEs are accompanied by type IV radio bursts 6.

Understanding the timing of type IV long duration bursts and the CMEs in an incremental manner will help in the design and timing of the ongoing and future space programs accordingly, so as to lessen the impact of these on such missions and ultimately on the life forms and the civilization on Earth.

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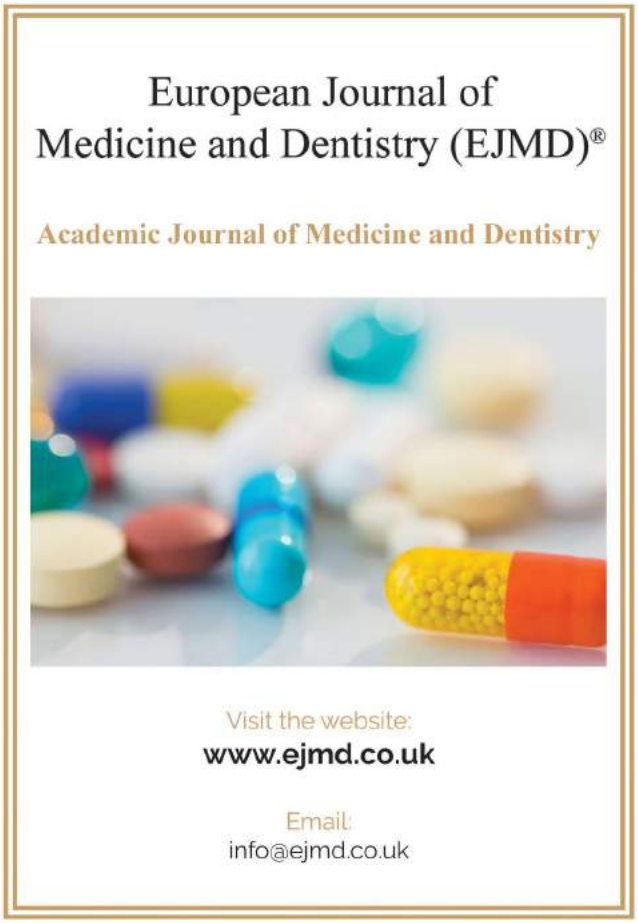

Climate Change: Reducing Carbon Emission from Aeroplanes

Carbon emission from commercial aircrafts could be reduced by about 16 % through better use of wind direction

Commercial aircrafts use lot of fuels to generate sufficient power to sustain flight. The burning of aviation fuels contributes in greenhouse gases in the atmosphere which in turn is responsible for global warming and climate change. Currently, carbon emission from aeroplanes constitutes about 2.4% of all man-made sources of CO2. This figure is likely to grow with growth in aviation sector. Hence the imperative to explore novel ways to reduce carbon emission from airliners and to enhance efficiency. Several ways have been thought of to reduce the carbon emission from aeroplanes. One such is to take the advantage of direction of the wind especially in the long-haul flights.

The idea of using wind direction in aviation to reduce fuel use is not new but it had limitations. Advances in space and atmospheric sciences has now enabled full satellite coverage and global atmospheric dataset. The research team of University of Reading has found that the transatlantic flights between London and New York could save up to 16% of fuel through better use of wind direction. The team analysed about 35000 transatlantic flights between 1 December 2019 and 29 February 2020 and used optimal control theory to find the minimum time routes. The findings indicated to a gap of hundreds of kilometres between typical actual flight paths and fuel optimised paths. This update could help reduce carbon emission in short term without involving any new capital outlay for technological advances.

Source:

Wells CA, Williams PD., et al 2021. Reducing transatlantic flight emissions by fuel-optimised routing. Environmental Research Letters, Volume 16, Number 2. Published 26 January 2021.
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Burden of Disease: How COVID-19 has Affected Life Expectancy

In countries like UK, USA and Italy which are badly hit by the COVID-19 pandemic, the life expectancy has reduced by at least 1.2-1.3 years.

Diseases and risk factors lead to premature deaths and disabilities and result in 'burden' on the people and the society. This limits people living long life in full health. There are several dimensions of the disease burden such as economic and financial, pain and human suffering or loss of time in full health for the individuals. As a quantitative concept, the burden due to a particular disease can be estimated in terms of DALY (Disability Adjusted Life Years) which is defined as sum of years of life lost (YLL) due to premature deaths and years of life lived with disability (YLD) in the population under consideration.

The COVID-19 pandemic has led to very significant burden on the people and the society worldwide. The burden due to COVID-19 has several dimensions but here, we are referring to "loss of healthy years of life" as measured in terms of DALY and its associated measures especially effects on life expectancy at birth in different countries.

In England and Wales, there were 57 419 excess COVID-19 related deaths in the first 47 weeks of 2020. 55% of the victims were men. Increased age and being men were associated with higher risk of death. Life expectancy reduced by 1.2 years for men and 0.9 years for women from 2019 baseline1. Older people living in care homes in the UK have higher mortality than older people living in the general population. A study conducted on care home residents in Scotland found that the life expectancy fell by about six months during the pandemic 2.

