Paxlovid and Lagevrio for Treatment of Covid-19

Molli Sarpong

Leach College of Nursing, University of St. Francis

NURS 613: Evidence-Based Practice in Healthcare

Sunya Watson

February 25, 2024

Paxlovid and Lagevrio for Treatment of Covid-19

Over the centuries, there have been many life altering events that have occurred and, in most instances, changed the way that human beings exist on this planet. Recently, a pandemic originally labeled as severe acute respiratory syndrome (SARS) human coronavirus and now commonly known as Covid-19, has shaken the human population to its core. Healthcare practices, policies, and procedures have all changed to accommodate the ever-changing situation caused by this new virus. This novel virus is known to cause illnesses such as pneumonia (PNA), fever, and breathing difficulty, which can potentially lead to respiratory failure. The diseases listed along with others have become more frequent and virulent leading to millions of deaths across the world.

Initially, there were no set treatments known to help treat Covid-19, especially in patients who experienced kind of response to the viral infection commonly known as a cytokine storm. These patients were the ones most likely to need ventilator support and have the highest mortality rate of all patients diagnosed with Covid-19 (Montazersaheb et al., 2022). However, as the years passed several medications became the standard treatment for Covid-19 patients: Remdesivir, Paxlovid, and Lagevrio being the only options now available (Health and Human Services [HHS], 2024). Currently, Paxlovid and Lagevrio are the only oral option for antiviral treatment available for Covid-19 at this particular time (HHS, 2024).

To better address the growing needs in healthcare regarding Covid-19, a question was asked to determine the efficacy and safety of the oral anti-viral medications currently on the market. Using the outline of Patient (P), Intervention (I), Compare (C), Outcome (O), and Time (T) or PICOT, the following question was posed: For patients diagnosed with Covid-19 and at high risk for severe disease, how does treatment with Paxlovid and/or Lagevrio compared to

standard of care reduce the severity of symptoms and length of their viral syndrome throughout their Covid-19 infection? Appendix A provides a more thorough breakdown of the PICOT question.

Currently, there are several research studies that have shown improvement of symptoms after initiation of oral antiviral medications; however, these therapies are still relatively new and further research should be done to identify their efficacy and safety margins. Also, in many facilities, such as Advocate Health Care, intravenous therapy of Remdesivir is used as front-line treatment prior the initiation of oral treatment (Offit, 2023). The purpose behind posing this question is to determine whether making oral antiviral treatments first-line treatment is a safe and effective way to reduce the possibility of severe covid symptoms in patient diagnosed with Covid-19.

Medications and Research

Paxlovid is the brand name of one of medication and contains two separate medications that were combined to create a treatment against Covid-19. The active anti-viral agents in Paxlovid are Nirmatrelvir and Ritonavir; Nirmatrelvir is a protease inhibitor that prevents viral replication (National Institutes of Health [NIH], 2023). Ritonavir is used as a "booster" to reduce the rapid breakdown Nirmatrelvir and has been used in the past as a boosting agent for anti-viral human-immunodeficiency virus (HIV) protease inhibitor medications (NIH, 2023). Only with the booster does Nirmatrelvir reach therapeutic concentrations to target the Covid-19 virus (NIH, 2023). The dosing of the two medications is dependent on the patient's renal function, where standard dosing is 300 mg of Nirmatrelvir, and 100 mg of Ritonavir are to be taken together twice a day for five consecutive days (NIH, 2023). Whereas renal dosing consists of 150 mg

Nirmatrelvir and 100 mg Ritonavir to be taken together twice a day for five consecutive days (NIH, 2023).

Lagevrio contains the active ingredient Molnupiravir, which is a ribonucleoside that causes viral mutations and lethal mutagenesis of the Covid-19 virus (U.S. Food and Drug Administration [USFDA], 2021). The dosing of this medication consists of 800 mg of Molnupiravir twice a day for five consecutive days (USFDA, 2021). As of now, there are no further dosing considerations for renal or hepatic impairment. However, this antiviral agent has been found to not be as clinically effective as Paxlovid and should be considered as the secondary option when Paxlovid or Remdesivir are not available at the time (USFDA, 2021).

Research Process and Data Collection

For the literature search, several different databases were searched in order to acquire different articles that addressed the PICOT question. The need for the articles to be within the last five years was not a concern, as Covid-19 oral antivirals have not been around long enough to fall outside of this range. Many of the articles that would have been useful were not accessible, however there were still some that were free through library access using EBSCO host. Overall, PubMed seemed to have the most applicable research studies available regarding both medications. Cochrane was the second most helpful in finding articles for this PICOT question, however there was a problem with many of them being systematic reviews instead of true research articles. Appendix B provides a greater understanding of the process in which different articles were chosen to help address the question created to determine the efficacy and safety of Paxlovid and Lagevrio.

Six articles were selected to help address the PICOT question. Each article will be broken down to better determine their value in addressing the issue illustrated in the originally stated

PICOT. Table 1 gives more information on the first article that was chosen to provide better insight on information needed to answer the PICOT question.

