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EXPLORE™
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Biowarfare and Biodefense

Thousands of different microorganisms can affect the health, safety, and economic stability of entire populations. Many medical and government organizations have created lists of pathogenic microorganisms most relevant to their missions. For example, the Centers for Disease Control and Prevention (CDC) maintains an ever-changing list of notifiable diseases; the National Institute of Allergy and Infectious Disease (NIAID) lists agents used for bio-warfare, and the Department of Health and Human Services (HHS) maintains a list of critical human pathogens.

Using microorganisms as harmful biological agents in the context of biological warfare (biowarfare), bioterrorism, and bio-crime are becoming more realistic. Biowarfare (BW) refers to the intentional use of biological agents (e.g., bacteria, viruses, fungi, and toxins) as weapons in war scenarios. BW agents can be deadlier than other conventional weapon systems. This is because even minute quantities of BW agents can cause mass casualties and/or fatalities, depending on the agent used, and the type of weaponization performed on the agent.

The recent COVID-19 pandemic has significantly changed our way of living and impacted the global economy. Global communication systems and technology and modern means of transportation have led to rapid spread of infectious diseases. In the past three decades, more than forty infectious diseases have emerged. Biosafety has fast emerged as a major challenge worldwide. The SARS-CoV infection spread globally following its emergence in China in July 2003. Another variant of Influenza Virus A, H7N9, emerged in Eastern China. Simultaneously, H1N1 Swine Flu Virus emerged in South America and subsequently reported in China. MERS or Middle East respiratory syndrome emerged in 2015 in China. In 1976, Ebola was first discovered in Central Africa. Biological pathogens can be artificially modified to enhance characteristics in terms

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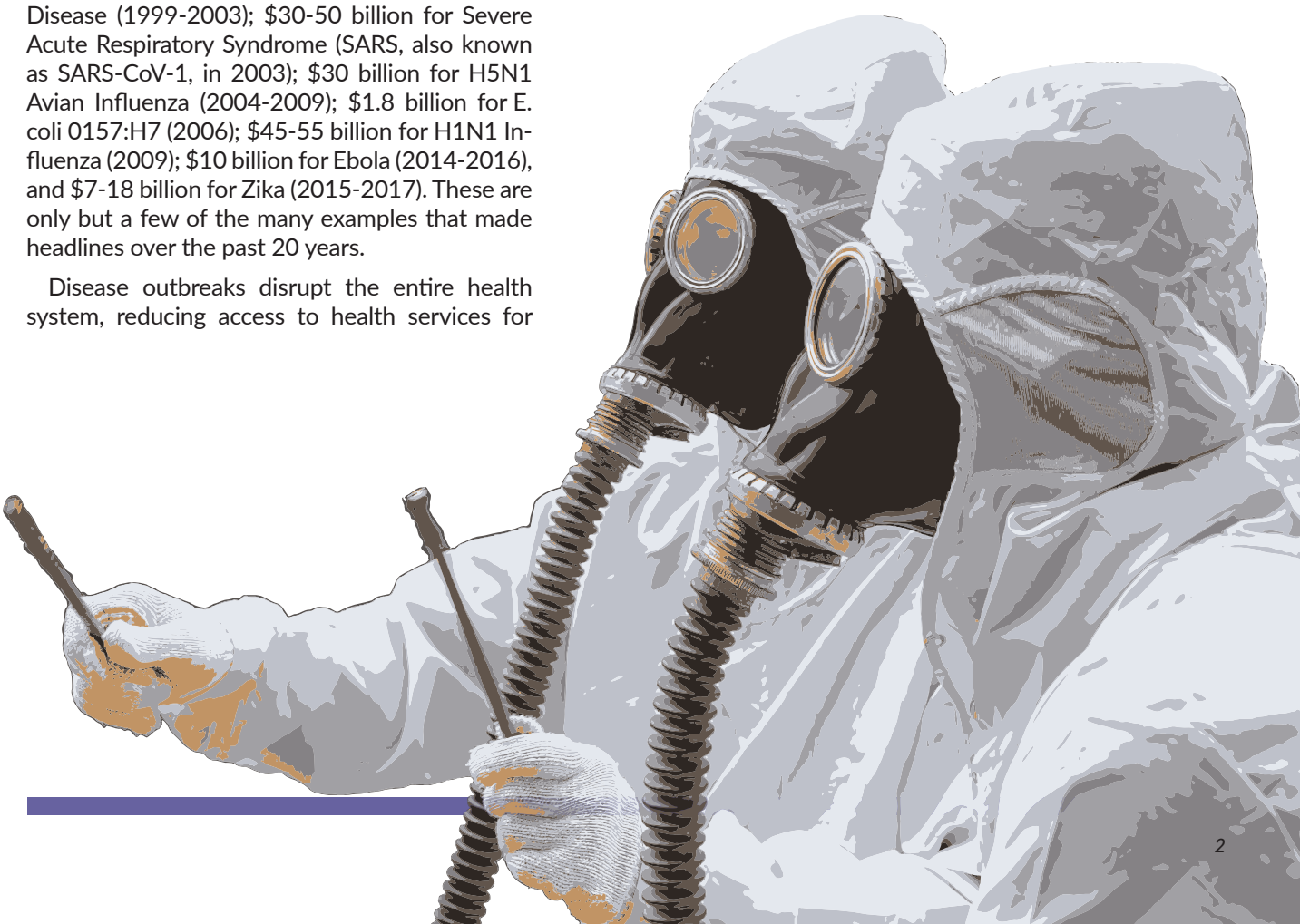
of genetic alterations, toxicity, and immunological impact. The genetic modification leads to a novel pattern of dominant gene expression, also termed as "gain-of-function" mutations. Any escape of these genetically altered pathogens will have multiple negative impacts on the external environment, threatening the health of humans, animals and plants, causing increased morbidity and mortality. The necessity for biosafety is greater than that at any other time in the past.

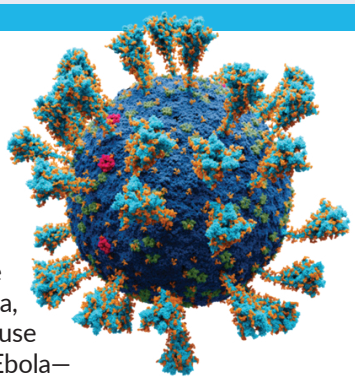
When disasters occur, America swings into action. We spend time and resources focused on doing whatever we can, whatever it takes to save lives. Unfortunately, we also often give in to our desires to put the latest disaster behind us, forgetting about the illness and death caused by diseases that spread faster than we can control them. We want so much to believe that pandemics occur only once in a century and that we have the resources to easily make up for our losses afterward. But the economic impacts of biological events are staggering: $200 million for Lyme Disease (2002); $10-15 billion for Foot and Mouth Disease (1999-2003); $30-50 billion for Severe Acute Respiratory Syndrome (SARS, also known as SARS-CoV-1, in 2003); $30 billion for H5N1 Avian Influenza (2004-2009); $1.8 billion for E. coli 0157:H7 (2006); $45-55 billion for H1N1 Influenza (2009); $10 billion for Ebola (2014-2016), and $7-18 billion for Zika (2015-2017). These are only but a few of the many examples that made headlines over the past 20 years.

