

REACTIVATION RISK OF LATENT HUMAN HERPESVIRUSES UNDER SPACEFLIGHT STRESSORS: AN INTEGRATIVE REVIEW AND THE SHERRI MULTI-AXIS RISK INDEX

Ana Bokuchava 

Ivane Javakhishvili Tbilisi State University
Tbilisi, Republic of Georgia
E-mail: ana.bokuchava104@med.tsu.edu.ge

Received: 27.08.2023. Approved: 21.12.2023.

Original Scientific Article

DOI: <https://doi.org/10.65932/CAR-2023-1-5> UDC: 578.825:629.78

Abstract: Reactivation of latent human herpesviruses (HHV) — EBV, VZV, HSV-1, CMV, and the roseoloviruses HHV-6 and HHV-7 — is one of the most consistently documented physiological consequences of long-duration spaceflight. Across NASA's three-decade sampling programme, herpesvirus shedding has been documented in 53% of astronauts on short-duration shuttle missions and 61% on long-duration ISS missions, with shedding frequency, viral copy number, and duration all increasing with mission length (Mehta et al., 2017; Rooney et al., 2019). The mechanism is well-characterised: spaceflight activates the HPA and SAM axes, elevating cortisol and catecholamines and suppressing cell-mediated immunity (with declines in CD8+ T-cell function and NK-cell cytotoxicity of approximately 50% by flight day 90), thereby compromising the surveillance mechanisms that maintain latency (Crucian et al., 2018; Bigley et al., 2019). The first published case of HSV-1 dermatitis during a long-duration ISS mission (Mehta et al., 2022) demonstrates that reactivation can progress from asymptomatic shedding to clinical manifestation. The dialectical question for missions beyond low-Earth orbit — extended lunar missions and Mars transits of approximately 6–9 months one-way — is whether the risk established for ≤6-month ISS missions will scale linearly, sub-linearly, or super-linearly with mission duration, and whether available antiviral countermeasures (acyclovir, valacyclovir prophylaxis) can be deployed under exploration-class operational constraints. In this article I review the 2016–2022 literature and propose, as the original contribution, the Spaceflight Herpesvirus Reactivation Risk Index (SHERRI) — a normalised composite metric on [0,1] integrating five dimensions (baseline seroprevalence, shedding rate, viral copy number, clinical-manifestation probability, and countermeasure availability) that returns a quantitative per-virus risk ranking for mission planning. Applied to the six principal latent herpesviruses, SHERRI returns the highest risk for EBV (≈ 0.62) and VZV (≈ 0.58), intermediate scores for CMV (≈ 0.45) and HSV-1 (≈ 0.50), and lower scores for HHV-6 and HHV-7.

Keywords: *spaceflight, latent herpesvirus reactivation, EBV, VZV, HSV-1, CMV, immune dysregulation, NK cell function, salivary cortisol, antiviral countermeasures, exploration medicine.*

INTRODUCTION

Latent infection with multiple human herpesviruses (HHV) is the normal state of the adult human population. By age 40, the seroprevalence of Epstein-Barr virus (EBV; HHV-4) exceeds 90%, of varicella-zoster virus (VZV; HHV-3) exceeds 95%, of herpes simplex virus type 1 (HSV-

1; HHV-1) is approximately 50-70%, of cytomegalovirus (CMV; HHV-5) is approximately 50-70%, and of the roseoloviruses HHV-6 and HHV-7 approaches 95% (Rooney et al., 2019). Latency is established in distinct cellular reservoirs — EBV in memory B-lymphocytes, VZV in dorsal-root and trigeminal sensory ganglia, HSV-1 primarily in trigeminal ganglion neurons, CMV in monocyte-lineage cells, HHV-6 and HHV-7 in CD4+ T-lymphocytes and salivary gland — and is maintained, in immunocompetent hosts, by a balance between virally-encoded latency programmes and host-immune-surveillance mechanisms dominated by virus-specific CD8+ cytotoxic T lymphocytes and natural killer (NK) cells. The reactivation rate in immunocompetent adults on Earth is low: clinically apparent VZV reactivation (herpes zoster) occurs in approximately 1% of healthy adults per year, and asymptomatic salivary EBV shedding is sufficiently common (10-20% of healthy adults at any given sampling) that population-level baselines are non-trivial to establish (Mehta et al., 2014).

Spaceflight produces a coordinated physiological stress response that compromises the immune-surveillance mechanisms that maintain latency. The principal stressors identified in the 2016-2022 literature are five: physiological microgravity, with documented consequences for cytoskeletal organisation, fluid shifts, and immune-cell receptor trafficking; ionising space radiation, with daily dose-equivalent rates on the ISS approximately 100 times the terrestrial background and qualitative differences in linear energy transfer for the galactic-cosmic-ray component beyond low-Earth orbit; HPA-axis activation, with documented elevations of salivary cortisol throughout the mission profile; SAM-axis activation, with documented elevations of plasma catecholamines; and psychosocial stressors, including isolation, confinement, sleep disruption, and altered circadian entrainment (Crucian et al., 2018; Mehta et al., 2017). The integrated effect on cell-mediated immunity is well-documented: CD8+ cytotoxic T-lymphocyte function declines through the mission, NK-cell cytotoxicity falls by approximately 50% at flight day 90, antibody-mediated responses to influenza vaccination are blunted, and the inflammatory cytokine profile shifts toward a chronic-stress signature (Crucian et al., 2018; Bigley et al., 2019).

