Infections in long-duration space missions

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As government space agencies and private companies announce plans for deep space exploration and colonisation, prioritisation of medical preparedness is becoming crucial. Among all medical conditions, infections pose one of the biggest threats to astronaut health and mission success. To gain a comprehensive understanding of these risks, we review the measured and estimated incidence of infections in space, effect of space environment on the human immune system and microbial behaviour, current preventive and management strategies for infections, and future perspectives for diagnosis and treatment. This information will enable space agencies to enhance their comprehension of the risk of infection in space, highlight gaps in knowledge, aid better crew preparation, and potentially contribute to sepsis management in terrestrial settings, including not only isolated or austere environments but also conventional clinical settings.

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Introduction

As private corporations and governmental space agencies plan long-duration spaceflights to the Moon and Mars, understanding the physiological effects and medical risks of such missions is becoming increasingly pressing. Such missions present substantial challenges for maintaining the health and wellbeing of crew members owing to isolation, delayed communications, scarce resources and on board medical skills, shortages in consumables, and exposure to the space environment, radiation, and microgravity.[1–3]

Among the medical conditions that threaten astronauts during long-duration space missions beyond low Earth orbit, sepsis and infections have the highest negative effect on mission success and are associated with some of the lowest survivability.[1,4–6] The risk of infections is increased in space because of multiple factors, including environmental contamination, changes in microbial behaviour, and a weakened immune system, and indeed, serious infections have historically occurred on multiple occasions during spaceflight.[3,4,7]

During spaceflight, even minor illnesses that have minimal effects on Earth can have substantial consequences. For example, simple upper respiratory infections can lead to mission delays, considerable costs, and reduced crew wellbeing and performance, potentially resulting in premature termination of the mission or loss of crew life.[7] However, understanding of the risk of infection in spaceflight and the steps that can be taken to mitigate these conditions remains limited.[1,7,8]

Therefore, we prepared a comprehensive narrative Review in accordance with PRISMA guidelines aiming to consolidate the existing knowledge about the risks of infections encountered during space missions, with a focus on future long-duration interplanetary expeditions to the Moon and Mars. Our search algorithms are provided in the appendix p 1 and the study selection is shown in figure 1. We synthesised the current data on alterations observed in the immune system and microbial behaviour in the unique microgravity and radiation environment of space. Additionally, we highlight current and future perspectives related to the prevention, diagnosis, and treatment of infections in space. Beyond having direct applicability in space medicine, this Review could improve the understanding and management of infections on Earth, particularly in austere and isolated environments.

Measured and expected risks during spaceflight

The incidence of infections in space is increased when compared with that in terrestrial settings, owing to a combination of factors summarised in figure 2.[7,8]

Measured incidence of infections in historical spaceflight

Approximately 620 people have flown to space to this date, for missions ranging from a few minutes to 437 days. Currently, most missions are flown on board the International Space Station (ISS), which is a large laboratory orbiting Earth at an altitude of approximately 250 miles and a speed of 17 500 miles per h. In the history of spaceflight, instances of severe medical events, including infections, have been recorded. In the 1970s and 1980s, three station evacuations were conducted owing to suspected appendicitis, prostatitis, and dysrhythmias.[9] A study of symptoms across 46 long-duration ISS missions (totalling over 20 flight-years) reported an incidence of 12 (all minor) events of infections, which represent an overall estimated rate of 0·6 events per person per flight-year.[10]

Proliferation of opportunistic bacteria is a concern, with crew members, food, and personal items being the most common sources of pathogens on board.[10–12] Viral reactivation is also widely reported in astronauts. For example, one study revealed that viral shedding of at least one herpes virus (which include cytomegalovirus, Epstein-Barr virus, herpes virus, and varicella-zoster virus [VZV]) in the saliva or urine affects 53·0% of astronauts during short-duration spaceflights and 61·0% during long-duration ISS missions.[12] Recently, the risk of reactivation of SARS-CoV-2 and severe COVID-19 infection in space was also described.[13] Stress-related chronic activation of the hypothalamus-pituitary-adrenal and sympathetic-adrenal-medullary axes (leading to glucocorticoid release) are hypothesised to be partly responsible for the decreased cell-mediated immunity in these conditions.[12]