Table 1

Article one: Paxlovid in high-risk patients

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19	
Name of Authors	Hammond, J., Leister-Tebbe, H., Gardner, A., Abreu, P., Bao, W., Wisemandle, W., Baniecki, M., Hendrick, V. M., Damle, B., Simón-Campos, A., Pypstra, R., & Rusnak, J. M.
Date Published	April 14th, 2022.
Journal Article Published in	The New England Journal of Medicine
Level of Evidence	Level II
Hypothesis, Question, or Purpose of Study	To determine the effectiveness of Paxlovid in preventing hospitalization and death through 28 days of Covid-19 infection (Hammond et al., 2022).
Design	Double-blind, randomized, controlled trial where patients were assigned in a 1:1 ratio active drug versus placebo to determine effectiveness of Paxlovid treatment (Hammond et al., 2022). An interactive response technology system was used to place patients in either the experimental group or the placebo group (Hammond et al., 2022).
Data Collection Instruments/Procedures	The main analysis compared the patients in both groups for hospitalization and/or death by day 28 of the study using the Kaplan-Meier method (Hammond et al., 2022). A z-test was used for the comparisons, with standard errors estimated using Greenwood's formula (Hammond et al., 2022). Changes in viral load from the base line analysis were compared between both groups using an analysis of covariance (ANCOVA) model (Hammond et al., 2022). The predetermined significance level for early termination was 0.002 for efficacy and 0.9184 for futility (Hammond et al., 2022).
Statistical Results or Findings	1) For patients treated within 3 days of symptom onset, patients treated with Paxlovid had a 0.77% rate of hospitalization with no deaths reported (Hammond et al., 2022). In the placebo group, they had a 7.01% rate of hospitalization with 7 deaths (Hammond et al., 2022). In this there was a relative risk reduction of 89.21% when administering Paxlovid (Hammond et al., 2022). 2) For patients treated within 5 days of symptom onset, patients treated with Paxlovid had a 0.77% rate of hospitalization and the placebo group had a 6.31% rate of hospitalization or death (Hammond et al., 2022). This equated

	to a risk reduction of 87.8% when administering Paxlovid (Hammond et al., 2022). 3) The only significant adverse event in both groups was dysgeusia (Hammond et al., 2022). 4) Through day 34, there were 13 deaths among the placebo group and no deaths in the study group (Hammond et al., 2022).
Implications and Conclusions of Study	1) Overall, treatment with Paxlovid caused an 88.9% reduction of risk for severe disease (Hammond et al., 2022). 2) With the results that were collected, the efficacy of Paxlovid was proven to be positive (Hammond et al., 2022). 3) Paxlovid has the potential to have drug-drug interactions in patients that have multiple medications, and this may pose a risk for patients in the high-risk category (Hammond et al., 2022).

Overall, this first article showed a positive response to Paxlovid treatment, whether given within the first 3 days or first 5 days of symptom onset. With patients that are at high risk for severe disease, this would be a beneficial treatment in helping to prevent hospitalization or deaths. Table 2 will give further information on the second article that was chosen to give better insight into the information needed to address the PICOT question.

Table 2

Article two: Paxlovid against Omicron in Geriatric population.

Safety and Efficacy of Paxlovid Against Omicron Variants of Coronavirus Disease 2019 in Elderly Patients	
Name of Authors	Weng, C., Xie, R., Han, G., Yuan, Y., Li, S., Wang, C., Wang, X., Jiang, W., & Jiang, L.
Date Published	January 25, 2023.
Journal Article Published in	Infectious Diseases and Therapy.
Level of Evidence	Level IV.
Hypothesis, Question, or Purpose of Study	To clarify the effectiveness and safety margins of Paxlovid treatment in the elderly population diagnosed with Covid-19 Omicron variant (Weng et al., 2023).
Design	A total of 163 patients were followed, aged over 60 years and diagnosed with mild to moderate Covid-19 disease (Weng et al., 2023). This was a single-center, retrospective study where the medical records of the aforementioned patients were followed through their hospital stay (Weng et al., 2023). 82

	patients in the group received Paxlovid treatment, the other 81 received standard of care treatment (Weng et al., 2023). The primary endpoint was the length of the patient's hospitalization, secondary endpoint was adverse events in either group through day 21 (Weng et al., 2023).
Data Collection Instruments/Procedures	The severity of pulmonary involvement was evaluated on chest computed tomography (CT) scans to determine a visual severity score throughout the course of the patient's Covid-19 infection (Weng et al., 2023). Means for the continuous values were compared using t tests and Mann-Whitney U tests (Weng et al., 2023).
Statistical Results or Findings	The duration of hospitalization was reduced in Paxlovid treatment, the viral shedding was also reduced in the treatment group as compared to the control group (Weng et al., 2023). A higher percentage of patients in the control group required supportive treatment than those in the treatment group (Weng et al., 2023). Only one patient in the treatment group progressed to severe disease, whereas four patients progressed to severe in the control group (Weng et al., 2023). Only in the control group was there a death of one patient (Weng et al., 2023).
Implications and Conclusions of Study	Paxlovid is found to be effective in reducing the length of Covid-19 disease, especially in the at-risk population of geriatrics. Oral antivirals such as Paxlovid would be helpful in preventing the need for hospitalization in this population of patients.

In review, the second article had evidence that showed that Paxlovid was helpful in preventing the need for the geriatric population to be admitted to hospital. However, this study was found to have some limitations, such as having such a small sample size, as well as this was only an observational study; a randomized-controlled trial would have been more effective in determining the effectiveness of Paxlovid in treating Covid-19 in the geriatric population (Weng et al., 2023). One concerning factor that was seen in this study was the evidence of Covid-19 rebound, however Weng et al. (2023) states that the follow-up period after the study was short. Table 3 gives additional information into an article that was chosen to determine the efficacy of Paxlovid in treating Covid-19.

Table 3

Article 3: Efficacy and safety of Paxlovid in adult population.

