

**Cost-Effectiveness Analysis of Prophylaxis Duration Following Lung Transplantation for
CMV Mismatch and Non-Mismatch Recipients**

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Abstract

Survival following lung transplantation is lower than survival following all other solid organ transplants. Chronic rejection, graft failure, and opportunistic infections all contribute to these poor outcomes. One such opportunistic infection is cytomegalovirus (CMV). CMV is one of the most common infections after lung transplant and can cause direct effects (viremia and disease), and indirect effects including increased risk of acute cellular rejection, and death. Donor CMV serology positive, recipient negative (D+/R-) patients have the highest risk for developing CMV, for which they receive extended valganciclovir prophylaxis. Longer prophylaxis durations, however, may lead to an increased risk of infection due to resistant CMV, and no standardized guidelines exist for prophylaxis duration. To investigate the effect of duration length on survival, a cost-effectiveness analysis of mismatch and non-mismatch patients was performed, where non-mismatch patients received 6 months of prophylaxis and mismatch patients received either 1 or 2 years. A Markov-state transition model was used, with month-long cycles over a five-year time horizon, a 3% discount rate, and took a healthcare system perspective. Health states of no CMV, sensitive and resistant CMV viremia, sensitive and resistant CMV disease, and death are modeled, with possible episodes of acute cellular rejection in each state. Outcomes included life-years gained and quality-adjusted life-years (QALYs). The model showed that increasing prophylaxis duration resulted in gains in both life-years and QALYs. Incremental cost-effectiveness ratios were

\$110,510 per life-year gained and \$150,280 per QALY. Continued prophylaxis for 5 years after transplant increases the ICER to \$153,862 per life-year gained, and \$203,756 per QALY. These results show that extended valganciclovir prophylaxis for mismatch patients is associated with gains of life-years and QALYs and is economically reasonable. As only a limited number of lungs are available, and the demand outweighs the supply, extended prophylaxis would result in these organs being used to their greatest benefit, and could decrease the need for re-transplants, showing a clear public health impact.

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1.0 Introduction

1.1 Lung Transplantation and Cytomegalovirus

Lung transplantations have been regularly performed since the 1980s, though first performed in 1963 by Dr. Thomas Hardy [1]. It is treatment option for a variety of diseases resulting in end-stage lung disease when other treatments are either not an option or unsuccessful [2]. More recently, clinical, surgical, and pharmacological advances have improved outcomes for patients undergoing lung transplantation. In 2000, patients had a 50% 2-year survival post-transplant; by 2014, they had a 50% 6-year survival after transplantation [3]. More patients receive lung transplants each year, and more people are on the waiting list to receive a transplant. In 2018, 2,565 lung transplants were performed in the United States, and the number of people on the waiting list grew by 233 [4].

Some improvements in outcomes can be attributed to the US implementation of the lung allocation score (LAS) in 2003, which provided a new system for donor lung allocation [2]. Under the LAS, allocation is done on the basis of medical need and benefit, rather than on time on the waiting list [2, 3]. The LAS considers a number of factors, including pre- and post-transplant survival; age, geography, blood type compatibility, and waiting time when making allocation decisions [4].

However, multiple challenges surrounding lung transplantation remain. There are still too few donors relative to the length of the waiting list. As a result, some wait-listed patients die before receiving a transplant – in 2018, 365 people either died on the waitlist, or became too sick to be transplanted [1, 4, 5]. Because of immunosuppression use following transplantation, both graft failure and chronic rejection contribute to post-transplant mortality, as do opportunistic infections [1, 3].

One such opportunistic infection is cytomegalovirus (CMV). CMV is the most common opportunistic infection following lung transplantation [6, 7]. CMV incidence following lung transplantation is higher than in other solid organ transplants; without prophylaxis, the incidence is estimated to range from 54 – 92% [8]. The most important risk factor associated with CMV acquisition following transplant is donor +, recipient – (D+/R-) serostatus [8]. CMV can be present as infection, or the more serious disease. CMV infection is generally defined by a positive culture, associated with active replication and shedding of the virus, while CMV disease is defined by CMV presence within cell preparations or tissue [9].