Disease outbreaks disrupt the entire health system, reducing access to health services for all diseases and conditions, which leads to even greater mortality and further economic depression. In addition to loss of life, epidemics and pandemics devastate economies. Estimated costs of past events include a loss of over US$40 billion in productivity from the 2003 SARS epidemic.

For COVID-19, the United States alone has sustained about $16 trillion in economic losses; losses that continue the longer the pandemic prolongs. Billions and trillions in losses are difficult to recover.

COVID-19 is not the end of the biological threat. It is one among many. While we must address this clear and present danger, we cannot do so to the exclusion of all other biological threats. As expected, unimpeded, the biological threat will only increase over time. We should assume that large-scale biological events affecting our national security, public health, and economic well-being are always imminent and plan accordingly. The Nation cannot afford to wait until COVID-19 disappears.





Dangers of Covid-19 Variants

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Mutations are part of a virus' lifespan when one is given enough time and people to infect, of which SARS-CoV-2 has had many — specifically, some 250 million cases and counting. INDIA experienced an unprecedented increase in COVID -19 cases beginning late March 2021 with over a million new infections reported in every three days. Sequencing the strain it was found that the mutant strain first observed in India in December 2020, B1.167.2, was dominant. When Covid-19 infections broke out in Wuhan, China, that first strain was a "wild type" virus. This was the strain used by scientists across the world to develop testing kits, treatment plans, and even vaccines. All viruses, including SARS-CoV-2, the virus that causes COVID-19, change over time. Most changes have little to no impact on the virus' properties. However, some changes may affect the virus's characteristics, such as how easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures. But some mutations are serious, so that usually countries need to reimagine their public health measures.

The variants of concern— Alpha (B.1.1.7first identified in the UK), Beta (B.1.351,South Africa), Gamma (P. 1.2, Brazil), Delta(B.1.617.2, India) and C. 1.2 — are different from all other countless variants for this very reason. It was inevitable that a more contagious variant would emerge. This was evident with the Alpha variant before the Delta variant. Research shows the Delta variant is much more infectious. Someone with the Alpha variant — the first detected coronavirus variant — could infect two other people, where as the Delta, the estimate is closer to five or more[1]. And those carrying the Delta virus have a higher viral load, meaning they're carrying more of the virus that could spread to others.

As of May 19, 2021, the delta variant had been detected in 43 countries across six continents . The Centers for Disease Control and Prevention (CDC) described Delta as more transmissible than the common cold and influenza, as well as the viruses that cause smallpox, MERS, SARS, and Ebola— and called it as contagious as chickenpox[2]. Because of this increased transmissibility, Delta has become the dominant variant worldwide. It accounts for more than 98.8 percent of COVID-19 cases in the United States According to a new study from the journal Nature, people with the Delta variant can transmit the virus for almost 2 days before experiencing any symptoms. Pre-symptomatic transmission may account for nearly 75 percent of Delta variant infections. This change could be a key feature driving the most recent surge in COVID-19 cases, a new study in the journal Nature suggests. Presymptomatic transmission was a feature of previous coronavirus variants, but the research suggests the gap between receiving a positive test to feeling systems was just 0.8 days. With the Delta variant, it's 1.8 days[3].

The Delta variant has certain significant mutations in the spike protein of the virus— the pointy elements that give it the shape of a crown (which is why it's called the coronavirus). These spikes are like hooks that have to find the receptors in a human cell to link with. Studies have shown that these spikes hook onto receptors called ACE-2. Once these spike proteins can unlock the cells, the infection spreads by replicating the genetic code of the virus. Some key mutations in the Delta variant .Vaccinated people with rare "breakthrough" infections may also be able to transmit the virus as easily as unvaccinated people because of elevated viral loads. A CDC study shows protection from the vaccines may decline over time as the wildly contagious delta variant surges across the country. Once delta became the dominant strain in the U.S., vaccine effectiveness against infection decreased from 91% to 66%[4].

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Performance evaluation of SteriSpace™ using computation fluid dynamics

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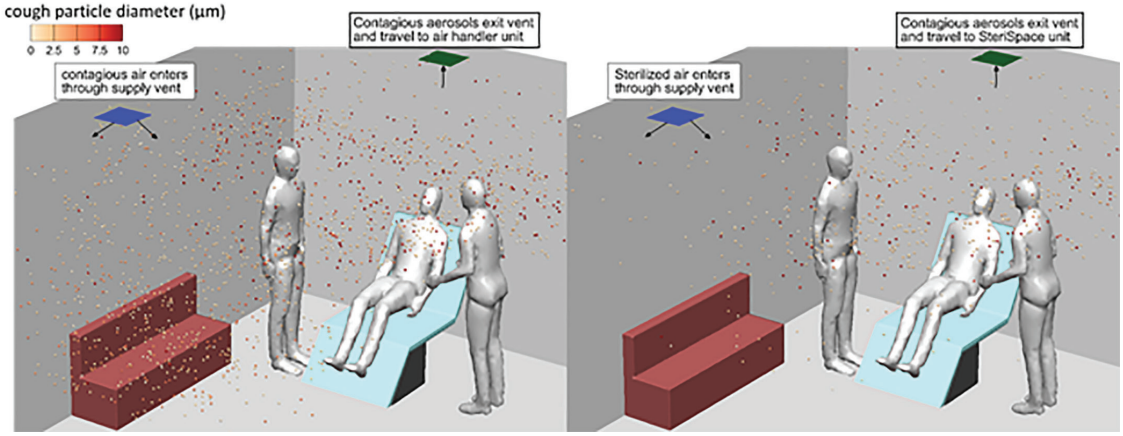
Ventilation in buildings is the movement of conditioned air (hot or cold) in enclosed spaces that provides thermal comfort to occupants and controls air quality. The COVID-19 pandemic has drawn attention to the significance of indoor air quality and how the air moves during the circulation process. The air movement is also connected to physical distancing measures that were used in establishments that reopened, such as restaurants, schools and music halls.

Contaminants, especially aerosols, remain airborne for prolonged periods and travel long distances, increasing the risk of infection to occupants in an indoor space. The airflow dynamics plays and important role in determining the movement and concentration of particles, and is affected by ventilation airflow rate, pressure differences and temperature changes. Computational fluid dynamics (CFD) can be used to predict the air flow patterns in an indoor space to optimally determine the location of the return ducts such that most of the pathogens exit the room.

All heating, ventilating and air-conditioning (HVAC) systems distribute a combination of outdoor (fresh) air and indoor air to reduce energy consumption. Air inside a room is either exhausted, re-conditioned and resupplied or can escape (passive relief) through gaps. The recirculated air carries contaminants that are smaller than 1 micron and air filters in the HVAC systems are often ineffective in removing pathogens that are very small. These pathogens are then distributed to other spaces in the building and increase the risk of infection to other occupants.