Efficacy and Safety of Paxlovid in severe adult patients with SARS-Cov-2 infection: a multicenter randomized controlled study.	
Name of Authors	Liu, J., Pan, X., Zhang, S., Li, M., Ma, K., Fan, C., Lv, Y., Guan, X., Yang, Y., Ye, X., Deng, X., Wang, Y., Qin, L., Xia, Z., Ge, Z., Zhou, Q., Zhang, X., Ling, Y., Qi, T., Wen, Z., Huang, S., Zhang, L., Wang, T., Liu, Y., Huang, Y., Li, W., Du, H., Chen, Y., Xu, Y., Zhao, Q., Zhao, R., Annane, D., Qu, J., Chen, D.
Date Published	February 6, 2023.
Journal Article Published in	The Lancet Regional Health – Western Pacific.
Level of Evidence	Level II.
Hypothesis, Question, or Purpose of Study	To study the efficacy and safety of Paxlovid in hospitalized adult patients with Omicron variant of Covid-19 infection and comorbidities (Liu et al., 2023).
Design	Open-label, multicenter, randomized controlled trial where hospitalized patients with severe comorbidities assigned in a one-to-one ratio to either receive Paxlovid or standard of care treatment (Liu et. al., 2023). Primary endpoint was 28-day all-course mortality; secondary endpoint included in-hospital mortality, progression to severe Covid-19 within 14 days and proportion of acute exacerbation from a chronic disease within 14 days (Liu et al., 2023).
Data Collection Instruments/Procedures	The Shapiro-Wilk test was used to test for normal distributions, independent Student t-test or the Wilcoxon-rank-sum test were used to perform comparison of quantitative data (Liu et al., 2023). The chi-square test, the exact probability method and the Cochrane-Mantel-Haenszel (CMH) test were used for additional comparison of quantitative data (Liu et al., 2023). Bonferroni correction for alpha was used to adjust confidence intervals; the survival time and duration of Covid-19 was plotted using the Kaplan-Meier curve (Liu et al., 2023).
Statistical Results or Findings	Paxlovid treatment was not found to decrease the 28-day mortality rate in patients diagnosed with Covid-19; there was no difference between the groups in terms of length of time for Covid-19 clearance (Liu et al., 2023). 8 patients died in the control group and 5 died in the treatment group (Liu et al., 2023). Although it was not within the purpose of the study, it was found that the Covid-19 vaccine was more successful in reducing the disease-related hospitalizations and deaths from the viral syndrome (Liu et al., 2023).
Implications and Conclusions of Study	There is a possibility that Paxlovid may not have as great of an effect in reducing the mortality rate in patients, especially those will multiple comorbidities. However, vaccines were

	found to be highly effective in preventing the need for hospitalization and reducing mortality in patients diagnosed with Covid-19.

Although this study had several limitations, it was found that neither the treatment nor control group had a significant difference in the mortality rate, over a timeframe of 28 days. Although, the use of preventative therapy, such as vaccinations, was found to be highly useful in reducing the mortality rate in patients that have several comorbidities. There was no significant difference between the two groups in terms of adverse events between the groups, therefore there is no question as to whether the medication was found to be safe. Some limitations of the study include the fact that no placebo was included in the study as there was an urgent need at the time for reliable and randomized study data to determine the efficacy of the medication (Liu et al., 2023). Additionally, it was found that as the virus mutates the mortality decreases, which could naturally skew the results of the study (Liu et al., 2023). Table 4 will provide information on a research study done for Lagevrio versus Paxlovid.

Table 4

Article four: Safety and efficacy of Lagevrio versus Paxlovid.

Antiviral efficacy of molnupiravir versus ritonavir-boosted nirmatrelvir in patients with early symptomatic Covid-19 (PLATCOV): an open-label, phase 2, randomized, controlled, adaptive trial.	
Name of Authors	Schilling, W. H., Jittamala, P., Watson, J. A., Boyd, S., Luvira, V., Siripoon, T., Ngamprasertchai, T., Batty, E. M., Cruz, C., Callery, J. J., Singh, S., Saroj, M., Kruabkontho, V., Ngernseng, T., Tanglakmankhong, N., Tubprasert, J., Abdad, M. Y., Madmanee, W., Kouhathong, J.,Suwannasin, K., Pagornrat, W., Piaraksa, N., Hanboonkunupakarn, P., Hanboonkunupakarn, B., Poovorawan, K., Potaporn, M., Srisubat, A., Loharjun, B., Taylor, W., Chotivanich, V., Chotivanich, K., Imwong, M., Pukrittayakamee, S., Dondorp, A., Day, N., Teixeira, M., Piyaphanee, W., Phumratanaprapin, W., & White, N.
Date Published	October 12, 2023
Journal Article Published in	The Lancet Infectious Diseases.
Level of Evidence	Level II.

Hypothesis, Question, or Purpose of Study	To compare the different antiviral therapies that are now available (Schilling et al., 2023).
Design	Open-label, multicenter, phase 2, randomized, controlled and adaptive pharmacometrics platform trial (Schilling et al., 2023). The patients were assigned randomly, the primary endpoint was the rate of viral clearance (Schilling et al., 2023).
Data Collection Instruments/Procedures	The TaqCheck SARS-CoV-2 Fast PCR Assay was used to quantify viral loads (Schilling et al., 2023). The rate of viral clearance was expressed as a slope coefficient and estimated using Bayesian hierarchical linear model (Schilling et al., 2023). Treatment effect was determined by the change in viral clearance (Schilling et al., 2023). Viral rebound was studied using the Fisher exact test (Schilling et al., 2023).
Statistical Results or Findings	The average time required to halve the viral load was shorter in duration in Paxlovid as compared to Lagevrio (Schilling et al., 2023). However, there was a higher proportion of patients receiving Paxlovid that experienced viral rebound (Schilling et al., 2023). No patients in either group developing serious disease, were hospitalized, or died as a result of their Covid-19 infection (Schilling et al., 2023).
Implications and Conclusions of Study	When comparing the two medications, it appears that Paxlovid is more effective; however, the medication does post the risk of the patient having viral rebound syndrome. Both medications were found to be safe and could be options for patients to help prevent progression of their Covid-19 symptoms.

This research study did a very good job in demonstrating the effectiveness of both antiviral treatments for Covid-19. Even though both effective, it was found that Paxlovid accelerated the clearance rate of viral load more effectively than Lagevrio (Schilling et al., 2023). One concerning factor of this study was that all patients used in the research were low risk, which brings to question whether the same results would occur in high-risk patients diagnosed with Covid-19. Table 5 compares Lagevrio and Paxlovid to determine the efficacy and safety of the medication in treating Covid-19.

