THE CLINICAL IMPACT OF RESPIRATORY VIRUSES

THE CLINICAL IMPACT OF HOSPITALIZATION DUE TO RESPIRATORY SYNCYTIAL VIRUS AND HUMAN METAPNEUMOVIRUS AS COMPARED TO INFLUENZA A IN THE ADULT POPULATION

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**Abstract**

**Background:** Respiratory Syncytial Virus (RSV) and Human Metapneumovirus (hMPV) are major respiratory pathogens in children, and are increasingly recognized as causes of significant illness in the adult population, particularly in seniors. Furthering our understanding of the clinical context of these illnesses will inform policy and practice on how best to use treatment and preventative measures when they become available. **Methods:** First, we conducted a retrospective chart review of adult patients hospitalized with RSV, hMPV, or Influenza A (2011-2016) at St. Joseph’s Healthcare Hamilton. All RSV and hMPV inpatients were included in the study, and a random sample of inpatients with Influenza A in each year were then selected. Second, we conducted an analysis of The FOREVER cohort (2011-2014), a linked laboratory and administrative data set that included the three major acute care centres in the Hamilton/Niagara Region. Outcomes were length of hospital stay, mortality, and changes in disposition post-hospitalization. **Results:** Patients with RSV (p<0.001) and hMPV (P=0.04) were observed to be older than those with influenza A and be more likely to reside in long term care facilities. Moreover, patients that were hospitalized with RSV and hMPV had longer lengths of hospital stay and higher odds of mortality after controlling for age, sex, and comorbid conditions in multi-variable models. There were no differences observed in changes of disposition following hospitalization between the three infections groups. There was a high level agreement between the two methodologies with regard to baseline characteristics, length of stay, and mortality. Differences were observed in the proportions of patients that were admitted to the ICU during their hospital stay and the proportion that were discharged to long term care facilities. **Conclusions:** RSV and hMPV in adult inpatients was half as common as Influenza A, and had comparable, if not worse outcomes.

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# **Chapter 1: Introduction**

Respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) are respiratory illnesses that pose a large burden in all populations. While RSV and hMPV are most studied in the pediatric population, these viruses are also capable of causing significant disease in the adult populations, especially in those with chronic conditions and in the elderly. Herein, we will explore how these viruses cause disease, their burden in adult populations, and gaps in this body of literature.

## **Respiratory Syncytial Virus (RSV)**

RSV is transmitted through close or direct contact with an individual that already has the infection, with the most common mode of transmission being large particle aerosols. RSV is incubated for two to eight days. An adult can shed the virus for three to seven days after infection while immunocompromised patients can be contagious for up to four weeks (1). Most children experience RSV before the age of two, however, they do not acquire complete immunity to the virus so reinfection later in life is possible. It is also possible that viral immune evasion through antigenic drift plays a significant role in the possibility of reinfection (2). Both the innate and adaptive immune response are important in the body’s process of clearing RSV infection. First, RSV interacts with the monocyte receptor CD14+, eliciting inflammation in the respiratory tract. RSV then inhibits T-Cell proliferation and inhibits the overall host response to the virus (3).

 Respiratory syncytial virus is a single-stranded, negative sense RNA virus. Once in the cell, an RNA strand, complementary to innate mRNA must be transcribed to form positive sense RNA which can then be translated into proteins. Infection occurs when the virus binds to cell surface glycosaminoglycans (4). The surface of the virus is coated with three glycoproteins: the attachment glycoprotein (G) which binds to receptors on airway epithelial cells (Cx3C chemokine receptor 1) inducing cell signaling and the fusion glycoprotein (F) which binds to nucleolin. The F protein facilitates a pH-independent fusion of virus to viral membrane which allows for the virus to gain access to the cell’s cytoplasm (2). Additionally, it is involved in the formation of syncytia between cells, leading to characteristic, *in vitro* RSV cytopathic effect (4). The final surface glycoprotein, the SH protein inhibits cell apoptosis. When G protein is removed from the surface, attenuated virus still is formed. Whereas when F protein is removed from surface, no virus is detected therefore it is a popular target for vaccinations as well as antiviral therapy. There are two non-structural proteins, NS1 and NS2, which are associated with the RSV virus. These proteins are involved in the inhibition of the host’s immune response as well as apoptosis inhibition (2).

There are two serotypes of RSV, A and B that are characterized by different antigenic reactivity of monoclonal antibodies. The viruses are distinct due to varying nucleotide sequences, reactivity patterns with monoclonal antibodies, and different responses to specific antisera. Within each subgroup, variation in the G protein has been observed (5, 6). There is no consensus on which serotype of RSV, A or B, is more severe. Many studies have come to the conclusion that they are equally as severe, whereas others have argued that one or the other leads to worse outcomes. Variables that have been used to demonstrate this are percentage of patients that require mechanical ventilation, and ICU admission (7). The predominant serotype has been shown to change from year to year (6). Some models have proposed a cyclical nature to the shift in predominant serotype. One explanation for this shift is that individuals develop transient immunity to the predominating serotype that can last for up to two years (8).

While RSV does inhibit part of the initial immune response, following recognition by the host cell via toll-like-receptors a change in gene expression occurs. Dendritic cells up regulate cytokines, chemokines, and cell surface molecules. Many of these cells signal an influx of natural killer cells, granulocytes, monocytes, macrophages, etc. that have antiviral properties and begin the adaptive immune response (2). Some important cytokines that are involved in this response are: interleukin (IL)–1b, a chemoattractant for neutrophils that enhances phagocytosis, tumor necrosis factor–a (TNF-a), which is associated with shock and neutrophil chemotaxis in the lungs, IL-6, which is associated with production of acute-phase reactants, fever, and antibody production, IL-8, which is the most potent neutrophil chemoattractant, and IL-12, which induces both the differentiation of CD4+ T cell responses to Th1 and the activation of NK cells (3). Following this innate response to the RSV virus, clearance of the infection is correlated to humoral immunity mediated control and Th1 cell mediated immune response (1). As part of the adaptive immune response, serum immunoglobulin A and G, respectively clear the infection from the upper and lower respiratory track (2). This can be noted when comparing the immune response in children to the elderly. Children typically elicit a restricted humoral response to the virus, whereas adults elicit a broader neutralizing and antibody response (9).

## **Human Metapneumovirus (hMPV)**

Human metapneumovirus was discovered in 2001 and has since been grouped with many of the other influenza-like-illnesses. The virus belongs to the same family as RSV but is part of a separate genus. Human MPV is a negative sense, single stranded RNA virus and undergoes same transcription and translation process as RSV. The cytopathic effects of hMPV are indistinguishable from RSV, as previously stated when epithelial cells in the airway are infected they form syncytia which can lead to obstruction of the airway and difficulty breathing (10). There are some key differences in the genomes of the pathogens that lead to their distinction, namely the absence of the non-structural proteins that are found in RSV. The three transmembrane glycoproteins that are apart of the hMPV are analogous to proteins in the RSV virus. First, the small hydrophobic protein which is implicated in inhibition of the innate and adaptive immune response. Second, a heavy glycosylated putative attachment protein which binds to the cell. Finally, the fusion glycoprotein which mediates viral fusions and entry of viral RNA into the cell. Additionally, there are a matrix protein lines (M2-1 M2-2), which are also present in RSV which play a role in budding and viral assembly (10). Notably, hMPV lacks the non-structural genes that are found in RSV, which indicates that there is a different mechanism for immune system evasion (3).

There are four subtypes of hMPV that are in circulation. The predominant serotypes vary from season to season. The pattern of this variation is not well established (11). The differences in the types of the virus are found in the SH protein and the G proteins, while the F protein is well conserved between serotypes. Differences in the virulence of the serotypes have been reported to be associated with genetic variability in the G protein (12).

Repeated infections with hMPV are common throughout life, as they are with RSV. Again, incomplete adaptive immunity is frequently pointed to as the primary culprit for this but antigenic drift leading to genetic variability in the virus is also a reasonable cause. It has been reported, that while RSV is capable of inhibiting CD4+ T-cell, production it is not as clear that hMPV is. However, the G protein of hMPV has been described to inhibit cell signaling and the innate immune response, possibly also inhibiting CD8+ T-cell production (13).

Following infection with hMPV, dendritic cells up-regulate different cytokines through interactions with toll-like receptors (14). The primary cytokine that is up-regulated following infection is IFN-α, which aids in restricting viral replication (3). The absence of the cytokines that are produced in an RSV infection leads to a weaker pro-inflammatory immune response. Clearance of the virus, correlates to an accumulation of cytotoxic CD8+ t-cells, which are recruited by IFN signaling. It has been shown that in older mice, CD4+ T-cells may also play an important role in clearance of the virus. Much of the innate and adaptive immune response to hMPV is poorly understood and more research is needed in order to produce effective vaccines and treatment (15).

## **Seasonality of RSV and hMPV:**

In North America the RSV and hMPV season are comparable and typically last from October to May. The seasons coincide with rainy seasons but do not perfectly overlap with influenza season. The peak of seasons between the two illnesses vary, the annual RSV epidemics peak between the months of October and January, while hMPV is observed to peak one to two months later in the season (10, 16). The more temperate the environment, the longer the duration of the season usually is. For example, the season is longer in the American South than it is in Southern Canada (17). Some studies have suggested that RSV and hMPV circulate in cyclical epidemics that are anti-cyclical with respect to each other (16). Within a season, the different serotypes of RSV and hMPV are reported to co-circulate with different serotypes being predominant each year (8).

## **Prevention and treatment of RSV and hMPV:**

The best current treatment of RSV and hMPV in all populations is supportive treatment such as intravenous fluids, oxygen, and mechanical ventilation if needed. There is only one antiviral for treatment of both illnesses, ribavirin, a nucleoside analog. However, the efficacy of ribavirin is not considered to be significant, and has not been well explored in patients with hMPV (18). There are antivirals targeting the F fusion protein for both RSV and hMPV that are being developed, but are still being tested in clinical trials (19).

There are prophylactic treatments for RSV that have been proven to be effective. Palivizumab is a virus neutralizing monoclonal antibody. The antibody binds to antigenic A site of the F protein which prevents fusion of the virus to the cell in turn this inhibits the neucleocapsid from gaining entry into the cell. Furthermore, if the virus does gain entry into one cell it prevents the spread of the virus between cells, and limits syncytia formation (20). Motavizumab is a derivative of palivizumab that has higher binding affinity for the F protein (21). While these monoclonal antibodies are highly effective, it is only approved for use in high risk infants, e.g. premature infants, those with chronic lung disease, or those that are immunocompromised. This is because while effective, it is expensive totaling upwards of 5,000 dollars per patient per RSV season for full protection (22). In the pediatric population, a more cost effective solution to controlling RSV is needed, and as will be explored later, a vaccine is also indicated in the adult population. New monoclonal antibodies targeting the F protein as well as the G protein are in development, however none are yet to be licensed (21, 23). Using glucocorticosteriods to treat infection has been shown to lead to increased viral replication and exacerbated illness (24)

Monoclonal antibodies targeting the F protein in hMPV are being developed similar to palivizumab for the high risk infant population. However, like palivizumab they will likely be expensive and not a good solution for the general population. An RNAi antibody has been shown to reduce HA titers in mice. The reduced viral load leads to a reduced severity of infection, but does not inhibit viral growth and does not prevent infection (19).

With the knowledge of RSV and hMPV in the pediatric population, treatment and prevention of illness have been a priority. One of the early attempts that was made to make a RSV vaccine, was through the inactivation of formalin. This is a similar practice to how the influenza vaccine was first developed. However, this resulted in exacerbated illness and the death of two children. It is thought that this was due to mediation by non-neutralizing antibodies that form immune complexes and lead to lung damage (25). Additionally, an exacerbated immune response through poor toll-like receptor stimulation, and increased T helper type 2 responses lead to a more significant inflammatory response. Since the first unsuccessful vaccine attempt, no vaccine has been brought to the market. There are 16 candidates for RSV vaccines that are currently being developed. The candidate vaccines fall into the categories of live-attenuated, subunit, vectored, and immune-stimulant vaccines. The vaccines are mostly in phase 1 clinical trials, with one subunit vaccine entering phase 3 clinical trials (26). The subunit RSV-F vaccine (the most advanced in testing) is being tested for the age categories of 2-6, 18-49, and greater than 60. While it does not address illness in the highest risk population (infants under the age of two), it is a promising candidate for the adult and elderly populations. Similar to Palivizumab, this vaccine candidate targets the F glycoprotein that is suspected to mediate viral entry into the host’s cells (26, 27).

Similar to the formalin inactivated RSV vaccine which caused increased severity of disease, in mouse models, the formalin inactivated hMPV vaccine that was developed had similar results. While not at the same stages as RSV vaccines, there are many hMPV vaccines that are being developed. The different types of vaccines are: subunit proteins, virus like particles, live attenuated viruses, chimeric vaccines, and cytotoxic t-lymphocyte epitopes. As with RSV, the F protein is a common target for many of these vaccines (19). The chimeric vaccine for hMPV, which is a live attenuated vaccine is the only candidate that has been tested in clinical trials. Unfortunately, the clinical trial (phase 2) was terminated early due to the apparent over-attenuation of the vaccine (28).

## **Epidemiology RSV and hMPV in the Adult Population:**

RSV was discovered in 1956, at this time it was quickly recognized to be an important pathogen in the pediatric population. Between its discovery and the early 1990’s the virus became recognized as contributing to infection in long-term care facilities and in nursing homes, however it was not until the 1990’s and early 2000’s that RSV began to be recognized as a pathogen in the overall adult population (29). This recognition was largely due to the development of improved diagnostic tests, namely, reverse transcriptase – polymerase chain reactions (RT-PCR) that allowed for the rapid detection of lower levels of virus (30). Adults typically have lower viral loads than children making the traditional diagnostic methods less specific and sensitive.

 Falsey et al. examined the different methods of diagnosis that were efficient and had adequate sensitivity and specificity. First, viral culture, which was the primary method of diagnosis at the time of the study, and when RSV was starting to be considered an important pathogen in the adult population, was determined to be highly insensitive and non-specific. The authors found that only 39% of all true positives were detected through viral culture as compared to serology testing. The second method that they explored was serology. While serology was found to be the best result for identifying disease, it is an inefficient method for case management due to the lengthy diagnostic time. In their study, the authors argued that their development of the RT-PCR was the best compromise between the two previous diagnostic strategies. The results of the study found that in hospitalized adults, the test had 69% sensitivity and 99% specificity and in outpatient adults, the test had 77% sensitivity and 99% specificity as compared to serology (30). Overall, this finding has allowed for a more significant exploration of RSV in the adult population.

