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The Integrated Medical Model: A probabilistic simulation model predicting in-flight medical risks

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The Integrated Medical Model (IMM) is a probabilistic model that uses simulation to predict human spaceflight mission medical risk. Given a specific mission and crew scenario, medical events are simulated using Monte Carlo methodology to provide estimates of resource utilization, probability of evacuation, probability of loss of crew, and the amount of mission time lost due to illness. Mission and crew scenarios are defined by mission length, extravehicular activity (EVA) schedule, and crew characteristics including: sex, coronary artery calcium score, contacts, dental crowns, history of abdominal surgery, and EVA eligibility.

The Integrated Medical Evidence Database (iMED) houses the model inputs for 100 medical conditions using in-flight, analog, and terrestrial medical data. Inputs include incidence, event durations, resource utilization, and crew functional impairment. Severity of conditions is addressed by defining statistical distributions on the dichotomized best and worst-case scenarios for each condition. The outcome distributions for conditions are bounded by the treatment extremes of the fully treated scenario – in which all required resources are available – and the untreated scenario – in which no required resources are available. Upon occurrence of a simulated medical event, treatment availability is assessed, and outcomes are

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generated depending on the status of the affected crewmember at the time of onset, including any pre-existing functional impairments or ongoing treatment of concurrent conditions.

The main IMM outcomes, including probability of evacuation and loss of crew life, time lost due to medical events, and resource utilization, are useful in informing mission planning decisions. To date, the IMM has been used to assess mission-specific risks with and without certain crewmember characteristics, to determine the impact of eliminating certain resources from the mission medical kit, and to design medical kits that maximally benefit crew health while meeting mass and volume constraints.

I. Introduction

SERIOUS medical consequences associated with the extreme space environment represent a potentially significant limiting factor for long-duration human spaceflight. Given the relative dearth of opportunities to study the physiologic effects of the space environment and the difficulties in mimicking such conditions through analog environments, computational models serve to augment space medicine research, assess risk, prioritize funding decisions, and ultimately aid in mitigating potential hazards to astronaut health. Many of these models produce simulations that answer targeted questions about human physiologic changes in response to spaceflight and the microgravity environment.[1-8] To complement these efforts, a broad view of in-flight astronaut health and resource usage is useful to program, project, and mission planners in establishing meaningful mission parameters for crew health and safety. Assad et al. published a deterministic model of astronaut health and resource utilization for long-duration spaceflight that provides an aggregate estimate of astronaut health and the mass of medical consumables used during the mission.[9] The Integrated Medical Model (IMM) expands upon these capabilities by providing a measure of quality time lost during the mission due to medical events, the probability of evacuation, the probability of loss of crew life, and resource utilization. Granularity at the medical condition level and resource type level is also achieved and provides information about drivers of evacuation, loss of crew, and overall poor health.

As a quantitative, evidence-based decision support tool that integrates organizational knowledge, published literature, and in-flight medical event data, the IMM provides comparative estimates of in-flight medical risks and resource utilization between different mission profiles, crew profiles, and medical kits. This probabilistic simulation uses Monte Carlo methodology with input from medical condition incidence data, medical condition outcome data, and treatment data on 100 medical conditions that have either occurred in flight or are of considerable concern to human spaceflight. Using these medical inputs, combined with crew and mission characteristics, the IMM generates a large number of simulated missions to predict the amount of time lost during the mission due to medical events, the probability of evacuation, the probability of a loss of crew life, and an estimate of resources required. As certain medical conditions have higher likelihoods if an individual has an associated risk factor (e.g., use of contacts is correlated with a greater risk of corneal ulcer), the IMM takes as input a crew profile defining several risk factors, including sex, presence of contacts, presence of coronary artery calcium, presence of crowns, and history of abdominal surgery. Further, medical conditions associated with space adaptation (SA) are modeled to occur only once in flight.

