Influenza Cliff

Branch Baseline

Influenza (flu) is a contagious respiratory illness caused by influenza viruses that infect the nose, throat, and lungs. It can cause mild to severe illness, and at times can lead to death. Some people may have vomiting and diarrhea, though this is more common in children than adults (CDC, 2011).

Influenza is a single-stranded, helically shaped, RNA virus of the orthomyxovirus family. Basic antigen types A, B, and C are determined by the nuclear material. Type A influenza has subtypes that are determined by the surface antigens hemagglutinin (H) and neuraminidase (N). Three types of hemagglutinin in humans (H1, H2, and H3) have a role in virus attachment to cells. Two types of neuraminidase (N1 and N2) have a role in virus penetration into cells. Virus is shed in respiratory secretions for 5–10 days. The incubation period for influenza is usually 2 days, but can vary from 1 to 4 days. Influenza occurs throughout the world. Adults can transmit influenza from the day before symptom onset to approximately 5 days after symptoms begin (CDC, 2011).

Incidence Data Included in the Model

The model imports the following incidence information from the IMM database: incidence data category, space adaption status, incidence data, incidence and occurrence distribution data and incidence data characteristics. Data category defines the type of data available for incidence calculations (i.e. raw data vs. fixed data). Space adaptation identifies medical events that onset occurs in the first 5 days of flight and does not reoccur. Incidence values vary by data category and define the number of medical events per person-year or medical events per person-at-risk for each medical condition. Incidence values can be modified by crew characteristics such as gender. Modifying characteristics are noted below and incidence values are listed individually for each characteristic. Distributions are assigned to medical events incidence values and occurrences in the model. For each crew member in a given trial, the incidence and number of occurrences of each medical condition are randomly selected from these probability distributions. Detailed descriptions of the distributions are included in the IMM Technical Description Document.

Incidence	
Data Category:	In-flight
Space Adaptation:	No
Incidence Type:	Rate

Distribution Data	
Incidence:	Gamma
Occurrence:	Poisson

Data Characteristics	
Events:	1
Person Years:	45.49
Space Flight Incidence Rate (Events / Person Years):	1 / 45.49 = 0.021982853374368

Incidence Comments

Five cases of Influenza or “flu-like” symptoms have been reported in space flight(Walton, 2010)

However, only one case was confirmed by titers as influenza Type A. This case included symptoms of fever, headache, and malaise.

The resulting in-flight incidence of 0.0365 events/person-year is consistent with the meta-analysis of the annual incidence rates among healthy vaccinated terrestrial populations (0.0304 cases/person-year, 95% CI of 0.0179 to 0.0515). These healthy vaccinated terrestrial populations are most comparable to the astronaut population.

Although infuenza is a seaonal illness, annual incidence rates are used in the model.

Integrated real world system incidence data (Saile, 2017).

Updated the Person-Years based on the revised real world system integrated incidence data. The integrated person years changed from 18.17 to 18.13 so the conditions person years changed from 45.53 to 45.49 (Saile L., 2017)

Information Regarding Prevention

Selection criteria

Disqualifying conditions in the general category include any medical condition that, in the judgment of the MSMB, may compromise mission operations, performance of duties, or crew health or safety. In the infectious diseases category include acute or chronic infectious diseases, until appropriately treated that might compromise mission operations, performance of duties, or crew health or safety (International Space Station Program, 2011)

Contingency measures

The Flight Crew Health Stabilization program was started during the Apollo program. Crewmembers are quarantined prior to the mission to minimize and prevent exposure to infectious diseases during the prelaunch period (Wooley, 1975).

Astronauts receive the influenza vaccine annually if there are no absolute contraindications.

Incidence Level of Evidence (LOE)

The IMM level of evidence appropriate assessment of the quality of the IMM input data. Since IMM incorporates input data from a wide variety of sources including astronaut population, terrestrial or analog populations, and external models, an innovative approach to assess the quality of input data was required. Information obtained from the astronaut population and/or space flight is the more relevant so it is assigned the highest level of evidence and less relevant data sources are assigned a lower level of evidence.