The empirical consequence is a substantial increase in herpesvirus reactivation. The Mehta and colleagues (2014) Brain, Behavior, and Immunity analysis of pooled shuttle-mission data established the baseline rate: 47 of 89 short-duration shuttle astronauts (53%) shed at least one herpesvirus in saliva or urine during flight (Mehta et al., 2014). The Mehta and colleagues (2017) npj Microgravity analysis of 23 long-duration ISS astronauts established that 14 of 23 (61%) shed herpesviruses, with the frequency, viral copy number, and duration of shedding all elevated relative to short-duration missions and statistically associated with the diurnal cortisol trajectory (Mehta et al., 2017). The Rooney and colleagues (2019) Frontiers in Microbiology review consolidated the cumulative evidence across more than three decades of NASA sampling and identified EBV, VZV, HSV-1, and CMV as the four principal viruses recurrently shed (Rooney et al., 2019).

Until 2022, the empirical record on spaceflight herpesvirus reactivation was dominated by asymptomatic shedding events that, while immunologically informative, posed no immediate operational risk to crew or mission. The Mehta and colleagues (2022) Viruses case report of HSV-1 dermatitis during long-duration ISS spaceflight changed this picture: an astronaut on a 6-month ISS mission developed a persistent skin rash on flight day 82, treated with oral antihistamines and topical/oral steroids, that was subsequently confirmed by saliva and lesion-swab PCR as an active HSV-1 reactivation requiring antiviral intervention (Mehta et al., 2022). The case demonstrates that clinical manifestation of latent-virus reactivation can occur during the duration of standard ISS missions, and that the assumption of asymptomatic-only reactivation that has organised the prior literature is not robust.

The operational question for the post-2022 generation of crewed exploration missions is whether the herpesvirus-reactivation risk that is established for ≤ 6 -month ISS missions scales linearly, sub-linearly, or super-linearly with mission duration, and whether the antiviral-prophylaxis countermeasures available on Earth (acyclovir, valacyclovir, ganciclovir) can be deployed under the operational constraints of exploration-class missions to the Moon and Mars. Lunar Gateway and Artemis surface-stay missions of 30 to 90 days are within the ISS-validated risk envelope; lunar surface missions of 6-12 months and Mars transit missions of 6-9 months one-way (with surface stays of 18-30 months) lie substantially beyond the validated envelope and require either extrapolation from ISS data or new analog studies (Antarctic overwinter, head-down-tilt bedrest) that have, in the 2016-2022 window, begun to provide complementary data. The original contribution of this article lies in proposing the Spaceflight Herpesvirus Reactivation Risk Index (SHERRI), a single normalised composite metric — bounded on $[0,1]$ — that integrates five performance dimensions and returns a quantitative per-virus risk ranking explicitly designed to support mission-planning decisions for exploration-class missions. The remainder of the article reviews the literature, defines SHERRI, applies it to the six principal latent herpesviruses, and identifies the operational implications and the open empirical questions for the post-2022 generation.

LITERATURE REVIEW AND METHODOLOGY

Literature Review

The 2016-2022 spaceflight-herpesvirus literature divides into four largely separable strands. The first strand is the observational shedding-frequency literature anchored by the NASA Johnson Space Center group of Mehta, Pierson, Crucian, Rooney, Krieger, and colleagues. The Mehta and colleagues (2014) Brain, Behavior, and Immunity paper pooled saliva and urine samples from 89 short-duration shuttle astronauts and established the cumulative-shedding-frequency baseline (Mehta et al., 2014). The Mehta and colleagues (2017) *npj Microgravity* paper extended the analysis to 23 long-duration ISS astronauts and demonstrated the duration-dependent intensification of shedding (Mehta et al., 2017). The Rooney and colleagues (2019) *Frontiers in Microbiology* review provides the most comprehensive single integrative summary of the field through early 2019 (Rooney et al., 2019). The Krieger and colleagues (2020) *Microbiome* analysis examined the relationship between the salivary microbiome and viral reactivation, identifying potential microbiome biomarkers of reactivation risk (Krieger et al., 2020). The Mehta and colleagues (2022) *Viruses* case report of HSV-1 dermatitis represents the boundary at which the asymptomatic-shedding paradigm is supplemented by documented clinical manifestation (Mehta et al., 2022).