The IMM goes beyond more traditional risk management tools in that it not only models risk, it also models risk mitigations in the form of medical condition treatment, and subsequent clinical outcomes based on medical resource mitigations available. The IMM also accounts for events unique to the spaceflight environment, such as solar particle events (SPE), which expose the crew to radiation, and extravehicular activities (EVAs), or 'spacewalks', that may lead to associated conditions and adverse medical outcomes. The model exhibits sufficient flexibility to allow for additional mission event types should data be made available. Currently, the input data is baselined to the International Space Station; however, the IMM is designed to be extensible, to support research, and to support capability development in order to enable long-term exploration class missions.

II. Methods

The IMM is implemented in MATLAB and draws model inputs from user-defined scripts and an SQL database.[10] In concept, the IMM architecture follows the practices of probabilistic risk assessment (PRA).[11] However, the implementation of the IMM diverges from strict PRA implementation to accommodate the broad assumptions required to implement medical treatment and outcome simulations. These enhancements maintain appropriate statistical

practices and result in a robust and extensible tool. Figures 1 and 2 provide overviews of model inputs and simulation flow, respectively.

A. Model Inputs

A SQL database called the integrated Medical Evidence Database (iMED) houses the medical-condition-model inputs. Within the database, clinical subject matter experts (SMEs) populate and maintain data on 100 medical conditions that have either occurred in flight or are of considerable concern or interest to human spaceflight. The following section outlines the data housed in the iMED and used by the model.

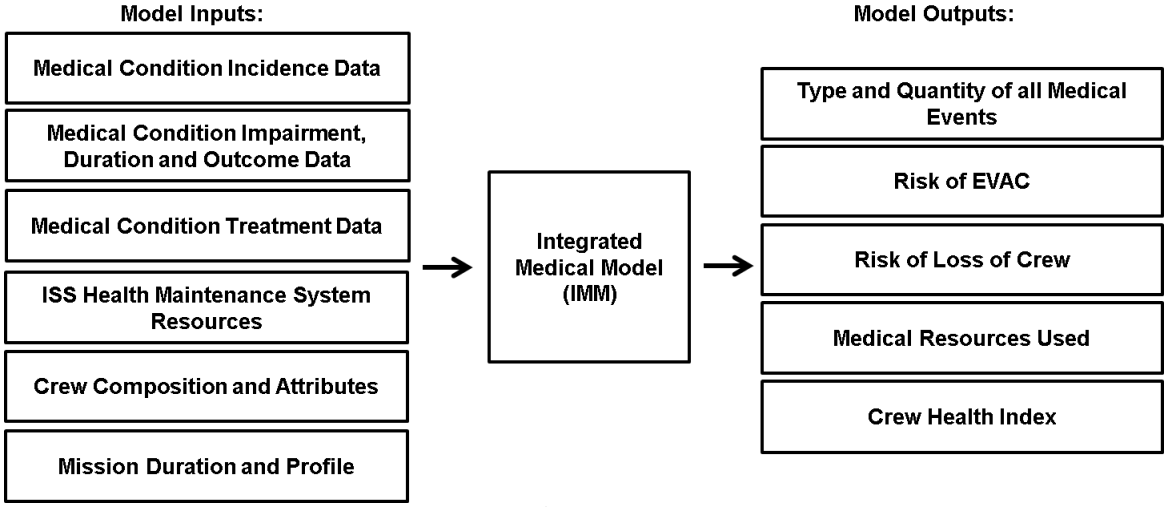

Figure 1. Summary of IMM inputs and outputs.

1. User-defined

Model users must define the mission, number of crew, and certain crewmember characteristics including sex, presence of dental crowns, presence of contact lenses, presence of coronary artery calcium (CAC), and history of abdominal surgery. An EVA schedule must also be defined for each crewmember. These crew characteristics indicate the appropriate incidence data for applicable medical conditions associated with crew-health-risk factors.