United States is among the worst affected countries. It is estimated that the US life expectancy in 2020 will reduce by 1.13 years due to COVID-19. The reduction in life expectancy for the Black and Latino ethnic groups will be 3-4 times higher. This trend is likely to continue in 2021. As a result, the gap in life expectancies between White and Black population will widen 3. According to a rough estimate, years of life lost (YLLs) due to COVID-19 deaths in the USA is about 1.2 million 4 implying about 1.2 million people would have lived for another one year in absence of the pandemic.

In Italy, as on 28 April 2020, total years of life lost (YLLs) due premature deaths attributed to COVID-19 was 81,718 (in males) and 39,096 (in females) which along with YLLD amounted to 2.01 DALYs per 1000 population. The burden was highest among 80-89 years age group 5.

The above estimates of the disease burden due to COVID-19 is limited due to the fact that the disease is still ongoing and available data is limited in almost all settings. In due course, the GBD estimate attributable to COVID-19 would be quantified to give clearer picture. However, in countries like UK, USA and Italy which are badly hit by the pandemic, the life expectancy has reduced by at least 1.2-1.3 years. It may take decades in future before this gap is bridged.

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Genetics of COVID-19: Why Some People Develop Severe Symptoms

Advanced age and comorbidities are known to be high risk factors for COVID-19. Does genetic make-up predispose some people making them more susceptible to severe symptoms? Conversely, does genetic make-up enable some people to have innate immunity making them immune against COVID-19 implying such people may not require vaccines. Identifying people with genetic susceptibility (by way of genome analysis) may provide for a more efficient personalised/precision medicine approach to combat this pandemic and other high burden diseases like cancer.

COVID-19 is known to disproportionately affect elderly and people with comorbidities however there seems to be another pattern. Apparently, some people are genetically more prone and predisposed to develop severe life-threatening symptoms 1 as indicated in the reported cases like three brothers in similar age group (who lived separately and were normal health wise) succumbing to COVID-19 2. This small group of people suffer hyperinflammation, clinical deterioration and multiple organ failure caused due to development Cytokine Storm (CS) in which Interleukin-6 (IL-6) is a central mediator. Two common gene polymorphisms that predispose to hyperinflammation are Familial Mediterranean Fever (FMF) and Glucose-6-phosphate Dehydrogenase (G6PD) deficiency which combined with obesity increases the risk further 3.

A systematic review links susceptibility to genetic variants in immune response genes. Forty genes were found to be associated with susceptibility and 21 of these genes had relation with development of severe symptom 4. Another study supports the view that ACE2 gene polymorphism contributes to susceptibility to COVID-19 5. The virus responsible for COVID-19 uses the angiotensin-converting enzyme 2 (ACE2) receptor protein present on the cell surface to enter the cell. Any variation in the ACE2 gene would have strong bearing on predisposition to COVID. The role of host-genetics in susceptibility to COVID-19 is investigated at the level of structural variants (SV) in a study reported in preprint recently by Sahajpal NS, et al. In this study, the researchers performed genome analysis on 37 severely ill COVID-19 patients. This patient-centric investigation identified 11 large structural variants involving 38 genes with a potential role in development of severe symptoms of COVID-19 6.

The fast-evolving knowledge base about role of host-genetics in COVID-19 disease progression may indicate appropriate shift of focus towards targeted approach to prevention and treatment of COVID-19. It may be possible to think of precisely targeted interventions to unique genetic-makeup of individuals 7. The personalised, precise treatments or interventions however would require genome analysis data at individual level. There may be issue of privacy to deal with however, in the long run, this may prove to be more effective cost wise too.

Currently, there are some commercial organisations that provide personal services covering basic health predispositions for individuals. However, more organised efforts in the public sector would be needed to build the knowledge base and infrastructure for personalised precision medicine to be a reality. GEN-COVID Multicentre Study 8 that aim to derive individual level phenotypic and genotypic data though biobanking and health records to make the data available to COVID-19 researchers worldwide is a step forward in this direction.