In 2013, Falsey et al. aimed to establish RSV as a global pathogen in the adult population, in doing so, the authors also identified the global burden of hMPV. The authors did this through analyzing a large, randomized control trial comparing adjuvanted and non-adjuvanted influenza vaccine in the adult population. Influenza A was found to be the most common pathogen accounting for 35% of illness in the sample, the second most significant illness was rhinovirus accounting for 25.6% of illness in the sample. RSV (12.8%) and HMPV (10%) were the third and fourth most common causes of influenza-like-illness. Finally, coronavirus, adenovirus, and parainfluenza accounted for the majority of the remaining illnesses. From this study it was found that individuals with moderate to severe RSV were more likely to be hospitalized than individuals with other viral pathogens (31). In Ontario, Canada, the report Ontario Burden of Infections Disease Study was in agreement with the global study, were RSV was reported to be the 11th most significant pathogen contributing to disease, and the third most significant viral pathogen contributing to disease after influenza and rhinovirus. Human MPV was not in the top 20 pathogens in Ontario (32). The previous two studies built on evidence from few prior studies and have been built up on in the years that followed.

Prior to the development of molecular diagnostic tests, three cohort studies were done exploring the burden of RSV in the adult population: Dowell (sample size=47), Falsey (sample size=147), Vikerfofs (sample size=57) (33-35). In the studies done by Dowell and Vikerfofs, they stated that it was important to consider RSV in the differential diagnosis for influenza, but that it was unlikely to be observed in cases were the individual was not already sick (33, 34). In the study done by Falsey et al. the authors were some of the first to report that RSV was a serious concern in the elderly, community dwelling populations (35).

Following their initial, smaller cohort study, Falsey et al. performed the first large cohort study exploring the burden of RSV in the adult population between the years of 1999 and 2003 in Rochester NY (36). In this study there were three populations that were included: first was healthy, community dwelling, elderly (>65 years of age) individuals that did not require hospital admission; the second was in adults (>18 years of age) with chronic health conditions; and the third was a cohort of adults who were hospitalized with either RSV or influenza A (36). In all populations RSV was compared to influenza, which is a better studied and more well understood disease in the adult population. Among the community dwelling population, it was found that RSV developed annually in 3-7%of elderly adults, and in the high risk adult population it was found to develop annually in 4-10% of people studies. In both of these populations, RSV presented similarly to non-pandemic influenza. In the hospital population, the primary outcomes that were explored were length of stay, ICU, mortality, and disposition following hospitalization. In this population there was a high percentage of individuals with chronic conditions, namely cardiopulmonary conditions. The mean length of stay was 14 days for patients with RSV and 8 days for patients with influenza. The percent of those that were admitted to the ICU was slightly higher in the RSV population than the influenza population, 15% and 12% respectively. Rates of mechanical ventilation were similar to those that were admitted to the ICU. The final outcomes the study considered where mortality and disposition. There was 8% and 7% mortality in the RSV and influenza population respectively, and 5% of RSV patients and 6% of influenza patients required higher levels of care at discharge than at admission to hospital. This study, is still referenced as the primary source describing RSV in the adult community dwelling population. The study had one of the largest sample sizes to date, was a prospective study, and included the largest number of outcomes. It was the first study to show that the burden of RSV was similar to non-pandemic influenza in the adult population, and along with the limited number of previous studies showed, that RSV is a concern in the adult and elderly population and that there is a need for vaccination and treatment for RSV both generally, but also in this specific population.

When hMPV was discovered in 2001, colleagues of Falsey, took advantage of the large number of samples that were used to compare RSV to influenza to explore this newly discovered disease (37). In their sample of 1386 hospitalized patients, over the four winters of study, 118 hMPV infections were detected. This number represented 8.5% of those tested and 8.0% of the illnesses evaluated. Clinically, the authors found that those with hMPV had a mean length of hospital stay was 9 days, 13% of those with hMPV were admitted to the ICU, 11% required mechanical ventilation, and there was 6% mortality. These outcomes were comparable to the outcomes of influenza A and RSV that were previously reported. In the community-dwelling populations, healthy-elderly and adults with chronic illness, the incidence ranged from 2.2% to 10.5% of influenza-like-illnesses annually. Many of these infections were asymptomatic. In the cases that were symptomatic, a proportion was associated with secondary infections such as influenza A and coronaviruses. This study concluded that hMPV was also a concern in the adult population, and that vaccine development would be beneficial. Disposition following diagnosis was not included in the retrospective analysis of the cohort. This was the first large cohort study to make an attempt at quantifying the burden of hMPV in the adult population (37).

Following this large cohort study conducted at the turn of the century, others have continued to explore the burden of RSV and hMPV globally. Many of the authors have used influenza as a comparator as it is a well-studied illness and it is better understood in adults in? the general population.

 Widmer et al. published two cohort studies comparing RSV and hMPV. In the first of these studies, the authors explored rates of RSV, hMPV, and influenza in adults over the age of 50 years. In their results, over the course of 3 years (2006-2009), they found similar rates of hospitalization for all three viruses. With regards to RSV, they found that patients who were hospitalized with their illness, were more likely to be older, or immunocompromised than those with influenza. Additionally, hMPV patients were more likely to be older, have cardiovascular disease, were less likely to be smokers, and were more likely to have received influenza vaccine than influenza patients. Finally, while minimal, the authors found that hospitalization rates of RSV and hMPV were higher than hospitalization rates of influenza in adults aged ≥65 years. They suggested that this was likely due to successful vaccination of the older population in the United States (38).

In the second study conducted by Widmer et al. rates of hospitalization for RSV and hMPV in the adult population (> 18 years of age) were compared across a single season(39). In this study, the authors did not use influenza as a comparator. Of the 1,248 samples that were tested, RSV was detected in 32 and hMPV was detected in 33 through RT-PCR. Respectively, 24 and 27 of those that tested positive were hospitalized with their identified illnesses. Comorbidities were detected in 87% of all individuals that presented to the care center. Of those that were hospitalized the median length of stay for patients with RSV was 4 days, 17% of those participants were admitted to the ICU, 4% required mechanical ventilation and all-cause mortality was reported in 4% as well. Individuals with hMPV had marginally shorter lengths of stay (median =3 days), and 7.4% were admitted to the ICU. The need for mechanical ventilation and all-cause mortality was not experienced by anyone in this population. This study was the first prospective cohort study to estimate the burden of disease of hMPV (39). The primary limitations of this study was that it only spanned a single year and had a small sample size. However, with those limitations in mind, the authors report that during the pandemic influenza season (2009-2010) they observed similar rates of hospitalization for RSV and hMPV to those reported by others for pandemic influenza (10/10,000)(39).

Since the study by Widmer et al. published in 2014, no cohort studies on hMPV have been reported. Three researchers have explored RSV and have began to quantify predictors of severity of illness. From 2009-2011, Lee et al. compared RSV to influenza across three centers in Hong Kong in the adult population using immunofluorescence assays (40). In this study, the authors explore predictors of all-cause mortality, respiratory failure requiring ventilator support, and hospitalization duration. The findings of the study showed that advanced age, radiographic pneumonia, underlying chronic lung disease, requirement for ventilation, bacterial superinfection, an elevated urea level and white blood cell count were all independently associated with poorer survival in RSV. RSV was more frequently associated with underlying chronic lung disease than influenza. In this study they found that 11.1% of RSV patients and 6.2% of influenza patients require mechanical ventilation support once hospitalized. In summary, higher morbidity and similar morality rates were reported for RSV compared to influenza, for RSV the 30- day all-cause mortality rate was 9.1% and for influenza it was 8.0%. There were not significant changes between 30-day and 60-day mortality (40).

Most recently, Park et al., attempted to build a scale for differentiation between severe RSV and self-limiting RSV upon hospital admission. They defined severe or life threatening RSV as requiring admission to ICU, need for mechanical ventilation care, or in hospital death. While self-limiting illness was considered hospital admission without need for higher level care. Using 227 RSV patients the authors developed a scale to predict life threatening RSV with 82% sensitivity and 72% specificity. The primary variables that were included in the scale were: lower respiratory tract infection, chronic respiratory disease, bacterial co-infections and fever. While this scale has not been validated in any other population, it was the first study that was done attempting to quantify how symptoms of individuals that are hospitalized predict and effect long term outcomes (41).

Finally, there has been one cohort study done in a Canadian population exploring RSV conducted between September 2012 and June 2013. McGeer et al. conducted a prospective, one season, four centre cohort study in adults over the age of 18. The researchers were interested in the outcomes of length of stay, ICU admission, need for mechanical ventilation, and in-hospital all-cause mortality. Eighty-six patients were included in the study, and they found that nearly all (97%) had chronic conditions, 15% were admitted to the ICU, 9% required mechanical ventilation, and 6% experienced all-cause mortality. Primarily, this study aimed to explore if their findings regarding RSV were comparable to those found in other studies. McGeers findings were that RSV is more prominent in individuals that are older that have underlying chronic conditions, such as cardiopulmonary diseases, or are immunocompromised. This study was in agreement with other studies confirming that RSV is a significant problem in the adult population (42).

In summary, the previously described studies detail that RSV and hMPV are concerns in the high-risk adult population and in the elderly population. The studies that have been done, point out that RSV and hMPV are associated with a risk of mortality and poor hospital outcomes. In more recent years, researchers have attempted to develop models to predict worse outcomes as a result of RSV for if and when effective vaccines become available. This information will allow for more effective use of the vaccine, and lead to more lives saved.

In the pediatric population RSV and hMPV present as a more severe illness as compared to influenza, due to the physical obstruction of smaller airways. However, in the adult population, the presentation of the illness is very similar, with RSV leading to slightly worse outcomes in most of the studies summarized. The similarity in the presentation of illness between RSV/hMPV and influenza, has contributed to the under recognition of these illnesses. The most reported symptoms associated with the viruses are coughing, labored breathing, weakness, sputum production, sore throat, muscle and joint pain, and in some cases fever (29, 36, 38, 39, 42).

## **Influenza A as a Comparator:**

Influenza is well recognized as a concern in the adult and elderly populations and has been thoroughly studied. Influenza is a good comparator illness for RSV and hMPV because of the similarities in the presentations of the illnesses and its ability to cause annual epidemics. Influenza viruses are single- stranded, negative sense RNA virus. In the adult and in the elderly population, two most common symptoms of influenza are cough and fever. There are four types of influenza (A, B, C, and D) that are categorized by their various nucleoproteins. Influenza A and B are the most common circulating serotypes of the virus, they evolve quickly and there are typically many co-circulating serotypes of these viruses, this trend contributes to the need for an annual flu vaccine.

The innate and adaptive immune responses to influenza have been well studied. Similar to RSV and hMPV when host cells are infected, the innate immune system recognizes the virus through toll-like receptors and in addition through the retinoic acid inducible gene I. This recognition initiates the immune response and leads to the production of cytokines. Type I interferons and pro-inflammatory cytokines are secreted to protect against influenza infection (43). The pro inflammatory cytokines then enhance IgM antibody responses and recruit CD4+ T cells to the site of infection which leads to the clearance of the infection(44).

Hospitalization as a result of influenza infections is strongly associated with age and presence of chronic conditions. This is consistent with what is known about RSV and hMPV (45). One of the primary differences between influenza and the previously discussed viruses is the availability of moderately effective vaccines. The first attempt at making an influenza vaccine was done in 1936. Since then, many different types of influenza vaccines that target different strains of the virus have been developed. In typical season, the vaccine effectiveness of the current seasonal (46) influenza vaccine ranges between 20 and 60 percent. The effectives of the individual vaccine may vary based on age, race, and other factors. In the elderly population the influenza vaccines are notably less effective. Receiving an influenza vaccine decreases an individual’s risk of hospitalization, protects high risk populations such as infants, and can reduce the duration and severity of illness if influenza is contracted. Additionally, the influenza vaccination has been associated with reducing the need for increased levels of care following hospitalization (47).

Another key difference between RSV/hMPV and influenza is the availability of effective antiviral treatments. While there have been contradictory results on the effectiveness of antivirals, most suggest that they are effective if administered early in illness (48). The most common antivirals are oseltamivir and zanamivir, both are reversible neuraminidase inhibitors. Neuraminidase, is a glycoprotein in the nuclear envelope of influenza virus that plays a large role in viral infection and spread throughout the body. The drugs are designed to have a higher affinity for neuraminidases as compared to human neuraminidases inhibiting virus spread (49). These drugs are not effective against RSV or hMPV because the viruses do not have surface neuraminidase glycoproteins. Antivirals have been shown to reduce the severity of illness, probability of ICU admission, hospital length of stay, and the risk of death (50). Prompt antiviral treatment has been shown to decrease the need for extended care following hospitalization in the elderly population. Exploring options to minimize the risk of hospitalizations and that continue to allow the elderly population to live independently is of interest to improve quality of life, and limit economic burdens to the health care system of interest (51).

Trends in antiviral use have changed since they became available. Prior to the influenza pandemic during the 2009-2010 season, only 30-40% of the Canadian adult population that presented to the hospital with influenza was prescribed an antiviral medication, with the most common antiviral medication being oseltamivir. During the pandemic antiviral use increased to between 80 and 90% in the adult and elderly population, and following the pandemic the percentage of adults that were prescribed antivirals fell to about 75% (52).

Overall, influenza A has shown to be a good comparator for RSV and hMPV. As summarized briefly, there is a large body of evidence that suggests it is a serious concern in the adult and elderly populations. Furthermore, it has moderately effective measures of prevention and treatment that have been developed over the last 100 years. Changes in the use of these treatments overtime has likely changed how RSV and hMPV compare now and in the future to influenza A.

## **RSV and hMPV in the Pediatric Population:**

In North America, RSV is the leading cause of hospitalization in children under one, and globally it is the leading cause of hospitalization for children under the age of five. By the age of 2 years old, virtually all children have been infected, and of those, 2% require hospitalization. RSV is one of the leading causes of death in infants worldwide. Mortality is estimated to be between 66,000-160,000 children under the age of five died from RSV or RSV complications since 2005 (53). Developed countries predominate these statistics therefore there are likely deaths in developing countries that have gone unaccounted for.

Infection is more severe in children because they have high surface area-to-volume ratio in airways so the airways are easily obstructed by the formation of syncytia as a result of RSV. Outcomes for children with single or multiple RSV infections can include: chronic sequelae (asthma), chronic bronchitis, chronic obstructive pulmonary disease, pulmonary hypertension, and idiopathic pulmonary fibrosis (53, 54). In Canada in 1997, it was reported that 18 million dollars a year are spent by the medical system on hospitalization of children due to RSV. This number only accounts for the pediatric population and costs that fall on the health cares system. It does not account for lost income/productivity for parents out of work due to children’s illness which would increase the total cost of RSV significantly (53).