2. Incidence Rates

In-flight data inform the medical condition incidence data for the medical conditions simulated in the IMM wherever possible. The NASA Lifetime Surveillance of Astronaut Health (LSAH) and information from published literature provides the IMM with in-flight data.[12-14] The current version of the model uses in-flight data from shuttle missions STS 1-114, except STS-51-L (Challenger) and STS-107 (Columbia), International Space Station expeditions 1-13, Apollo, Skylab, and Shuttle/Mir. Data from some later flights inform medical condition inputs related to visual impairment and intracranial pressure (VIIP).

Where observational data are insufficient to adequately define the in-flight medical risk, the IMM uses terrestrial analog and general population data, Bayesian updates to pre- and postflight astronaut data from terrestrial data[15], analog condition terrestrial data, and external probabilistic modules to model and estimate medical-event likelihoods. Acquisition of terrestrial incidence is through analog and general population published literature. For some medical conditions, such as the occurrence of in-flight renal stones, Bayesian updates can be made to terrestrial data. External models are used to estimate incidence of very rare, but high impact, events, such as the a bone-fracture-risk model.[16] The current list of the IMM medical conditions, along with the incidence data source type (i.e., in-flight data, terrestrial data, Bayesian updates to terrestrial data, or external model data), and the distributions sampled for each incidence rate may be found in the Appendix. Medical conditions associated with causative mission events and risk factors affecting medical condition likelihoods, are also indicated.

3. Scenario

The severity of a medical condition occurrence is modeled as a best- or worst-case event scenario with medical event outcomes defined separately for each scenario. Outcomes associated with these two scenarios represent the best and worst possible outcomes for the affected crewmember given defined resource, treatment, and environmental constraints. The probability of a best or worst-case scenario is specified in the iMED as being uniformly distributed over a range defined by clinical SMEs and informed by the literature for each of the medical conditions.

4. Treatment

The IMM models mitigations to the medical risks in the form of treatments. Resource types and quantities used to model medical risk mitigation in the IMM are derived from the International Space Station (ISS) Health Maintenance System. A treatment is defined for each medical condition/scenario combination and consists of required quantities of medical resources, the per day dosage, and a resource category, if applicable. The resource is assigned to a category so that in the event of an insufficient quantity of a primary resource, a suitable alternate may be considered from the same category during simulation. The iMED contains an alternative resource table that lists equivalent dosages for resources within the same category. Treatments are defined by clinical SMEs to reflect acceptable medical standards of care.

5. Outcomes

Medical event outcomes are defined in the iMED for each medical event/scenario combination for the situation where sufficient medical resources are available to treat the medical condition and the situation where insufficient resources are available. These outcomes include functional impairments, durations, the probability that an evacuation should be considered (pEVAC), and the probability of loss of crew life (meaning one or more crew) (pLOCL). Functional impairments and durations, and pEVAC and pLOCL are generated using beta-pert distributions. Functional impairments (FI) and durations (DT) are defined for each of three clinical phases: diagnosis and initial treatment (Clinical Phase 1), ongoing treatment and convalescence (Clinical Phase 2), and permanent impairment for the remainder of the mission (Clinical Phase 3). FI and DT are specified as ranges (min and max) assuming a Beta-Pert distribution with the midpoint serving as the most likely value. FI, DT, and end state outcome (pLOCL and pEVAC) specifications are ascertained from a combination of impairment guidelines, best evidence from ground-based analog populations, and clinical SME experience with the medical condition.[17] It should be noted that evacuation and loss of crew life endstate data is not drawn from in-flight data, as these events are rare. As end-state outcomes are largely impacted by medical resource limitations, their specification relies heavily on clinical expertise within the NASA community.