Table 5

Article 5: Lagevrio and Paxlovid versus Covid-19

Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalized patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort-study.	
Name of Authors	Wong, C. K., Au, I. C., Lau, K. T., Lau, E. H., Cowling, B. J., & Leung, G. M
Date Published	December 5, 2023.
Journal Article Published in	Lancet Infectious Disease.
Level of Evidence	Level IV.
Hypothesis, Question, or Purpose of Study	To evaluate the effectiveness of Lagevrio and Paxlovid in hospitalized patients diagnosed with Covid-19 during an Omicron outbreak (Wong et al., 2023).
Design	Retrospective cohort study of adult hospitalized patients diagnosed with Covid-19 upon admission without oxygen needs (Wong et al., 2023). For mortality rates, data was taken from the Hong Kong death registry (Wong et al., 2023). 1856 patients were assigned to Lagevrio with equal amounts of controlled patients; 890 patients were given Paxlovid, with equal amounts of control patients (Wong et al., 2023). Primary outcome was all-cause mortality, secondary was composite outcome of disease progression and time required to reach low viral burden (Wong et al., 2023).
Data Collection Instruments/Procedures	Rubin's rules were used to pool the treatment effects and were estimated using the different datasets; standardized mean difference (SMD) was used to assess the balance of each baseline covariate (Wong et al., 2023). Hazard ratios with 95% confidence intervals were used for each outcome between Paxlovid and Lagevrio using Cox-regression models (Wong et al., 2023). A cluster-robust sandwich variance-covariance estimator was used in all Cox regression models to account for the correlation seen in the propensity-score matches (Wong et al., 2023).
Statistical Results or Findings	The time needed to reach low viral burden was shorter among patients receiving Paxlovid and Lagevrio as compared to those getting standard of care treatment (Wong et al., 2023). There were no significant differences in the length of stay for patients receiving Paxlovid and their corresponding control group; however, there was a significantly shorter hospital stay for patients taking Lagevrio as opposed to their control group (Wong et al., 2023). By day 7, the proportion of patient's mortality was lower in those receiving oral antivirals as opposed to their respective control groups; the same statistics were seen by day 28 (Wong et al., 2023).
Implications and Conclusions of Study	The use of either Paxlovid or Lagevrio were seen to have a reduction in mortality rates as opposed to those not receiving oral antivirals; therefore, it would be beneficial to begins

	patients with oral antivirals early on in their course of Covid-19 to improve patient outcomes.

Even though article four presented the concept that Paxlovid was more effective than Lagevrio, it can be seen through this article that both are effective in improving patient outcomes. This research study did have some limitations, such as the fact that it was an observational study done on patients through their electron health records (EHR), instead of a controlled study where a placebo could have been used. Also, this research was only done in patients that were hospitalized within Hong Kong hospitals and not in any other area; as such, the results may be skewed as only a single population of patients were used for this research. Table 6 will provide information abou7t the comparison of intravenous Remdesivir (RDV) versus oral Paxlovid.

Table 6

Article 6: Intravenous RDV versus oral Paxlovid.

Effectiveness of Oral Nirmatrelvir/Ritonavir vs. Intravenous Three-Day Remdesivir in Preventing Progression to Severe COVID-19: A Single-Center, Prospective, Comparative, Real-Life Study	
Name of Authors	Basoulis, D., Tsakanikas, A., Gkoufa, A., Bitsani, A., Karamanakos, G., Mastrogianni, E., Georgakopoulou, V. E., Makrodimitri, S., Voutsinas, P.-M., Lamprou, P., Kontos, A., Tsiakas, S., Gamaletsou, M. N., Marinaki, S., & Sipsas, N. V.
Date Published	July 7, 2023
Journal Article Published in	Viruses
Level of Evidence	Level IV.
Hypothesis, Question, or Purpose of Study	To determine the efficacy of both antivirals in preventing hospitalization and/or death in patients diagnosed with Covid-19 (Basoulis et al., 2023).
Design	Prospective observational study performed in Laiko General Hospital; data was taken from patients that were immunocompromised or had more than one comorbidity and were tested positive for Covid-19 (Basoulis et al., 2023). Primary outcome of the study was hospitalization within 30 days; secondary outcome was mortality at 30 days, length of hospital stays and mortality rate at 90 days (Basoulis et al., 2023). 356 patients received RDV, 165 received Paxlovid (Basoulis et al., 2023).

Data Collection Instruments/Procedures	Normality of distribution was examined using Kolmogorov-Smirnov test; Group comparisons were examined using Student's t-test and Mann-Whitney U test, chi-square test was used for categorical variables (Basoulis et al., 2023). Multivariable analysis was performed using binary logistic regression; Kaplan-Meier survival curve was used to examine differences in hospitalization length of stays (Basoulis et al., 2023).
Statistical Results or Findings	1.4% (5 patients) in the RDV group and 0.6% (1 patient) in the Paxlovid group died within 30 days of hospitalization (Basoulis et al., 2023). 1.4% (5 patients) in RDV group and 1.2% (2 patients) in the Paxlovid group died by 90 days of hospitalization (Basoulis et al., 2023). Both antivirals were found to have a 97.1% of efficacy in preventing mortality; early administration of antiviral treatment was associated with lower mortality rates in immunocompromised and high-risk patients (Basoulis et al., 2023). Both RDV and Paxlovid were found to have the same efficacy (Basoulis et al., 2023).
Implications and Conclusions of Study	Antiviral treatment was found to be effective in preventing severe disease in high-risk patients, which would be an effective method to reduce mortality rates in patients. For patients that do not need to be hospitalized, oral antivirals would be beneficial to keep them from needing to be hospitalized.

Reviewing the different articles presented, the majority identified that the use of either Paxlovid or Lagevrio provided beneficial outcomes in patients diagnosed with Covid-19. This particular study did have several limitations, such as the fact that it was an observational study that had no control group to compare it to. Additionally, no data was collected on the tolerability of the medications, although there were no patients in either group that terminated treatment early because of symptoms (Basoulis et al., 2023). Lastly, this was only a single-center trial and may not represent the same results in different countries or locations (Basoulis et al., 2023).

State of the Science Summary

Overall, after reviewing all the articles that were not meta-analyses or systematic reviews, it can be seen that there is a consensus that the use of oral antivirals were effective in improving patient outcomes. However, there was a trend where Paxlovid was found to be more effective in

treating Covid-19 than Lagevrio; Paxlovid was also found to have a higher rate of rebound symptoms after the five-day course of treatment was completed (Schilling et al., 2023). Attempts to find research studies that examined the safety and efficacy of Lagevrio on its own has proven very challenging. Even though there were many articles comparing the two medications to determine which was more effective in treating Covid-19. This may be due to the fact that Paxlovid has been fully approved by the FDA, whereas Lagevrio is still only under emergency use authorization (Food and Drug Administration [FDA], 2023).