For **PRISMA guidelines**, see https://www.prisma-statement.org/

See Online for appendix

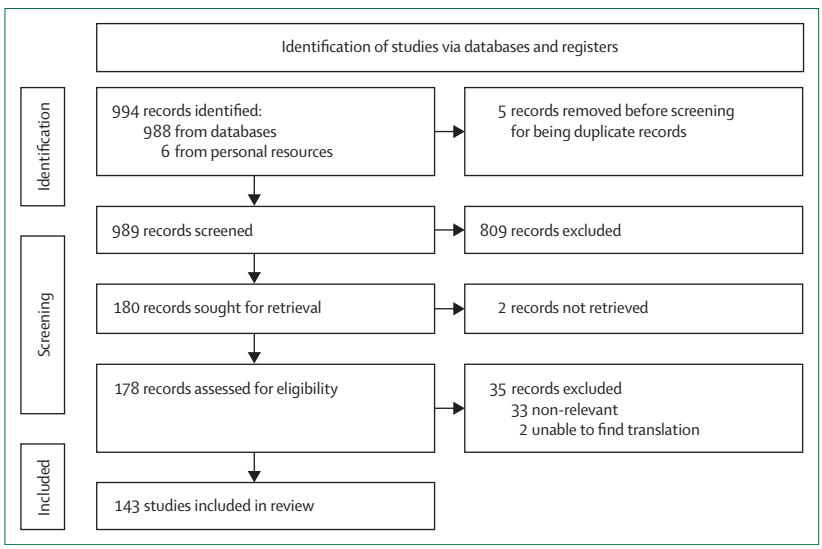

Figure 1: **PRISMA flow diagram for inclusion or exclusion of articles**

Expected incidence during long-duration space missions in the future

Moon missions as part of the National Aeronautics and Space Administration (NASA) Artemis programme include 30-day missions, with two crew members remaining in lunar orbit and two others exploring the surface. Mars missions outlined in the (now cancelled) NASA Constellation programme included 900-day six-person crew missions. The medical risks associated with long-duration interplanetary spaceflights of the future have been discussed by several expert panels.[5] For example, Tran and colleagues listed the ten conditions of highest concern for space operations, among which sepsis ranked eighth.[6] Robertson and colleagues estimated that sepsis and infections have some of the lowest survivability (ranked 25th among 30 conditions) and highest negative effect on the mission (ranked first of 30 conditions).[1]

The probability of medical events most likely to occur during such future missions can be estimated by examining large case series from ground-analogue populations and military and civilian populations and using the data collected over 150 person-years of accumulated spaceflight experience.[9] For example, the risk of acute appendicitis is 1–2 per 100 000 person-days, which would be equivalent to 1–2 cases every 45 years for a six-person space crew.[4] Overall, the estimated incidence of infection events during a 950-day six-crew Mars mission could be as high as 90, with respiratory, skin, and subcutaneous tissue infections topping the list.[5]

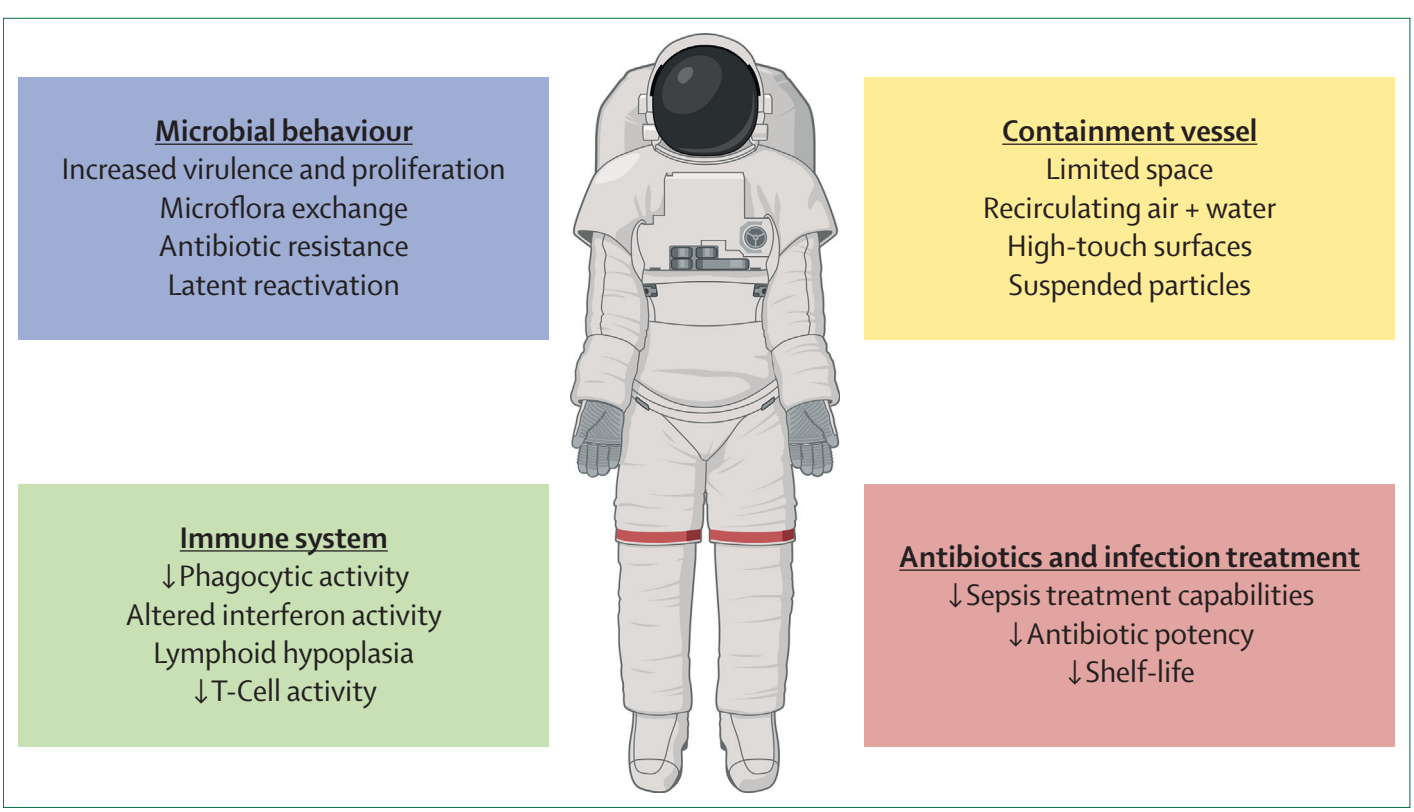

Figure 2: **Summary of key factors that contribute to increased risk of infections in the space environment**
The factors have been categorised in terms of the features of the spacecraft environment, changes in microbial behaviour, the immune system, and treatment capability. The figure has been generated using BioRender (https://biorender.com/).