The air sterilization technology, SteriSpace destroys airborne biological pathogens and can be a stand-alone unit for a room or integrated into a building air handling system, and can be customized for different configurations. A CFD study simulated and compared the dispersion of pathogens released by an infected patient sitting in a clinic room with a conventional HVAC system and in a clinic room with the SteriSpace system. A higher particle concentration (30%

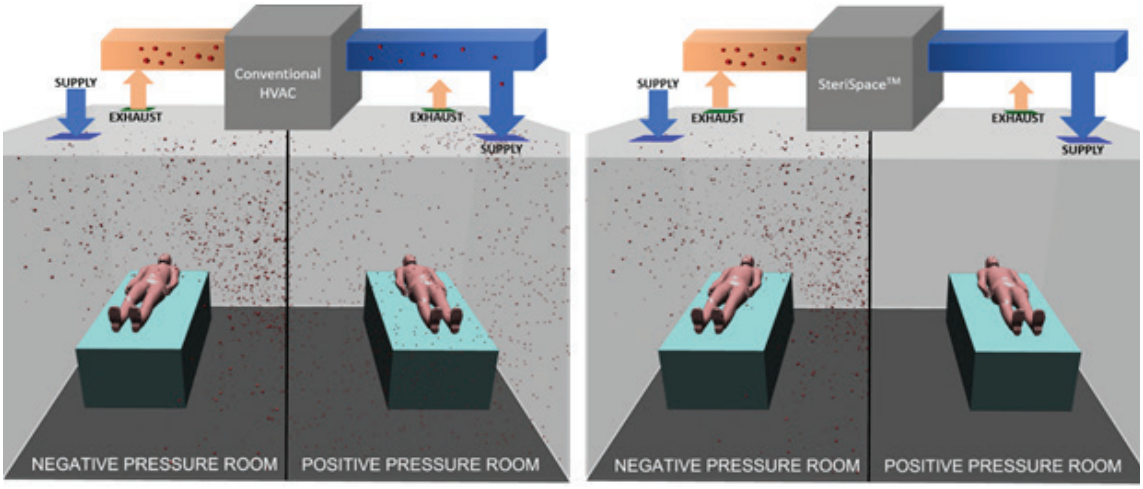


more) was removed by the SteriSpace system compared to a conventional ventilation system. A small percentage of exhausted pathogens were reintroduced through the supply duct to the room that were not treated by the conventional HVAC system. However, SteriSpace technology treated all pathogens passing through the supply duct. It was shown that more airborne particles would contaminate a room without SteriSpace, increasing the risk of infection.

The SteriSpace technology can also be used in patient isolation shelters to prevent the transmission of the Coronavirus to unaffected people. CFD was used to simulate an isolation system for a negative pressure room (airborne infectious isolation (AII) room) and a positive pressure room, whereby an infectious patient was located in the AII room.

In a conventional HVAC system, some contaminants exhausted from the AII room were introduced in the positive pressure room due to inefficient filtering of the pathogens. The airborne pathogens in the positive pressure room increased with time as respiratory particles traveled through the ventilation system and increased the risk of infection to occupants in that space. However, when a SteriSpace system was linked to the isolation system, the exhausted pathogens were treated and only clean, sterile air was supplied to the positive pressure room, ensuring the safety of the patient. Additionally, the SteriSpace system operated at a higher flowrate than the conventional ventilation system and hence make-up air was required to maintain the pressure inside the rooms.

The findings of these studies can be generalized to any scenario where a centralized ventilation system is employed for thermal comfort and air quality control. If air in a subspace of a building is contaminated, the SteriSpace system will remove the contaminants at a faster rate and will also ensure that the removed air is treated so that occupants in other subspaces of the building are not compromised.



Importance of ventilation in the fight against COVID

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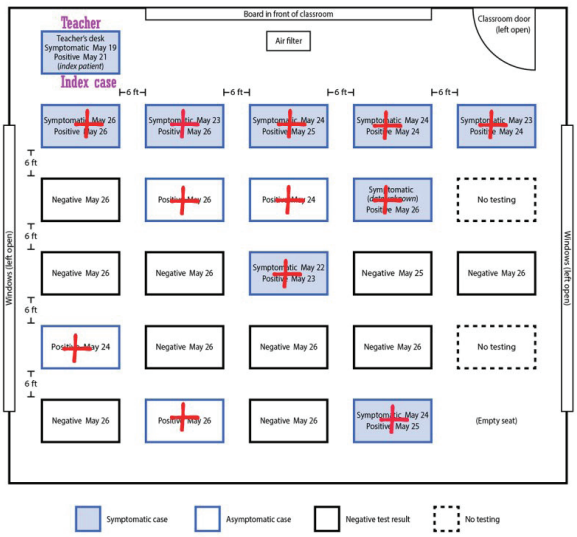
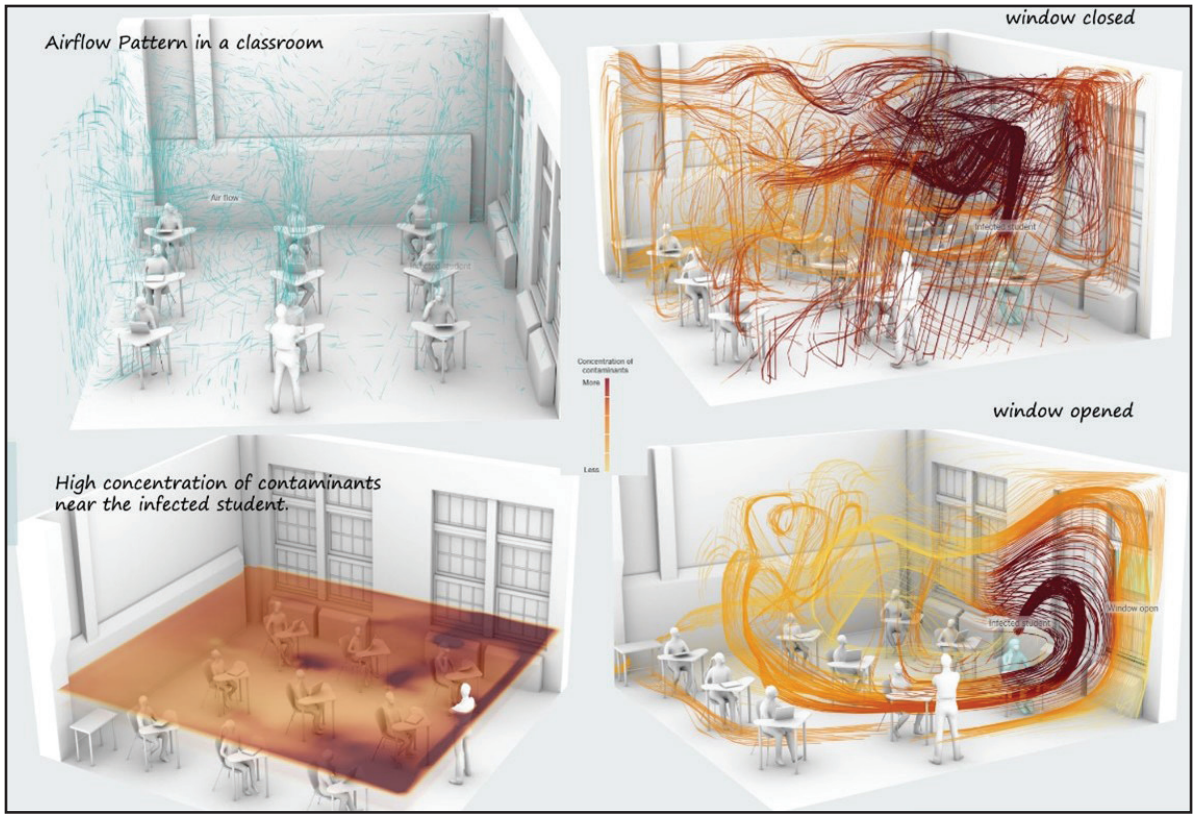
The unknown disease first detected in Wuhan China in 2019 so far infected over 235 million and killed over 4.8 million people so far globally. Newer variants of the coronavirus that causes COVID-19 , the disease now known as,like Alpha and Delta are highly contagious, infecting far more people than the original virus.