Throughout all of the articles presented, the majority consensus showed that the use of oral antivirals showed an increase in positive outcomes for the patients diagnosed with Covid-19. However, in the third article it was identified through a randomized and controlled trial where the use of Paxlovid was compared to standard care treatment. This possibility that there may be no clinical significance in the reduction is concerning when knowing that there is yet another surge in Covid-19 infections. According to Storey (2024), a recent study has shown that in patients that received Paxlovid, there were high rates of rebound Covid-19 that led the patients to have recurrence of their old symptoms or worsening of their old symptoms that required hospitalization. Storey (2024) also states that the research stated that patients with long Covid exhibited similar symptoms to those patients that didn't receive treatment for their illness.

There were equal amounts of level II and level IV studies, with either experimental research performed or an observation study. Tleyjeh et al. (2021) discussed the problems associated with observational studies in determining effectiveness of treatment for Covid-19, specifically stating the possibility of confounding factors and bias skewing results. These factors place the study at risk of not having appropriate scientific merit to have appropriate conclusions on the efficacy of different treatments for Covid-19 (Tleyjeh et al., 2021). Thus, going forward, it

would be beneficial if additional level IV studies were performed to better assess the efficacy of the oral antiviral treatments Paxlovid and Lagevrio.

Throughout all the studies performed on studying Paxlovid, the main complaint from patients was dysgeusia (Miller, 2023). This symptom has created a colloquial term labeled as "Paxlovid mouth," where the patient experiences a bitter taste in their mouth resulting from the fact that the medication is excreted in the salivary glands (Miller, 2023). In the studies, there wasn't any other major side effect that was spread throughout all studies.

The Centers for Disease Control [CDC] (2024) identifies the three antivirals that are currently being used are the most effective and trusted treatment currently for Covid-19. Specifically, the medications target different areas of the virus to prevent it from being able to continue multiplying within the body, helping to prevent the patient from experiencing severe disease that may require them to be hospitalized (CDC, 2024). As a result, this treatment is already considered as the standard plan of care for patients that are diagnosed with Covid-19. Walgreens has even initiated a program where the pharmacists can prescribe Paxlovid to patients that have tested positive for Covid-19 following a rapid antigen test (Walgreens, 2024). Walgreens pharmacists have a series of questions to rule our patient with renal or hepatic dysfunction (Walgreens, 2024).

Lagevrio has a particular benefit over Paxlovid in that it currently has no known drug-drug interactions (Merck, 2023). For patients that are unable to swallow, however do not need to be hospitalized for their symptoms, Lagevrio also has the benefit of being a capsule that can be opened and administered via a nasogastric tube or gastric tube (Merck, 2023).

Change in Clinical Practice

Currently, the guidelines state that when a patient has severe Covid-19, which requires hospitalization, then RDV should be prescribed over the oral antiviral options (University of California [UC], 2023). Therefore, the final option for patients diagnosed with Covid-19, with regards to treatment, is Lagevrio (UC, 2023). In order to make the treatment for Covid-19 more effective in patients, both hospitalized and outpatients, new policy guidelines should be created. Appendix C will demonstrate a new guideline policy that can be initiated to incorporate the updated evidence-based practice guidelines.

Since the beginning of the pandemic, a lot of research has gone into the proper prescribing and administration guidelines for the multiple antivirals now available. Nearly every population of healthcare workers and various scientists worked together to research new medications and appropriate treatment options to conquer the ever-evolving virus known as Covid-19. To help direct change in practice moving forward, the same group of people can be utilized to create new policies and guidelines. These updated policies and guidelines will affect all patients diagnosed with Covid-19, or patients testing negative but presenting with a high suspicion of Covid-19 infection, Evidence from the FDA, and drug manufacturers, such as Pfizer, will be utilized to provide safe and effective treatment guidelines.

One of the concerns regarding the intravenous option is the fact that since there have been resurgences of different variants, RDV now has a shortage in supply (Rizvi, 2021). In the beginning of the pandemic, shortages such as that seen currently with RDV, led practitioners to make heart-breaking decisions about which patients should receive treatment. Changes need to be made in treatment guidelines to ensure that such practices do not continue, leading to an increase in patient deaths due to inappropriate treatment of Covid-19.

To determine how to create this change in practice, a strategy must first be created. Table 7 will identify objectives for the implementation of the change in practice guidelines.

Table 7

Developing a Change Strategy

Objectives	Method/Plan	Responsibility	Completion Date	Measurable Outcomes
Decrease in unnecessary admissions to complete RDV treatment.	If patients are stable for discharge, Paxlovid and other symptom relieving medications can be prescribed instead.	Emergency Care Physicians and Emergency Care Nurse Practitioners.	04/01/2024	Decrease in observation patient admissions for RDV therapy.
Increase patients' availability to receive Paxlovid after being prescribed by physician.	Acquiring funding to have packages of Paxlovid available to patients in the same way relief packages were handed out in the beginning of the pandemic.	Management and stockholders of the hospital network can work with legislators.	04/01/2024	Increase in patients being compliant with Paxlovid treatment.
When Paxlovid is contraindicated because of drug-drug interactions, other oral antivirals such as Lagevrio can be used instead of admitted for RDV.	Providing educational materials to the physicians and nurse practitioners on the other oral antivirals that are currently approved to treat Covid-19.	Management and the staff educators. The pharmacists and drug representatives could also play a crucial role.	04/01/2024	Increase in prescribing of other oral antivirals other than Paxlovid for patients diagnosed with Covid-19.
In patient's that cannot swallow, Lagevrio be prescribed	Educating physicians that Lagevrio is a capsule and can	Educators, Pharmacists and Drug representatives.	04/01/2024	Increase in prescribing of Lagevrio in patients that

instead of RDV if possible.	be opened to be administered via a nasogastric tube or a gastric tube (Merck, 2023).			cannot swallow and use nasogastric or gastric tubes for enteral feedings and medication administration.