The human immune system in space

Overview of the immune system

The human immune system can be divided into two branches—innate immunity, which is characterised by non-specific cellular responses; and adaptive immunity, which is characterised by immunological memory and specific cellular reactions.[7] The innate immune system involves rapid-response cells such as neutrophils, mast cells, eosinophils, and basophils and soluble components such as complement and acute-phase proteins. Adaptive immunity can be further subcategorised as cellular immunity, involving T-cell responses, and humoral immunity, involving B-cell and antibody activity. Cytokines, such as interferons, interleukins, and growth factors, are biological molecules that are secreted by some immune cells to establish a specific response from other cells. Immunity requires a careful balance: autoinflammatory or autoimmune conditions can arise when immune activity is high, whereas an immunocompromised state can follow when immune activity is low.[3,7] Spaceflight can alter the immune system to induce either of these states—an elevated innate response or an impaired adaptive response, or both (figure 3).[7,14–16] For instance, the NASA Twins Study, conducted during a 1-year mission on the ISS, revealed substantial variations in gene expression patterns related to immune response pathways, DNA methylation patterns controlling T-cell responses, and plasma cytokine signatures, indicating reduced cellular responsiveness and increased inflammation.[14–16]

The following sections describe how the various components of the immune system are affected by spaceflight.

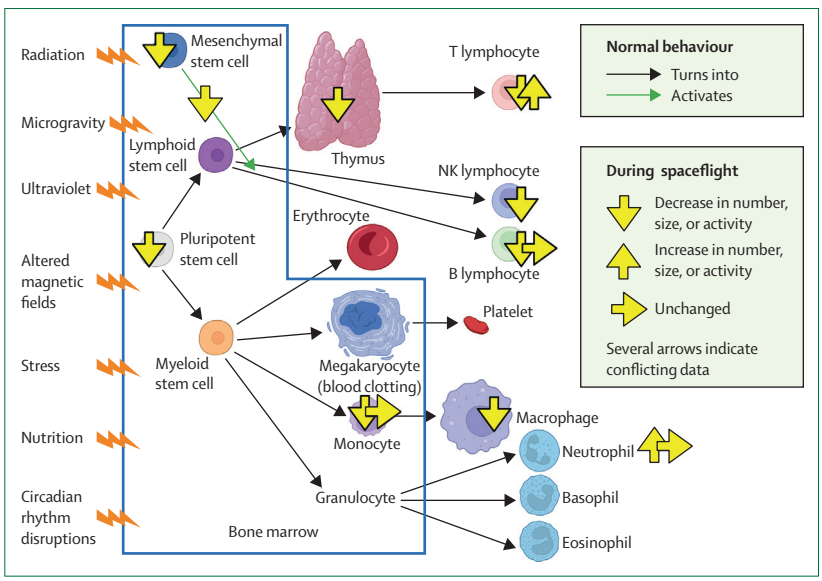

Figure 3: **Summary of changes observed in the immune system in space environment**
During spaceflight, cellular and innate immunity display observable changes, mostly marked by decreased function, whereas changes in humoral immunity are less clear. The figure has been generated using BioRender (https://biorender.com/).

Lymphoid organs

Lymphoid organs are the sites of production and maturation of lymphoid and myeloid cells. These are divided into primary lymphoid organs (bone marrow and thymus) and secondary lymphoid organs (lymph nodes, spleen, tonsils, and some tissues in mucous membrane layers such as the intestine). Maturation of stem cell precursors into lymphocytes is controlled by interactions in the bone marrow environment, involving cells such as mesenchymal stem cells.[17] During spaceflight, the numbers of murine bone marrow haematopoietic stem and progenitor cells decrease.[18] Simulated microgravity is associated with inhibited proliferation of murine mesenchymal stem cells and reduced gene expression of CXC motif chemokine ligand 12 (CXCL12) in human mesenchymal stem cells.[19] Both these factors most likely contribute to the observed impaired activity of haematopoietic stem cells. The thymus is known to undergo atrophy in spaceflight, possibly due to an increased glucocorticoid stress response.[17] In turn, this cellular disruption might contribute to the observed reduction in the function of T cells.[7,14]

Overall changes in leukocytes

Multiple studies in animals and humans have indicated that white cell counts change substantially in space, with some conflicting data.[7,16] Blood samples taken from ten cosmonauts who were 150 days into spaceflight showed an increase in their relative count of lymphocytes, but no changes in the relative counts of neutrophils and monocytes.[16] Contrastingly, blood samples taken from a single ISS crew member across 191 flight-days showed a steady reduction in the overall white cell count, with specific reduction in the neutrophil, lymphocyte, and monocyte subsets.[7] Of note, however, the white cell count rebounded to the preflight levels in the phase immediately after landing,[7,16] which is possibly secondary to the stress response to re-entry and landing.[16] The effects of non-ionising radiofrequency radiations (used in spacecraft communication systems) on the immune cells remain under active investigation.[20]

Phagocytes and innate immunity

Innate immunity is characterised by a non-specific cellular response to invading pathogens. The primary goal of innate immunity is to directly destroy the pathogen while initiating the generation of memory B and T cells for faster responses to future infections.[3] Phagocytes are a type of innate immune cells and include neutrophils and monocytes, which can migrate to peripheral tissues and mature into macrophages.