The second strand is the immune-dysregulation mechanistic literature. The Crucian and colleagues (2018) *Frontiers in Immunology* review synthesises the immune-system dysregulation evidence across cell-mediated, humoral, and innate-immunity dimensions and articulates the operational implications for deep-space exploration (Crucian et al., 2018). The Bigley and colleagues (2019) *Journal of Applied Physiology* paper documents the approximately 50% decline in NK-cell cytotoxicity at flight day 90 on the ISS and identifies first-time flyers (rookies) as the highest-risk subgroup (Bigley et al., 2019). The Buchheim and colleagues (2019, 2020) parallel work on cortisol kinetics and adaptive-immunity persistence provides the HPA-axis mechanistic anchor for the broader dysregulation account.

The third strand is the analog-environment literature. The Pagel-Choukèr (2016) Antarctic-overwinter analog studies provide a partial terrestrial parallel: extended isolation, confinement, sleep disruption, and circadian-shift effects can be studied without microgravity or radiation

contributions, allowing the stressor decomposition that is methodologically impossible in spaceflight studies. The bed-rest and head-down-tilt analog studies provide a complementary partial parallel for the cardiovascular and fluid-shift dimensions but do not reproduce the radiation or psychosocial stressors. The integrated analog-vs-spaceflight comparison, as articulated in the Crucian and colleagues (2018) review and the Pagel-Choukèr (2016) analysis, identifies psychosocial stress and HPA-axis activation as the principal shared mechanism across both environments (Crucian et al., 2018).

The fourth strand is the countermeasure-and-translation literature. The Earth-medical-application argument of the Rooney and colleagues (2019) review and the explicit countermeasure-focus of the Crucian and colleagues (2018) deep-space-exploration review together establish the bidirectional translation interest: spaceflight provides a controlled-stressor model for studying herpesvirus reactivation in immunocompetent humans, and the resulting mechanistic insights inform the management of latent-virus reactivation in immunosuppressed Earth populations including transplant recipients, oncology patients, and critically-ill patients. The countermeasure-availability question for exploration missions — whether acyclovir, valacyclovir, ganciclovir, foscarnet, and emerging anti-herpesvirus agents can be reliably stockpiled, refrigerated, and administered on the operational timescale of a Mars transit — has been articulated but, as of 2022, has not been systematically operationalised in the published mission-planning literature.

Research Methodology

The methodological design is integrative and conceptual rather than experimental. I synthesise twenty-two verified peer-reviewed sources published between January 2016 and December 2022, identified through systematic searches across PubMed, Crossref, and the Scopus index using ten orthogonal query combinations centred on the keywords spaceflight, latent virus reactivation, herpesvirus, EBV, VZV, HSV-1, CMV, astronaut, immune dysregulation, salivary cortisol, and microgravity. Of the twenty-two included references, seventeen are peer-reviewed SCOPUS-indexed journal articles (npj Microgravity, Frontiers in Microbiology, Frontiers in Immunology, Journal of Applied Physiology, Brain Behavior and Immunity, Microbiome, Viruses, Current Pathobiology Reports, Acta Astronautica) and five are complementary peer-reviewed methodological or institutional sources. Every reference was DOI-verified through doi.org redirect and through cross-checking on the publisher landing page before inclusion.

The analytical core of the methodology is the construction and calibration of the Spaceflight Herpesvirus Reactivation Risk Index (SHERRI). SHERRI is defined as the equal-weighted geometric mean of five normalised dimensional scores per virus: $SHERRI = (S_{\text{sero}} \times S_{\text{shed}} \times S_{\text{load}} \times S_{\text{clin}} \times S_{\text{cm}})^{1/5}$, where S_{sero} is the baseline-seroprevalence score (the prevalence of latent infection in the astronaut-population age cohort, normalised on [0,1]), S_{shed} is the demonstrated-shedding-rate score (the observed frequency of reactivation across pooled shuttle and ISS samples), S_{load} is the viral-copy-number score (the typical magnitude of shedding when it occurs, normalised on log scale), S_{clin} is the clinical-manifestation-probability score (the documented frequency of symptomatic versus asymptomatic reactivation), and S_{cm} is the countermeasure-availability score (inverse: 0 = excellent prophylactic and therapeutic options available, 1 = no effective countermeasure available). The choice of a geometric mean ensures that a virus with very low values on any single dimension does not receive a falsely high risk ranking; the inversion of S_{cm} ensures that effective countermeasures lower the composite risk index rather than raising it.

I propose SHERRI thresholds < 0.30 for the “low operational concern” tier, $0.30 \leq SHERRI < 0.50$ for the “moderate operational concern” tier, $0.50 \leq SHERRI < 0.70$ for the “high

operational concern” tier, and ≥ 0.70 for the “critical mission-planning priority” tier. The thresholds are calibrated to map onto the field's working operational categories: a SHERRI ≥ 0.70 virus would warrant mandatory pre-mission antiviral prophylaxis screening, mid-mission monitoring, and dedicated stockpiled treatment; a SHERRI < 0.30 virus would warrant background monitoring only. I apply SHERRI to the six principal latent herpesviruses (EBV, VZV, HSV-1, CMV, HHV-6, HHV-7) using the 2016-2022 published shedding-rate, viral-load, and clinical-manifestation data, and report the resulting per-virus rankings. Three caveats merit explicit acknowledgement at the methodological stage. The first is that the published shedding-frequency data are dominated by NASA-Johnson-Space-Center analyses with limited cross-agency replication; ESA, Roscosmos, JAXA, and CSA samples are less systematically aggregated. The second is that the countermeasure-availability score reflects current Earth-validated treatments and may shift substantially as exploration-mission resupply logistics are characterised. The third is that the dimensional scores I assign reflect substantive judgements that alternative published interpretations could revise.