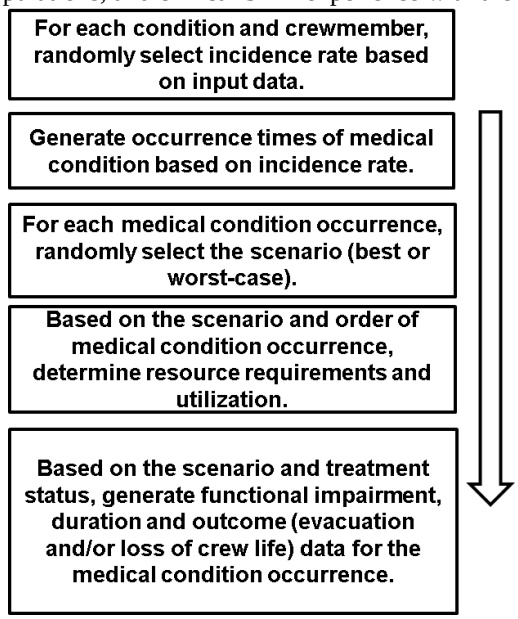

Figure 2. Overview of IMM simulation.

B. Simulation

6. Medical Condition Occurrences

SA conditions are simulated to occur at most once during the mission and, with the exception of conditions associated with VIIP, occur within the first 5 days. The incidence of a SA condition is defined in the iMED as an incidence proportion (IP) or events per person task. The IP is either fixed or generated from a Beta distribution, and the occurrence of the event is drawn from a Bernoulli distribution defined by the IP. If the SA medical condition occurs, the time-of-occurrence is then generated from a Beta-Pert distribution specified in the iMED.

For each scheduled EVA for a crewmember, an EVA-associated medical event occurrence is drawn from a Bernoulli distribution defined by the medical condition IP, which is either fixed or generated from a Beta distribution. If the event occurs, the time-of-occurrence is the start time of the scheduled EVA.

The only condition currently in the model that is associated with SPEs is acute radiation syndrome (ARS). An SPE incidence is generated from a gamma distribution defined in the iMED, and SPEs are simulated as a Poisson process with time between events generated via an exponential distribution with lambda equal to the incidence rate (IR). The SPE schedule is generated in this way at the beginning of every

mission. If an SPE occurs, all crewmembers are at risk for ARS. ARS occurrences are predicted from a Bernoulli distribution defined by a fixed incidence proportion.

For general conditions (non-EVA, non-SPE, and non-SA), medical event occurrences are simulated as a Poisson process with time between events generated via an exponential distribution with lambda equal to the incidence rate. For all medical condition occurrences, the best-case or worst-case scenario type is generated from a Bernoulli distribution.

7. Treatment

Within the simulation, medical resources used to treat each medical event are taken out of the medical kit the order of medical event occurrence. While the resource types and quantities are specified model inputs, these treatments may be modified within the simulation to account for remaining mission time (for example, if the medical event occurs near the end of the mission), or to account for overlap with treatment of concurrent conditions within the same crewmember. If a required resource is unavailable or the quantity is insufficient and an alternative is specified in the iMED, the alternate will be used as the mitigation. Note that medical event outcomes are simulated from statistical distributions that are specified for the situation where all required resources are available (fully treated) and also when no required resources are available (untreated). To predict outcomes for a medical event where some but not all of the required essential resources are available to treat the medical event, a partial treatment scheme is employed that allows for a continuum between the fully-treated and untreated situations. To address partial treatment outcomes between these two extremes, we use a resource availability factor (RAF), calculated as the proportion of required resources available, to generate statistical distributions that are shifted between the fully treated and completely untreated distributions (Figure 3).

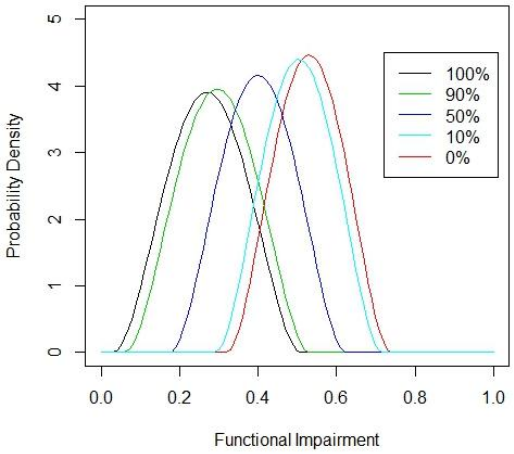

Figure 3. Sample statistical distributions for functional impairment (FI) for varying RAF values ranging from 100% (all required resources available) to 0% (no required resources available).