In the pediatric population, hMPV has been described as a significant cause of influenza-like-illness. It as been reported to cause between four and 20 percent of respiratory illness in the pediatric population. Due to the identical pathogenic presentation of hMPV to RSV, similar concerns of airway obstruction are present. Most infections occur during the first year of life, and it has been shown that virtually all children are infected prior to the age of 5 years old (55). There are minor differences that have been reported between hMPV and RSV. Clinically hMPV is very similar to RSV with lower rates of wheezing observed (56). It has been reported that there is a greater association between hMPV and fever than between RSV and fever, while RSV is more likely to be associated with rhinorrhea. Patients that are hospitalized with hMPV are typically older than patients hospitalized with RSV (57, 58). Both RSV and hMPV are reported to be significant causes of pneumonia and bronchitis as well as upper respiratory tract infections. As is the case for RSV, severe prematurity is associated with higher risk of infection with hMPV in children under the age of five (59). Additionally, being male and having asthma have also been shown to increase the likelihood of a child getting hMPV (60).

## **Current Study Design:**

Herein we conducted a two-part study. First, a retrospectivechart review was carried out on patient’s medical records for patients that were admitted to one Hamilton hospital between 2011 and 2016 with RSV, hMPV, or Influenza A. Second, we analyzed the Institute of Clinical and Evaluative Sciences (ICES) linked laboratory and administrative data set for all major adult Hamilton, Ontario hospitals. In the Hamilton Regional Lsaboratory Medicine Program’s Regional Virology laboratory, which serves the Hamilton/Niagara region of Ontario, all nasopharyngeal swabs were tested with multiplex polymerase chain reactions during the indicated time frame. This laboratory testing allows us to make a consistent and accurate comparison of RSV, hMPV, and Influenza A. Moreover, it allowed for the true establishment of the clinical burdens of these viruses among hospitalized patients. Through this study the aim was to answer three questions: First, are there baseline differences in patients hospitalized with the respiratory syncytial virus, human metapneumovirus, and influenza A. Second, are there differences between infection groups in how patients are managed in hospital and the outcomes they experienced during and following hospitalization? Finally, is the large administrative data set representative of the results found in the retrospective chart reviews? These questions expand on the current body of literature, through comparing all three viruses, RSV, hMPV, and Influenza A in a post- 2009 influenza pandemic era, where management of influenza in hospitalized patients has improved significantly. Additionally, it will be the first study to be done comparing all three viruses in a Canadian population with this large of a sample size.

All RSV cases (173) and all hMPV cases (125) from during this time were considered for inclusion and 20 randomly selected influenza cases from each of the corresponding study years were used as comparators. The outcomes that were recorded are length of stay, ICU admission, remaining in hospital at 30 days, 30-day mortality, readmission to hospital within 30 days, discharge to same level of care, transfer to rehabilitation facility with future intent to send home, discharge to home with increased level of care, and discharge to long-term care after having resided at home.

For the second part of this thesis, we performed a secondary analysis on the linked laboratory and administrative ICES data set. This data set included the entire Hamilton ON adult population (> 18 years of age) who were hospitalized with RSV, hMPV or influenza A over the same time span as the retrospective chart reviews. Hospitals that will be included in this analysis are: St. Joseph’s Healthcare Hamilton, The Juravinski Hospital, and Hamilton General Hospital. The data set included the co-variables sex, age, comorbid conditions (Charlson Comorbidity Index), and disposition at time of hospitalization and the outcomes mortality, length of hospital stay, and disposition following hospitalization at 30 days (remains in hospital, discharge with increased home supports, discharge to rehab facility, discharge to long term care, and hospital readmission within 30 days).

In this study, it was of interest to account for a significant number of comorbid conditions in the multivariable models that were proposed. The Charlson comorbidity index is commonly selected due to its wide-spread use, and repeated verification. The Charlson index was also selected due to its simplicity. (61).

By including both components in this thesis, we were able to better establish the clinical course of these illness in Hamilton ON, and to make conclusions that are potentially more generalizable to a larger Ontario/Canadian population. Additionally, much of the data is being used to draw conclusions about the state of respiratory viruses in the province. Therefore, being able to validate this data set with high level chart reviews will allow for stronger conclusions to be drawn in the future. The chart reviews will provide a more specific look at individuals while the ICES data set will provide higher level variables that will encompass a larger population. Together they can be compared and analyzed for hospital specific concerns, as well as individual, and population concerns.

# **Chapter 2: The Clinical Impact of RSV and hMPV as Compared to Influenza A: A Retrospective Chart Review**

In this study, an inception cohort of patients hospitalized with of Respiratory Syncytial Virus (RSV), human Metapneumovirus (hMPV), and Influenza A was used to compare patient outcomes of through retrospective chart reviews at a single acute-care hospital in Hamilton, Ontario. Outcomes of patients were compared across infection groups in order to understand the burden of disease among patients hospitalized with the distinct viruses.

## **Methods:**

### **Sample selection:**

Using the Hamilton Region Laboratory Medicine Program’s Virology Laboratory information system, all respiratory virus multiplex reverse transcriptase polymerase chain reactions (RT-PCR) tests in the 18 years or older population between January 1, 2011 and December 31, 2016 were selected. Cases were selected for further consideration if, they were admitted inpatients to St. Joseph’s Healthcare Hamilton (Hamilton, ON) between January 1, 2011 and December 31, 2016, and if their RT-PCR test from a nasopharyngeal swab was positive for RSV, hMPV, or influenza A. Testing for respiratory viruses is done at the prescribing physician’s discretion or if patients presented with febrile respiratory illness, however no viruses is tested for independently. If multiple respiratory viruses were detected with virus other than the indicated viruses, individuals were included. All cases of RSV and hMPV across the indicated years were considered for inclusion in the study. A random selection of Influenza A cases, stratified by year, were chosen using a random number generator in Excel 2016. For each year, 20 cases were then selected to be included in the study. In total, the cases selected represented 36.6% of the overall population hospitalized with Influenza A. The yearly representativeness varied from year to year due to the changing prevalence of seasonal influenza. The representativeness of the population that was hospitalized with Influenza A was 31%, 59%, 53%, 23%, 27%, and 29% in the years 2011, 2012, 2013, 2014, 2015 and 2016 respectively. Research Ethics board approval was obtained from the Hamilton integrated Research Ethics Board (HiREB).

### **Data Extraction:**

Of the cases selected for chart reviews, individual identification numbers were blinded to viral etiology for data extraction. The variables pertaining to comorbidities, list of medications, and outcomes were extracted without knowledge of the illness that led to hospitalization in order to reduce confirmation bias.

For all selected cases, data was extracted from each patient’s electronic medical record (EMR). Reasons for exclusion were: no mention of illness in medical record, no medical record found, no RT-PCR result documented in medical record, the identified PCR test result was associated with outpatient medical care, insufficient details of variables of interest in patient chart (<50%), or did not have RSV, hMPV, or Influenza A. Those with hospital acquired infections were defined as patients with a positive RT-PCR test greater than 3 days following admission. Those with hospital acquired infections were assessed separately due to the unique nature of their illness.

 Demographic variables that were collected were sex (male or female), age, community status, and comorbid conditions. Community status was defined as living independently, living with supports (Community Care Access Centre support, support in house from nurse or family), or living in long-term care. Comorbidity data was collected in the context of Charlson Comorbidity Scores (62).

Symptoms were categorized as: cough, fever, wheezing, labored breathing, sore throat, congestion/rhinorrhea, myalgia, and other. If patient’s symptoms were described as “upper respiratory track symptoms”, they were coded in the chart review process as having a cough and sore throat. If symptoms were described as “community acquired pneumonia”, patient symptoms were considered to have, fever, labored breathing, and myalgia (63). For the clinical diagnosis’s of “respiratory failure” and “COPD exacerbation” that were given in place of symptoms, labored breathing was assigned as the sole symptom in the data extraction process. Bacterial co-infections were defined as positive culture collected from any site. Chest X-ray results were recorded as normal for patient or acutely abnormal. The acute abnormalities were recorded as infiltrates present, lobar pneumonia or definite bacterial pneumonia, pulmonary edema, or other. Any use of antiviral medication, namely oseltamivir (Tamiflu), or antimicrobial medications were also recorded.

Finally, hospital outcomes were documented. Changes in a patient’s disposition following hospitalization were recorded. This was done through recording disposition at time of admission which, as previously stated, was recorded as either resides independently, lives with supports, or resides in a long term care facility or nursing home. Outcomes following hospitalization, that were considered a change in disposition were: remaining in hospital at 30 days, mortality in hospital, discharge to long term care, discharge with increased level of care (e.g. change in CCAC support, moved in with family member, transfer to palliative care in nursing home), and transfer to rehabilitation with intent to send home following rehabilitation. If there was no change in disposition, this was also recorded. To the extent possible in chart reviews, hospital readmission within 30 days of discharge was recorded. This only captured patients re-admitted to the same institution.

Following chart reviews all recorded data was reviewed to ensure that there were no discrepancies in the chart review. If discrepancies were found, for example one patient was recorded as having two non-compatible outcomes, the individual chart was revisited to reconcile the discrepancy. Outliers for the continuous variables of age and length of stay were assessed through the development of histograms and box plots in SPSS.

### **Analysis:**

Descriptive statistics were reported to determine study sample characteristics. All continuous variables were reported as medians and ranges. Dichotomous variables were reported as values and percentages. Patients with hospital acquired infections were stratified and only reported on in a descriptive capacity. Wilcoxon rank sum tests were used to compare continuous variables. Associations between dichotomous variables were quantified with chi squared tests and quantified with odds ratios. Multivariable logistic regression models were built to evaluate dichotomous outcomes of ICU admission, mortality, severe disease defined as mortality or ICU admission, change in disposition that resulted in a higher level of care following discharge or at 30 days (remaining in hospital, transfer to rehabilitation, transfer to long-term care), and hospital readmission within 30 days of discharge. Length of stay was evaluated through a cox proportional hazard model. Models were built on the bases of biological plausibility. The event was defined as discharge from the hospital, those that remained in hospital at 30 days and those that experience mortality were censored. Statistical significance was considered to be p values less than 0.05. Results were reported as odds ratios or hazard ratios with 95% confidence intervals. Virus, sex, age, hospital and Charlson Comorbidity scores were included in all models. Comorbidity scores were included as a continuous variable. RSV and hMPV were compared to Influenza A. In the model considering change in disposition following hospital discharge, disposition prior to hospitalization was included. Complete case analysis was used. Goodness of fit was assessed through Hosmer-Lemeshow test statistics. Multicollinearity was assessed through standard error estimates, anything less than 2 was consider acceptable. All analysis of data was conducted in SPSS 24.

## **Results:**

Between January 1, 2011 and December 31, 2016, 5,046 patients were tested by RT-PCR for respiratory viruses at St. Joseph Healthcare Hamilton. The viruses tested included: Influenza A, Influenza B, Respiratory Syncytial Virus, human Metapneumovirus, Para Influenza (types 1, 2, and 3), Adenovirus, and Entero/Rhinovirus (2013-2016). Influenza A was the most prevalent virus over the identified years, with the exception of 2016, when more cases of Entero/Rhinovirus were observed (Table 1).

**Table 1. All Respiratory Viruses by Year**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Mean Age (Years)** | **Total Males across all years(%)** | **Total Number of Cases** |
| **All years** | **2011** | **2012** | **2013** | **2014** | **2015** | **2016** |
| **Total Number of Respiratory PCR tests** | 67.7 | 2476 (50) | 5046 | 698 | 661 | 710 | 937 | 1032 | 1007 |
| **Influenza A** | 66.6 | 167 (45.7) | 366 | 64 | 33 | 37 | 86 | 77 | 69 |
| **Influenza B** | 65.7 | 58 (49.2) | 118 | 8 | 20 | 6 | 46 | 16 | 22 |
| **RSV** | 75.5 | 68 (39.3) | 173 | 28 | 19 | 38 | 20 | 40 | 28 |
| **hMPV** | 70.1 | 56 (44) | 126 | 21 | 22 | 21 | 15 | 31 | 16 |
| **ParaInfluenza (Types 1, 2 or 3)** | 69.9 | 60 (50.4) | 119 | 22 | 10 | 21 | 15 | 32 | 19 |
| **Adenovirus**  | 77.7 | 1 (50) | 2 | 1 | 0 | 0 | 0 | 0 | 1 |
|  **Enetro/rhinovirus\*** | 65.2 | 140 (50.9) | 252 | NA | NA | 34 | 60 | 74 | 84 |
| **Negative for all Specimens** | 67.4 | 1932 (49.6) | 3893 | 551 | 555 | 554 | 698 | 764 | 771 |

**\***Molecular Testing Only Available after September 2013

Overall, 419 patient medical records were identified through the laboratory information system to be included in the retrospective chart review. Eighty-two patients were excluded during the chart review process. Fifty-three patients were excluded for insufficient information in their medical records. Insufficient information was defined as medical records containing less than 50% of the variables identified for extraction. Furthermore, 17 patients were excluded from inclusion because they had no medical record in the St. Joseph’s Healthcare Hamilton’s electronic medical record system, 7 patients were excluded because no RT-PCR test was present in their medical records (possibly because they were outpatients who were wrongly recorded as being inpatient), and 2 patients were identified as having received outpatient care. In total the random sampling of patients included in the analysis with Influenza A represented 25.7% of the population hospitalized with Influenza A from 2011 to 2016. The randomly selected sample was determined to be representative of the overall influenza A infected population through comparing the median age and the proportion male of the total population and the sample (Table 2). An addition 27 patients were analyzed separately as their infections met the definition of hospital acquired infections. Of these patients, 11 had hospital acquired influenza A, 7 had hospital acquired RSV, and 9 had hospital acquired hMPV. Ultimately, 309 individuals were included in the final analysis (Figure 1).

5,046 Patients admitted to hospital with respiratory viruses

* 4,399 Patients excluded for not have RSV, hMPV or Influenza A
* 246 Patients with Influenza A not selected in Random Selection Process

173 patients with RSV

108 patients with hMPV

120 patients with Influenza A

Chart Reviews

* 60 Patients excluded for incomplete medical records
* 17 Patients EMR could not be located
* 2 Patients were wrongly classified as inpatient
* One identified patient did not have the appropriate illness recorded in medical record

134 patients with RSV

99 patients with hMPV

105 patients with Influenza A

27 exuded for Hospital Acquired infections

Final: 127 patients with RSV

 90 patients with hMPV

 94 patients with Influenza A

**Figure 1.** Patient tested episodes for RSV, hMPV, and Influenza A included in the study.

### **Community Acquired Infections:**

Median age was similar across all three virus-infected patient groups, however patients with RSV were more likely to be older than those with Influenza A (p<0.001) and hMPV (p=0.06), while not statistically significantly when compared to hMPV (Table 2). For each illness the cohorts were 40 to 47% male, but no difference in sex was observed between infection groups. The full cohort encompassed a population with a high level of comorbid conditions with greater than 90% of the population having at least one documented comorbidity. Those with RSV were more likely to have at least one comorbid condition compared to those with Influenza A (OR: 4.9, 95%CI: 1.0 to 24.4), no other differences were observed between infection. The most common comorbidity, given that individuals were hospitalized with RSV, hMPV, or Influenza A, was pulmonary disease including COPD, asthma, or obstructive sleep apnea. A high percentage of the population also had cardiac comorbidities and renal disease (Table 2). The median Charlson Comorbidity score for all three patient groups was observed to be 2, with a range for those with influenza A was 0-6 while the range for those with RSV and hMPV was 0-9.