After spaceflight, neutrophils display elevated activity and highly exacerbated secretion of proinflammatory cytokines in response to fungal antigen stimulation.[16] The proliferation rate and absolute number of murine macrophages, in addition to murine monocyte-to-macrophage differentiation, appear to decrease in spaceflight.[21] Altered precursor cell activity can underlie these effects, as research using murine bone marrow cells suggests that spaceflight can affect precursor cell responses to macrophage colony

stimulating factor, ultimately contributing to the reduction in the numbers of some blood cell types, including macrophages.[22]

B cells

B cells play a crucial role in producing antibodies that enable the immune system to respond rapidly to secondary infections, reactivation of viruses, and vaccine responses. However, the effect of spaceflight on humoral immunity, specifically B cells, is less explored than its effects on innate immunity. The B-cell count seems to remain unaffected in space.[23,24] However, the concentration of IgA in the serum, which is associated with mucosal defence against pathogens, increases during spaceflight, as compared with the preflight values,[24] which could indicate a response to pathogen exposure through mucosal surfaces, such as the shedding of latent herpes virus by other crew members.[12,25]

T cells

T cells have diverse functions within the immune system.[7] These cells are crucial facilitators of B-cell function, leading to antibody production and recognition of re-infecting organisms. T cells can be subdivided into $CD8^+$ T cells, which are responsible for the cytotoxic killing of pathogens, and $CD4^+$ T cells, which are responsible for interacting with other components of the immune system.[7]

$CD4^+$ T-cell proliferation, function, and cytokine expression is negatively affected by spaceflight.[7,14,17] In contrast, the absolute number of cytotoxic $CD8^+$ T cells increases during and after spaceflight.[7,14,16] These $CD8^+$ T cells display reduced function, particularly against cytomegalovirus and Epstein-Barr virus, which are hypothesised to contribute to the pathophysiology underlying the reactivation of herpes viruses.[12]

γδ T cells constitute a subgroup of T cells that is crucial for stimulating inflammatory reactions in both lymphoid and myeloid cell lineages. These cells play a pivotal role in the initial stages of both the inflammatory and immune responses, through multiple molecular pathways. Unlike their αβ T-cell counterparts, γδ T cells do not rely on MHC molecules for recognising exogenous and tumour antigens.[26] As a result, γδ T cells are classified as innate immune cells. A 45-day head-down bed rest study reported an increase in γδ T cells from 29·0% to 35·0%, suggesting an enhanced inflammatory and immune response.[26]

Regulatory T cells are a subtype of $CD4^+$ T cells that can mediate immune tolerance through a multitude of immunomodulatory mechanisms, such as promoting the suppression of conventional T cells.[7,14] Simulated microgravity appears to enhance regulatory T-cell function, suggesting an enhanced immunosuppressive response.[27]

Soluble markers of immunity

A study on 13 astronauts on board the ISS showed increased plasma concentrations of cytokines such as IL-3, IL-7, and IL-15.[28] IL-3 is secreted by T cells and promotes the proliferation of myeloid lineage cells, such as granulocytes; IL-7 is integral to T-cell and B-cell development; and IL-15 causes proliferation of natural killer cells;[28] these markers point to a state of inflammation during spaceflight. Another potential biomarker for immune competency during spaceflight is cell-free mitochondrial DNA. The NASA Twins Study confirmed that cell-free mitochondrial DNA increased during the 1-year flight, thus proposing it as a marker of physiological stress.[29] This conclusion was supported by analysing blood samples of 14 astronauts who were on short-duration missions.[30]

Microbial behaviour in space

Of the more than 100 bacterial strains and over 30 filamentous fungal species isolated inside the ISS,[31,32] those of potential concern for human health were identified as *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Serratia marcescens*, and several representatives of the *Bacillus*, *Mycobacterium*, and *Aspergillus* genii.[3,31,33]

Cosmic radiation, microgravity, increased solar ultraviolet radiation, altered gravity field, vast temperature gradients, and the vacuum environment are typical conditions associated with spaceflight (figure 4).[1,3,34] Upon exposure to these conditions, microorganisms transferred from Earth to spacecrafts can undergo many physical and behavioural alterations, also known as bacterial adaptive response.[7,34–36] Additionally, the non-ionising radiofrequency radiation (used, for example, in telecommunication systems) increases the antibiotic resistance of bacteria.[37]

The two main sources of ionising radiation in deep space are galactic cosmic radiation (highly energetic particles, primarily protons and heavy ions, originating from outside the solar system, sometimes abbreviated as HZE for high [H] atomic number [Z] and energy [E]) and solar particle events (sudden bursts of solar radiation, primarily consisting of high-energy protons, electrons, and alpha particles). The effect of these radiations on microorganisms depends on several factors, with linear energy transfer (the energy transmitted by a charged particle on a unit length track) being one of the key parameters, along with dose and duration of exposure.[38] These two types of ionising radiations induce their mutagenic and toxic effects on human cells and microorganisms through direct DNA damage and indirect mechanisms (generation of free radicals).[39]

Some microorganisms can survive in the vacuum of space for years, and vacuum has intrinsic mutagenic properties.[39,40] The concern is that these microorganisms could again come in contact with spacesuits during spacewalks, be brought back into the space stations or habitats, and potentially affect human health.