8. Outcomes

Functional impairments and clinical phase durations, and probabilities of loss of crew and evacuation are generated from Beta-Pert distributions. Loss of crew and evacuation are simulated from Bernoulli distributions using the generated probabilities. Simulated outcomes for a given medical event may affect downstream events on the timeline. If a medical condition results in an evacuation or loss of crew life, no further medical events may occur for the affected crewmember. Furthermore, a crewmember in Clinical Phases 1 and 2 of a medical event may not experience a second concurrent occurrence of the identical medical event during that time.

9. Outputs

Primary outcomes describing the impact of medical events on the mission are measured by the Crew Health Index (CHI), probability of evacuation (pEVAC), probability of loss of crew life (pLOCL), and total medical events (TME). The CHI is a function of quality-adjusted life years lost due to medical events. Given n overlapping functional impairments $<f_1,f_2, f_3,\ldots,f_n>$ at a point in time within a crewmember due to medical events, the overall functional impairment f_{total} can be calculated using function: $f_{total} = 1-(1-f_1)\times(1-f_2) \times (1-f_3) \times \ldots \times (1-f_n)$. The quality time lost is calculated as the product of f_{total} and the duration of the time interval over which the functional impairment is applied. Total quality time lost (QTL) over a mission is calculated as the sum of products of the functional impairments and durations. The CHI is an estimate of total jcrew health and is calculated in the following way: $CHI = 100\%\times(1-QTL_{total}/(L\times c))$ where c is the number of crew, L is the mission length in hours, and QTL_{total} is the total amount of quality time lost for all crewmembers on a mission. The contributions of individual medical conditions to each primary output, as well as descriptive statistics on the individual resources used are also available.

III. Results

Example results from 100k trials for an ISS 6-month Design Reference Mission (DRM) with a 4-male, 2-female crew are provided here. Crew risk factors include: 1 crewmember with a CAC score greater than zero, 3 crewmembers

with contacts, 2 crewmembers with crowns, 1 crewmember with a history of abdominal surgery, and 2 crewmembers who perform 6 EVAs each. Three risk mitigation scenarios are modeled: one in which no medical resources are available, one in which the ISS Health Maintenance System is available (with no resupply), and one in which unlimited quantities of consumables in the ISS Health Maintenance System are available. A summary of these outputs can be found in Table 1, and the distributions that some of these outputs assume can be seen in Figures 4-5. The outputs provided here are for the crewmembers as an aggregate. As is expected, the worst CHI, pEVAC and pLOCL outcomes occur in the untreated scenario, with outcomes improving as more resources become available. Notably, total medical events (TME) are reduced in the scenario where no medical resources are available. This is reflective of the increased precedence of early termination of crewmembers' missions due to death or evacuation. For comparison, CHI data from an exploration-class Mars 2.5-year DRM is provided in Figure 6 with available medical resources derived from the ISS Health Maintenance System and with an identical crew profile to the ISS DRM with the exception that 2 crewmembers perform 2 EVAs per week each. Figure 7 provides a comparison of CHI on the ISS 6-month and Mars 2.5-year DRMS with limited quantities of ISS Health Maintenance System resources available.

Table 1. ISS 6 month, 6 crew mission.

	No Medical Resources			**ISS Health Maintenance System**			**Unlimited Medical Resources**		
	Mean	95% Confidence Interval		Mean	95% Confidence Interval		Mean	95% Confidence Interval	
		Lower Bound	Upper Bound		Lower Bound	Upper Bound		Lower Bound	Upper Bound
TME	98.3	73	122	106	87	126	106	87	126
CHI	59.2	43.36	71.25	94.93	84.32	98.46	94.98	84.44	98.47
pEVAC	66.9	66.57	67.14	5.57	5.43	5.72	4.93	4.8	5.07
pLOCL	2.89	2.78	2.99	0.44	0.4	0.49	0.45	0.41	0.49