**Table 2: Demographics**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Influenza A** | **RSV** | **hMPV** |
|  | Total Hospitalized Population | Randomly Selected Sample |  |
|  | (n=366) | (n=94) | (n=125) | (n=90) |
| Male (%) | 168 (45.8) | 44 (46.8) | 50 (40) | 37 (41.1) |
| Median Age (range) | 69.94(19.5-101.5) | 71.55(19.9-94.1) | 78.9(20.1-97.1)\* | 75.05(19.8-96.4) |
| **Disposition Prior to Hospitalization** |  |
| Lived Independently (%) | NA | 66 (70.2) | 55 (44)\* | 41 (45.6)\* |
| Lived with Support (%) | NA | 16 (17.0) | 44 (35.2)\* | 25 (27.8)\* |
| Resides in Long term care (%) | NA | 10 (10.6) | 23 (18.4)\* | 15 (16.7)\* |
| **Comorbidities** |  |
| Any (%) | NA | 87 (92.6) | 123 (98.4)\* | 88 (97.8) |
| Cardiac Disease (%) | NA | 26 (27.7) | 49 (39.2) | 29 (32.2) |
| Pulmonary Disease (%) | NA | 39 (41.5) | 70 (56) | 38 (42.2) |
| Diabetes Mellitus (%) | NA | 19 (19.1) | 24 (19.2) | 25 (19.5) |
| Cancer (%) | NA | 9 (9.6) | 19 (15.2) | 15 (16.7) |
| Renal Disease (%) | NA | 17 (18.1) | 29 (23.2) | 15 (16.7) |

\* indicates that RSV or hMPV are statistically significantly different from Influenza A (p<0.05)

† Indicates that hMPV is significantly different from RSV (p<0.05)

Living disposition of patients prior to hospitalization varied among those hospitalized with Influenza A as compared to those hospitalized with RSV and hMPV. Individuals with RSV (OR: 3.3, 95% CI: 1.7 to 6.5) and hMPV (OR: 2.5, 95% CI: 1.2 to 5.3) were more likely to require support to live prior to hospitalization when compared to Influenza A. Of those included in the cohort, 10.6%, 18.0%, and 16.7% hospitalized with Influenza A, RSV, and hMPV respectively resided in long-term care prior to hospitalization. Again those with RSV (OR:2.8, 95% CI: 1.2 to 6.3) and hMPV (OR:2.4, 95% CI:1.0 to 5.8) had higher odds of residing in long term care compared to those with Influenza A. No difference in living conditions prior to hospitalization was observed between those hospitalized with RSV and hMPV (OR:0.96, 95% CI:0.35 to 2.65).

Upon admission to the hospital the most common symptoms were difficult or labored breathing and coughing. A high percentage of patients also had fever, and rhinorrhea/congestion. Two patients that presented to the emergency room were intubated on arrival, therefore their symptoms were not recorded.

**Table 3: Hospital Admission**

|  |  |  |  |
| --- | --- | --- | --- |
|   | **Influenza A** | **RSV** | **hMPV** |
| **Symptoms upon Admission** |  |
|  Cough (%) | 55 (58.5) | 75 (60) | 60 (66.7) |
|  Fever (%) | 30 (31.9) | 33 (26.4) | 28 (31.1) |
|  Wheezing (%) | 10 (10.6) | 23 (18.4) | 13 (14.4) |
|  Difficult or Labored Breathing (%) | 60 (63.8) | 93 (74.4) | 63 (70) |
|  Sore Throat (%) | 3 (3.2) | 5 (4.0) | 2 (2.2) |
|  Congestion/ Sputum Production (%) | 23 (24.5) | 40 (32.0) | 34 (37.8) |
|  Myalgias (%) | 15 (16.0) | 14 (11.2) | 9 (10) |
| **Co-Infection** |  |
|  Viral (%) | 2 (2.1) | 4 (3.2) | 0 (0) |
|  Bacterial (%) | 16 (12.5) | 24 (19.2) | 8 (8.9) † |
| **Chest X-Ray Results** |  |
|  Abnormal Results (%) | 44 (46.8) | 54 (43.2) | 38 (42.2) |
|  Infiltrates Observed (%) | 18 (40.9) | 18 (33.3) | 10 (26.3) |
|  Consolidation Observed (%) | 6 (13.6) | 6 (11.1) | 2 (5.3) |
|  Pulmonary Edema (%) | 7 (15.9) | 22 (40.7)\* | 15 (39.5)\* |
|  Other (%) | 13 (29.5) | 9 (16.6) | 11 (28.9) |
| **Medication Use** |  |  |  |
|  Antiviral Medication (%) | 64 (68.1) | 14 (11.2)\* | 4 (4.4)\* |
|  Antimicrobial Medication (%) | 54 (57.4) | 88 (70.4) | 65 (72.2)\* |

\* Indicates that RSV or hMPV are statistically significantly different from Influenza A (p<0.05)

† Indicates that hMPV is significantly different from RSV (p<0.05)

Viral co-infections were observed among four individuals in the cohort. Two patients were infected with Influenza A and RSV; those patients were included in the descriptive statistics as part of the Influenza A cohort in order to avoid redundancy. Two additional patients had viral co-infections, along with their RSV positive RT-PCR tests, one tested positive for Enterovirus/rhinovirus, and the other with Parainfluenza. Bacterial Co-infections were confirmed by culture in 15.5% of the cohort. Respectively, 12.5%, 19.2%, and 8.9% of those with Influenza A, RSV, and hMPV had a positive culture at any site including respiratory, blood, urine etc. at the same time as their viral RT-PCR test.

No differences in the proportions of acutely abnormal X-rays were observed between patients hospitalized with Influenza A, RSV, or hMPV, respectively, of whom 46.8%, 43.2%, and 42.2% had some form of an abnormal finding in their chest X-ray results. A higher proportion of those with Influenza A had infiltrates and consolidations observed on their chest X-rays. Contrastingly, those with RSV and hMPV had higher proportions of pulmonary edema than those with Influenza A.

When admitted to the hospital, patients with Influenza A were much more likely to be prescribed oseltamivir (Tamiflu), which is only effective against Influenza A, compared to those with RSV and hMPV. Furthermore, antimicrobial use was frequent among individuals hospitalized with these respiratory viruses.

Hospital outcomes were first evaluated in a uni-variable analysis (Table 4). No statistically significant differences between proportions of ICU admission and all-cause mortality where observed between patients hospitalized with RSV, hMPV, and Influenza A. Admission to the ICU was observed in 14 patients with Influenza A, 12 with RSV, and 10 with hMPV. High levels of mortality were not observed in this cohort, however mortality was observed more frequently in patients with RSV (OR:3.57, 95%CI: 0.75 to 16.9) and hMPV (OR: 3.3, 95%CI: 0.65 to 16.7) compared to those with Influenza A, although it was not significant. For all three viruses there was a high level of overlap between those that experienced mortality and those that were admitted to the ICU. While not statistically significant, those with RSV were most likely to experience severe illness defined as ICU admission or Death compared to Influenza A (OR: 1.2, 95%CI: 0.58 to 2.4) and hMPV (OR: 1.2, 95%CI: 0.60 to 2.5).

**Table 4: Outcomes**

|  |  |  |  |
| --- | --- | --- | --- |
|   | **Influenza A** | **RSV** | **hMPV** |
| **In Hospital Outcomes** |   |
|  Median Length of Stay^ | 4 (1-30) | 8 (1-30)\* | 5 (1-30) |
|  ICU Admission (%) | 14 (14.9) | 20 (16) | 10 (11.1) |
|  Mechanical Ventilation (%) | 11 (11.7) | 15 (12) | 8 (8.9) |
|  All Cause 30 Day Mortality (%) | 2 (2.1) | 9 (7.2) | 6 (6.7) |
|  Remained in Hospital after 30 days (%) | 7 (7.4) | 13 (10.4) | 5 (5.6) |
| **Disposition at Discharge** |  |
|  Discharge to Same Level of Care (%) | 71 (75.5) | 79 (63.2) | 68 (75.5) |
|  Discharge to Increased Level of Care (%) | 9 (9.6) | 23 (18.4) | 9 (10) |
|  Discharge to Long-Term Care (%) | 0 (0) | 0 (0) | 1 (1.1) |
|  Discharge to Rehab Facility (%) | 5 (5.3) | 1 (0.78) | 1 (1.1) |
|  30 Day Hospital Readmission (%) | 5 (5.3) | 17 (13.6) | 5 (5.6) |

\* indicates that RSV or hMPV are statistically significantly different from Influenza A (p<0.05)

† Indicates that hMPV is significantly different from RSV (p<0.05)

^Length of stay and all other outcomes were censored at 30 days

Change in level of care at 30 days, based on uni-variable analyses was not observed to be different between the viruses. Similarly, when considering proportions of 30-day hospital readmission, no difference was observed between those with each of the viruses, however, a higher proportion of those with RSV were re-admitted to the hospital than those with hMPV or Influenza A. The final hospital outcome evaluated was patient length of stay. Median Length of stay was 8 days, 5 days, and 4 days for RSV, hMPV, and Influenza A respectively. Those with RSV had distinctly longer hospital stays than those with Influenza A (P<0.001) and hMPV (P<0.001). No difference was observed between the median length of hospital stays for patients with hMPV and Influenza A (P=0.15).

**Table 5. Multivariable Logistic Regression Models**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **ICU Admission** | **Mortality** | **Severe Illness** | **Increase in Care requirements** | **30-Day Hospital Readmission** |
|  | Adjusted Odds Ratio (95%CI, p value) |
| **Respiratory Virus** |  |  |  |  |  |
|  Influenza A | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
|  RSV | 1.24 (0.57-2.71) | 2.78 (0.56-13.83) | 1.24 (0.59-2.62) | 0.58 (0.24-1.41) | 2.98 (1.03-8.6)\* |
|  hMPV | 0.74 (0.30-1.84) | 2.95 (0.56-15.53) | 0.98 (0.43-2.36) | 0.37 (0.13-1.09) | 1.11 (0.30-4.02) |
| **Sex** |  |  |  |  |  |
|  Male | 2.07 (1.05- 3.97)\* | 3.52 (1.85-10.42)\* | 2.09 (1.13-3.85)\* | 1.19 (0.54-2.59) | 0.98 (0.43-2.23) |
| **Age** | 0.98 (0.96-0.99)\* | 1.03 (1.0- 1.07)\* | 0.99 (0.97-1.01) | 0.99(0.97-1.02) | 0.99 (0.96-1.02) |
| **Charlson Comorbidity Score** | 1.17 (0.98-1.41) | 1.19 (0.92-1.52) | 1.12 (0.94-1.33) | 1.57 (0.94-1.42) | 0.99 (0.78-1.26) |
| **Community Status** |  |  |  |  |  |
| Living independently | N/A | N/A | N/A | 1.0 (reference) | N/A |
| Living with Supports | N/A | N/A | N/A | 2.62 (1.03-6.67)\* | N/A |
| Living in Long-Term Care | N/A | N/A | N/A | 4.52 (1.56-13.04)\* | N/A |

\* indicates that variable was statistically significant in adjusted models (p<0.05)

In adjusted logistic regression models, no differences were detected between viruses for hospital outcomes, with the exception of 30-day hospital readmission, which, when corrected for age, sex, and Charlson comorbidity score, individuals with RSV were more likely to be re- admitted to the hospital than those with Influenza A (OR: 2.9, 95%CI: 1.03 to 8.60, P=0.049) (Table 5). In the adjusted models, male sex was significantly associated with ICU admission, mortality, severe disease, and increase in care requirements after, with female patients being less likely to experience these worse outcomes. No other variables were significant in the adjusted models for ICU admission, mortality, severe disease, or increase in care requirements was observed. Charlson comorbidity scores, were marginally insignificant in being associated with worse outcomes of for all multivariable logistic regression models, therefore it is possible that comorbid conditions are significant and our study did not demonstrate the power necessary to show the results. Finally, after adjusting for age, sex, comorbidity score, and virus, the only predictor of transitioning to requiring a higher level of care following hospitalization was requiring support to live at home prior to hospitalization or already residing in long-term care. Hosmer-Lemeshow tests were insignificant for all models indicating an adequate fit (Appendix 1.1-1.5).

Median lengths of stay were determined to be different in univariable analysis, however, no significant difference was observed in the adjusted Cox proportional hazards model. While not significant, those with RSV had a lower hazard ratio of being discharged than those with Influenza A (HR:0.79, 95%CI: 0.59 to 1.06, P=0.12), indicating RSV may result in longer hospital stays, no difference was observed between hMPV and Influenza A. Comorbidity scores and age were significantly associated with extending hospital stay, with higher Charlson comorbidity scores and older age reducing the hazard ratio of being discharge (Table 6.) Sex was not significantly associated with discharge in this model.

**Table 6. Adjusted Length of Stay Cox Proportional Hazard Model**

|  |  |
| --- | --- |
| **Variable** | **Length of stay**Adjusted Hazard Ratio (95%CI) |
| **Respiratory Virus** |   |
|  Influenza A | 1.0 (reference) |
|  RSV | 0.79 (0.59- 1.06) |
|  hMPV | 1.04 (0.81-1.49) |
| **Male Sex**  | 0.92 (0.72-1.76) |
| **Age by Decade** | 0.92 (0.86-0.98)\* |
| **Charlson Comorbidity Score** | 0.93 (0.86-1.00)\* |

\* indicates that variable was statistically significant in adjusted models (p<0.05)

### **Hospital Acquired Infections:**

Of those identified with hospital- acquired infections (n=27), 11 had Influenza A, 7 had RSV, and 9 had hMPV. The demographics of the population were similar to those with community acquired infections, with 48% of the patients being male, the median age being 65.9, and the median Charlson comorbidity score equal to 2. The majority of patients were admitted from living independently or living with supports at home (n=25), while 2 were admitted from long-term care facilities. The proportion of patients in this cohort with culture confirmed bacterial infections was 44% and 55% had abnormal chest X-rays. The most frequent abnormality observed on chest X-rays was a consolidation (n=8). In this cohort, an over prescription of antimicrobial agents was not observed. The length of stay for patients in this cohort was significantly longer than those in the community acquired cohort, with 62.9% of patients remaining in the hospital when censored at 30 days following positive RT-PCR result. Ten patients were either in the ICU at the time of respiratory infection, or admitted to the ICU during their hospitalization, however during the 30 days following the acquisition of the viral infection, only one (4%) experienced all-cause mortality. Among those discharged prior to 30 days (n=9), one was readmitted to the hospital within 30 days of discharge.