After initiating the change in practice, the policies should be evaluated for efficacy. The process of evaluation will be demonstrated in table 8.

Table 8

Evaluation Plan

Measurable Outcomes	Method and Tools for Measuring	Responsibility	Timelines
Decrease in observation patient admissions for RDV therapy.	Admission rates for stable patients with Covid-19 decrease; increase in prescribing of Paxlovid for stable patients.	Emergency Care Physicians and Nurse Practitioners.	Will evaluate through 3-months span after initiation of plan.
Increase in patients being compliant with Paxlovid treatment.	Providing patients with funding options via the manufacturer websites. Asking Pfizer for samples for patients that are low income.	Pharmacists, Registered Nurses, Physicians, and Social Workers.	Will evaluate through 3-months after initiation of the plan.
Increase in prescribing of other oral antivirals other than Paxlovid for patients diagnosed with Covid-19.	Reaching out to drug representatives and drug companies for additional information regarding prescribing information for both Paxlovid and Lagevrio.	Pharmacists, Educators, Drug companies, Nurse managers and Nurse Educators.	Will evaluate through 3-months after the initiation of the plan.
Increase in prescribing of Lagevrio in patients that cannot swallow and use nasogastric or gastric tubes for	Having educators, pharmacists and drug companies provide additional information regarding the administration of	Pharmacists, Educators, Drug Companies, Nurse managers and Nurse educators.	Will evaluate through 3-months after the initiation of the plan.

enteral feedings and medication administration.	the different oral antivirals that are currently available.		

Resources Needed to Create Change

At the beginning of the pandemic, when patients presented to the emergency department for signs and symptoms of Covid-19, many patients were given a relief package. Furlan & Caramelli (2021) spoke about the packages that included medications to treat symptoms that were associated with Covid-19, such as ondansetron for nausea and loperamide for diarrhea. The government funded the creation of these packages that were handed to patients that weren't critical enough to be admitted to the hospital for their Covid-19 symptoms and were sent home (Furlan & Caramelli, 2021).

Now that Paxlovid has been removed from the category of emergency use authorization and has been fully approved by the FDA, prescriptions costs have skyrocketed. Even with insurance, the cost of Paxlovid may be hard for some patients to be able to afford after being diagnosed with Covid-19 (Erman, 2023). As a result, funding needs to be made available to allow patients to have greater access to Paxlovid; the availability to Paxlovid can be easily increased by making relief packages like those that were first seen in the beginning of the pandemic.

Pfizer has several different programs that both the physicians, as well as the patients, can sign up for to help pay for the costs of Paxlovid (Pfizer, 2023a). Through December 2024, patients that are currently enrolled in Medicare, Medicaid, Tricare, and those that are uninsured can received Paxlovid for free through the United States Government's Patient Assistance Program (Pfizer, 2023a). Social workers can help the patients not only sign up for insurance, as well helping the patients fill out the appropriate paperwork to obtain the medication for free (Pfizer, 2023a).

In addition, Merck is the company that designed/created Lagevrio for the treatment of Covid-19 (Merck, 2023). Currently, there are no known drug-drug interactions for Lagevrio, which makes the possibility that this medication will be a safer option for patients that have several other chronic medications (Merck, 20123). Having drug representatives and pharmacists educating physicians and nurse practitioners on prescribing information about Lagevrio will help to increase the prescribing rates of this oral antiviral for Covid-19.

After reviewing all data, Paxlovid was found to be the drug of choice when treating Covid-19 with oral antivirals. Currently, many patients are being admitted to the hospital for the sole purpose of RDV administration instead of oral medications in hopes that patients will have faster recovery. However, many of these patients would have benefited from being discharged home with oral medications to recuperate outside of the hospital. As a result of these findings, a new protocol was designed to possibly correct this shortcoming found within the healthcare system today.

References

Basoulis, D., Tsakanikas, A., Gkoufa, A., Bitsani, A., Karamanakos, G., Mastrogianni, E., Georgakopoulou, V. E., Makrodimitri, S., Voutsinas, P.-M., Lamprou, P., Kontos, A., Tsiakas, S., Gamaletsou, M. N., Marinaki, S., & Sipsas, N. V. (2023). Effectiveness of oral nirmatrelvir/ritonavir vs. intravenous three-day remdesivir in preventing progression to severe COVID-19: A single-center, prospective, comparative, real-life study. *Viruses*, *15*(7), 1515–1525. https://doi.org/10.3390/v15071515

Centers for Disease Control. (2024). *Covid-19 treatments and medications*. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/your-health/treatments-for-severe-illness.html

Erman, M. (2023). *Pfizer to price covid treatment paxlovid at $1,390 per course* . Reuters. https://www.reuters.com/business/healthcare-pharmaceuticals/pfizer-price-covid-19-drug-paxlovid-1400-five-day-course-wsj-2023-10-18/

Fineout-Overholt, E. & Johnson, S. (2023). Asking Compelling Clinical Questions. In Melnyk, B. & Fineout-Overholt, E., *Evidence-Based Practice in Nursing & Healthcare a Guide to Best Practice* (5th ed.). Wolters Kluwer.

Food and Drug Administration. (2023). *Information for healthcare providers: LAGEVRIOTM (molnupiravir)*. Food and Drug Administration. https://www.fda.gov/media/155055/download#:~:text=LAGEVRIO%20is%20authorized%20for%20emergency,not%20accessible%20or%20clinically%20appropriate.