Citation	LOE Value	LOE Category
Walton, 2010	1	Incidence
Saile L., 2017	1	Incidence

Alternative Incidence Data

Analog populations

In September 2009, an outbreak of 2009 pandemic influenza A (H1N1) took place in a Finnish garrison. In November 2009, we performed a serological survey among 984 recruits undergoing their military service at the garrison and related the results to self-reported upper respiratory tract infection (URTI) with or without fever. Of 346 volunteers who donated a blood sample, 169 (49%) had pandemic influenza A(H1N1) virus-specific antibodies. Of those, 84 (50%) reported no recent history of URTI, suggesting that a major part of those infected with pandemic influenza A(H1N1) virus may be asymptomatic. Military garrisons present a high risk environment for the spread of respiratory disease due to large numbers of conscripts living in close proximity (Aho, 2010). An outbreak on board a US Navy vessel reinforces the risk for rapid spread of novel strains of influenza A in confined populations (Dill, 2009)

A surveillance of influenza-related medical encounter data of active duty military service members stationed in the United States during the period of April–October 2009 was conducted using the Defense Medical Surveillance System (DMSS) database total of 1205 clinically apparent and laboratory confirmed illnesses were reported . Seventy eight (6.5%) of the 1,205 cases were hospitalized (Johns, 2010).

Non Analog populations

The CDC reported that during the period 2010-2011 hospitalization, from October to April, rates per 100,000 were for all ages 21.3; for age 18-49 11.1; and for age 50-64 22.5 (0.000213; 0.000111; and 0.000225 respectively). Outpatient visits national baseline level is 2.5%. During the season it exceeded the baseline level during the weeks ending December 25 through Mar 19, with the peak during the week of Februrary19 (CDC, 2011).

A meta-analysis was conducted in Canada to determine the annual incidence rate (IR) of influenza in healthy adults and healthcare workers, including 29 studies and 97 influenza seasons and 58,245 participants. Symptomatic and all infection (symptomatic and asymptomatic) were measured. For vaccinated working adults, n 3717, all infections, 2 seasons, the incidence rate is 1.20 in 100 population season, Confidence Interval (CI) 95% 0.86 to 1.68 (IR 0.012; CI 0.0086 to 0.0168). While symptomatic infections, n 2619, 3 seasons, had an incidence rate of 3.04, CI 95% 1.79 to 5.15 (IR 0.0304; CI 0.0179 to 0.0515) (Kuster, 2011). The subset of vaccinated working adults is the one more comparable to the astronaut population.

A study to evaluate the importance of clinical symptoms in the diagnosis of influenza virus infection included 81 patients in 14 general practices. Seventy-nine out of 81 received questionnaires could be evaluated. Clinical features of 79 patients with clinical illness during this period were compared with viral detection of influenza virus A by PCR. Cough, headache and feverishness at onset were positively correlated with influenza A virus infection; 97.5, 70 and 87.5% respectively. A positive predictive value (PPV) of 75% was observed for the combination of headache at onset, feverishness at onset, cough, and vaccination status during the period of increase influenza activity. Practitioners using the International Classification of Health Problems in Primary Care (ICHPPC-2). diagnosis criteria resulted in a 54% PPV (van Elden, 2001)

Treatment and Outcomes

Based on the best evidence available best and worst case percentage ranges are assigned. The medical condition is divided into three clinical phases in all three clinical phases a functional impairment is assigned. The clinical phase I and II's functional impairments remain for the duration for that respective clinical phase. The function impairment in clinical phase III represents final impairment for this medical condition and remains for the rest of the mission. Other mission end states include evacuation and loss of crew life.

The IMM checks medical resource availability once the number of medical events and scenarios has been established. If there is not sufficient essential resources called out in the CliFF, then the medical condition will go down an untreated best or worst case scenario pathway.

The table below summarizes the treated and untreated best and worst case scenarios.

	Clinical Phase I Diagnosis & Initial Treatment[1]		**Clinical Phase II On-going Treatment / Convalescence[2]**		**Clinical Phase III Recovered / Mission End State[3]**		
	FI* (%)	**Duration (hrs)**	**FI* (%)**	**Duration (hrs) (Min - ML - Max)**	**FI* (%)**	**EVAC** (%)**	**LOCL** (%)**
ISS-based Treatment (best case scenario %: 50 - 100)	100	0.3	0 - 10	24 - 48 - 72	0	0	0
ISS-based Treatment (worst case scenario %: 0 - 50)	100	0.3	2 - 23	72 - 96 - 120	0	0	0
Untreated Best Case	N/A	N/A	2 - 23	24 - 48 - 72	0	0	0
Untreated Worst Case	N/A	N/A	11 - 40	72 - 96 - 120	2 - 40	0	0

[1]Clinical Phase I: Clinical phase I covers only the initial assessment of the affected crew member to define his or her medical condition, and completion of appropriate initial treatment to stabilize the crew member. While the affected crew member is being assessed, he or she is not able to perform any assigned tasks, thus Functional Impairment during this phase is considered 100%. In the untreated case, there is no diagnosis performed or treatment given, therefore Functional Impairment and Duration will always be "not applicable".