Two new studies show how the COVID -19 have been evolving to be very efficiently spreading through air[1, 2]. Most scientists now agree that the corona virus is transmitted mostly airborne. The findings indicates how the virus is adapting to make it more formidable. The study showed that small aerosols traveled much longer distances than larger droplets and the Alpha variant was much more likely to cause new infections via aerosol transmission. The second study found that people infected with Alpha exhaled about 43 times more virus into tiny aerosols than those infected with older variants. The Alpha variant proved to be twice as transmissible as the original virus, and the Delta variant has mutations that turbocharged its contagiousness even more. As the virus continues to change, newer variants may turn out to be even more transmissible, experts said.

People infected with the Alpha variant had copious amounts of virus in their nose and throat, much more than those infected with the original virus. But even after adjusting for that difference, those infected with the variant released about 18 times as much virus into the smallest aerosols.

The ultratransmissibility of the variants may come down to a mix of factors. It may be that lower doses of the variants are required for infection, or that the variants replicate faster, or that more of the variant virus is exhaled into aerosols — or all three. The importance of ventilation and clean air is very high on the fight against any airborne disease like COVID-19. One good example is a study put out recently by the CDC that looked at an outbreak that occurred in late May in an elementary school in California. On the surface, it looked like the school was doing a lot of things right.[3] They were masking. They were spacing out desks. And yet a teacher there passed the virus on to half the class. Now, this teacher wasn't vaccinated and had gone to work with really mild allergy-like symptoms. At brief points during the day, the teacher took their mask off to read out loud to the class. The teacher got a coronavirus test and it came back positive. And yeah, then soon after, half the class ended up testing positive, too. And it wasn't just kids in that one classroom(figure siblings of students





and even fully vaccinated parents. In fact, all told, there were 27 people infected. The bottom line is, these strategies aren't perfect on their own, but the more protections you can layer on in schools, the better the chance that you can curb the spread of the virus. New York Times in a recent article beautifully shown how the virus travel in a closed class room. [4]. They worked with an engineering firm and experts specializing in buildings systems to better understand the simple steps schools can take to reduce exposure in the classroom. The modelling shows how fast a room can be contaminated by a infected patient.(figure 2).

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Is there a link connecting COVID-19 and prostate cancer in the long term? Possible biologic intersections

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Introduction:

The COVID-19 pandemic caused by the rapid spread of SARS-CoV-2 infection has affected all nations of the world with more than 216,303,376 confirmed cases, including 4,498,451 deaths as of 31st August 2021 (WHO report). Although COVID-19 is seen as a disease that primarily affects the lungs, long-term consequences are possible due to the multi-system inflammatory syndrome (MIS) that can prevail in COVID-19 patients. MIS effects of COVID-19 have been documented in most, if not all, body systems. Oxidative stress resulting from COVID-19 associated chronic inflammation can cause significant DNA damage, gene fusion and organ injury resulting in neoplastic transformation. A pattern noticed since the initial days of the COVID-19 outbreak in China and seen repeating itself around the world, is that the disease burden and adverse outcomes are disproportionately higher in men, especially men of color [2, 3]. It is also known that CaP disproportionately affects men of color at nearly twice the rate of men of European ancestry. A recent New York State Department of Health report stated that the incidence of CaP and its mortality among men of color is highest in Erie County than elsewhere in the state excluding NYC . Given that the burden of CaP and COVID-19 related MIS are likely to be higher in men, the potential for devastating long-term consequences like neoplastic transformation in the prostate or rapid progression of pre-existing CaP are likely to be much higher in men. Thus, it is important to understand the long-term consequences of COVID-19 in men by looking for biological factors that may predispose to malignancy including unique gene fusions and chronic inflammation. This review summarizes recent developments and provides just-in-time considerations of our current understanding in this area and proposes a link that could potentially initiate CaP in men due to COVID-19 infection or advance rapid progression of pre-existing CaP in men.

Gender differences in rate of occurrence and mortality from COVID-19:

The trend emerging from data around the globe clearly indicate that men are at higher risk of infection, hospitalization and mortality from COVID-19 with SARS-CoV-2 than women [4-6]. Initially reported from China this gender difference in now confirmed with data emerging from France, Germany, Iran, Italy, South Korea, UK, and USA. Furthermore, a recent meta-analysis, that included 59,254 patients from 61 studies, confirmed the same observation [7]. Additionally, Italian epidemiological data suggest an even higher 3:1 male: female ratio for SARS CoV-2 infection [8]. In our own backyard, in the state of New York as of June 14th 2020, mortality by gender was reported to be 42% for females vs. 58% for males (https://www.syracuse.com/coronavirus-ny/). In a case series of COVID-19 patients hospitalized in New York City, 60.3% of inpatients were male, 66.5% of inpatients who required ICU admission were male, and mortality rates were consistently higher for males across all age groups older than 20 years [9].

Hence knowing that this gender difference exists in COVID-19 infection and mortality careful consideration of public health policies to manage the long-term consequence of exposure to this virus should be put in place.