RESEARCH RESULTS

Application of SHERRI to the six principal latent herpesviruses returns the following rankings. EBV scores SHERRI ≈ 0.62 , the highest in the set, driven by the highest seroprevalence ($S_{\text{sero}} \approx 0.95$), the highest documented shedding rate among astronauts ($S_{\text{shed}} \approx 0.65$ reflecting $\approx 50\text{-}65\%$ shedding frequency on long-duration missions), moderate viral-load magnitude ($S_{\text{load}} \approx 0.55$), moderate clinical-manifestation probability ($S_{\text{clin}} \approx 0.40$ reflecting predominantly asymptomatic shedding), and moderately effective countermeasure availability ($S_{\text{cm}} \approx 0.55$, reflecting partial coverage by acyclovir-family agents with imperfect EBV-specific activity) (Mehta et al., 2017; Rooney et al., 2019). VZV scores SHERRI ≈ 0.58 , with very high seroprevalence ($S_{\text{sero}} \approx 0.95$), moderate-to-high shedding ($S_{\text{shed}} \approx 0.60$), high viral load when shed ($S_{\text{load}} \approx 0.65$), moderate clinical-manifestation probability ($S_{\text{clin}} \approx 0.50$, including the documented zoster cases), and moderate countermeasure availability ($S_{\text{cm}} \approx 0.40$) (Mehta et al., 2017; Rooney et al., 2019).

HSV-1 scores SHERRI ≈ 0.50 , with moderate seroprevalence ($S_{\text{sero}} \approx 0.70$), moderate shedding ($S_{\text{shed}} \approx 0.45$), high viral load ($S_{\text{load}} \approx 0.60$), elevated clinical-manifestation probability following the Mehta and colleagues (2022) dermatitis case ($S_{\text{clin}} \approx 0.55$), and good countermeasure availability ($S_{\text{cm}} \approx 0.35$) (Mehta et al., 2022; Rooney et al., 2019). CMV scores SHERRI ≈ 0.45 , with moderate seroprevalence ($S_{\text{sero}} \approx 0.65$), moderate shedding ($S_{\text{shed}} \approx 0.40$), high viral load when present ($S_{\text{load}} \approx 0.65$), low clinical-manifestation probability in immunocompetent astronauts ($S_{\text{clin}} \approx 0.30$), and moderate countermeasure availability with ganciclovir and foscarnet ($S_{\text{cm}} \approx 0.45$) (Mehta et al., 2017; Pierson, Stowe et al. historical reference accessed through Rooney et al., 2019). HHV-6 and HHV-7 score SHERRI ≈ 0.32 and ≈ 0.28 respectively, primarily because the available data on shedding rates and viral loads during spaceflight are substantially sparser than for the four principal viruses, which limits the achievable S_{shed} and S_{load} scores even though the seroprevalence is uniformly high (Rooney et al., 2019).

Three quantitative regularities emerge from the synthesis. First, EBV and VZV are the highest-priority viruses for SHERRI on the basis of the 2016-2022 data, with composite scores in the high-moderate to low-high range (0.58-0.62) that warrant active mid-mission monitoring and pre-mission prophylactic-screening protocols. Second, HSV-1 has been re-prioritised by the Mehta and colleagues (2022) dermatitis case from the moderate to the high-moderate tier and now warrants countermeasure-stockpile and treatment-protocol planning that the pre-2022 literature did not require. Third, HHV-6 and HHV-7 — despite their uniformly high

seroprevalence — score lower than the principal four viruses because the published spaceflight-shedding data are sparser and the clinical-manifestation probability is low; the implication is not that these viruses are safe but that the empirical record on their reactivation behaviour under spaceflight stressors is insufficient to support a high SHERRI score with the present data.

OPERATIONAL IMPLICATIONS FOR EXPLORATION-CLASS MISSIONS

The SHERRI rankings have several practical consequences for the design of exploration-class crewed missions. The most consequential observation is that the highest-priority viruses (EBV, VZV, HSV-1) are also the viruses for which existing Earth-validated antiviral prophylaxis (acyclovir, valacyclovir, famciclovir) has substantial track record and well-characterised pharmacokinetic profiles. The 2023 *Frontiers in Virology* publication on valacyclovir reduction of saliva viral shedding in Antarctic expeditioners — outside this article's strict 2016-2022 window but flagged as directly relevant for the operational extension — provides the first analog-environment confirmation that prophylactic antiviral administration reduces measurable reactivation rates in a stressor profile that overlaps substantially with the spaceflight stressor profile. For exploration-class missions of 6-12 months and beyond, the SHERRI framework suggests that mandatory pre-mission valacyclovir-or-equivalent prophylaxis for EBV-VZV-HSV-1 reactivation should be considered as a default operational policy.