Furlan, L., & Caramelli, B. (2021). The regrettable story of the “covid kit” and the “early treatment of covid-19” in Brazil. *The Lancet Regional Health - Americas*, *4*, 100089. https://doi.org/10.1016/j.lana.2021.100089

Hammond, J., Leister-Tebbe, H., Gardner, A., Abreu, P., Bao, W., Wisemandle, W., Baniecki, M., Hendrick, V. M., Damle, B., Simón-Campos, A., Pypstra, R., & Rusnak, J. M. (2022). Oral Nirmatrelvir for high-risk, nonhospitalized adults with covid-19. *New England Journal of Medicine*, *386*(15), 1397–1408. https://doi.org/10.1056/nejmoa2118542

Health and Human Services. (2024). *What are the possible treatment options for covid-19?*. Treatment Options for COVID-19 | HHS/ASPR. https://aspr.hhs.gov/COVID-19/Treatments/Pages/Possible-Treatment-Options-for-COVID19.aspx

Liu, J., Pan, X., Zhang, S., Li, M., Ma, K., Fan, C., Lv, Y., Guan, X., Yang, Y., Ye, X., Deng, X., Wang, Y., Qin, L., Xia, Z., Ge, Z., Zhou, Q., Zhang, X., Ling, Y., Qi, T., … Chen, D. (2023). Efficacy and safety of PAXLOVID in severe adult patients with SARS-COV-2 infection: A Multicenter randomized controlled study. *The Lancet Regional Health - Western Pacific*, *33*, 100694–100705. https://doi.org/10.1016/j.lanwpc.2023.100694

Merck. (2023). *Information for healthcare providers: LAGEVRIOTM (molnupiravir)*. Lagevrio. https://www.lagevrio.com/hcp/

Miller, K. (2023). *Is "Paxlovid mouth" dangerous?* Health. https://www.health.com/condition/infectious-diseases/coronavirus/what-is-paxlovid-mouth-bitter-metallic-taste-side-effects#:~:text=Paxlovid%20mouth%2C%20which%20falls%20under,no%20official%20Paxlovid%20mouth%20treatments.

Montazersaheb, S., Hosseiniyan Khatibi, S. M., Hejazi, M. S., Tarhriz, V., Farjami, A., Ghasemian Sorbeni, F., Farahzadi, R., & Ghasemnejad, T. (2022). Covid-19 infection: An

overview on cytokine storm and related interventions. *Virology Journal*, *19*(1). https://doi.org/10.1186/s12985-022-01814-1

National Institutes of Health. (2023). *Ritonavir-boosted Nirmatrelvir (paxlovid)*. https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/

Offit, P. (2023). *In the journals: Oral form Remdesivir vs. paxlovid for treatment of covid-19*. Children's Hospital of Philadelphia. https://www.chop.edu/news/journals-oral-form-remdesivir-vs-paxlovid-treatment-covid-19#:~:text=Currently%2C%20the%20first%20choice%20for,can%20only%20be%20administered%20intravenously.

Pfizer. (2023a). *PaxcessTM: PaxlovidTM (Nirmatrelvir Tablets; ritonavir tablets)*. PAXLOVID. https://www.paxlovid.com/paxcess

Pfizer. (2023b). *Fact sheet for healthcare providers: Paxlovid*. New York, New York; Federal Drug Administration. https://www.fda.gov/media/155050/download

Rizvi, Z. (2021). *Gilead first: How a monopoly on Remdesivir lead to rationing*. Public Citizen. https://www.citizen.org/article/gilead-first/#:~:text=Remdesivir%20is%20in%20shortage.,effectiveness%2C%20remdesivir%20is%20being%20rationed.

Schilling, W. H., Jittamala, P., Watson, J. A., Boyd, S., Luvira, V., Siripoon, T., Ngamprasertchai, T., Batty, E. M., Cruz, C., Callery, J. J., Singh, S., Saroj, M., Kruabkontho, V., Ngernseng, T., Tanglakmankhong, N., Tubprasert, J., Abdad, M. Y., Madmanee, W., Kouhathong, J., … Loharjun, B. (2023). Antiviral efficacy of molnupiravir versus ritonavir-boosted nirmatrelvir in patients with early

symptomatic COVID-19 (PLATCOV): An open-label, phase 2, randomised, controlled, Adaptive Trial. *The Lancet Infectious Diseases*, *24*(1), 36–45. https://doi.org/10.1016/s1473-3099(23)00493-0

Storey, D. (2024). *Study reveals paxlovid does little to stave off long covid*. Psychiatrist.com. https://www.psychiatrist.com/news/study-reveals-paxlovid-does-little-to-stave-off-long-covid/

Tleyjeh, I. M., Kashour, T., Mandrekar, J., & Petitti, D. B. (2021). Overlooked shortcomings of observational studies of interventions in coronavirus disease 2019: An Illustrated Review for the clinician. *Open Forum Infectious Diseases*, *8*(8). https://doi.org/10.1093/ofid/ofab317

University of California. (2023). *Covid-19 medicines that can help*. ucsfhealth.org. https://www.ucsfhealth.org/education/covid-19-medicines-that-can-help

U.S. Food and Drug Administration. (2021). *Coronavirus (COVID-19) update: FDA authorizes additional oral antiviral for treatment of covid-19 in certain adults*. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain.

Walgreens. (2024). *Paxlovid – covid-19 antiviral treatment*. https://www.walgreens.com/findcare/covid19/paxlovid

Weng, C., Xie, R., Han, G., Yuan, Y., Li, S., Wang, C., Wang, X., Jiang, W., & Jiang, L. (2023). Safety and efficacy of Paxlovid against Omicron variants of coronavirus disease 2019 in elderly patients. *Infectious Diseases and Therapy*, *12*(2), 649–662. https://doi.org/10.1007/s40121-023-00760-x

Wong, C. K., Au, I. C., Lau, K. T., Lau, E. H., Cowling, B. J., & Leung, G. M. (2023). Real-world effectiveness of early molnupiravir or nirmatrelvir–ritonavir in hospitalised patients with covid-19 without supplemental oxygen requirement on admission during Hong Kong's Omicron Ba.2 Wave: A retrospective cohort study. *The Lancet Infectious Diseases*, *22*(12), 1681–1693. https://doi.org/10.1016/s1473-3099(22)00507-2

Appendix A

Intervention
In patients diagnosed with Covid-19 (P), how does Paxlovid and Lagevrio (I) compared to standard care treatment (C) affect the patient outcomes (O) within their duration of illness (T).