Gender-differences in SARSCoV-2 diseases are hormones to be blamed:

It is well known among Immunologist and Virologist that men are more susceptible to virus infection and produce lower levels of antibodies than women. The prevailing model for classification of hormonal influence on immune responses suggests that testosterone and progesterone decrease immune responses while estrogens can enhance immune responses[10]. Women are also known to have a stronger innate immune system, which confers quick and broad protection to viral infections. Could this difference be due to the activity of male and female steroid hormones, available evidence indicates so. It is well know that that steroid hormones testosterone, estrogen, and progesterone, and their corresponding nuclear hormone receptors, modulate downstream signaling that arouses different effects and responses from the immune system [10, 11]. Innate immune cells like macrophages, monocytes, mast cells, and dendritic cells play a vital role in this process. The recognition of antigen by the innate immune cells involves the protein sensors of RNA viruses, such as SARS-CoV-2, that are encoded by genes belonging to the family of Toll-like receptors (TLRs) located on the X-chromosome. TLR7 and TLR8 can detect single-stranded RNA. Due to its bi-allelic expression, women have higher levels of TLR7 contributing to stronger innate immune responses and faster clearance of the virus as opposed to men where the virus lingers for a longer time. In addition to TLR7, several other immune regulatory genes located on the X-chromosome (e.g., TLR8, FOXP3, CXCR3, and CD40L) contribute to stronger immune response against viruses in women [11-14]. Women also show higher levels of type-1 interferon genes that are critical to jump-starting innate immune response following a viral challenge [11, 15]. A gender difference is also reported with regard to viral shedding [16]. Time to clearance of SARS-CoV-2 was found to be significantly earlier in females compared to male COVID-19 patients[16]. Also, within families with more than one infected family member, females cleared the virus faster[16]. A recent meta-analysis of COVID-19 patients explained key immunological differences in males and females that affect susceptibility. The study found higher prevalence of immune mediators that are associated with adverse outcomes of SARS-CoV-2 in men, including TNFSF13B, CCL14, CCL23, IL-7, IL-16, and IL-18. A comparison of adaptive immune responses between males and females demonstrates that, females have higher levels of CD4/CD8 ratios [17]. Interestingly several proinflammatory and antiviral genes expressed by cytotoxic T cells carry estrogen receptor elements in their promoter and contribute to stronger cytotoxic response in females [11, 18]. In summary, females exhibit robust innate and adaptive immune responses to viral infections leading to a scenario where the SARS-CoV-2 virus could be persistent in the system causing devastation in disease outcome in men and present itself with immense potential for long term sequelae.

Potential role of COVID-19 in the Molecular Pathogenesis of CaP.

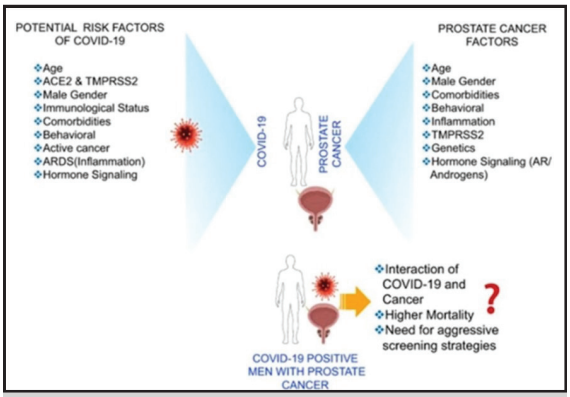


Figure 1. Adopted from Chakravarty et al. [1]. Men are at an elevated risk of SARS-CoV-2 infection than women. Common risk factors involved in COVID-19 mortality, CaP risk, and theoretical justification for aggressive clinical management of COVID-19 in prostate cancer patients in the post-pandemic era or if the infection reoccurs

Accumulating evidence supports common risk factors for both COVID-19 and CaP (Figure.1). Comorbidities such as hypertension, diabetes, alcoholism and smoking that substantially influence the severity of COVID-19 are also known

to influence the development progression and outcomes of CaP [19-24]. Interestingly, the most significant common risk factor for both diseases is age. The risk for CaP increases in men above the age of 50, and notably, this is the age group that is most susceptible to complications and mortality from COVID-19 [6, 8, 25-31].

Cellular Mediators of COVID-19 and Potential Association with CaP:

Another factor linking COVID-19 and CaP is the high expression levels of the host proteolytic enzyme, TMPRSS2, associated with both the diseases [2]. TMPRSS2 plays a pivotal role in the activation of SARS-CoV-2. Entry of SARS-CoV-2 into host cells depends on the protease activity of TMPRSS2 [32-37], and, coincidentally, TMPRSS2 expression is regulated by androgen/androgen receptor (AR) signaling [38-44]. The S glycoprotein of SARS-CoV-2 is cleaved by TMPRSS2 leading to virus activation, representing one of the essential host factors for SARS-CoV-2 pathogenicity (Figure. 2) [45]. Compared to the relatively low levels of ACE-2 expression found in a wide range of body tissues, TMPRSS2 shows similar broad tissue distribution but with relatively higher expression levels [37, 46]. TMPRSS2 is highly expressed in urogenital tissues like prostate, seminal vesicles, testis, epididymis, and kidney [47] and as noted above, TMPRSS2 expression is regulated by androgen/AR signaling [38-44]. In the prostate, TMPRSS2 is expressed primarily in the luminal cells of the prostate and in a large proportion of CaP tumors, is fused with erythroblast transformation specific (ETS) transcription factors, predominantly ETS related gene (ERG) and ETS variant transcription factor 1 (ETV1) [44, 48-50]. Gene fusions between TMPRSS2 and ERG are found in approximately 50% of CaP cases [44, 48-50]. TMPRSS2 is expressed at high levels in both primary and metastatic CaP. Several studies demonstrated the presence of androgen responsive (AR) elements in the promoter/enhancer and intron regions of the TMPRSS2 gene[38-44]. A significantly positive correlation for the expression of AR and TMPRSS2 was seen in both primary and metastatic castrate resistant CaP [51]. These findings support the premise that higher levels of androgens could induce greater expression of TMPRSS2, which could increase susceptibility to SARS-CoV-2 infection and severity of COVID-19. Interestingly, a recent study showed that ACE-2 expression is higher in men and may be regulated by androgen/AR signaling [6]. Furthermore, AR and ACE-2 co-expression was observed in a wide range of different tissues. Other investigators showed the presence of ACE-2 expressing cell clusters within the prostate and testis [52].

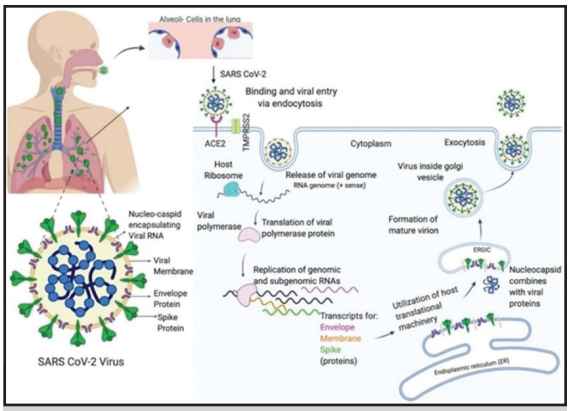


Figure 2. Adopted from Chakravarty et al. [1]. Regulation of TMPRSS2 gene transcription and process of severe acute respiratory syndrome coronavirus 2 entry into target cells. TMPRSS2:ERG gene fusion is associated with prostate cancer development. SARS-CoV-2 engages ACE2 as the entry receptor and uses TMPRSS2 for spike protein priming.