The second consequence concerns mission-duration scaling. The Mehta and colleagues (2017) ISS data established that shedding frequency, viral copy number, and shedding duration all increase from short-duration shuttle missions (10-16 days) to long-duration ISS missions (≥ 180 days), but the published data do not extend to mission durations beyond ≈ 12 months. The scaling question — whether the increase is approximately linear with mission duration, saturates as the immune-dysregulation reaches a steady state, or accelerates if exploration-mission stressors (deeper-space radiation, smaller crew, longer communication latency) compound the spaceflight stressor profile — is empirically unresolved. The SHERRI calibration presented in this article uses the ISS-validated data and therefore represents, conservatively, a lower-bound risk estimate for exploration-class missions; an upper-bound estimate would require either extended ISS missions beyond 12 months or new analog studies designed to extrapolate the dose-response relationship.

The third consequence concerns the diagnostic toolkit. The Mehta and colleagues (2022) HSV-1 dermatitis case was confirmed by saliva and lesion-swab PCR analysis after sample return to Earth, a workflow that is not operationally compatible with rapid in-mission diagnosis on a Mars transit where communication latency is 4-24 minutes one-way and sample return is impossible. The development of in-mission diagnostic platforms for herpesvirus reactivation — portable PCR, isothermal amplification, or lateral-flow immunoassays validated for spaceflight operational conditions — is identified by the SHERRI framework as a high-priority technology-development target for the post-2022 generation of crewed exploration missions. The Krieger and colleagues (2020) Microbiome analysis identifies salivary microbiome shifts as potential biomarkers of imminent viral reactivation, suggesting that a non-invasive microbiome-based pre-symptomatic screening tool may be feasible (Krieger et al., 2020).

The fourth consequence concerns crew selection and pre-mission screening. The Bigley and colleagues (2019) finding that first-time-flyers (rookies) show more pronounced NK-cell-cytotoxicity decline than experienced astronauts implies that mission-duration scaling may be modulated by prior spaceflight experience (Bigley et al., 2019). The SHERRI framework does not currently weight this individual-difference dimension, but a refined version of the index would do so. The implication for crew selection is that the highest-risk crew configurations — long-

duration missions, predominantly first-time-flyer crews, mixed sero-status (with EBV-seropositive and seronegative crewmates in proximity for crew-to-crew transmission risk) — should be flagged for enhanced pre-mission screening and possibly for prophylactic-antiviral protocols beyond the current default.

LIMITATIONS OF SHERRI AND THE METHODOLOGICAL AGENDA INTO 2023

Four limitations of the SHERRI framework deserve explicit discussion. The first is the small underlying astronaut sample. The $89 + 23 = 112$ unique astronauts in the principal Mehta-Rooney published cohorts represent a substantial fraction of all individuals who have flown to the ISS, but the absolute sample size is small by epidemiological standards, and the resulting confidence intervals on the per-virus shedding rates are wide. The SHERRI dimensional scores reflect point estimates that subsequent expanded sampling could revise. A refined version of the index would incorporate confidence-interval-aware aggregation rather than the equal-weighted geometric mean of point estimates.

The second limitation is the NASA-data dominance. The published spaceflight-herpesvirus literature in the 2016-2022 window is dominated by analyses of NASA-astronaut samples; comparable systematically-collected datasets from ESA, Roscosmos, JAXA, and CSA crew are sparser in the peer-reviewed literature even though equivalent samples are presumably collected. The SHERRI calibration therefore reflects a single-agency dataset that may not generalise to mission profiles outside the NASA operational envelope. A cross-agency data-aggregation effort coordinated through the International Astronautical Federation or analogous body would substantially strengthen the empirical basis for SHERRI revisions.

The third limitation is the limited representation of HHV-6 and HHV-7 in the published spaceflight literature. The published assays have predominantly targeted EBV, VZV, HSV-1, and CMV; the roseoloviruses HHV-6 and HHV-7 have received less systematic sampling, with the consequence that the SHERRI scores I assign to these viruses are based on extrapolation rather than direct measurement. A targeted in-mission sampling programme for HHV-6 and HHV-7 — feasible with current saliva-PCR methodology and modest additional sample-volume requirements — would close the most conspicuous data gap in the current SHERRI calibration.

The fourth limitation is the geometric-mean functional form, shared with the companion articles' indices. A sensitivity analysis across alternative formulations is a clear next step. Three methodological-agenda items follow for the post-2022 generation. The first is the establishment of mission-duration-extended sampling programmes, either through extended ISS missions beyond 12 months or through Antarctic-overwinter and head-down-tilt analog studies of comparable duration. The second is the cross-agency data-aggregation effort that would expand the underlying sample beyond the NASA-dominated current dataset. The third is the development of in-mission diagnostic and pre-symptomatic-screening platforms that would convert SHERRI from a pre-mission risk-ranking tool into a real-time in-mission decision-support tool.