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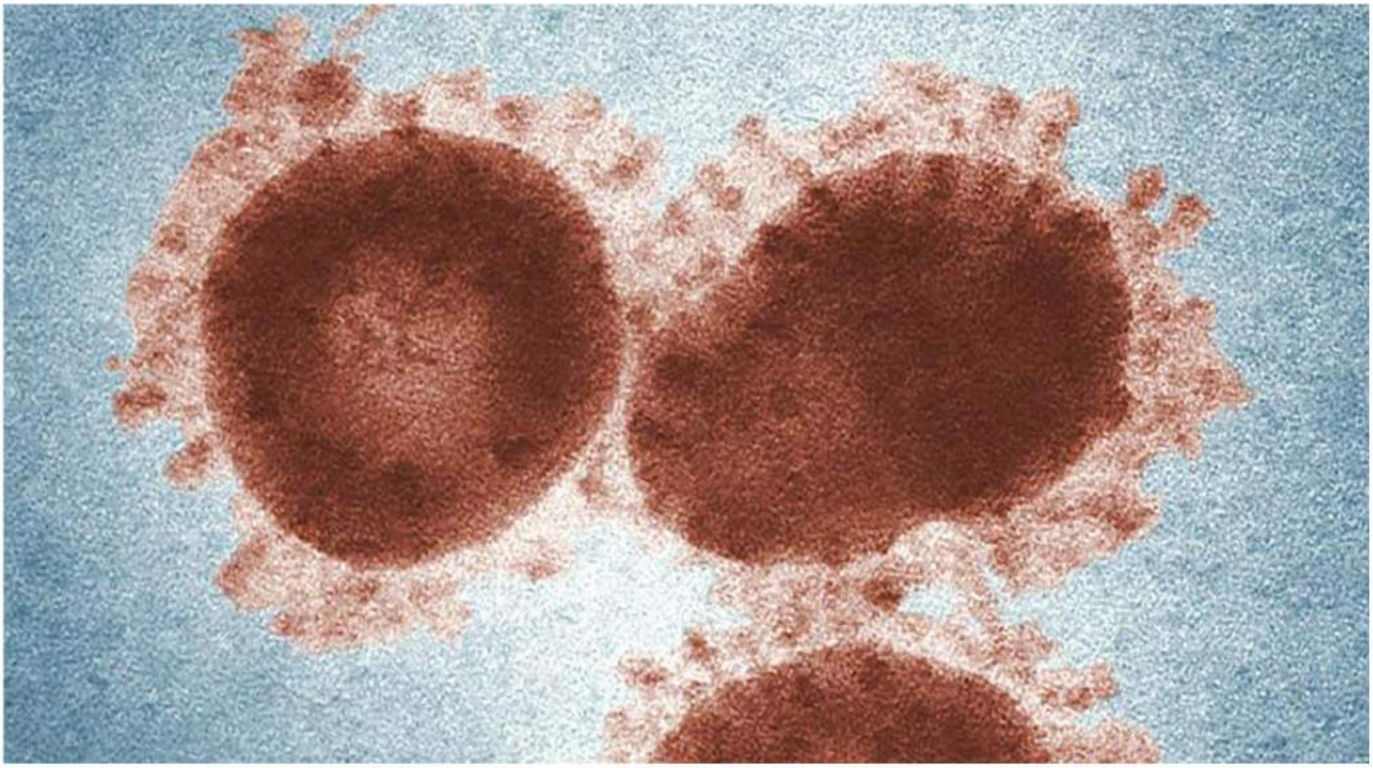
Thapsigargin (TG): A Potential Anti-cancer and Broad-spectrum Anti-viral Agent That May be Effective Against SARS-CoV-2

The plant derived agent, Thapsigargin (TG) has been used in traditional medicine for long time. TG has shown promises as a potential anti-cancer drug because of its biological property to inhibit the sarcoplasmic/endoplasmic reticulum Ca2+ ATPase (SERCA) pump which is necessary for cell to be viable. Its prodrug has completed phase 1 of clinical trial. According to a latest research report, TG has shown broad-spectrum antiviral property against a range of human viruses in preclinical trials. The results suggest TG may be used as inhibitor against SARS-CoV-2, the novel coronavirus responsible for COVID-19.

Thapsigargin (TG), a plant derived agent from the common weed Thapsia garganica (Apiaceae) which is native to the Mediterranean. The plant is highly toxic to cattle and sheep and hence is called "deadly carrot". The resins derived from this plant has been used in traditional medicine for various ailments for centuries.



The cytotoxic property of thapsigargin is due to its ability to inhibit sarcoplasmic/endoplasmic reticulum Ca2+ ATPase (SERCA) pump thereby making the cells non-viable. This made TG a potential anticancer candidate (1). Its prodrug Mipsagargin has completed phase 1 of clinical trial but no results have been posted yet (2).

At non-cytotoxic levels, thapsigargin is found to have antiviral property against Influenza A virus in animal models (3). Further research has shown TG to be highly effective against respiratory syncytial virus (RSV), common cold coronavirus OC43, SARS-CoV-2 and influenza A virus in primary human cells, thus making thapsigargin a potential broad-spectrum anti-viral agent for the treatment of viral diseases in humans (4). This development offers a new strategic tool to deal with COVID-19 caused by SARS-CoV-2 virus and is very significant in view of the tough situation presented by the pandemic (4,5). However, it needs to undergo mandatory clinical trials to meet the required safety and efficacy standards, before being considered for its use in treating COVID-19 infected patients.

Earlier, BX795 had shown potential as a broad-spectrum antiviral agent for use in humans (6). BX795 acts by inhibiting protein kinase B (AKT) phosphorylation and the subsequent hyperphosphorylation of 4EBP1. It has shown antiviral property against herpes simplex virus (HSV) and has also been shown to suppress inflammatory responses (7). However, no clinical trial seems to be underway for this agent to take it forward. More recently, yet another agent. diABZI (a STING agonist) has shown antiviral property against coronavirus infection (8).

These molecules show a promising hope as broad anti-viral agents in the treatment of COVID-19. However, each of these need to undergo the required clinical trials to prove their safety and efficacy before being approved for use in humans as medicine.