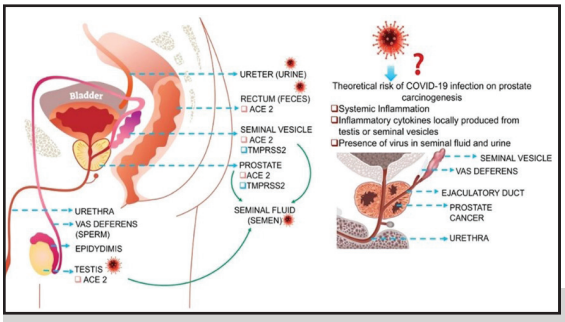
COVID-19 Induced Inflammation, TMPRSS2, and CaP:

Repeated gene arrangements are common in CaP, and catastrophic chromosome rearrangements are characteristic of CaP carcinogenesis [53-56]. Inflammation-induced oxidative stress is an essential driver of oncogenic TMPRSS2:ERG fusions [57]. It has also been demonstrated that treatment of CaP cells with TNF-α induced a robust inflammatory response that resulted in DNA breaks and de novo genomic arrangements mediated by a non-homologous end joining process [57]. Other studies demonstrate that systemic and pelvic inflammation with subsequent production of pro-inflammatory cytokines (IL-1, IL-6, IL-8, and MCP-1) can accelerate the progression of existing CaP [58-60]. Interestingly, elevated levels of IL-1 and IL-6 are also associated with SARS-CoV-2 infection [61, 62]. TNF-α levels are elevated in the

blood and tissues of patients with SARS-CoV-2 infection and in conjunction with IL-1β, IL-6, IL-8, and MCP-1 are major contributors to the immunopathology COVID-19 [63, 64]. Based upon these observations it can be envisioned that the prostate can be seriously affected, including the induction of CaP or the progression of existing disease, by the high levels of pro-inflammatory cytokines produced during COVID-19. Emerging data demonstrate that SARS-CoV-2 infections can adversely affect the genitourinary tract [47] supporting our premise that SARS-CoV-2 can infect the prostate producing chronic inflammation and subsequent induction and progression of CaP. During COVID-19, SARS-CoV-2 can be detected in semen and with observed delayed clearance of virus from the testes, there is concern that the urogenital tract, including the prostate, could serve as a reservoir for SARS-Cov-2 [65-67].

COVID-19 Induced Inflammation from Adjacent Tissues may Augment CaP:

Inflammation is a driver of CaP carcinogenesis [68]. Anatomically, the prostate is located beneath the bladder, close to the seminal vesicles and the rectum. The presence of SARS-CoV-2 demonstrated in semen, testes and feces of infected men suggests that the anatomically adjacent prostate is subject to the inflammatory milieu generated during COVID-19. Semen is produced by secretions from the seminal vesicles, prostate, and testes. The vas deferens, the duct that carries sperm from the testes, enters the ejaculatory duct and then passes through the prostate to the urethra. This route could result in the dissemination of pro-inflammatory cytokines to the prostate leading to potential carcinogenesis of CaP and its progression. The seminal vesicles express ACE-2 and TMPRSS2 and can be targets of SARS-CoV-2 infection also producing an inflammatory milieu adjacent to the prostate [69-71]. Other routes for the introduction of pro-inflammatory cytokines to the prostate include the arteries that supply systemic blood and through the ducts that connect the prostate with the seminal vesicles (Figure. 3). Finally, as already mentioned, the prostate can be directly infected by SARS-Cov-2 resulting in high local levels of pro-inflammatory cytokines ultimately leading to direct carcinogenesis and progression of CaP [72].



Adopted from Chakravarty et al [1]. Pictorial illustration of the hypothetical risks and possible routes of spread of SARS-CoV-2 to the prostate.(a) This is based on tissue level expression of a TMPRSS2 and ACE2; and(b) the presence of virus in body fluids such as urine, semen, and feces. Systemic or tissue derived inflammation, during COVID-19, has the potential to accelerate pre-existing prostate cancer resulting in an aggressive phenotype and therefore represents a potential risk factor for prostate cancer patients.

Men of Color are more susceptible to the Incidence and Outcomes of COVID-19 and CaP:

COVID-19 has disproportionately affected people of color globally. While this may be attributed, in part, to socioeconomic factors including access to healthcare, genetic and physiological variables among different ethnicities may contribute to differential host responses to COVID-19. Significant racial variances also exist in CaP incidence and outcomes, with African American men experiencing a higher incidence (186.8 vs 107.0 per 100,000) and mortality rate (40.8 vs 18.2 per 100,000) than European American men [73]. Multiple factors including, cultural, socioeconomic, psychosocial, and healthcare access disproportionately influence higher cancer burdens and poor disease outcomes in African American men [74, 75]. However, tumor biology also appears to contribute to this disparity as a recent study concluded that significant biological differences in CaP could be attributed to a man's racial ancestry [76]. In this study African American men demonstrated higher expression of genes related to inflammation (IL33,

IFNG, CCL4, CD3, ICOSLG), and lower expression of genes related to genetic mismatch repair (MSH2, MSH6, $p < 0.001$ for all) [76].

In conclusion with a higher prevalence COVID-19 in men, and the dual role of the TMPRSS2 gene in infection with SARS-Cov-2 and CaP, plus the high levels of inflammation produced during COVID-19, we regretfully postulate increases in the prevalence and severity of CaP, in men particularly men of color, in the post-COVID-19 era. Therefore, with known risk to develop CaP because of COVID-19 we need on a priority basis to initiate studies that address this looming critical issue which could provide a basis for identifying at risk men and even be translated to new strategies to prevent and treat COVID-19 associated CaP in men.

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An Overview of Catheter-Associated Urinary Tract Infections

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Urinary catheterization accounts for 80% of hospital-acquired urinary tract infections (UTIs), and prolonged catheterization significantly increases the risk of developing catheter-associated urinary tract infections (CAUTIs) (1). CAUTIs are one of the most common health care-associated infections worldwide, accounting for over 1 million cases annually (2-5). Catheter insertion often leads to damage and inflammation of protective bladder mucosa, disrupting natural barriers and allowing for bacterial colonization and subsequent infection (6). Each successive day of catheterization increases the risk of urine colonization by up to 8%, such that virtually all patients catheterized for greater than 30 days will experience bacteriuria (bacterial presence in urine), and the majority of patients with long-term catheters will experience at least one CAUTI (7-9). Thus, long-term catheter administration should only be considered when absolutely necessary due to the introduced risk of infection.

Frequent overuse of indwelling catheters during hospitalization (21 to 50% of patients) has led many patients to be placed at risk for a multitude of complications. In patient populations residing in nursing homes and long term-care facilities it has been recorded that up to 13% of men and 12% of women have an indwelling urinary catheter upon admission (10). Due to such high incidence, medical intervention required for these infections also presents a source of substantial financial burden, as every incidence of CAUTI is associated with the medical cost of $750-$1000, collectively resulting in over $340 million in healthcare expenses each year in the U.S. (11). Furthermore, bacteremia (bacterial presence in the bloodstream), a common secondary complication of CAUTI, is estimated to cost approximately $2,900 per incidence (12). These costs are expected to continually rise due to ongoing advances in preventive medicine that extend life expectancy, thereby increasing the elderly population who make up the majority of those requiring catheters (2, 13).