Hospital outbreaks are difficult to declare based on the method of data collection, however, in 2011, all 6 hospital acquired infections were determined to be Influenza A and occurred between weeks 2 and 5; in 2015, 5 cases of hMPV were documented in weeks 16 and 17, and in 2016, 3 cases of RSV were recorded during the same week. It is possible that these events were hospital outbreaks. All other cases of hospital acquired infection are not well correlated to the cases we have captured in this study.

## **Discussion:**

This study demonstrates that there were a significant number of cases of RSV and hMPV over the course of the six years at a single acute care hospital. There were few differences observed between the clinical courses of patients hospitalized with RSV, hMPV, and Influenza A, indicating that all contribute to disease in the general adult population. However, the difference in prevalence of diseases indicates that Influenza A likely poses the largest burden of disease in the adult and elderly population. These findings are comparable to others that have previously studied these viruses (36, 38). This study adds to the body of literature that exists by including hMPV in the comparison between RSV and Influenza A, which few have done, and demonstrating similar outcomes.

There was little distinction observed between the clinical presentation of each virus, with similar rates of symptoms present and chest X-ray abnormalities. Rates of infiltrates and consolidations being observed on chest S-rays were similar across all three illnesses, however those with hMPV appeared to have fewer consolidations observed on X-ray. Notably, pulmonary edema was more common among individuals with RSV and hMPV, this is inconsistent with the recent study published stating that acute myocardial infraction (MI) was more frequent following Influenza A than RSV infections (64). It is possible that this difference stems from the older study population that was hospitalized with RSV compared to Influenza A. However, acute MI was not captured as a variable of interest in this chart review.

While few differences were observed between the clinical presentation of individuals with the distinct viruses, higher rates of antimicrobial usage were observed in patients with RSV and hMPV. When considering those with chest X-ray abnormalities or confirmed bacterial co-infections, antimicrobial prescription rates represented an over prescription of agents by 25.9% for Influenza A, 45.5% for RSV, and 69.2% for hMPV for cases that did not have definite or possible bacterial co-infections. Physician reasoning for starting antimicrobials was not captured in retrospective chart reviews making this trend hard to describe, though through observation it seems to suggest that a diagnosis of Influenza A results in a lower usage of antimicrobials as compared to RSV and especially hMPV. There are many possible explanations for this distinction, first it is possible that as prescription rates of antiviral medications has increased this has directly impacted prescription rates for antimicrobials in patients with influenza. It is also possible that those with RSV and hMPV do appear to be sicker when in the hospital suggesting their infections may have bacterial origin and may require treatment. Even in a hospital that routinely tests for all viral infections, antimicrobials are routinely over prescribed for respiratory viruses but most commonly in viruses that are not routinely tested for. It is possible that many antimicrobials may have been discontinued following detection of virus through PCR. As others have described, this study also suggests that using PCR testing for respiratory viruses could reduce over-prescription of antimicrobial medications (65).

Many of the differences observed between the populations hospitalized with the indicated viruses were observed at baseline, prior to hospitalization. This included differences in age, sex, and the likelihood of having at least one comorbid condition. These differences could explain differences between univariable and multivariable analysis. In univariable analysis, those hospitalized with RSV were more likely to have longer lengths of stay. However, when considered in the Cox proportional hazards model, after adjusting for age, sex, and comorbid conditions, RSV was insignificant in extending hospital length of stay and differences between viruses did not persist. While it is possible that RSV may extend hospital length of stay due to the reduced hazard ratio of discharge, age and Charlson comorbidity index scores were significant in extending hospital length of stay specifying that the differences that existed at baseline likely explain why patients with RSV had longer hospital stays.

 Though not significant in multivariable models, there were higher mortality in patients hospitalized with RSV and hMPV as compared with those with Influenza A. This is distinct from prior cohort studies that reported more congruent proportions of all-cause mortality between viruses, even when high levels of comorbid conditions and older age were present (36, 38). It is possible that this difference is a result of better hospital management of Influenza A in recent years. Our study demonstrated high levels of antiviral usage among those hospitalized with Influenza A, consistent with others findings on use of antivirals following the 2009 Influenza H1N1 pandemic (52).

 The only significant distinction in outcomes between RSV, hMPV, and Influenza A, was the higher rates of 30-day readmission among patients originally admitted with RSV. It is possible that this was due to higher rates of pulmonary disease in those with RSV, namely COPD, which is controlled for via Charlson Score, but not as an independent variable. However, this finding indicates that those with RSV do cause significant primary and secondary hospitalizations and that prevention of illness or more effective management (such as antivirals in future) during the original hospitalization could reduce the burden of RSV on the healthcare system.

 Transition in levels of care required following hospitalization was difficult to capture in a retrospective study, nevertheless, it did not appear to differ between viruses. In multi-variable models the only significant predictors of requiring a higher levels of care following hospitalization were requiring supports to live or residing in LTC prior to hospitalization. When considering variables that suggested greater utilization of healthcare services, the largest proportion that required higher level of care where those that remained in hospital beyond 30 days. This is consistent with hospitalization being a significant cause of transition in care, and preventing hospitalization due to any respiratory virus should be a priority in the adult and elderly population (51).

 Hospital acquired infections were shown to contribute to outcomes for patients in this study. Roughly equal proportions of patients with RSV, hMPV, and Influenza A were observed to have acquired their illness while in the hospital. All infection groups experienced poor outcomes. Better hospital management strategies for all illness would likely reduce this burden of disease.

Strengths of this study include considering RSV, hMPV, and Influenza A infection in a hospital setting that routinely tests for all three viruses with RT-PCR. Additionally, this study included hMPV which has not been considered in many of the previous studies comparing RSV and Influenza A. Furthermore, this study six full years following 2009 Influenza pandemic which allowed us to include a moderately large sample size.

There are some limitations of this study, primarily this data was collected retrospectively from chart reviews, which limited the information that could be obtained. Second, this study was conducted at one hospital that is specialized in respiratory conditions and dialysis for kidney disease, explaining high levels of pulmonary and renal comorbid conditions. Conducting the study in this population possibly represents an over estimate of the burden of disease in a more general adult population that could be hospitalized with one of the three viruses. Finally, while likely representative of the total population admitted with Influenza A only 25% of patients were ultimately included in the study.

From this study we can conclude that being hospitalized from RSV is about half as common as Influenza A and that being hospitalized from hMPV is about a quarter as common. RSV appears to be contribute to similar if not worse outcomes in the general adult population while hMPV appears to have similar or slightly better outcomes as compared to Influenza A. These viruses contribute a significant burden of disease to the population and better prevention and management of all respiratory viruses should be a priority to improve the health of individuals.

# **Chapter 3: Comparing RSV and hMPV to Influenza A with the Use of Administrative and Laboratory Data**

The aim of this study was to compare the baseline characteristics and clinical outcomes of adult patients hospitalized with RSV, hMPV, and influenza A in the years following the 2009 influenza A pandemic. Influenza A is known to cause significant illness in the adult and elderly population while, in this population, RSV and particularly hMPV are less well recognized causes of disease. A few studies have compared all three viruses, most of which have concluded that similar outcomes were observed between infection groups (36-39).

The Institution of Clinical and Evaluative Science (ICES) administrative data was used to capture all patients hospitalized in Hamilton, ON from January 1, 2011 to May 31, 2014. Three acute care hospitals were included in this analysis, each with varying patient populations: St. Joseph Healthcare Hamilton, which is the regional centre for patients with respiratory diseases and has a dialysis centre; Hamilton General Hospital, which is the major trauma centre for the region; and The Juravinksi Hospital which is the cancer treatment centre for the region. All three hospitals also have general medicine and surgery in addition to their specializations. Therefore, while these hospital’s specializations do not explicitly define the patient populations included in this study they may indicate why some patients may choose one hospital over another in a non-random way. Moreover, these hospital distinctions give us an understanding of the independent comorbid conditions of patients included in this study. By including all three major hospitals, a larger, more generalizable sample was included in the study. All patient samples were tested at the same laboratory using multiplex PCR tests.

 In this analysis we aim to expand on the findings of a retrospective chart review carried out at a single site in Hamilton ON. This retrospective chart review will allow us to validate the analysis of the administrative data.

## **Methods:**

### **Sample Selection:**

Respiratory virus testing results were ascertained from Hamilton sites of the Flu and Other Respiratory Viruses Research (FOREVER) Cohort. As of June 2018, the FOREVER Cohort included results of all respiratory virus testing conducted by 11 Public Health Ontario laboratories and eight academic hospital-based laboratories between May 1, 2009 and May 31, 2014. From this cohort, patients with RSV, hMPV, and Influenza A who were admitted to St. Joseph Healthcare Hamilton (n=416), Hamilton General Hospital (n=297), or The Juravinski Hospital (n=291), as identified through the Institutional Information System, between January 1, 2011 and May 31, 2014, where included. All respiratory samples from the Hamilton Regional Laboratory, during this time frame, were tested with multiplex RT-PCR at the Hamilton Regional Laboratory Medicine Program’s Regional Virology/Molecular Laboratory, located at St. Joseph’s Healthcare Hamilton. The use of data in this project was authorized under section 45 of Ontario’s Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

 Patients included in the analysis must first have had a valid identification number that facilitates linking laboratory data to administrative data, they must have been over the age of 18, and they must have tested positive for RSV, hMPV, or Influenza A during the designated time frame. Patients with missing age or birthdate, sex, or with postal codes from outside of Ontario were excluded due to incomplete information. Patients were included if this was their first hospitalization in their episode of care. If the date of the positive PCR test was within 3 days following admission to the hospital patients were defined as having community acquired infection and those with a positive PCR after 3 days of hospitalization were defined as having hospital acquired infections.

### **Measures and outcomes:**

Hospital admissions were defined as episodes of care which included transfer to a different hospital within 6 hours, or readmission to same hospital within 48 hours. All episodes of care were censored at 30 days. The dataset was not unique by patient, with 18 patients having more than one episode of care. There were patients (n<5) with additional episodes of care within 30 days of discharge from the first for a distinct respiratory pathogen. For these patients, their second admission was excluded from the analysis. For those that had a second episode of care within the same season that was beyond 30 days following discharge of the first, and those that that had a second episode of care in a different season all episodes were included in the analysis. Age, sex, Charlson Comorbidity score, and hospital were included for all patients. Charlson Comorbidity scores were calculated using *International Classification of Disease, 10th Revision* (ICD-10) codes on the index date of admission to the hospital(62, 66). These variables were collected from the Discharge Abstract Database of the Canadian Institute for Health Information. Patients living condition prior to admission was defined as either residing in long-term care (LTC) or not. Residing in long-term care was defined as patients who had an Ontario Drug Benefit claim that was from an LTC facility within one-year of hospital admission, if there was a physician billing with a LTC flag, or if there was a documented assessment date in the Continuing Care Reporting System-LTC database.

All outcomes were censored at 30-days post specimen collection, these included ICU admission, all-cause mortality, length of stay (LOS), remaining in hospital at 30 days, discharge to LTC, and discharge to rehabilitation facility. ICU admission, all cause mortality, LOS, remaining in hospital at 30 days, discharge to LTC, and 30-day readmission were collected from the Database of the Canadian Institute for Health Information dataset. Admission to a rehabilitation facility was identified through the National Rehabilitation Service database. Patients who were admitted to rehabilitation within 7 days of discharge from the hospital were considered. Furthermore, patients who were admitted to a rehabilitation for reasons that suggested they were likely in rehabilitation prior to hospitalization were excluded. Conditions that warranted this exclusion included joint replacement, leg amputation, etc. (n < 5).

### **Analysis:**

Descriptive statistics were reported to determine study sample characteristics. All continuous variables were reported as medians and ranges. Dichotomous variables were reported as counts and frequencies. Descriptive statistics were stratified by hospital and results for patients hospitalized at St. Joseph Healthcare Hamilton were compared to the prior chart review study for validation. Patients with hospital-acquired infections were not included in the primary analyses and only reported, separately, in a descriptive capacity. Complete case analysis was conducted. Wilcoxon rank sum tests were used to compare continuous variables. Associations between dichotomous variables were examined with chi squared tests and quantified with odds ratios. Multivariable logistic regression models were built to evaluate dichotomous outcomes of ICU admission, mortality, severe disease (defined as mortality or ICU admission), change in disposition that resulted in a higher level of care following discharge or at 30 days (remaining in hospital, transfer to rehabilitation, transfer to long-term care), and hospital readmission within 30 days of discharge. Length of stay was evaluated through a Cox proportional hazards model. The event was defined as discharge from the hospital, those that remained in hospital at 30 days and those that experienced mortality were censored. Statistical significance was considered to be p values less than 0.05. Results were reported as odds ratios or hazard ratios with 95% confidence intervals. Sex, age, hospital, and Charlson Comorbidity scores were included in all models. Comorbidity scores and age were included as continuous variables. In the model considering change in disposition following hospital discharge, living condition prior to hospitalization was included. Models were built on the basis of biological plausibility. Goodness of fit was assessed through Hosmer-Lemeshow test statistics. For Cox proportional hazard models, AIC with and without covariates were compared to assess fit of model. Multicollinearity was assessed through standard error estimates, anything less than 2 was consider acceptable. All analysis of data from the administrative cohort was conducted in SAS enterprise 7.1.

## **Results:**

### **Community Acquired Infections:**

Between January 1, 2011 and May 31, 2014, 1,003 patients from the community or LTC facilities were admitted to one of the three major acute care hospitals in Hamilton, Ontario with RSV, hMPV, or Influenza A. Influenza A was the most common illness while RSV and hMPV were each half as common. Similar proportions of each sex were infected across infection groups, and females were over represented (56.2%). Patients with RSV (P<0.001) and hMPV (P=0.04) were more likely to be older than those with Influenza A, and those with RSV were more likely to be older than those with hMPV (P<0.001) (Table 1). A higher proportion of patients presented to St. Joseph’s Healthcare Hamilton (n=416), the regional care centre for respiratory diseases and dialysis, with the indicated infections than presented to the other two hospitals (The Jurivinski Hospital=297, Hamilton General Hospital=291) included in the study. No significant differences in the proportions of patients with each virus were observed between hospitals; however, patients with RSV and hMPV did appear to be more likely to be admitted to The Juravinski Hospital (RSV: OR:1.26, 95% CI: 0.86 to 1.84; hMPV: OR:1.38, 95% CI: 0.93 to 2.04) compared to Hamilton General Hospital (Table 1).