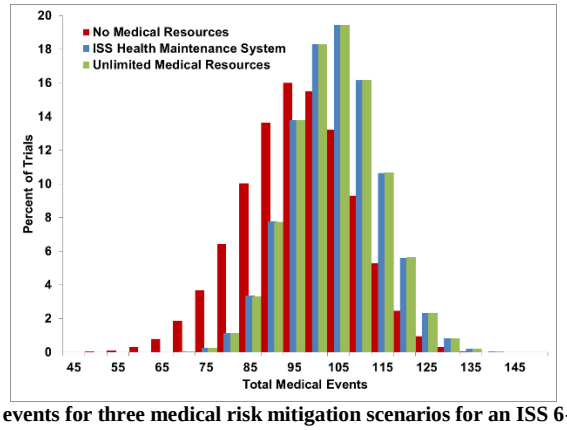

Figure 4. Total medical events for three medical risk mitigation scenarios for an ISS 6-month, 6-crew mission.

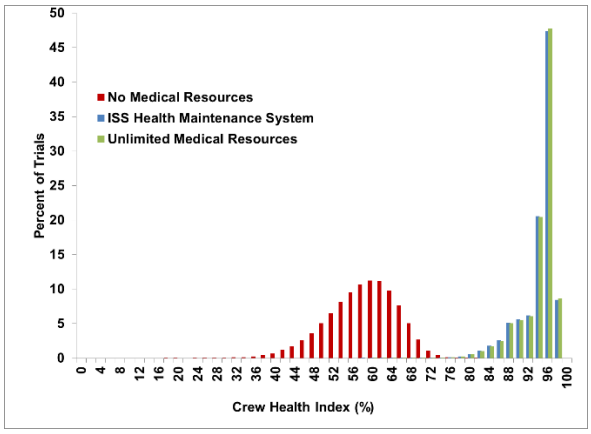

Figure 5. Crew health index over 100,000 trials for an ISS 6-month, 6-crew mission.

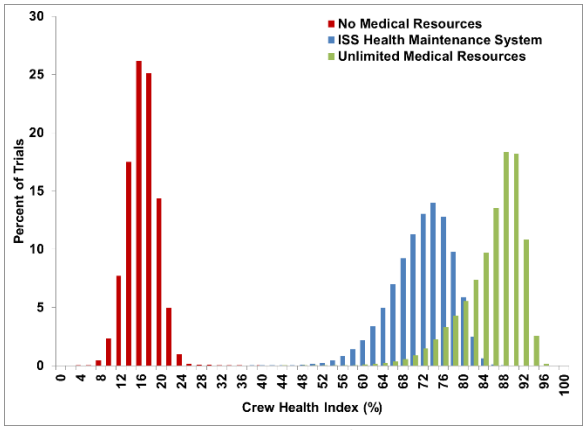

Figure 6. Crew health index over 100,000 trials for a Mars 2.5-year, 6-crew mission.

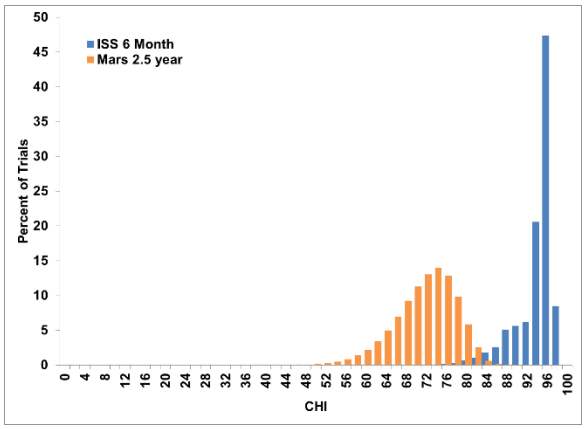

Figure 7. Crew Health Index comparison with limited quantities of resources from the ISS Health Maintenance System available on ISS 6-month and Mars 2.5-year missions.