Furthermore, the unique selection pressures in enclosed spacecraft environments with many high-touch surfaces and recirculation of air and water can contribute to increased microbial mutations and exchange of genetic material across species.[7,34,41–43] Altogether, these changes could potentially modify gene expression, reproduction rate, virulence, morphology, antibiotic resistance, biofilm

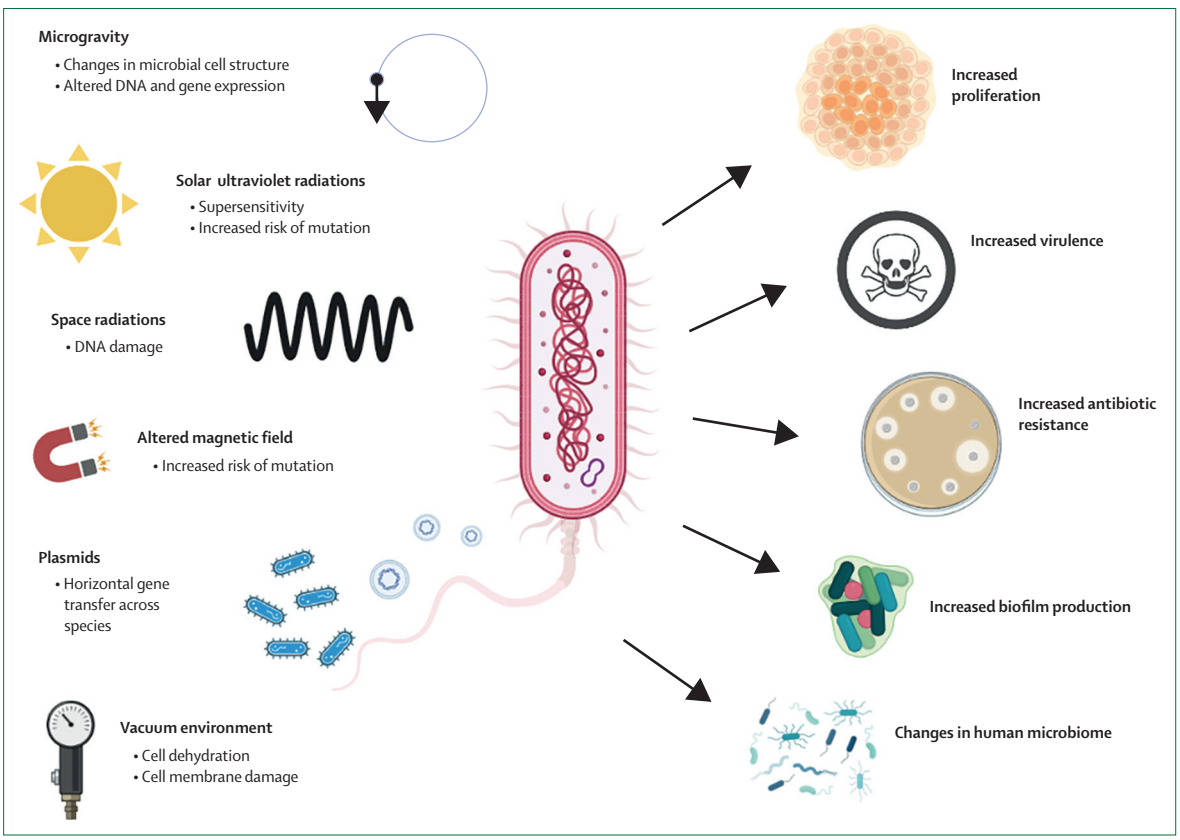

Figure 4: **Effects of spaceflight on microorganisms**
Cosmic radiation, microgravity, increased solar ultraviolet radiation, altered gravity field, vast temperature gradients, horizontal transfer of genetic material across species, and the vacuum environment can affect the microorganisms present inside spacecrafts. These factors can modify gene expression, the reproduction rate, virulence, morphology, antibiotic resistance, biofilm formation, and secondary metabolism of bacteria and fungi, thereby increasing the risk of infections. The figure has been generated using BioRender (https://biorender.com/).

formation, and secondary metabolism of bacteria and fungi in the space environment.[3,34,38]

Increased virulence

Increased virulence was reported, for example, in isolates of the fungus *Aspergillus fumigatus* obtained from the ISS, which were shown to be significantly more lethal than the controls for a larval zebrafish model.[44] Similar results were observed for the bacteria *Serratia marcescens* in a fruit fly model[45] and for *Salmonella enterica* serovar Typhimurium in a murine model.[46]