**Table 1. Demographics**

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | Influenza A | RSV | hMPV |
|  | 502 | 258 | 243 |
| Male (%) | 226 (45.0) | 103 (39.9) | 111 (45.6) |
| Median Age (Range) | 70 (18-101) | 79 (20-97)\* | 77 (18-103)\*† |
| **Hospital Site** |  |  |  |
| St. Joseph’s Healthcare Hamilton (%) | 201 (40.0) | 112 (43.4) | 103 (42.4) |
| Hamilton General Hospital (%) | 162 (32.3) | 62 (24.0) | 67 (27.5) |
| The Juravinski Hospital (%) | 140 (27.9) | 78 (30.2) | 79 (32.5) |
| **Disposition Prior to Hospitalization** |  |  |  |
| Residing Independently (%) | 472 (94.0) | 223 (86.4)\* | 211 (86.8)\* |
| Residing in Long Term Care (%) | 34 (6.7) | 38 (14.7)\* | 36 (14.8)\* |
| **Charlson Comorbidity Score (Min-Max)** | 1 (0-11) | 1 (0-9) | 1 (0-7) |

\* Indicates that RSV or hMPV are statistically significantly different from Influenza A (p<0.05)

 † Indicates that hMPV is significantly different from RSV (p<0.05)

Patients that were hospitalized with RSV and hMPV were more likely to reside in LTC facilities prior to hospitalization when compared to those with Influenza A. Accordingly, a higher proportion of individuals with RSV and hMPV had at least one comorbid condition (Figure 1). Among patients hospitalized with Influenza A, 45% had no comorbid conditions that were captured in Charlson Comorbidity index scores. The median Charlson Comorbidity index score was observed to be one in all infection groups (Table 1).

**Figure 1.** Patients with influenza A were more frequently admitted to the hospital with no comorbid conditions that are captured in the Charlson Comorbidity index.

There were many distinctions in hospital based outcomes observed between Influenza A, RSV, and hMPV in uni-variable analysis. Patients with RSV had distinctly longer lengths of stay than those with Influenza A (U=5.7, P<0.001), while no differences were observed between RSV and hMPV (0.49, P=0.62), or Influenza A and hMPV (U=0.28, P=0.77). Patients hospitalized with RSV and hMPV were more likely to be admitted to the ICU and experience 30-day all-cause mortality than those with Influenza A (Table 2). A small portion of individuals with one of the three viruses remained in the hospital at 30 days following admission; no differences in proportions between the infection groups were observed.

Patients that were admitted to one of the hospitals with Influenza A, RSV, or hMPV, that did not already reside in LTC prior to hospitalization, all had similar proportions of discharge to LTC within 30days of admission or remaining in hospital at 30 days following admission. Those with hMPV were less likely to require admission to a rehabilitation facility following admission, although no significant portion of persons with any illness required rehabilitation after discharge from hospital. Patients with each of the three viruses had similar rates of hospital readmission within 30 days of discharge.

**Table 2. Outcomes**

|  |  |  |  |
| --- | --- | --- | --- |
|   | **Influenza A** | **RSV** | **hMPV** |
| **In Hospital Outcomes** |   |
|  Median Length of Stay (min-max)^ | 4 (1-30) | 6 (1-30)\* | 5 (1-30) |
|  ICU Admission (%) | 75 (14.9) | 50 (19.5)\* | 41 (16.9)\* |
|  All Cause 30 Day Mortality (%) | 24 (4.7) | 27 (10.5)\* | 29 (11.9)\* |
|  Remained in Hospital after 30 days (%) | 15 (3.1) | 12 (4.5) | 11 (5.2) |
| **Disposition at Discharge** |   |
|  Discharge to Same Level of Care (%) | 391 (77.8) | 179 (69.9)\* | 170 (70.2)\* |
|  Discharge to Long-Term Care (%) | 22 (4.3) | 11(4.9) | 12 (4.3) |
|  Discharge to Rehabilitation Facility (%) | 15 (3.2) | 6 (2.7) | ≤ 5 (≤ 4.8)\* |
|  30 Day Hospital Readmission (%) | 45 (8.9) | 28 (10.9) | 22 (9.1) |

\* Indicates that RSV or hMPV are statistically significantly different from Influenza A (p<0.05)

† Indicates that hMPV is significantly different from RSV (p<0.05)

^ Length of stay and all other outcomes were censored at 30 days

Patients admitted to St. Joseph’s Healthcare Hamilton and included in the ICES database were compared to retrospective chart reviews for the same time period. All patients with RSV and hMPV were eligible for inclusion in the chart reviewed cohort, and a stratified by year, random sample of patients with Influenza A were included. Of those included in the final comparison, similar proportions of sex and median ages were observed between the chart reviewed cohort and the administrative data cohort. A higher proportion of patients were observed to have been admitted from LTC to the hospital in the chart reviewed cohort as compared to the administrative data cohort. There were discrepancies observed between the median Charlson Comorbidity index scores of patients amid the two cohorts.

**Table 3. Comparison of Chart reviewed Cohort and Administrative Data Cohort**

|  |  |  |  |
| --- | --- | --- | --- |
|   | Influenza A | RSV | hMPV |
|   | Chart Reviewed Data | Administrative data | Chart Reviewed Data | Administrative data | Chart Reviewed Data | Administrative data |
| **Demographics** |   |   |   |   |   |   |
| Population size | 35 | 201 | 66 | 112 | 59 | 103 |
| Male (%) | 16 (44) | 85 (42.8) | 29 (43.9) | 50 (44.6) | 26 (44.1) | 41 (39.8) |
| Age (Range) | 60.9 (19-91) | 69 (18- 101) | 79.8 (25 - 97) | 78 (20-97) | 73.1 (19-96) | 76 (19-96) |
| Charlson Comorbidity Score (Min-Max)  | 1 (0-5) | 1 (0-11) | 2 (0-7) | 1 (0-5) | 2 (0-7) | 2 (0-6) |
| Residing in LTC prior to Hospitalization | 2 (5.7) | 11 (5.4) | 14 (21.1)\* | 17 (15.2)\* | 9 (21.1)\* | 13 (12.6)\* |
| **Outcomes** |   |   |   |   |   |   |
| Length of Stay (Min-Max)^ | 4 (1-30) | 4 (1-30) | 7.5 (1-30) | 6(1-30) | 5 (1-30) | 5 (1-30) |
| ICU admission (%) | 5 (14.3) | 32 (15.9) | 10 (14.9)\* | 29 (25.9)\* | 7 (11.8)\* | 25 (24.3)\* |
| Mortality (%) | 1 (2.8) | ≤ 5 (≤ 2.5) | 5 (7.4)\* | 14 (12.5)\* | 5 (8.4) | 8 (7.7) |
| Remained in Hospital at 30 days | 3 (8.6) | 7 (3.4) | 7 (10.4) | ≤ 5 (≤ 4.5) | 1 (1.7) | ≤ 5 (≤ 4.8) |
| Discharge to LTC (%) | 0 (0) | ≤ 5 (≤ 2.5) | 0 (0) | ≤ 5 (≤ 4.5) | 1 (1.7) | ≤ 5 (≤ 4.8) |
| Discharge to Rehabilitation (%) | 3 (8.6) | ≤ 5 (≤ 2.5) | 1 (1.4) | 0 (0) | 1 (1.7) | ≤ 5 (≤ 4.8) |
| 30-day Hospital Readmission (%) | 3 (8.6) | 16 (7.9) | 9 (13.4) | 13 (11.6) | 2 (3.34)\* | 18 (17.4)\* |

\* Indicates differences observed in the chart reviewed and administrative data cohort (p<0.05)

^ Length of stay and all other outcomes were censored at 30 days.

Proportions of outcomes were compared between the two cohorts as well, with identical lengths of stay, and similar rates of mortality, observed. Higher rates of ICU admission were observed in the administrative cohort among patients with RSV and hMPV. Outcomes related to disposition following hospitalization varied between the two cohorts. Fewer patients remained in hospital at 30 days in the administrative data cohort as compared to the chart reviewed cohort, while more patients were discharged to LTC within 30 day of admission. Similar proportions of patients were discharged to rehabilitation facilities and similar readmission rates were observed between cohorts, with the notable exception that far more patients with hMPV were readmitted to the hospital in the administrative data cohort.

Sex was an insignificant predictor of all outcomes; however, males trended towards having worse outcomes. Age varied in its association with the ICU admission and mortality. Younger age was found to be associated with higher likelihood of ICU admission and older age was found to be associated with higher likelihood of mortality. When considering severe illness, defined as ICU admission or mortality, age was not a significant predictor. Higher Charlson Comorbidity index scores were associated with worse outcomes across all logistic regression models with the exception of requiring a higher level of care following discharge form the hospital. RSV was associated with higher rates of mortality and severe disease when compared to Influenza A, however, RSV was not observed to have an independent association with higher rates of ICU admission. Human MPV was associated with higher rates of mortality compared to Influenza A, but was not significantly associated with any of the other indicated outcomes. There were no significant differences in outcomes noted between hospitals. No differences between infections groups were observed in the multivariable logistic regression model for 30-day hospital readmission, with the only significant predictor for being readmitted to the hospital was a higher Charlson Comorbidity score.

**Table 4. Multivariable Logistic Regression Models**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **ICU Admission** | **Mortality** | **Severe Illness** | **Requirement of higher level of care**† | **30-Day Hospital Readmission** |
| Odds Ratio (95% CI) |
| **Respiratory Virus** |   |   |   |   |   |
|  Influenza A | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
|  RSV | 1.49 (0.98- 2.27) | 1.93 (1.08-3.49)\* | 1.60(1.10-2.34)\* | 0.92 (0.52-1.63) | 1.12 (0.67-1.88) |
|  hMPV | 1.27 (0.78-1.86) | 2.49 (1.40-4.436)\* | 1.435 (0.98-2.12) | 1.24 (0.72-2.16) | 1.00 (0.58-1.70) |
| **Sex** |   |   |   |   |   |
|  Male | 1.11 (0.78-1.56) | 1.01 (0.63-1.62) | 1.02 (0.74-1.39) | 0.83 (0.52-1.32) | 1.42 (0.93-2.18) |
| **Age by Year** | 0.98 (0.97-0.99)\* | 1.03 (1.01-1.05)\* | 0.99 (0.98-1.0) | 1.04 (1.02-1.06)\* | 1.00 (0.99-1.02) |
| **Charlson Comorbidity Score** | 1.31 (1.18-1.46)\* | 1.35 (1.19-1.55)\* | 1.36 (1.23-1.50)\* | 1.04 (0.87-1.23) | 1.16 (1.02-1.32)\* |
| **Hospital** |   |   |   |   |   |
| Hamilton General Hospital | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| St. Joseph Healthcare Hamilton | 1.32 (0.87-1.98) | 0.56 (0.31-1.02) | 1.01 (0.70-1.46) | 0.60 (0.35-1.05) | 1.52 (0.89-2.59) |
| The Jurivinksi | 0.66 (0.41-1.08) | 0.99 (0.56-1.77) | 0.72 (0.47-1.08) | 0.87 (0.50-1.05) | 1.15 (0.63-2.09) |
| **Community Status** |   |   |   |   |   |
| Living independently | N/A | N/A | N/A | 1.0 (reference) | N/A |
| Living in Long-Term Care | N/A | N/A | N/A | 0.07 (0.01-0.47)\* | N/A |

\* Indicates that variable was statistically significantly different in adjusted models (p<0.05)

† Model had a significant Hosmer-Lemeshow statistic (P<0.05)

Older age was associated with increased likelihood of requiring a higher level of care following hospital admission, and residing in LTC prior to hospital admission reduced the need for higher levels of care following discharge from the hospital. No differences were observed between infections groups, or those with more comorbid conditions. However, in the model accounting for increase in care requirements was poor (p<0.001) (Appendix 2.5).

Length of stay was assessed through a Cox proportional hazard model with the outcome of interest being discharge from the hospital (Table 4). Those with RSV (HR: 0.81 95%CI: 0.70 to 0.95, p=0.008) were less likely to be discharged from the hospital compared to those with Influenza A. Furthermore, while not significant, those with hMPV (HR: 0.88 95%CI: 0.74 to 1.04, p=0.13) also had a lower hazard ratio of discharge from hospital, correlating to longer lengths of stay. Older age and higher Charlson Comorbidity scores were significantly associated with longer hospital stays in the Cox proportional hazards model as well. Sex was not a statistically significant predictor of discharge from hospital in this model. A reduction in AIC was observed between models without covariates compared to with covariates indicating an adequate model fit. (Appendix 2.6).

**Table 5. Length of Stay Cox proportional Hazard Model**

|  |  |
| --- | --- |
| **Variable** | **Discharge from Hospital** |
| Hazard Ratio (95% CI) |
| **Respiratory Virus** |   |
|  Influenza A | 1.0 (reference) |
|  RSV | 0.81 (0.70- 0.95)\* |
|  hMPV | 0.88 ( 0.74 - 1.04) |
| **Sex** |  |
|  Male | 1.07 (0.94 - 1.21) |
| **Age by Year** | 0.98 (0.985 - 0.99)\* |
| **Charlson Comorbidity Score** | 0.87 (0.83 - 0.91)\* |
| **Hospital**  |  |
| Hamilton General Hospital | 1.0 (reference) |
| St. Joseph Healthcare Hamilton | 1.03 (0.88-1.20) |
| The Juravinski Hospital | 1.00 (0.84-1.18) |

\* Indicates that variable was statistically significantly different in adjusted models (p<0.05)

### **Hospital Acquired Infections:**

In the analysis of the administrative dataset, an additional 104 patients with hospital acquired infections were identified, of whom 66 had a positive test for Influenza A, 18 were positive for hMPV, and 20 patients tested positive for RSV. These infections occurred in roughly equal proportions across all three hospitals, and Influenza A was approximately 3 times as common as RSV and hMPV at each institution. As was observed in the community acquired sample, patients were more likely to be female. For patients with RSV, hMPV, and Influenza A, the median ages were 75, 73, and 75 years, respectively. Patients with RSV, hMPV and Influenza A had median Charlson Comorbidity scores of 2.5, 1, and 2 respectively.

 Thirty-day all-cause mortality amongst patients with hospital-acquired Influenza A, RSV, or hMPV was observed in 10 patients. Within each infection group, 15% of patients with RSV, 11% with hMPV and 7.6% with Influenza A died. A high portion of patients (n=36/104 =X%) were either in the ICU at the time of their respiratory virus testing or were admitted to the ICU within 30 days of their test. Additionally, 50% or more of patients in each infection group remained in hospital at 30 days following their positive respiratory test.