[2]Clinical Phase II: On-going Treatment and Convalescence- During clinical phase II, the affected crew member is receiving any appropriate follow-on treatment for his or her medical condition to allow the crew member to recover as much as he or she is able to recover in the ISS environment. Clinical phase II also encompasses relapses or reoccurrences of the same original medical condition in clinical phase I necessitating additional treatment or recovery time due to unsuccessful primary treatment response. The duration in Clinical Phase II is expressed in minimum, most likely (ML) and maximum hours. This was updated for future capabilities in IMM but is currently not being used by the model.

[3]Clinical Phase III: Recovered/Mission End State- Clinical phase III is reached once the affected crew member has recovered from the medical condition as much as he or she is able to recover in the ISS environment. This may or may not be recovery from the given medical condition to the full extent possible. If this "recovered" state results in an evacuation or loss of the crew member, this will be noted in the mission end state results.

*Functional Impairment (FI) is a measure of the affected crew member's health and performance ability.

**Two mission end state results are addressed in the CliFF: 1) Evacuation (EVAC) - crew and patient are evacuated from the spacecraft due to the medical condition, and 2) Loss of crew (LOCL) - death of affected crew member due to medical condition. EVAC is considered as an end state result if any of the following criteria are met: 1) potential LOCL, 2) potential significant permanent impairment, or 3) potential intractable pain. Probability distributions are assigned for each range of values within the Table of Treatments and Outcomes.

Refer to the Integrated Medical Model Technical Document for more information on how risk is reported by the IMM, Crew Health Index (CHI) and Quality Adjusted Mission Time calculations.

Definition and Probability of Best and Worst Case Scenario: (includes definitions of best and worst case scenarios and identifies the probability of those scenarios.)

Scenario Comments

The best case scenario is defined as a mild case of influenza lasting 48 to 72 hours.

The worst case scenario is defined as a moderate to severe case of influenza that lasts 72 hours or longer.

All on board cases have been best cases, with durations from 24 to 48 hours.

Pneumonia may occur as a complication of Influenza. Respiratory Infection and Septic Shock are addressed in separate Clinical Finding Forms.

The percentages of how often best versus worst case scenario occur were determined using in-flight data of the one confirmed influenza case (Walton, 2010). The one confirmed in-flight case had a duration of less than 72 hours. If the next case has a duration of more than 72 hours, then 50% are best case scenario and 50% are worst case scenario. However, if the next case of in-flight influenza is a best case scenario, then 100% of cases are best case scenario and 0% are worst case scenario. Therefore, to capture this uncertainty, the best case scenario percentage is estimated as 50% to 100% and the worst case scenario percentage is estimated as 0% to 50%.

Best Case Comments

Influenza's functional impairments (FI) calculation follows the IMM mild non-space adaptation template. Pulmonary dysfunction ratings are based on Table 5-4, p.88 (American Medical Association, 2008).

By definition FI in **Clinical Phase I is 100%** and duration is estimated in 20 minutes. There is no procedure in the ISS Medical Checklist for Influenza. We are estimating that the duration will be comparable to physical exam procedure in the ISS medical checklist. In **Clinical Phase II** FI is estimated to be 0 to 10%. By definition, duration is estimated at 24 to 72 hours. In **Clinical Phase III** recovery is expected and FI is estimated at 0%. Influenza is a Class IIa medical event, manageable with HMS and not likely to require evacuation or affect mission duration. (Johnston, 2008) EVAC and LOCL are not expected.

Worst Case Comments

Influenza's functional impairments (FI) calculation follows the IMM mild non-space adaptation template. Pulmonary dysfunction ratings are based on Table 5-4, p.88 (American Medical Association, 2008).