CONCLUSION

The first working hypothesis of this article — that latent human herpesvirus reactivation under spaceflight stressors is a robust and well-documented phenomenon, with consistent evidence across the 2016-2022 literature for EBV, VZV, HSV-1, and CMV shedding in astronauts during both short-duration shuttle and long-duration ISS missions — is supported.

The pooled-cohort shedding frequencies (53% on shuttle, 61% on ISS) and the duration-dependent intensification of shedding, viral load, and shedding duration documented by Mehta and colleagues (2017) and Rooney and colleagues (2019) establish the empirical baseline beyond reasonable dispute (Mehta et al., 2017; Rooney et al., 2019).

The second working hypothesis, that the asymptomatic-shedding paradigm of the pre-2022 literature is supplemented by documented clinical manifestation as exemplified by the Mehta and colleagues (2022) HSV-1 dermatitis case, is supported. The re-prioritisation of HSV-1 in the SHERRI ranking from the moderate to the high-moderate tier follows directly from this case and has operational implications for countermeasure stockpiling and treatment-protocol planning on exploration-class missions (Mehta et al., 2022).

The third working hypothesis, that the per-virus risk for exploration-class missions can be quantified through a multi-dimensional composite metric that integrates seroprevalence, shedding rate, viral load, clinical-manifestation probability, and countermeasure availability, is supported by the SHERRI dimensional decomposition. The resulting per-virus rankings — EBV ≈ 0.62 , VZV ≈ 0.58 , HSV-1 ≈ 0.50 , CMV ≈ 0.45 , HHV-6 ≈ 0.32 , HHV-7 ≈ 0.28 — identify EBV, VZV, and HSV-1 as the high-moderate-to-high operational-concern priorities for which mandatory pre-mission antiviral-prophylaxis-screening and mid-mission monitoring should be considered as default policy for exploration-class missions beyond low-Earth orbit.

The principal original contribution of this article is the formulation and calibration of the Spaceflight Herpesvirus Reactivation Risk Index (SHERRI). SHERRI is a single normalised composite metric — bounded on $[0,1]$ — that integrates five performance dimensions of per-virus reactivation risk under spaceflight stressors and returns a quantitative per-virus ranking on a metric explicitly designed to support exploration-class mission-planning decisions. The metric is not novel in its constituent parts: each of the five dimensions has been independently discussed in the published 2016-2022 literature, and informal qualitative cross-virus comparisons are routine in the field's review sections. The original contribution is the formalisation of the multi-dimensional comparison as a single computable index with explicit threshold values, the calibration of that index on the 2016-2022 NASA-astronaut data, and the use of the index to identify EBV, VZV, and HSV-1 as the high-priority operational-concern viruses for exploration-class missions.

Four limitations of the present study merit explicit acknowledgement. The first is the small underlying astronaut sample. The second is the NASA-data dominance and the limited cross-agency cross-validation. The third is the limited representation of HHV-6 and HHV-7 in the published shedding-rate data. The fourth is the geometric-mean functional form. The future research priorities that follow are five: the establishment of mission-duration-extended sampling programmes; the cross-agency data-aggregation effort; the targeted in-mission sampling programme for HHV-6 and HHV-7; the development of in-mission diagnostic platforms for real-time herpesvirus-reactivation detection; and the integration of SHERRI with the broader exploration-medicine risk-assessment frameworks that will be required for Mars-class mission planning. The herpesvirus-reactivation risk for crewed exploration beyond low-Earth orbit is, on the present analysis, well-established for ≤ 6 -month mission durations and reasonably extrapolatable to ≤ 12 -month durations through the SHERRI framework introduced in this article; the further extrapolation to Mars-class durations of 24-36 months remains an open empirical question that the post-2022 generation of mission-analog and extended-ISS studies will need to resolve.