 While it is difficult to identify hospital infection outbreaks retrospectively, three likely hospital outbreaks were identified during the time frame of our study. The first outbreak occurred at St. Joseph Healthcare Hamilton, where 6 cases of Influenza A were identified to have occurred in the same weeks of January 2011. Second, 14 cases of Influenza A were identified to have occurred over a three weeks in December of 2012 at The Juravinski Hospital. Finally, the last outbreak likely occurred in January 2013, at Hamilton General Hospital where 10 cases of Influenza A were identified in a 3-week time frame. Other cases had temporal relationships to other cases in the same hospital but no more than 3 cases of RSV, hMPV, or Influenza A were identified to have occurred within a similar time frame.

## **Discussion:**

 From January 1, 2011 to May 31, 2014, there was a significant number of patients admitted to St. Joseph’s Healthcare Hamilton, Hamilton General Hospital, and The Juravinski Hospital with RSV, hMPV, and Influenza A. Across all three hospitals, Influenza A was the most common virus but was associated with less clinically severe outcomes than those with RSV and hMPV. A majority of patients with RSV, hMPV, and Influenza A presented to St. Joseph’s Healthcare Hamilton. Patients with RSV and hMPV were more likely to present to The Juravinski Hospital as compared Hamilton General Hospital and those with Influenza A were more likely to do the opposite. This could indicate that patients who are immunocompromised were more likely to experience RSV and hMPV as compared to influenza A, based on the patient populations of these care centres, this has been shown in other studies (38).

 The chart reviewed cohort of patients that was used to validate a subgroup of the administrative data cohort showed a high level of agreement between the two cohorts. The variables of sex, median age, and proportions that experienced adverse outcomes were highly congruent between the cohorts. Patients in the administrative data set were observed to have lower Charlson Comorbidity index scores. Due to the different methods of data collection it is possible that not all comorbid conditions are well captured in the administrative data cohort and that chart reviews are better able to identify all comorbid conditions for patients. It is also possible that there was discrepancy in patients that were eligible for inclusion in our retrospective chart review as compared to those in the total population hospitalized with the different infections at St. Joseph Healthcare Hamilton. However, this difference was likely a systematic difference in the calculation of these scores which would not effect the overall results. Higher rates of mortality were observed in the administrative cohort which is likely due to the ability to track mortality beyond hospitalization (64). In the chart review, while we did define mortality to be 30-day all-cause mortality, we were only able to capture those that died in the hospital at one institution. Some additional discrepancies did exist between outcomes, namely pertaining to outcomes following hospitalization. One possible explanation for this is that there was a discrepancy in those that were captured as residing in LTC prior to hospitalization and therefore more new admissions to LTC were recorded at discharge. This discrepancy should be explored further to better understand how the different methodologies yielded different results.

At baseline, patients with RSV and hMPV were older, more likely to have at least one comorbid condition, and more likely to already be living in a LTC facility. These differences likely contribute to the observed worse outcomes in univariable analysis of patients with RSV and hMPV. However, in multivariable models, when sex, age, and comorbid conditions are controlled for, being hospitalized with RSV or hMPV was independently associated with higher mortality than Influenza A. RSV was also significantly associated with severe disease, defined as ICU admission or mortality, but was not significant in its association with ICU admission alone. Both RSV and hMPV were significantly associated with ICU admission in univariable analysis, however it is likely that after correcting for age and comorbid conditions, which are significant in the multivariable model, that these baseline characteristics can be considered as an explanation for this discrepancy.

Prior studies have reported similar proportions of mortality between patients with RSV, hMPV, Influenza A(29, 36, 37). In this study we found results that suggested RSV and hMPV were associated with worse mortality rates, there are many possible explanations for this. First it is possible that better hospital management has improved outcomes for patients with Influenza A in the years following the prior studies and mortality from Influenza A has been reduced (50, 52). Second, it is also possible that improved diagnostic tests for Influenza A have captured a larger population of patients with Influenza A that experience less severe illness. However, improvement in diagnostic tests for Influenza A have been paralleled with improvements in diagnostic tests for the other viruses as well, so they would likely have shown similar results if this alone was the cause (30, 67).

 There were no significant differences in outcomes associated with the different hospital institutions, and as stated above there was also no independent hospitals that trended to towards worse outcomes. While we expect distinct patient populations to have presented to the different hospitals, it is possible that their distinctions are accounted for in Charlson Comorbidity scores and that adding hospital to the model did not further account for their comorbid conditions. Multicollinearity was assessed in the independent models, and it was determined not to be a concern.

Age was associated with adverse outcomes in contrasting ways. Younger age was associated with higher likelihood of being admitted to the ICU, and older age was associated with higher odds of mortality. As others have shown, older age can be associated with less use of measures to extend life, which would explain this finding (68).

RSV was significantly different from Influenza A in both univariable and multivariable analysis with respect to length of hospitalization. This outcome is concordant with some of the other more severe outcomes addressed previously. No statistically significant differences in length of stay were observed between hMPV and Influenza A in univariable or multivariable analysis. However, those with hMPV had a reduced hazard ratio of discharge (HR: 0.88, 95%CI:0.74 to 1.04, P=0.13) compared to Influenza A, suggesting that they may remain in the hospital for a longer period of time.

Patients hospitalized with Influenza A, RSV, and hMPV had similar proportions of patients that remained in hospital at 30-days following admission, were discharged to rehabilitation or long term care facilities, and were readmitted to the hospital with 30-days of discharge. Requirement of higher level of care with in 30 days of discharge following hospitalization was defined as remaining in hospital at 30 days, being transferred to rehabilitation, or being discharged to long term care facilities. There was not a significant portion of any infection group that experienced these outcomes, and no virus was significantly associated with this outcome of increased care requirements in multiviariable models. By these measures all three viruses contributed similar burdens of illness to the healthcare system. Additionally, the model used to assess transition to higher levels of care was not associated with an adequate model fit statistic indicating that there are likely many other variables that contribute to these outcomes that were not accounted for in this study.

Hospital acquired infections accounted for a subset of patients with each infection. Influenza A was more frequent in this subgroup, and appeared to have lead to more widespread outbreaks at the distinct hospitals. There significantly higher proportions of mortality and ICU admission in this subgroup of patients. Others have demonstrated that prophylactic Oseltamivir (Tamiflu) should be considered for preventing nosocomial outbreaks in diverse patient settings(69, 70). Antiviral use could not be obtained for patients in this analysis, however efficient prophylaxis could likely reduce future nosocomial infections. The development of antivirals would likely help limit secondary and tertiary cases of RSV and hMPV that were observed among those with hospital acquired infections.

There are many strengths to this study. This study spanned a significant time frame and included a large sample size. Outcome information for all patients was available due to longitudinal method of data collection. For example, patients were able to be tracked between hospitals, and 30-day mortality beyond in hospital 30-day mortality was able to be captured. Furthermore, in this study we were able to include a diverse hospital population with patients from three separate hospitals. While comorbid conditions were not specifically ascertained, based on the patient populations within each hospital, it is likely that a number of immunocompromised patients along with those with pulmonary disease, renal disease, and cardiac disease were all represented in this study.

There were some limitations to this study. First, due to data that was used, there was not a significant amount of patient specific information that could reported, symptoms that patients presented to the hospital with, chest X-ray results, and the use of medications. Second, comorbid conditions were only captured as Charlson Comorbidity scores, while this scoring system is well validated, it is not exhaustive and does not include all comorbid conditions. Therefore, it is possible that some included patient’s comorbid conditions were not well captured. Additionally, this study took place in one mid-size metropolitan area, this could limit the generalizability of this study.

In this study, we conclude that while RSV and hMPV independently contribute fewer cases of illness than Influenza A, together they have a similar number of cases. We demonstrated that both RSV and hMPV have similar or worse outcomes compared to Influenza A with respect to mortality, ICU admission, length of stay, and disposition following hospitalization. This finding suggests that not only preventative measures, such as vaccines, for RSV and hMPV, but antiviral medication and better hospital management would likely reduce their burden of illness. Due to the similar mechanisms of these viruses, exploring vaccine prevention and antiviral medications that could treat both viruses would likely benefit the adult population.

# **Chapter 4: Discussion, and Conclusions**

Two different methodologies were used to address the same research questions each with their respective strengths and limitations. First, we conducted a series of highly detailed retrospective chart reviews and second we analyzed an administrative data set that had been linked to laboratory information system data. The research questions we aimed to answer were as follows: First, were there differences in patients hospitalized with the Respiratory Syncytial Virus (RSV), human Metapneumovirus (hMPV), and Influenza A? Second, were there differences between infection groups in how patients are managed in hospital and the outcomes they experienced? Finally, were the results obtained through the analysis of the large administrative data set comparable to the results found in the retrospective chart reviews?

In response to our first research question, with both methodologies, we were able to demonstrate that there were baseline differences between those hospitalized with RSV, hMPV, and Influenza A. We found that patients with RSV were older and more likely to have at least one comorbid condition as compared patients infected with the other two viruses. Additionally, those with RSV and hMPV were more likely to require support to live prior to hospitalization. The proportion of males hospitalized and the median age of patients in the independent infection groups were highly comparable. Male sex was significantly associated with ICU admission and mortality in the chart reviewed cohort. However, in the administrative data cohort, while male patients appeared to experience worse outcomes than female patients, sex was not significantly associated with any of the outcomes of interest. This discrepancy is likely due to a larger sample size and more specific results in the larger, more diverse cohort. Age had a concordant relationship with each of the outcomes discussed in this study between the two cohorts. Younger age was associated with higher odds of being admitted to the ICU while older age being associated with increased length of stay, mortality, and increased care requirements after hospitalization. It is possible that older age is associated with less use of measures to extend life, which would explain this discrepancy (68).

The retrospective chart review was carried out at St. Joseph Healthcare Hamilton. This lead to a large portion of patients with pulmonary disease, cardiac disease, and renal disease being included in the study. Patients with these conditions were observed to be the most likely to experience any of the respiratory viruses explored in this study, as a majority of patients elected St. Joseph Healthcare Hamilton to be their choice of healthcare institution. We likely expanded our population to include a larger portion of patients that have leukemia, lymphoma, and that are immunocompromised by including the additional care sites. Moreover, we included a larger sample of patients that did not have any comorbid conditions (24%). This study demonstrates that patients with many different comorbid conditions as well as no comorbid conditions are at risk of being hospitalized with RSV, hMPV, and Influenza A. Finally, based on the distribution of infection groups across the three hospitals included, it is likely that patients that are immunocompromised are more like to be infected with RSV and hMPV than Influenza A.

 As part of our second aim, establishing differences in patient’s outcomes, we found patients hospitalized with RSV were observed to have worse outcomes as compared to patients with Influenza A after controlling for differences in baseline characteristics. Outcomes were consistent between the two cohorts of patients, however the statistical power associated with the larger sample size from the administrative data cohort gave more precise estimates. Human MPV had more discrepancies between the results in the two cohorts when being compared to Influenza A. In the retrospective chart review, patients with hMPV appeared to fair better than those with Influenza A with respect to ICU admission, length of stay, and requiring increased levels of care after hospital admission. The opposite was observed in the administrative data cohort; however, the relationships were not statistically significant in either the chart review or administrative database.

 Prior authors have described hMPV as having similar lengths of stay to Influenza A and slightly shorter lengths of stay as those with RSV (36-38). It is likely that the length of stay was more accurately captured in the administrative data set due the longitudinal nature of the data (32). The discrepancies between chart reviewed patients and the administrative data set may also be due to the number of patients with hMPV who were excluded in the chart review process due to inadequate information in their patient records. In the results of the chart review analysis, patients with hMPV virus seemed to fair similarly or better than those with Influenza A, the opposite of what was observed with RSV. In the analysis of the administrative data, patients with hMPV seemed to fair more comparably as those hospitalized with RSV. Due to the similar clinical presentations and pathologies of RSV and hMPV these results are not unexpected and they are similar to what previous authors have described (10, 36-38).

Previously, similar mortality rates in hospitalized patients have been observed between RSV, hMPV, and Influenza A (36, 38). In our study, across both cohorts, a smaller proportion of patients with Influenza A experience mortality than those with RSV or hMPV. Additionally, in the administrative data cohort RSV and hMPV had statistically significant associations with mortality. It is possible that our methods of data collection, primarily use of the administrative data base, did a better job of capturing mortality than previous authors have. However, there have also been a number of years between when the previous papers were published and the years that we included in this study. Improved diagnostic tests and hospital management options, as well as increased vaccination rates for influenza have all been observed in this time period (52). While an increase in diagnostic capabilities for RSV and hMPV has been documented during this time frame as well, it has not been accompanied by new treatment options or preventative measures (26, 30). Specifically, in the adult population there is no cost-effective measure for preventing disease is available(22). Therefore, it is also possible that RSV and hMPV do result in worse outcome now as compared to when prior studies were published. This would suggest that RSV and hMPV would benefit from the same hospital management options, such as the development of effective antiviral medications, and vaccinations, that are continuously improving for influenza. In our retrospective chart review, we were able to account for antiviral usage, and compare it to a prior study carried out in the same institution. The comparison of these studies demonstrated an increase in the use of antiviral medications, and a decrease in the use of antimicrobial medications for patients with Influenza A (71). These tools would also likely contribute to reducing rates of ICU admission and decreasing hospital lengths of stay in those hospitalized with RSV and hMPV.

Finally, when comparing the two methodologies, similar results were observed. These two methodologies contrast the advantages of having a large sample size and a more diverse population as was ascertained from the large administrative data set with a smaller sample size and more specific details on individual characteristics of a patient’s course of care from retrospective chart reviews. From the administrative data we did not collect individual comorbid conditions and were unable to collect patient’s symptoms, chest X-ray results, and antiviral and antimicrobial medication use. The absence of these variables limits our ability to describe the exact clinical presentation of patients and the severity of their illnesses. Moreover, the chart reviews allowed us to explain how patients were managed in the hospital with medication and supportive care more thoroughly. However, the usage of the large administrative data set complements our retrospective chart reviews by expanding our original highly detailed information to include more patients spread across three healthcare institutions that care for distinct patient populations. Additionally, the laboratory information for patients hospitalized between April 1, 2014 and December 31, 2016 was not available in the administrative data set, so we were unable to exactly replicate the chart reviews in the analysis of the administrative data set.

The Hamilton Regional Laboratory Medicine Program’s Virology Laboratory’s testing of all nasopharyngeal samples with multiplex PCR testing over the course of several years offers a unique prospective in an adult population to compare respiratory viruses. In this study we were able to describe the prevalence in hospital of RSV and hMPV with respect to Influenza A. We demonstrated that while independently each virus is half as common as Influenza A, when added together across three institutions, a similar number of cases were observed. Many of these cases would not have been recognized at other institutions that do not routinely test for all of these viruses, which leads to an underestimate of the burden of these viruses in the adult and elderly populations. Currently patient care is not altered based on the diagnosis of RSV or hMPV, besides potential discontinuation of antimicrobial medications. Yet, it is important to understand how prevalent they are in communities in order to make an argument for the development of vaccines and antiviral medications. Additionally, when the vaccines and antivirals, that are being developed, do become available it will be important to be able to diagnosis these viruses in order to understand the efficacy of the preventative measures and treatment options. A vaccine would likely not be effective against both viruses, however, an antiviral medication may be able to treat both viruses. The F fusion protein is analogous in RSV and hMPV and therefore considering both viruses in the development of these medications could be beneficial.