To minimize CMV risk following lung transplantation, prophylaxis with antivirals like ganciclovir or valganciclovir is recommended [7, 9]. Generally, D+/R- patients receive between 3 and 6 months of prophylaxis after transplantation, though there is currently no consensus around optimal prophylaxis duration [7, 10]. Though prophylaxis can reduce CMV incidence, it also increases the risk of resistant CMV strains. An estimated 3 – 16% of cases are resistant, which is associated with decreased patient survival [11]. Resistant CMV is treated with IV Foscarnet, which is effective but associated with nephrotoxicity [9, 11]. Thus, any extended prophylaxis duration must be weighed against the increased risk of resistant CMV strains.

1.2 Introduction to Cost-Effectiveness Analysis

One way to investigate optimal prophylaxis duration following lung transplantation is to perform a cost-effectiveness analysis (CEA). CEAs compare the costs and effectiveness of one strategy, usually a treatment or some other intervention, to one or more alternatives [12, 13]. The comparison is the difference in costs between strategies divided by the difference in strategy effectiveness to calculate the incremental cost-effectiveness ratio (ICER). Effectiveness can be measured in different ways – some examples include deaths averted, number of cases of a disease prevented, or quality-adjusted life-years (QALYs) [13].

QALYs are the most commonly used measurement of effectiveness, calculated by multiplying a health state utility values by the length of time a person spends in that state [12-14]. These utilities are elicited either directly, on a person-by-person basis, indirectly, through a preference-based questionnaire, or can be estimated from previously-published literature.

There are three common ways of directly eliciting a utility value – the standard gamble (SG), time trade-off (TTO), and visual analog scale (VAS). The SG poses the question of remaining in a certain health state, or “gambling,” with a probability of returning to full health and a corresponding probability of death [14]. This probability is then varied until the indifference point is reached – when there is no longer a preference between the current health state and the probability of death [14]. This probability then becomes a utility value – if a person were indifferent at a 60% chance of death, the utility is 0.60. The TTO offers the choice of continuing to live in a particular health state for the remaining life time, or living in perfect health for a shorter period of time [14]. Just as with the SG, this amount of time living in perfect health is varied until the indifference point is reached [13]. The utility score is then ascertained by dividing the amount of time at the point of indifference by the life expectancy [14]. If an indifference point of 7 years

was found, and the choice was between that and 10 years in current health, the utility score would be 0.70. The VAS is the simplest of the 3 direct elicitation methods. A scale is drawn with a single line, ranging from 0 – 100, and users are asked to mark on the scale their measurement for the health state being questioned [14]. If 73 were marked, for example, the utility score would then be 0.73.

Often, however, it is not feasible to perform a direct elicitation of a utility score. More commonly, indirect elicitation is performed using a generalized questionnaire. The two most frequently used are the EQ-5D and the SF-6D [14]. The EQ-5D contains 5 domains – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression – and within each domain, participants are asked to select whether they have no problems, slight problems, moderate problems, severe problems or extreme problems [15]. Using a validated calculation, these scores are then transformed into a utility score [14]. The SF-6D is a condensed version of the SF-36, a questionnaire from RAND that contains 8 domains and 2 summary scores [16, 17]. The domains included are physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health; the summary scores are the physical component score and the mental component score [16]. The SF-6D uses a subset of the questions from the SF-36, and comprises 18,000 health states [17]. Using a validated model, utility scores can then be obtained from the SF-36 for use in cost-effectiveness analyses [17].

There are times that neither direct or indirect elicitation of utility values are feasible, because the analysis being done uses retrospective data, rather than prospective. In these cases, the utility values will not come from any type of elicitation, but rather, will come from utility estimates used in previously published research studies or analyses.

1.3 Public Health Significance of CMV Following Lung Transplantation

The public health significance of lung transplant and maximizing mortality following transplantation is clear. The shortage of donor lungs is a problem on a population level – a shortage of donors means that there is an increased risk of death while on the transplant waiting list. Overall, < 2% of all eligible lungs are actually used in transplant in the US, often due to concerns about donor history, chest trauma, or other ICU complications [1]. This results in 10 – 13% of those on the waiting list dying before they can be transplanted [1]. Furthermore, the 5-year mortality following transplantation is around 55%, lower than many other solid organ transplants [1]. With limited donors and limited survival 5 years post-transplant, it is imperative that informed decisions about CMV treatment be investigated in order to maximize the efficacy of the donor organs transplanted, and to improve the post-transplant survival rates.