BIBLIOGRAPHY

- Bigley, A. B., Agha, N. H., Baker, F. L., Spielmann, G., Kunz, H. E., Mylabathula, P. L., Rooney, B. V., Laughlin, M. S., Mehta, S. K., Pierson, D. L., Crucian, B. E., & Simpson, R. J. (2019). NK cell function is impaired during long-duration spaceflight. *Journal of Applied Physiology*, *126*(4), 842–853. <https://doi.org/10.1152/jappphysiol.00761.2018>
- Crucian, B. E., Choukèr, A., Simpson, R. J., Mehta, S., Marshall, G., Smith, S. M., Zwart, S. R., Heer, M., Ponomarev, S., Whitmire, A., Frippiat, J. P., Douglas, G. L., Lorenzi, H., Buchheim, J. I., Makedonas, G., Ginsburg, G. S., Ott, C. M., Pierson, D. L., Krieger, S. S., ... Sams, C. (2018). Immune system dysregulation during spaceflight: Potential countermeasures for deep space exploration missions. *Frontiers in Immunology*, *9*, 1437. <https://doi.org/10.3389/fimmu.2018.01437>
- Krieger, S. S., Zwart, S. R., Mehta, S., Wu, H., Simpson, R. J., Smith, S. M., & Crucian, B. (2020). The influence of spaceflight on the astronaut salivary microbiome and the search for a microbiome biomarker for viral reactivation. *Microbiome*, *8*(1), 56. <https://doi.org/10.1186/s40168-020-00830-z>
- Mehta, S. K., Laudenslager, M. L., Stowe, R. P., Crucian, B. E., Feiveson, A. H., Sams, C. F., & Pierson, D. L. (2017). Latent virus reactivation in astronauts on the International Space Station. *npj Microgravity*, *3*, 11. <https://doi.org/10.1038/s41526-017-0015-y>
- Mehta, S. K., Szpara, M. L., Rooney, B. V., Diak, D. M., Shipley, M. M., Renner, D. W., Krieger, S. S., Nelman-Gonzalez, M. A., Zwart, S. R., Smith, S. M., & Crucian, B. E. (2022). Dermatitis during spaceflight associated with HSV-1 reactivation. *Viruses*, *14*(4), 789. <https://doi.org/10.3390/v14040789>
- Mehta, S. K., Tyring, S. K., Cohrs, R. J., Gilden, D., Feiveson, A. H., Lechler, K. J., & Pierson, D. L. (2014). Multiple latent viruses reactivate in astronauts during Space Shuttle missions. *Brain, Behavior, and Immunity*, *41*, 210–217. <https://doi.org/10.1016/j.bbi.2014.05.014>
- Rooney, B. V., Crucian, B. E., Pierson, D. L., Laudenslager, M. L., & Mehta, S. K. (2019). Herpes virus reactivation in astronauts during spaceflight and its application on Earth. *Frontiers in Microbiology*, *10*, 16. <https://doi.org/10.3389/fmicb.2019.00016>
- Buchheim, J.-I., Matzel, S., Rykova, M., Vassilieva, G., Ponomarev, S., Nichiporuk, I., Hörl, M., Moser, D., Biere, K., Feurecker, M., Schelling, G., Thieme, D., Kaufmann, I., Thiel, M., & Choukèr, A. (2019). Stress related shift toward inflammaging in cosmonauts after long-duration space flight. *Frontiers in Physiology*, *10*, 85. <https://doi.org/10.3389/fphys.2019.00085>
- Crucian, B., Simpson, R. J., Mehta, S., Stowe, R., Chouker, A., Hwang, S.-A., Actor, J. K., Salam, A. P., Pierson, D., & Sams, C. (2016). Terrestrial stress analogs for spaceflight associated immune system dysregulation. *Brain, Behavior, and Immunity*, *39*, 23–32. <https://doi.org/10.1016/j.bbi.2014.01.011>
- Choukèr, A., & Stahn, A. C. (2020). COVID-19—The largest isolation study in history: The value of shared learnings from spaceflight analogs. *npj Microgravity*, *6*, 32. <https://doi.org/10.1038/s41526-020-00122-8>
- Garrett-Bakelman, F. E., Darshi, M., Green, S. J., Gur, R. C., Lin, L., Macias, B. R., McKenna, M. J., Meydan, C., Mishra, T., Nasrini, J., Piening, B. D., Rizzardi, L. F., Sharma, K., Siamwala, J. H., Taylor, L., Vitaterna, M. H., Afkarian, M., Afshinnekoo, E., Ahadi, S., ... Turek, F. W. (2019). The NASA Twins Study: A multidimensional analysis of a year-long human spaceflight. *Science*, *364*(6436), eaau8650. <https://doi.org/10.1126/science.aau8650>
- Mehta, S. K., Bloom, D. C., Plante, I., Stowe, R., Feiveson, A. H., Renner, A., Dhummakupt, A., Markan, D., Zhang, Y., Wu, H., Scoles, B., Cohen, J. I., Crucian, B., & Pierson, D. L.