By definition FI in **Clinical Phase I is 100%** and duration is estimated in 20 minutes. There is no procedure in the ISS Medical Checklist for Influenza. We are estimating that the duration will be comparable to physical exam procedure in the ISS medical checklist. In **Clinical Phase II** FI is estimated to be 2 to 23%. Duration is estimated at 72 to 120 hours (CDC, 2011). In **Clinical Phase III** recovery is expected and FI is estimated at 0%. Influenza is a Class IIa medical event, manageable with HMS and not likely to require evacuation or affect mission duration. (Johnston, 2008). An influenza outbreak in 1999 caused 232 sick cases aboard a Navy ship. Ill crewmembers missed 106 working days. There was one MEDEVAC secondary to infection complications (1/232 = 0. 43%) (Earhart, 2001). EVAC and LOCL are not expected.

Untreated Best Case Comments

Influenza's functional impairments (FI) calculation follows the IMM mild non-space adaptation template. Pulmonary dysfunction ratings are based on Table 5-4, p.88 (American Medical Association, 2008).

During **Clinical Phase II** FI is estimated to be 2 to 23%. By definition, duration is estimated at 24 to 72 hours. In **Clinical Phase III** there is no treatment available; recovery is expected and FI is estimated at 0-10%. Influenza is a Class IIa medical event, manageable with HMS and not likely to require evacuation or affect mission duration. (Johnston, 2008) EVAC and LOCL are not expected.

Untreated Worst Case Comments

Influenza's functional impairments (FI) calculation follows the IMM mild non-space adaptation template. Pulmonary dysfunction ratings are based on Table 5-4, p.88 (American Medical Association, 2008).

During **Clinical Phase II** FI is estimated to be 11 to 40%. Duration is estimated at 72 to 120 hours (CDC, 2011). In **Clinical Phase III,** there is no treatment available. Full recovery is uncertain and FI is estimated at 2-40%. Influenza is a Class IIa medical event, manageable with HMS and not likely to require evacuation or affect mission duration. (Johnston, 2008)EVAC and LOCL are not expected.

Treatment and Options Level of Evidence (LOE)

The IMM level of evidence appropriate assessment of the quality of the IMM input data. Since IMM incorporates input data from a wide variety of sources including astronaut population, terrestrial or analog populations, and external models, an innovative approach to assess the quality of input data was required. Information obtained from the astronaut population and/or space flight is the more relevant so it is assigned the highest level of evidence and less relevant data sources are assigned a lower level of evidence.

Citation	LOE Value	LOE Category
American Medical Association, 2008	3	FI
Johnston, 2008	2	EVAC
Walton, 2010	1	BCWC

The Resource Table (RT)

Resource	Units Required Best Case	Units Required Worst Case	Units Available At Start Of Mission	Consumable	Essential	Rationale
Benzonatate (Tessalon Perles) 100mg	10	20	30	Yes	Yes	To suppress cough
Dextromethorphan (Robitussin) 15mg capsule	10	20	20	Yes	Yes	Cough expectorant
Sudafed 12 Hour (Pseudoephedrine) 120 mg	10	10	100	Yes	Yes	Reduce congestion
Tylenol (Acetaminophen) 325 mg	15	24	150	Yes	Yes	Pain/malaise relief

Resource Comments

In the United States, four antiviral agents are approved for preventing or treating influenza: amantadine, rimantadine, zanamivir (Relenza), and oseltamivir (Tamiflu). (CDC, 2011). None of them are available on board (Mission Operations Directorate (MOD), 2011).

Resources available on board are used for symptomatic relief of fever, malaise, and nasal congestion.

Required Resources Level of Evidence (LOE)

The IMM level of evidence appropriate assessment of the quality of the IMM input data. Since IMM incorporates input data from a wide variety of sources including astronaut population, terrestrial or analog populations, and external models, an innovative approach to assess the quality of input data was required. Information obtained from the astronaut population and/or space flight is the more relevant so it is assigned the highest level of evidence and less relevant data sources are assigned a lower level of evidence.

Citation	LOE Value	LOE Category
CDC, 2011	3	Resources
NASA Mission Operations Directorate (MOD), 2011	2	Resources

Level Of Evidence

Input Data	LOE Average
Incidence	1
Functional Impairment	3
Best Case / Worst Case	1
EVAC / LOCL	2
Resources	2.5
QUALITY OF EVIDENCE	**1.9**

Description	Range
Excellent	1-2
Good	2.1-3
Fair	3.1-4
Poor	4.1-5

Reference List

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