Table A1: Breakdown of PICOT Question

This PICOT question is an interventional question that addresses the treatment of an illness or disability (Fineout-Overholt & Johnson, 2023).

Appendix B

PICOT Worksheet and Search Strategy

1. Define the PICOT question:

(P) Patient/Problem: Patient's diagnosed with Covid-19 and at high risk for severe disease.

(I) Intervention: Treatment with Paxlovid and Lagevrio.

(C) Comparison: Standard of care treatment.

(O) Outcome: Severity of patient's symptoms and length of time symptoms last.

(T) Time: Throughout the length of their Covid-19 infection.

2. Write out the question:

For patients diagnosed with Covid-19 and at high risk for severe disease, how does treatment with Paxlovid and/or Lagevrio compared to standard of care reduce the severity of symptoms and length of their viral syndrome throughout their Covid-19 infection?

3. Type of question:

Therapy/Intervention

4. Types of studies to include in the search:

Randomized controlled trials, Cohort study, Case control studies, In Vitro/lab research,

5. List main topics and alternate terms from the PICO question that can be used for the search:

Efficacy of Paxlovid, Efficacy of Lagevrio, Safety of Paxlovid, Oral antivirals for Covid-19

6. List the inclusion criteria:

Patients diagnosed with Covid-19 and studies performed in the last five years.

7. List irrelevant terms to exclude from the search:

Opinions, meta-analysis, systematic review

8. List databases that to find articles regarding PICOT question:

PubMed, The New England Journal of Medicine, CINAHL, Cochrane Library, and Health Source.

Appendix C

Guidelines for Treatment of Covid—19

<table>
<tr><th colspan="3">University of St. Francis Healthcare Network</th></tr>
<tr><td colspan="2">Title: Guideline for Treatment of Covid-19 Patients; Inpatient & Outpatient Use of Oral Antivirals.</td><td>Document Number: 12345</td></tr>
<tr><td colspan="2">Document Type:
Guideline</td><td>Last Review: 02/01/2024</td></tr>
<tr><td>Patient Group:
Adults and Pediatric</td><td>Applies to:
Clinical Practice</td><td>Effective Date: 02/25/2024</td></tr>
<tr><td colspan="3">Purpose:
To establish an evidence-based Covid-19 treatment Guidelines and to provide guidance on the use of oral antivirals in patients diagnosed with Covid-19, both in the inpatient and outpatient setting. These recommendations are intended to serve as a guideline and cannot account for individual patient scenarios or replace/supplant physician judgement.</td></tr>
<tr><td colspan="3">Scope:
This guideline applies to University of St. Francis Healthcare Network outpatient, emergency department and inpatient units at any entity or facility owned and controlled by University of St. Francis Healthcare.</td></tr>
<tr><td colspan="3">----------</td></tr>
<tr><td colspan="3">Paxlovid: Ritonavir/Nirmatrelvir for inpatient and outpatient use.
An orally bioavailable protease inhibitor that is active against a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins (Pfizer, 2023b).</td></tr>
<tr><td colspan="2">Standard Regimen for Patients with No Renal/Hepatic Impairment</td><td>Adjusted Regiment for eGFR ≥ 30 to < 60 mL/min</td></tr>
<tr><td colspan="2">Nirmatrelvir 300mg with Ritonavir 100mg PO twice daily for 5 days.</td><td>Nirmatrelvir 150mg with Ritonavir 100mg PO twice a day for 5 days.</td></tr>
<tr><td colspan="3">Prioritize Paxlovid for the treatment of mild/moderate Covid disease and hold nonessential medications that may interact with the treatment course when possible before considering alternative therapy options.</td></tr>
<tr><td colspan="2">Inclusion Criteria:
*Covid confirmed, or high suspicion by clinic presentation
*Symptom onset within the last 5 days.
*Risk factor for severe Covid.</td><td>Exclusion Criteria:
*Severe hepatic impairment
*Severe renal impairment as defined by eGFR <30 mL/min.</td></tr>
<tr><td colspan="3">Clinical Pearls:
*Paxlovid is currently indicated for the management of patients ≥12 years of age and who weigh ≥40kg (Pfizer, 2023b).
*Paxlovid can be taken with or without food, should be swallowed whole and cannot be crushed or chewed (Pfizer, 2023b).
*Ritonavir is known to</td></tr>
</table>

<table>
<tr><td colspan="2">Monitoring Notes:
A daily comprehensive metabolic panel order should be checked by the pharmacist daily to verify safety of continuing Paxlovid therapy.</td></tr>
<tr><td colspan="2">----------</td></tr>
<tr><td colspan="2">Lagevrio: Molnupiravir for outpatient and inpatient use.
An enterally bioavailable investigational nucleoside analogue medication that is under Emergency-Use Authorization for the treatment of Covid-19 (Merck, 2023). Medication works by increasing the number of mutations in the virus' genetic material in a way that impairs the ability of Covid-19 to multiply (Merck, 2023).</td></tr>
<tr><td colspan="2">Lagevrio should only be chosen when patient is contraindicated to take Paxlovid due to interactions or lack of supply.</td></tr>
<tr><td colspan="2">Dosing information:
*Lagevrio is taken as 800 mg (4 tablets of 200mg) every 12 hours for 5 consecutive days (Merck, 2023).
*This medication is provided in capsule form and can be opened and sprinkled on food for patients with dysphagia or placed in nasogastric or gastric tube for enteral administration of this medication (Merck, 2023).</td></tr>
<tr><td>Inclusion Criteria:
*Patients ≥ 18 years of age for whom an alternative treatment is not accessible or clinically appropriate (Merck, 2023).
*Patients must weigh at least 40 kg (Merck, 2023).
*Symptoms need to have started within less than 5 days from medication initiation (Merck, 2023).
*Must have one risk factor for developing severe disease (Merck, 2023).</td><td>Exclusion Criteria:
*Patient is < 18 years of age (Merck, 2023).
*Pregnant patients as there is known embryo-fetal toxicity in animal studies (Merck, 2023).</td></tr>
</table>

Table C1: Policy Guidelines for Oral Antiviral Administration in Covid-19 Patients.