IV. Conclusions

Effective risk management is an integral aspect of human spaceflight and is critical to program and project success. The IMM serves as a quantitative, objective tool for risk managers and mission planners by providing aggregate risks that can be compared across mission profiles as well as more granular information such as medical conditions, crew characteristics, and mitigations most influential to those risks. For example, the IMM has been used to determine the impact of certain resources being unavailable, the impact of crewmember medical attributes, and which consumable resources are most sought on a long-duration mission. Information from the IMM has also been

used for a medical kit optimization routine that generates medical kits to meet mass and volume constraints while maximizing CHI or minimizing pLOCL and pEVAC for specified mission and crew profile constraints.[18]

The IMM was initially developed for ISS planning, and model inputs were baselined to the ISS. To make the model more meaningful for exploration-class mission, some model outputs could be reconsidered. For example, on exploration missions, evacuation is not possible in the same sense as was intended when the parameter was initially developed. A loss-of-mission output metric might be more meaningful in the context of exploration missions and this development is currently underway. Further, the complexities of multiple co-morbidities and the effects of a crewmember with a communicable medical condition on the probability that other crewmembers contract the same illness are not modeled. Future work might also include modeling ISS countermeasures beyond medical resources, such as the advanced resistive exercise device (ARED) and treadmill, modeling the failure of medical risk mitigations, modeling radiation risks beyond those associated with SPEs, and modeling vehicle environmental systems with medical condition correlates.

Appendix

Medical Condition	Incidence Data Source	Incidence Distribution	Risk factors
Abdominal Injury	Terrestrial	Gamma	
Abdominal Wall Hernia	Terrestrial	Gamma	
Abnormal Uterine Bleeding	Terrestrial	Fixed	Sex
Acute Arthritis	Terrestrial	Fixed	Sex
Acute Cholecystitis/Biliary Colic	Astronaut pre- and postflight data, Terrestrial data	Lognormal	Sex
Acute Compartment Syndrome	Terrestrial	Fixed	Sex
Acute Diverticulitis	Terrestrial	Fixed	
Acute Glaucoma	Terrestrial	Fixed	Sex
Acute Pancreatitis	Terrestrial	Fixed	
Acute Prostatitis	Terrestrial	Fixed	Sex
Acute Radiation Syndrome	Terrestrial	Fixed	SPE
Acute Sinusitis	In-flight	Gamma	
Allergic Reaction (mild to moderate)	In-flight	Gamma	
Altitude Sickness	Terrestrial	Lognormal	
Anaphylaxis	Terrestrial	Fixed	
Angina/Myocardial Infarction	Terrestrial	Fixed	Sex
Ankle Sprain/Strain	In-flight	Gamma	
Anxiety	Terrestrial	Fixed	Sex
Appendicitis	Astronaut pre- and postflight data, Terrestrial data	Lognormal	
Atrial Fibrillation/ Atrial Flutter	Astronaut pre- and postflight data, Terrestrial data	Lognormal	Sex
Back Injury	In-flight	Gamma	
Back Pain (Space Adaptation)	In-flight	Beta	
Barotrauma (ear/sinus block)	In-flight	Gamma	
Behavioral Emergency	Terrestrial	Fixed	
Burns secondary to Fire	External model	Fixed	
Cardiogenic Shock secondary to Myocardial Infarction	Terrestrial	Fixed	Sex
Chest Injury	Terrestrial	Gamma	
Choking/Obstructed Airway	In-flight	Gamma	
Constipation (space adaptation)	In-flight	Beta	
Decompression Sickness Secondary to Extravehicular Activity	Terrestrial	Beta	EVA
Dental : Exposed Pulp	Terrestrial	Fixed	
Dental Caries	Astronaut pre- and postflight data, Terrestrial data	Lognormal	
Dental: Abscess	Astronaut pre- and postflight data, Terrestrial data	Lognormal	
Dental: Avulsion (Tooth Loss)	Terrestrial	Fixed	