Increased proliferation

Studies have indicated increased growth and biomass of microorganisms in space,[3,33,34,47] including those of strains of *A fumigatus* and *Aspergillus niger* isolated from the ISS.[32,33] Microbial reproductive patterns in space have a reduced lag phase, amplified exponential phase, and substantially higher stationary concentration.[39]

Increased biofilm production

Biofilms are communities of bacteria and yeasts that grow on surfaces, embedded in a self-produced matrix.[7] Microbial cells are often more resistant to antibiotics and antifungals than those that are not present in biofilms.[34] Spaceflight can enhance the formation of biofilms in some microorganisms, which is thought to be DNA damage related,[31,34,48] and indeed, biofilms have been found in substantial quantities in space stations.[7,34] Besides the risks posed to human health, several studies have also highlighted the capability of microorganisms in biofilms to infiltrate spacecraft systems and affect their structural integrity.[3,49,50] The accumulation and adaptability of microorganisms during longer missions further exacerbate the dangers that the microorganisms present to both astronauts and spacecraft machinery.[36]

Increased antibiotic resistance

Numerous studies have highlighted rising antibiotic resistance in space, which could be secondary to genetic mutations and horizontal gene transfer across species.[34] For example, measurements carried out in the 1980s indicated that the minimum inhibitory concentrations against *S aureus* for some antibiotics doubled in spaceflight as compared with those observed in the ground controls.[51] Schiwon and colleagues investigated bacterial isolates

from both the ISS and Antarctic research station in Concordia, Antartica.[52] Although the bacterial species identified at both the locations were highly similar, 25 (86·2%) of 29 ISS isolates displayed resistance to one or more antibiotics, whereas only 24 (43·6%) of 55 Antarctic isolates displayed such resistance. Additionally, 25 (86·2%) of 29 ISS isolates carried relaxase or transfer genes encoded on plasmids, or both, which can facilitate the transfer of antimicrobial resistance genes between microorganisms.[52]

A study examined the transcriptomic response of *Escherichia coli* cultured aboard the ISS and exposed to varying levels of gentamicin.[41] A comparison with control samples on Earth revealed that the space-flown bacteria displayed enhanced adaptation to higher antibiotic concentrations. This adaptation was characterised by the upregulation of over 50 genes related to stress response, oxidative stress, and starvation.[41]

Changes in the human microbiome

The human gut microbiome plays a crucial role in shaping physiological responses and immune function.[53,54] However, spaceflight has been linked to changes in the gut microbiome.[15,34,55,56] To mitigate these changes, astronauts currently receive probiotics.[14,34] The skin microbiome is also subject to changes in spaceflight. The *Malassezia* species, which is thought to be the causative organism of seborrheic dermatitis, has repeatedly been shown to increase in number during spaceflight.[57] The isolated and unique ISS environment also contributes to skin microbiota changes; exchange of bacteria between crew has been observed in addition to astronaut skin microbiomes resembling those of ISS surfaces.[57] Additionally, fibroblasts, the cells partly responsible for skin healing, display impaired migration under simulated microgravity conditions, which can leave damaged skin exposed to the environment;[58] an effective in-vitro countermeasure is platelet-rich plasma, which contains growth factors and cytokines from platelet granules.[58]

Current preventive and prophylactic measures against infections

Space agencies maintain stringent medical standards for astronauts. NASA, for example, implements various prophylactic measures, including vaccinations; preflight quarantine; preflight physical conditioning; inflight nutritional, behavioural, and psychological countermeasures; and regular monitoring, to optimise astronaut health.[7,8,14]

Measures for controlling infections are strictly enforced on board the ISS as well to minimise the risk of contamination. These measures include hand hygiene and regular disinfection of high-touch surfaces.[8] A continuous high-efficiency particulate air filtration system is also in place on board the ISS to reduce the risk and transmission of infections.[7,8,14] Recycled water is filtered and sterilised to a high standard.[7,14] To prevent the adverse effects of vitamin deficiency, particularly on the immune system, astronauts receive multivitamin supplements, probiotics, and a functional enriched diet that is supplemented in omega-3 fatty acids, minerals, antioxidants, polyphenols, and flavonoids.[14,34,59] Vitamin A deficiency, for example, can hinder optimal cell-mediated immune responses.[60] Vitamin D plays a role in the Toll-like receptor response pathway of phagocytosis.[61] Regular exercise of moderate intensity is also encouraged among astronauts as it promotes better immunity, in particular, reducing the risk of latent virus reactivation.[62,63] For deep space missions, astronauts are recommended to undergo a preflight screening for herpes virus serology. If the astronauts test positive for VZV, then the VZV Shingrix vaccine is administered to them to minimise the risk of latent reactivation.[59] Since 2013, use of Zostavax for VZV in astronauts as a prophylactic countermeasure has resulted in reduced VZV reactivation in spaceflight.[64] Moreover, inflight influenza vaccine response showed no substantial difference in the measured immune response inflight and the response on Earth.[15] This research opens new avenues for potential inflight preventive vaccine countermeasures.