The invading uropathogens that cause CAUTI commonly originate from the host's own native microflora and/or fecal contaminants that colonize the periurethral area (2). However, introduction of transitory microflora that originate from healthcare personnel when handling the catheter can also lead to infection (2, 4, 14). Bacteria can be introduced into the bladder during initial catheter insertion through the catheter lumen or along the catheter-urethral interface (15).

Catheterization can have adverse effects on the bladder environment. The initial insertion of the catheter causes the disruption of the urothelium and has the propensity to induce a robust inflammatory cascade, resulting in the release of numerous host proteins, including fibrinogen (16). The catheter rapidly becomes coated in a conditioning film comprised of fibrinogen along with other host proteins, which creates an optimal surface for the attachment of invading uropathogens, promoting their successive biofilm formation (16, 17). The presence of an indwelling catheter can also cause urinary retention (insufficient drainage of the bladder), resulting in an accumulation of 10-100 ml of stagnant urine that can then act as a reservoir for bacterial growth (18).

The microbiology of CAUTI is dynamic, involving a continual turnover of organisms, with patients acquiring new organisms at a rate of about 3–7% per day (19, 20). Early colonizers include Escherichia coli, Enteroccoccus spp., Pseudomonas aerugi-

nosa, Klebsiella pneumonia, Enterobacter spp., and coagulase-negative Staphylococcus spp. (21, 22). Some early colonizers, such as Enterococcus spp., E. coli, and P. aeruginosa remain present during long-term catheterization. Additionally, there are other organisms not often encountered during short-term catheterization that become more common with long-term catheter use, including Proteus mirabilis, Providencia spp., and Morganella morganii (21, 22). Several studies have shown that these bacterial organisms most frequently exist as biofilms on the catheter surface (23). CAUTI biofilms are often polymicrobial, meaning there are multiple bacterial species that make up the biofilm community (24).

Biofilm formation is a critical contributor to CAUTI pathogenesis due to providing increased resistance against both antimicrobial agents and host defense mechanisms which results in increased persistence of infection in the host (25, 26). Biofilm formation is a multistep process, involving irreversible microbial attachment to a substrate, development of microcolonies, the production of extracellular polymeric substances (EPS), maturation, and dispersal, which is thought to contribute to persistent infection during CAUTI and dissemination to the bloodstream (27-31). The biofilm effectively acts as a physical barrier that prevents the diffusion of antimicrobials either by binding and chemically inhibiting the antimicrobial molecules or by limiting their rate of infiltration (32, 33). The biofilm-associated bacteria also experience reduced growth rates and are less metabolically active, which limits the efficacy of many antimicrobial agents (34). The environment that immediately surrounds the biofilm may also provide conditions that further protect the biofilm-associated bacteria (35). As a result, biofilm formation on catheters poses a serious challenge due to the increased resistance of biofilm-associated organisms to antimicrobial agents (28, 29, 36, 37).

These infections are also typically complicated by the formation of bladder and kidney stones (urolithiasis) developed from mature urinary crystals. Bacterial urease activity (ability to hydrolyze urea into carbon dioxide and ammonia) introduces ammonia into the urine and thereby raises the pH and initiates the precipitation of anions and cations, resulting in the formation of struvite (MgNH3PO4) or apatite (CaPO4) crystals (38). These crystals can become embedded in the biofilm material and create crystalline biofilm structures that often cause encrustation of the catheter and block urine flow. This resulting urinary blockage, as well as the presence of mature stones, pose a serious risk to patients as they have the potential to cause permanent renal damage and may progress to life-threatening bacteremia and sepsis (1, 39-41).

Therefore, once a CAUTI is diagnosed, it is recommended that the catheter be fully removed or replaced by a new catheter and followed by systemic antibiotic treatment (42, 43). There are different diagnostic criteria depending on the patient population, but diagnosis usually involves having 2 or more signs and symptoms of infection, such as: hematuria (blood in urine), fever, suprapubic or flank pain, acute change in mental status with leukocytosis (higher than normal white blood cell count), and hypotension (low blood pressure) (44). Initial empiric antibiotic therapy can be broad spectrum, however the following need to be considered: factors that increase the risk of drug resistance, prior antimicrobial agents, and local resistance patterns (4, 45). Antibiotic selections should of course be further optimized after receiving culture and susceptibility results (43). Treatment duration should also be limited to 7 to 14 days, depending upon treatment response (46). The success of antibiotic therapies is however being challenged due to the emergence and rapid increase of multi-drug resistant (MDR) bacterial strains (47-50). If treatment fails, unresolved CAUTIs can lead to the onset of secondary bloodstream infections, which results in further morbidity and mortality (34-38). Therefore, the discovery of new therapeutic strategies for CAUTI is critical to successfully reduce poor outcomes and mortality.

However, treatment is also limited by the presence of the biofilm causing recurrence of infection. Bacterial cells within biofilms can be up to 1000 times more resistant to antimicrobial insult than their planktonic counterparts (51). Thus, while antibiotic therapy may successfully eliminate planktonic bacteria, the surviving biofilm can then shed and disperse additional planktonic cells, resulting in a cycle of recurrent acute infection which is difficult to eradicate (19-22). Therefore, ongoing research in the field should take a combinatorial approach, including administration of universal standard preventative practices in health care settings, the discovery of new therapeutic treatments, as well as the discovery of novel strategies for the prevention of bacterial biofilm formation on catheter surfaces and for the disruption of existing biofilms.

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A NEW STANDARD FOR AIR

Fully Scalable Advanced Air Sterilization System

The only technology on the market with Military Grade Air-Sterilization with an effectiveness of 99.9999% (6-log kill).

SteriSpace uses a patented compressive heating technology to eliminate airborne biological pathogens, such as bacteria, viruses, and hardy bacterial spores in an airstream.

SteriSpace Applications

- **Military BioSafety and BioSecurity**
- **Educational Institutions**
- **Industrial & Commercial shelters**
- **Healthcare Facilities**

SteriSpace

SteriSpace®

In 2021, You First Services expanded its Air Sterilization Program to include the extensive design and development of scale-up SteriSpace units with flow rates of 1200 CFM and 5000 CFM to address airborne contamination in larger volume spaces. The development and testing of the 1200 CFM SteriSpace unit is forecasted to be complete by the end of the 2021 calendar year, closely followed by the completion of the design and development of 5000 CFM SteriSpace unit. The scale-up SteriSpace units will offer more cost-effective solutions in larger industrial and commercial applications.

The YFS team attended the Army USA conference in October 2021, and has made in-roads with a large military prime contractor to provide complete, joint, turnkey solutions against biological agent decontamination to address biosecurity and biosafety. The capability of the SteriSpace technology with its highly effective kill-rate of 99.9999% against biological threats, has been recognized as the "missing piece of the puzzle" in military Chemical, Biological, Radiologic and Nuclear (CBRN) defense.