Medical Condition	Incidence Data Source	Incidence Distribution	Risk factors
Dental: Crown Loss	Terrestrial	Fixed	Crowns
Dental: Filling Loss	Terrestrial	Fixed	
Depression	Terrestrial	Fixed	Sex
Diarrhea	In-flight	Gamma	
Elbow Dislocation	Terrestrial	Fixed	
Elbow Sprain/Strain	In-flight	Gamma	
Eye Abrasion (foreign body)	In-flight	Gamma	
Eye Chemical Burn	In-flight	Gamma	
Eye Corneal Ulcer	Terrestrial	Fixed	Contacts
Eye Infection	In-flight	Gamma	
Eye Penetration (foreign body)	Terrestrial	Fixed	
Finger Dislocation	In-flight	Gamma	
Fingernail Delamination	In-flight	Beta	EVA
Gastroenteritis	In-flight	Gamma	
Head Injury	Terrestrial	Gamma	
Headache (CO2 induced)	In-flight	Gamma	
Headache (Late)	In-flight	Gamma	
Headache (space adaptation)	In-flight	Beta	
Hearing Loss	In-flight	Gamma	
Hemorrhoids	In-flight	Gamma	
Herpes Zoster Reactivation (shingles)	In-flight	Gamma	
Hip Sprain/Strain	In-flight	Gamma	
Hip/Proximal Femur Fracture	External model	Lognormal	Sex
Hypertension	Terrestrial	Fixed	
Indigestion	In-flight	Gamma	
Influenza	In-flight	Gamma	
Insomnia (space adaptation)	In-flight	Beta	
Knee Sprain/Strain	In-flight	Gamma	
Late Insomnia	In-flight	Gamma	
Lower Extremity (LE) Stress Fracture	Terrestrial	Fixed	Sex
Lumbar Spine Fracture	External model	Lognormal	Sex
Medication Overdose/Adverse Reaction	In-flight	Gamma	
Mouth Ulcer	In-flight	Gamma	
Nasal Congestion (space adaptation)	In-flight	Beta	
Neck Injury	In-flight	Gamma	
Nephrolithiasis	Astronaut pre- and postflight data, Terrestrial data	Lognormal	
Neurogenic Shock	Terrestrial	Fixed	
Nose bleed (space adaptation)	In-flight	Beta	
Otitis Externa	In-flight	Gamma	

Medical Condition	Incidence Data Source	Incidence Distribution	Risk factors
Otitis Media	In-flight	Gamma	
Paresthesias	In-flight	Beta	EVA
Pharyngitis	In-flight	Gamma	
Respiratory Infection	In-flight	Gamma	
Retinal Detachment	Terrestrial	Fixed	Sex
Seizures	Astronaut pre- and postflight data, Terrestrial data	Lognormal	
Sepsis	Terrestrial	Fixed	
Shoulder Dislocation	Terrestrial	Fixed	
Shoulder Sprain/Strain	In-flight	Gamma	
Skin Abrasion	In-flight	Gamma	
Skin Infection	In-flight	Gamma	
Skin Laceration	In-flight	Gamma	
Skin Rash	In-flight	Gamma	
Small Bowel Obstruction	Terrestrial	Fixed	History of abdominal surgery
Smoke Inhalation	External model	Fixed	
Space Motion Sickness (space adaptation)	In-flight	Beta	
Stroke (cerebrovascular accident)	Astronaut pre- and postflight data, Terrestrial data	Lognormal	Sex
Sudden Cardiac Arrest	Terrestrial	Fixed	Coronary artery calcium
Toxic Exposure: Ammonia	External model	Fixed	
Traumatic Hypovolemic Shock	Terrestrial	Fixed	
Urinary Incontinence (space adaptation)	In-flight	Beta	Sex
Urinary Retention (space adaptation)	In-flight	Beta	Sex
Urinary Tract Infection	In-flight	Gamma	Sex
Vaginal Yeast Infection	Terrestrial	Gamma	Sex
Visual Impairment and Intracranial Pressure (VIIP)(space adaptation)	In-flight	Beta	
Wrist Fracture	External model	Lognormal	
Wrist Sprain/Strain	In-flight	Gamma	

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