Overall through comparing RSV and hMPV to influenza A with two distinct methodologies we were able to demonstrate similar or worse morbidity and mortality between the different infection groups. RSV and hMPV remain under detected viruses due to laboratory practices, and it is important that we recognize them in order to develop and use vaccines and antivirals effectively as they become available. Laboratories should continue to innovate new ways of detecting respiratory viruses that are cost effective. This will contribute to more accurate administrative data that captures larger geographic regions. As administrative data becomes more accurate it will inevitably be used in the future to make recommendations towards what drugs are developed. Vaccines and antiviral medications should be developed with both the pediatric and adult populations in mind, as both would benefit from the prevention of these illnesses. Finally, while this study was able to answer questions about patients admitted to hospital with RSV and hMPV it did not capture the prevalence of these viruses in the community, and the outcomes of patients that experience less severe illness. Therefore, more should be done to understand the total prevalence of the viruses in the community in order to understand the total burden of these illnesses.

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|  |  |
| --- | --- |
| **Appendix 1: Chart Reviewed Cohort Goodness of Fit Analyses**  |  |
|  |
| **Appendix 1.1 ICU Admission Logistic Regression Model Goodness of Fit Statistics** |
| Partition for the Hosmer and Lemeshow Test |
|   | Total | ICU Admission | No ICU admission |
| Group |   | Observed | Expected | Observed | Expected |
| 1 | 31 | 0 | 1.647 | 31 | 29.353 |
| 2 | 31 | 2 | 2.314 | 29 | 28.686 |
| 3 | 31 | 4 | 2.762 | 27 | 28.238 |
| 4 | 31 | 5 | 3.124 | 26 | 27.876 |
| 5 | 31 | 3 | 3.625 | 28 | 27.375 |
| 6 | 31 | 7 | 4.318 | 24 | 26.682 |
| 7 | 31 | 5 | 4.896 | 26 | 26.104 |
| 8 | 31 | 3 | 5.728 | 28 | 25.272 |
| 9 | 31 | 6 | 6.728 | 25 | 24.272 |
| 10 | 31 | 9 | 8.858 | 22 | 22.142 |
| Hosmer and Lemeshow Goodness-of-Fit Test |  |   |   |
|  |  |  |
| Chi-square | df | Sig. |  |  |  |
| 7.404 | 8 | 0.494 |  |  |  |
|  |  |  |  |  |  |
| **Appendix 1.2 Mortality Logistic Regression Model Goodness of Fit Statistics** |
| Partition for the Hosmer and Lemeshow Test |
| Group | Total | Mortality Experience | Alive |
| Observed | Expected | Observed | Expected |
| 1 | 31 | 0 | 0.139 | 31 | 30.861 |
| 2 | 31 | 0 | 0.344 | 31 | 30.656 |
| 3 | 31 | 1 | 0.569 | 30 | 30.431 |
| 4 | 31 | 1 | 0.766 | 30 | 30.234 |
| 5 | 31 | 1 | 1.002 | 30 | 29.998 |
| 6 | 31 | 0 | 1.253 | 31 | 29.747 |
| 7 | 31 | 3 | 1.634 | 28 | 29.366 |
| 8 | 31 | 2 | 2.209 | 29 | 28.791 |
| 9 | 31 | 2 | 3.364 | 29 | 27.636 |
| 10 | 32 | 7 | 5.72 | 25 | 26.28 |
| Hosmer and Lemeshow Goodness-of-Fit Test |  |  |  |
|  |  |  |
| Chi-square | df | Sig. |  |  |  |
| 4.395 | 8 | 0.82 |  |  |  |
|  |  |  |  |  |  |
| **Appendix 1.3 Severe Illness Logistic Regression Model Goodness of Fit Statistics** |
| Partition for the Hosmer and Lemeshow Test |
| Group | Total | Experiences Severe Illness | Did not Experience Severe Illness |
| Observed | Expected | Observed | Expected |
| 1 | 31 | 2 | 2.824 | 29 | 28.176 |
| 2 | 31 | 4 | 3.246 | 27 | 27.754 |
| 3 | 31 | 4 | 3.572 | 27 | 27.428 |
| 4 | 31 | 6 | 3.967 | 25 | 27.033 |
| 5 | 31 | 4 | 4.4 | 27 | 26.6 |
| 6 | 31 | 4 | 5.044 | 27 | 25.956 |
| 7 | 31 | 5 | 5.901 | 26 | 25.099 |
| 8 | 31 | 7 | 6.563 | 24 | 24.437 |
| 9 | 31 | 7 | 7.336 | 24 | 23.664 |
| 10 | 32 | 9 | 9.147 | 23 | 22.853 |
| Hosmer and Lemeshow Goodness-of-Fit Test |  |  |  |
|  |  |  |
| Chi-square | df | Sig. |  |  |  |
| 2.243 | 8 | 0.973 |  |  |  |
|  |  |  |  |  |  |
| **Appendix 1.4 Increase in Level of Care Requirements Logistic Regression Model Goodness of Fit Statistics** |
| Partition for the Hosmer and Lemeshow Test |
| Group | Total | Required Increased Levels of Care | Required Same levels of care |
| Observed | Expected | Observed | Expected |
| 1 | 30 | 0 | 0.903 | 30 | 29.097 |
| 2 | 30 | 1 | 1.318 | 29 | 28.682 |
| 3 | 30 | 4 | 1.685 | 26 | 28.315 |
| 4 | 30 | 2 | 2.023 | 28 | 27.977 |
| 5 | 30 | 2 | 2.324 | 28 | 27.676 |
| 6 | 30 | 1 | 2.83 | 29 | 27.17 |
| 7 | 30 | 4 | 3.517 | 26 | 26.483 |
| 8 | 30 | 6 | 4.24 | 24 | 25.76 |
| 9 | 30 | 6 | 5.634 | 24 | 24.366 |
| 10 | 27 | 6 | 7.526 | 21 | 19.474 |
| Hosmer and Lemeshow Goodness-of-Fit Test |  |  |  |
|  |  |  |
| Chi-square | df | Sig. |  |  |  |
| 7.119 | 8 | 0.524 |  |  |  |
|  |  |  |  |  |  |
| **Appendix 1.5 Readmission to the Hospital Logistic Regression Model Goodness of Fit Statistics** |
| Partition for the Hosmer and Lemeshow Test |
| Group | Total | 30 Day Hospital Readmission | No 30 day Hospital Readmission |
| Observed | Expected | Observed | Expected |
| 1 | 31 | 1 | 1.376 | 30 | 29.624 |
| 2 | 31 | 1 | 1.491 | 30 | 29.509 |
| 3 | 31 | 3 | 1.568 | 28 | 29.432 |
| 4 | 31 | 0 | 1.7 | 31 | 29.3 |
| 5 | 31 | 1 | 1.849 | 30 | 29.151 |
| 6 | 31 | 4 | 2.242 | 27 | 28.758 |
| 7 | 31 | 4 | 3.627 | 27 | 27.373 |
| 8 | 31 | 4 | 3.892 | 27 | 27.108 |
| 9 | 31 | 2 | 4.173 | 29 | 26.827 |
| 10 | 32 | 7 | 5.083 | 25 | 26.917 |
| Hosmer and Lemeshow Goodness-of-Fit Test |  |  |  |
|  |  |  |
| Chi-square | df | Sig. |  |  |  |
| 7.568 | 8 | 0.477 |  |  |  |
|  |  |  |  |  |  |
| **Appendix 1.6 Length of Stay Cox Proportional Hazards Model Goodness of Fit Statistics** |
| Model Fit Statistics |  |  |  |
| Criterion | Without | With |  |  |  |
| Covariates | Covariates |  |  |  |
| -2 LOG liklihood | 2728.01 | 2707.08 |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| **Appendix 2: Administrative Data Cohort Goodness of Fit Analyses**  |
|  |  |  |  |  |  |
| **Appendix 2.1 ICU Admission Logistic Regression Model Goodness of Fit Statistics** |
| Partition for the Hosmer and Lemeshow Test |
| Group | Total | ICU admission | No ICU admission |
|
| Observed | Expected | Observed | Expected |
| 1 | 100 | 6 | 6.27 | 94 | 93.73 |
| 2 | 100 | 9 | 8.63 | 91 | 91.37 |
| 3 | 100 | 6 | 10.48 | 94 | 89.52 |
| 4 | 101 | 9 | 12.54 | 92 | 88.46 |
| 5 | 100 | 13 | 14.04 | 87 | 85.96 |
| 6 | 101 | 19 | 16.09 | 82 | 84.91 |
| 7 | 100 | 23 | 17.91 | 77 | 82.09 |
| 8 | 101 | 22 | 20.86 | 79 | 80.14 |
| 9 | 100 | 28 | 24.46 | 72 | 75.54 |
| 10 | 96 | 30 | 33.69 | 66 | 62.31 |
| Hosmer and Lemeshow Goodness-of-Fit Test |  |  |  |
|  |  |  |
| Chi-Square | DF | Pr > ChiSq |  |  |  |
| 7.1685 | 8 | 0.5186 |  |  |  |
|  |  |  |  |  |  |
| **Appendix 2.2 Mortality Logistic Regression Model Goodness of Fit Statistics** |
| Partition for the Hosmer and Lemeshow Test |
| Group | Total | Expereinced Mortality  | Alive |
|
| Observed | Expected | Observed | Expected |
| 1 | 100 | 2 | 1.18 | 98 | 98.82 |
| 2 | 100 | 1 | 2.39 | 99 | 97.61 |
| 3 | 100 | 2 | 3.49 | 98 | 96.51 |
| 4 | 101 | 3 | 4.68 | 98 | 96.32 |
| 5 | 100 | 5 | 5.71 | 95 | 94.29 |
| 6 | 100 | 9 | 7.11 | 91 | 92.89 |
| 7 | 100 | 9 | 8.78 | 91 | 91.22 |
| 8 | 100 | 13 | 11.04 | 87 | 88.96 |
| 9 | 101 | 15 | 14.04 | 86 | 86.96 |
| 10 | 97 | 21 | 21.59 | 76 | 75.41 |
| Hosmer and Lemeshow Goodness-of-Fit Test |  |  |  |
|  |  |  |
| Chi-Square | DF | Pr > ChiSq |  |  |  |
| 3.8149 | 8 | 0.8734 |  |  |  |
|  |  |  |  |  |  |
| **Appendix 2.3 Severe Illness Logistic Regression Model Goodness of Fit Statistics** |
| Partition for the Hosmer and Lemeshow Test |
| Group | Total | Experienced Severe Illness | Did not Experience severe Illness |
|
| Observed | Expected | Observed | Expected |
| 1 | 100 | 7 | 10.5 | 93 | 89.5 |
| 2 | 101 | 16 | 13.59 | 85 | 87.41 |
| 3 | 100 | 20 | 15.16 | 80 | 84.84 |
| 4 | 100 | 8 | 16.64 | 92 | 83.36 |
| 5 | 102 | 16 | 19.09 | 86 | 82.91 |
| 6 | 100 | 21 | 21.09 | 79 | 78.91 |
| 7 | 100 | 26 | 23.19 | 74 | 76.81 |
| 8 | 100 | 31 | 25.85 | 69 | 74.15 |
| 9 | 100 | 32 | 30.31 | 68 | 69.69 |
| 10 | 96 | 40 | 41.59 | 56 | 54.41 |
| Hosmer and Lemeshow Goodness-of-Fit Test |  |  |  |
|  |  |  |
| Chi-Square | DF | Pr > ChiSq |  |  |  |
| 11.6846 | 8 | 0.1658 |  |  |  |
|  |  |  |  |  |  |
| **Appendix 2.4 Increase in Level of Care Requirements Logistic Regression Model Goodness of Fit Statistics** |
| Partition for the Hosmer and Lemeshow Test |
| Group | Total | Required Increase in level of Care | Required same Level of care |
|
| Observed | Expected | Observed | Expected |
| 1 | 100 | 1 | 0.86 | 99 | 99.14 |
| 2 | 100 | 10 | 2.02 | 90 | 97.98 |
| 3 | 100 | 2 | 3.83 | 98 | 96.17 |
| 4 | 100 | 4 | 5.3 | 96 | 94.7 |
| 5 | 100 | 8 | 6.79 | 92 | 93.21 |
| 6 | 101 | 0 | 8.57 | 101 | 92.43 |
| 7 | 100 | 4 | 10.4 | 96 | 89.6 |
| 8 | 100 | 11 | 12.36 | 89 | 87.64 |
| 9 | 100 | 9 | 14.7 | 91 | 85.3 |
| 10 | 98 | 35 | 19.17 | 63 | 78.83 |
| Hosmer and Lemeshow Goodness-of-Fit Test |  |  |  |
|  |  |  |
| Chi-Square | DF | Pr > ChiSq |  |  |  |
| 66.4466 | 8 | <.0001 |  |  |  |
|  |  |  |  |  |  |
| **Appendix 2.5 Readmission to the Hospital Logisitic Regression Model Goodness of Fit Statistics** |
| Partition for the Hosmer and Lemeshow Test |
| Group | Total | 30 Day Hospital Readmission | No 30 Day hospital Readmission |
|
| Observed | Expected | Observed | Expected |
| 1 | 100 | 7 | 5.44 | 93 | 94.56 |
| 2 | 100 | 4 | 6.39 | 96 | 93.61 |
| 3 | 100 | 13 | 7.08 | 87 | 92.92 |
| 4 | 100 | 6 | 7.8 | 94 | 92.2 |
| 5 | 102 | 4 | 8.72 | 98 | 93.28 |
| 6 | 100 | 10 | 9.29 | 90 | 90.71 |
| 7 | 102 | 5 | 10.28 | 97 | 91.72 |
| 8 | 100 | 15 | 11.18 | 85 | 88.82 |
| 9 | 100 | 15 | 12.87 | 85 | 87.13 |
| 10 | 95 | 16 | 15.95 | 79 | 79.05 |
| Hosmer and Lemeshow Goodness-of-Fit Test |  |  |  |
|  |  |  |
| Chi-Square | DF | Pr > ChiSq |  |  |  |
| 14.9479 | 8 | 0.0602 |  |  |  |
|  |  |  |  |  |  |
| **Appendix 2.6 Length of Stay Cox Proportional Hazards Model Goodness of Fit Statistics** |
| Model Fit Statistics |  |  |  |
| Criterion | Without | With |  |  |  |
| Covariates | Covariates |  |  |  |
| AIC | 10807.908 | 10729.931 |  |  |  |