Management of infections in space

Infection diagnosis

On board medical skills and resources are scarce in space, which poses challenges for diagnosing and managing medical conditions, including infections.[1,65] Telemedicine, which allows remote medical consultations and guidance, is extensively used in current spaceflight operations, but is only available in real time, within the immediate vicinity of Earth.[65,66] During missions to Mars, communication delays between Earth and the spacecraft can reach up to 20 min in each direction, making real-time communication and guidance impossible.[65,66] Besides clinical examination, additional diagnostic modalities are limited in space.[65] Although simple point-of-care blood analyses are available on the ISS, non-routine laboratory tests, such as those for inflammatory markers and cytokine panels and blood cultures, are currently challenging.[65,67] Imaging capabilities in space are also constrained, with ultrasound being the primary modality available.[68,69]

Antimicrobial agents

Antibiotics show decreased potency and reduced shelf life in space, when compared with that under Earth conditions.[70] For instance, a study showed that the clavulanate in amoxicillin–clavulanic acid lost 50·0% of its potency by day 534 in space.[70] This observation is especially of concern given the increased antibiotic resistance reported in multiple microorganisms, which we discussed in a previous section ("Increased antibiotic resistance"). In contrast to bacterial infections, viral infections typically resolve without intervention. However, whether specific antiviral treatments are necessary for prophylactic or curative purposes in the context of space-induced immunosuppression remains uncertain.[14,71] A case report of an astronaut who received valaciclovir inflight for a cold sore outbreak is published.[64]

Sepsis management in space

Severe infections can progress to sepsis, a condition characterised by hypovolemia, vasoplegia, and organ dysfunction. Managing sepsis in space would present substantial challenges due to factors such as microgravity-induced physiological changes, scarce equipment and supplies, and constraints in terms of the technical skills of the crew.[1,2,9,72] The administration of large volumes of intravenous fluids, a key aspect of sepsis resuscitation, is also unlikely to be feasible owing to stowage restrictions.[65] To address this limitation, a prototype device capable of generating intravenous fluids from on board drinking water was tested inflight in 2011.

Extended exposure to microgravity affects the cardiovascular system, leading to absolute and relative hypovolemia, reduced systemic vascular resistances, decreased maximum oxygen consumption (VO_{2max}), and potential alterations in cardiac function.[72] Furthermore, adrenergic receptors are also affected, with decreased sensitivity of alpha adrenergic receptors.[9,72] These changes have implications for the haemodynamic management of astronauts with sepsis, particularly when the astronaut requires administration of alpha agonist vasopressors such as adrenaline, noradrenaline, or phenylephrine.

To meet the oxygen supply needs for conditions such as pneumonia, concentrated oxygen could be generated using an on board concentrator, eliminating the need for bulky oxygen tanks.[65] In severe cases of sepsis, providing invasive and sustained organ support would prove to be highly challenging and be associated with a low likelihood of survival. However, invasive interventions such as mechanical ventilation, peritoneal dialysis, and vasopressor infusion could theoretically be considered.[9]

Future perspectives for infection prevention, diagnosis, and treatment

Potential preventive measures

Efforts are underway to explore pharmacological and non-pharmacological interventions that can modulate the immune system in space.[14,59,73] β Blockers, for example, can help to counteract the adverse immune consequences of sympathetic nervous system activation during spaceflight.[14] However, caution is advised before using immune system enhancers in space, as these drugs precipitate hyperactivation and autoimmunity in a dysregulated immune system.[73]

Preventive measures for surgical infectious conditions have also been investigated, including prophylactic surgeries such as appendicectomy and cholecystectomy.[4] Personalised administration of probiotics and faecal transplantation are other approaches that are being considered, as these approaches have shown promise in enhancing weakened immune responses and protecting astronaut gut flora.[55,59,74] Additionally, novel vaccination against specific bacterial strains such as *Pseudomonas aeruginosa* could be explored.[75]

Finally, cardiovascular deconditioning (which could precipitate haemodynamic instability in sepsis) is a primary concern of operational space medicine.[9] To mitigate this concern, the concept of generating (partial) artificial gravity through centrifugal force in rotating modules of the spacecraft has been proposed.[76]

Improving antibiotic availability and effectiveness

Enhancing antibiotic availability and effectiveness is crucial for managing infections during long-duration space missions in the future.[70] One potential approach is to generate antibiotics in situ during the mission, using bacterial cultures and precursor molecules.[77] Next, genomics-based approaches can provide rapid testing of bacterial samples to identify their susceptibility or resistance to specific antibiotics, rather than relying on conventional antimicrobial susceptibility testing.[78,79] Finally, nanotechnology has the potential to improve the bioavailability and effectiveness of antibiotics in space. For example, nanomaterials could protect antibiotics from degradation or enable the antibiotics to be delivered more efficiently to targeted areas by overcoming biofilm barriers.[80]

Intelligent medical systems

Integrating artificial intelligence (AI) into medical equipment can enhance on board medical expertise and provide diagnostic and therapeutic support for astronauts. For instance, AI-enabled ultrasound devices improve image acquisition, interpretation, and expand the range of applications of these devices.[81] These devices can automatically assess cardiac function and fluid volume status and detect abnormalities in lung ultrasound, in addition to offering real-time guidance during invasive procedures, such as regional anaesthesia or vascular access.