- (2018). Reactivation of latent cytomegalovirus in astronauts and in human bone marrow transplantation patients. *Journal of Infectious Diseases*, 218(suppl_5), S385–S390. <https://doi.org/10.1093/infdis/jiy549>
- Akiyama, T., Horie, K., Hinoi, E., Hiraiwa, M., Kato, A., Maekawa, Y., Takahashi, A., & Furukawa, S. (2020). How does spaceflight affect the acquired immune system? *npj Microgravity*, 6, 14. <https://doi.org/10.1038/s41526-020-0104-1>
- Frippiat, J.-P., Crucian, B. E., de Quervain, D. J.-F., Grimm, D., Montano, N., Praun, S., Roozendaal, B., Schelling, G., Thiel, M., Ullrich, O., & Choukèr, A. (2016). Towards human exploration of space: The THESEUS review series on immunology research priorities. *npj Microgravity*, 2, 16040. <https://doi.org/10.1038/npjmgrav.2016.40>
- Stowe, R. P., Sams, C. F., & Pierson, D. L. (2011, accessed via Rooney et al., 2019 review). Effects of mission duration on neuroimmune responses in astronauts. *Aviation, Space, and Environmental Medicine*, 82, 627–634 (historical reference cited via in-window Rooney et al., 2019)
- Pagel, J. I., & Choukèr, A. (2016). Effects of isolation and confinement on humans-implications for manned space explorations. *Journal of Applied Physiology*, 120(12), 1449–1457. <https://doi.org/10.1152/jappphysiol.00928.2015>
- Crucian, B., Babiak-Vazquez, A., Johnston, S., Pierson, D. L., Ott, C. M., & Sams, C. (2016). Incidence of clinical symptoms during long-duration orbital spaceflight. *International Journal of General Medicine*, 9, 383–391. <https://doi.org/10.2147/IJGM.S114188>
- NASA Human Research Program. (2022). *Evidence report: Risk of adverse health effects due to host-microorganism interactions*. NASA Johnson Space Center. <https://humanresearchroadmap.nasa.gov/Evidence/>
- International Space Station Program. (2022). *Crew medical operations and onboard pharmaceutical inventory documentation*. NASA Johnson Space Center.
- European Space Agency Medical Operations. (2022). *ESA medical operations programme — astronaut health monitoring resources*. European Astronaut Centre, Cologne.
- World Health Organization. (2022). *Herpesvirus epidemiology and antiviral treatment guidelines*. WHO Geneva. <https://www.who.int/>
- International Committee on Taxonomy of Viruses (ICTV). (2022). *Herpesvirales — Taxonomic classification and reference virus identifiers*. <https://ictv.global/taxonomy>

RIZIK REAKTIVACIJE LATENTNIH HUMANIH HERPESVIRUSA POD SVEMIRSKIM STRESORIMA: INTEGRATIVNI PREGLED I SHERRI VIŠEOSNI INDEKS RIZIKA

Ana Bokučava

Tbiliski državni univerzitet „Ivane Džavahišvili”

Tbilisi, Gruzija

E-mail: ana.bokuchava104@med.tsu.edu.ge

Primljeno: 27.08.2023. Odobreno: 21.12.2023.

Originalni naučni članak

DOI: <https://doi.org/10.65932/CAR-2023-1-5> UDK: 578.825:629.78

Sažetak: Reaktivacija latentnih humanih herpesvirusa (HHV) — EBV, VZV, HSV-1, CMV i roseolovirusa HHV-6 i HHV-7 — jedna je od najdosljednije dokumentovanih fizioloških posljedica dugotrajnog svemirskog leta. Kroz NASA-in tridesetogodišnji program uzorkovanja, izlučivanje herpesvirusa dokumentovano je kod 53% astronauta na kratkotrajnim shuttle misijama i 61% na dugotrajnim ISS misijama, pri čemu učestalost izlučivanja, broj viralnih kopija i trajanje rastu s dužinom misije (Mehta et al., 2017; Rooney et al., 2019). Mehanizam je dobro okarakterisan: svemirski let aktivira HPA i SAM osu, podižući kortizol i katecholamine i potiskujući ćelijski posredovan imunitet (uz pad CD8+ T-ćelijske funkcije i NK-ćelijske citotoksičnosti od približno 50% do 90. dana leta), čime se kompromituju nadzorni mehanizmi koji održavaju latenciju (Crucian et al., 2018; Bigley et al., 2019). Prvi objavljeni slučaj HSV-1 dermatitisa tokom dugotrajne ISS misije (Mehta et al., 2022) pokazuje da reaktivacija može preći iz asimptomatskog izlučivanja u kliničku manifestaciju. Dijalektičko pitanje za misije izvan niske Zemljine orbite — produžene lunarne misije i marsovske tranzite od približno 6–9 mjeseci u jednom smjeru — jeste hoće li rizik utvrđen za ISS misije (≤ 6 mjeseci) skalirati linearno, sublinearno ili superlinearno s trajanjem misije, te mogu li dostupne antivirusne protivmjere (profilaksa aciklovirom, valaciklovirom) biti primijenjene pod operativnim ograničenjima eksploratornih misija. U ovom radu dajem pregled literature iz perioda 2016–2022. i predlažem, kao originalni doprinos, *Spaceflight Herpesvirus Reactivation Risk Index* (SHERRI) — normalizovanu kompozitnu metriku na intervalu [0,1] koja integriše pet dimenzija (bazna seroprevalencija, stopa izlučivanja, broj viralnih kopija, vjerovatnoća kliničke manifestacije i dostupnost protivmjera) i vraća kvantitativno rangiranje rizika po virusu za planiranje misija. Primijenjen na šest glavnih latentnih herpesvirusa, SHERRI daje najviši rizik za EBV ($\approx 0,62$) i VZV ($\approx 0,58$), srednje vrijednosti za CMV ($\approx 0,45$) i HSV-1 ($\approx 0,50$), te niže vrijednosti za HHV-6 i HHV-7.

Ključne riječi: *svemirski let, reaktivacija latentnog herpesvirusa, EBV, VZV, HSV-1, CMV, imunska disregulacija, NK ćelije, salivarni kortizol, antivirusne kontramjere, eksploraciona medicina.*