You First Services is working towards including SteriSpace as part of the "requirements" in military defense to eliminate biological threats. SteriSpace will be part of a turnkey solution that currently offers CBRN Air Filtration Systems, Patient Isolation Shelters, Environmental Control Units (ECU) and Command and Control/Tactical Operation Integration Systems. Continued collaborations with military prime contractors will result in the integration of SteriSpace in Military Hospital Systems, Expeditionary Military Systems, Terrestrial Military Applications as well as Biological Safety Labs (BSL) within the Contiguous United States (CONUS) and Outside Contiguous United States (OCONUS) and anywhere potentially contaminated air streams exist.

GloTran®

Department of Veterans Affairs– Federal Supply Schedule: Contract Award

Effective November 1, 2021, GloTran Hydrogen Peroxide Gas Plasma Disinfection System was awarded a 5-year contract under the Federal Supply Schedule with the Department of Veteran Affairs. This Contract Award will include the VA as well as other federal agencies, state, and local governments, including tribal governments and educational institutions.

You First Services, Inc. will now diligently continue its efforts to support the VA Healthcare System to maximize resources and combat rising healthcare costs, by reducing waste and implementing the reuse of non-critical medical devices by safely and effectively disinfecting with GloTran.

Lubricity®

Marketing efforts for Lubricity – our pioneer dry mouth remedy, is now paying dividends with growth in both online and distributor sales. We expect exponential growth as we rigorously penetrate the Dental Service Organizations (DSO) and continue our efforts to collaborate with large dental and oncology and other healthcare distributors.

You First Services, Inc. received Program Approval for Continuing Education (PACE) by the Academy of General Dentistry (AGD) to offer quality dental education designed to improve the overall dental health care of the general public. The YFS team is currently developing the curriculum to offer CE credits for calendar year 2022.

MetaQil®

MetaQil is the only product on the market today, scientifically-designed to relieve taste disorders especially metallic taste – a common symptom experienced by patients undergoing cancer chemotherapy. Today, the You First Services team has successfully penetrated the Oncology market by introducing MetaQil to Oncology Centers nationwide, through an extensive Sample and Referral Program. In 2022, we hope to include MetaQil as part of the 'Standard of Care' protocol.

Additionally, You First Services has partnered with the American Cancer Society to launch MetaQil into their Hope Lodge charitable project. We continue to nurture the efforts of the American Cancer Society by bringing MetaQil to patients undergoing active chemotherapy.

Teeth Chatters PODCAST

We are excited to announce about the launch of podcast. TEETH CHATTERS where we chat about Oral Health & Systemic Health.

To commemorate World Arthritis Day and we have our first episode live:
https://lubricityinnovations.com/teeth-chatters-podcast/
Please take your time to visit our landing page and listen to the podcast. It is QUITE interesting...

ASSOCIATION OF THE UNITED STATES ARMY

Voice for the Army - Support for the Soldier

The Association of the United States Army (AUSA) held their annual meeting in Washington, DC from October 11th – 13th and it was attended by Dr. John Lordi, Dr. Himashini Perera, and Danny Forcucci. Further support from Joe Healy and Laura Cecala in the Sales Department made the tradeshow highly productive. The team at the show ended up having numerous in-person meetings with prospective contractors, some of which manufacture military shelters and are interested in integrating SteriSpace into their shelters to protect personnel from biological threats given the hostile environments where the shelters are deployed. During the tradeshow our team had virtual meetings from the corporate office with AUSA prospects who were not able to attend the show. Also, during the meeting Sean Dwyer and Hope Dunkleman in the Marketing Department conducted a geo-fencing campaign whereby everyone in the convention center were served SteriSpace advertisements on their cell phones. Our sales team is orking towards executing partnership deals with many organizations.

Lung Force

You First Services, Inc. participated in September's Lung Force Walk, with two of its products, SteriSpace and Lubricity, serving as event sponsors. The annual walk is one of American Lung Association's signature fundraising events, allowing its participants to raise awareness and funds to help defeat lung cancer and for lung health. The walk took place at Buffalo's Outer Harbor with over 200 people showing their support. The event functioned as a great way for YFS to reach out to the community of WNY. As a team, You First Services raised over $1,200 for the American Lung Foundation.

Our company shares the American Cancer Association's focus on air quality and the treatment of lung disease, making SteriSpace and Lubricity participation in this year's event the perfect way of helping both organizations realize these goals.

Aheimer's Association Walk

Alzheimer's is both a painful disease to not only go through but watch your loved ones endure. You First Services' Oral Healthcare products Metaqil and Lubricity are formulated to help ease some symptoms of this awful disease. Some medications can have a side effect of dry mouth or a bad metallic taste. YFS products help alleviate this annoyance from their ever-complicated lives.

Just under 1,500 people were in attendance for this walk at Buffalo's Outer Harbor on September 18, 2021. Our team was successful in building community brand awareness by distributing many product samples and gathering contact information for our growing contact list! As a company, we donated $2,324 to the Alzheimer's Association from team fundraising and others proceeds going directly to the foundation.

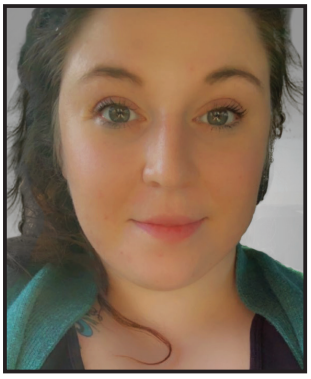
Getting the community to know about these helpful products that are right in their backyard is something that is a big push for YFS right now. Stay tuned for more YFS Holiday WNY Community Outreach efforts!

Welcome New Employees

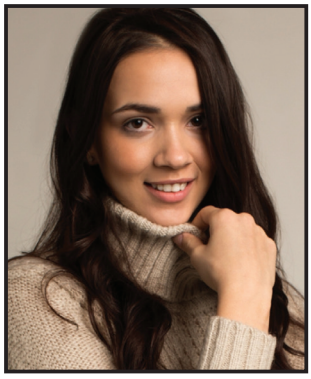
Lamont Humphrey
Quality Assurance & Regulatory Affairs Manager

Dan Forcucci
Director of Sales and Business Development

Laura Martin
Accountant

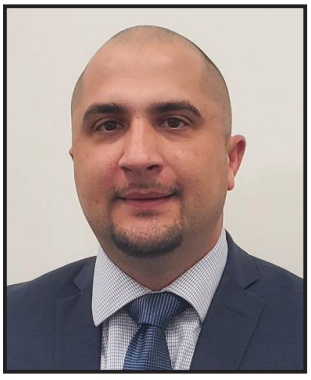


Hannah Vail
Quality Control Chemist



Vasilisa Mirinova
Digital Marketing Manager

Sara Juliano
Brand Ambassador



Indi Kormaku
Manager, Business Development and Marketing

Sean Dwyer
Marketing Manager

Hope Dunkleman
Digital Marketing Specialist