AI-based decision support systems can offer personalised recommendations for diagnosing and managing various conditions, including infections and sepsis, by utilising physiological modelling and analysing large volumes of routinely collected medical data.[2] These systems can predict sepsis, patient deterioration, and the need for admission to intensive care unit or mechanical ventilation and provide guidance on optimal management strategies.[2,82] Large language models can be useful for space health, supplementing the expertise of the crew with on-demand advice during emergency medical scenarios.[83]

Along those lines, a recent NASA publication highlighted the basic requirements for a precision space health system, a concept of an AI-driven space health infrastructure for space exploration missions of the future that is aimed at providing "predictive, preventative, participatory, and personalized" medical care to crew members.[2] Existing AI systems could be repurposed and novel algorithms, app, and models specific to space needs could be developed to achieve this vision.[2] For example, closed-loop AI systems that optimise the haemodynamic status in the perioperative period or intensive care unit could be adapted for space missions.

Search strategy and selection criteria

We searched the bibliographic databases PubMed and Google Scholar for articles published between Jan 1, 1970, and March 25, 2024. Search terms were related to the themes spaceflight, space medicine, space analogue environments, microgravity and microgravity models, infections, and the immune system. The specific search terms were a combination of the keywords "infection", "sepsis", "immunity" and "space", "spaceflight", or "astronaut". We considered in-vitro studies, human and animal research, journal articles, reviews, case reports, books and book chapters, and reports in English and French. We also examined publications from the NASA Technical Report Server, and from the authors' personal resources.
All authors individually screened the search results by title and abstract and compiled an inclusive list of potential articles of interest.
We categorised the review topics into six overarching themes:

- Epidemiology of infections, including incidence, prevalence, and risk factors
- Changes to the human immune system and their effect on the incidence of infection
- Microbial behaviour
- Infection prevention and prophylaxis
- Current diagnostic and management approaches
- Future directions for the prevention and management of infectious diseases

All articles that were deemed relevant to any theme by at least one author were included for full review. All authors independently read all selected articles and extracted any relevant information pertaining to the six pre-identified research themes.

Challenges in space research and directions for future research

In this Review, we highlight how infections represent one of the top priorities of the space medicine field and one of the greatest challenges that should be overcome to enable safe long-duration spaceflight.[1,7] However, conducting research in space or simulated space conditions presents numerous challenges and limitations, some of which could undermine the robustness or generalisability of the findings.[2] Space research is always restricted by small sample sizes, due to logistical constraints and costs. The understanding of human physiology during spaceflight, including the immune system, is still limited, with most available data only comparing preflight and postflight periods.[18,23] Most literature focus on short-duration missions, and there has been no substantial biomedical research conducted beyond the low Earth orbit.

The complexity of microorganism behaviour and technical difficulties associated with conducting experiments in extreme environments, such as maintaining sterile conditions, controlling variables, and ensuring accurate data collection, hinder the reproducibility of studies.[9,84] Some experiments or methods for collecting data might even be too risky for use on a spacecraft. However, many spaceflight analogue environments are available for research, including ground-based simulations (bed rest studies, dry immersion, and centrifuges), parabolic flights, drop towers, and ground-based laboratories in which some aspects of the space environment can be recreated (such as altered gravity or increased radiation).[84] However, these environments cannot fully replicate the exact conditions of space, including sustained microgravity, increased radiation, and other space-specific factors.[21,34] Many of these methods, such as parabolic flights and drop towers, provide only short durations of microgravity, which precludes studying the long-term effects on the immune system and microbial behaviour. Overall, the differences between simulated conditions and actual space environments can limit the applicability and accuracy of the findings, for example, by affecting the understanding of how bacteria and hosts interplay in the true space environment.[34]

Our Review highlights conflicting data for several of the research topics we explored, and numerous questions remain unanswered. The precise mechanisms by which microgravity influences human and bacterial physiology, including the effect on cell-cell adhesion, remain unclear.[3,85] Are some individuals genetically predisposed to have a more resilient immune system for space travel? What is the role of on board functional immune testing?[16] Can methods be developed to slow down drug degradation during the journey, ensuring the effectiveness of antibiotics when required?[70] Is generating antibiotics on-demand within the spacecraft a possibility?[77] What should be included in the medical kit aboard a spacecraft embarking on a 3-year mission to Mars?[65] How can organ support be provided in the event of sepsis and septic shock?[9]

Conclusions

The potential threat of severe infections during long-duration space missions is a matter of utmost importance. To facilitate deep space travel, the space medicine community should further their understanding of the risks associated with infections in space and develop optimal strategies to prepare crew members in effectively managing infections and sepsis. Multidisciplinary research is essential to address the issue of pathogenicity in space, to avoid Earth's non-pathogenic microorganisms from gaining pathogenic traits once in space, to avoid increasing the pathogenicity of Earth's pathogens and humans developing a frailer immune system with higher infection rates during space exploration, and to develop protective systems that guarantee the health and safety of space crew.[3,84] Addressing infection-related challenges not only holds importance for space exploration but also has valuable implications for preventing and managing infections on Earth, particularly in isolated or austere environments, but in more conventional clinical settings as well.

Contributors

Conceptualisation, methodology, and supervision: MK. Data collection and curation: RZ and DC. Formal analysis: all authors. Figures: RZ and MK. Original draft, writing, review, and editing: all authors. All authors have directly accessed and verified the underlying data reported in the manuscript. We did not make use of any AI-assisted technology in the writing of this article.

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MK received consulting fees from Philips Healthcare and speaker honoraria from GE Healthcare and Gilead. The other authors declare no competing interests.

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