2.0 Literature Review

To better understand the importance of proper CMV prophylaxis following lung transplantation, it is important to first understand the complicated relationship between lung transplantation, CMV, and graft failure. As stated earlier, CMV incidence is higher in lung transplant recipients, and those at highest risk are D+/R- [8]. CMV infection can develop after transplantation through transmission from a donor-positive organ, a donor-positive blood transfusion, or a reactivation of a latent infection in a positive transplant recipient [9]. CMV is associated with acute and chronic allograft rejection, but it is not clear if the relationship is causal [8, 11]. It is suspected that CMV infection of the vascular endothelium and smooth muscle cells likely plays a role in acute and chronic rejection; CMV also induces anti-endothelial cell antibodies, which may lead to the development of chronic rejection in the long term [11]. In lung transplant recipients, pneumonia is the most common presentation of CMV, though hepatitis, gastroenteritis, and colitis are also seen [9]. Furthermore, in lung transplant recipients, CMV is associated with bronchiolitis obliterans syndrome (BOS), which is progressive and the major factor affecting post-transplant mortality [7, 9, 11]. Once BOS is present, median survival is around 3 years [7]. Because BOS is progressive even with heightened treatment, prevention is key to increasing survival after lung transplant [11].

2.1 Prevention of CMV

There are 2 major strategies for preventing CMV infection – pre-emptive therapy, and prophylaxis.

Pre-emptive therapy relies on continual testing of patients following transplantation to identify infection before the emergence of disease [9]. If this strategy is used, its recommended that patients be monitored daily immediately following transplant, then weekly for 6 weeks, then every 2 weeks until 12 weeks post-op, and monthly following week 12 [8]. Pre-emptive therapy may be selected because only those who are actually sick are treated, and it can decrease costs and decrease the risks of resistant strains emerging [9]. However, there is still a cost associated with the increased monitoring, and it's possible that cases of CMV disease can still be present even though the infection escaped detection [11].

Thus, especially for D+/R- transplant recipients, prophylaxis is much more common. Most patients receive between 3 and 6 months of prophylaxis, though some receive less and some receive more [7]. Initially, the prophylaxis regimen was IV or oral ganciclovir for 1 – 3 months following transplant, now, the most commonly used regiment is IV ganciclovir followed by oral valganciclovir (valganciclovir), or just oral valganciclovir, for 3 – 6 months [7]. During this time, patients should still be monitored – every 2 weeks for the first 6 monthly, and then monthly after that [8]. The use of CMV hyperimmune globulin (CMV-IVIG) has improved outcomes when used in conjunction with valganciclovir prophylaxis, though not when used alone [11]. A major limitation of prophylaxis, however, especially in the short-term, is that almost half of at-risk patients develop CMV after prophylaxis is discontinued [7].

2.2 Treatment of CMV

CMV infection or disease can develop during prophylaxis, known as breakthrough CMV, or after prophylaxis has been discontinued. CMV infection and disease are generally treated with IV ganciclovir twice a day for 2 – 4 weeks, or until the viral load is reduced to levels below detection upon testing [8, 11]. Often, CMV IVIG will also be added as treatment, especially for treatment of pneumonia or colitis [11]. Recurrence, however, is common, and treatment should be repeated when that occurs [9].

Resistant CMV should be suspected when patients do not respond to IV ganciclovir treatment, or when there are persistent episodes of recurring infection either during prophylaxis or following its discontinuation [8, 11]. Foscarnet is generally used as treatment for resistant CMV, though a combination of Foscarnet and IV ganciclovir is sometimes used [8, 9, 11]. Typically, patients receive 21 days of Foscarnet, and then a lower maintenance dose of the drug for an additional 30 days [8]. Foscarnet is effective, but is associated with an increased risk of nephrotoxicity [9].

2.3 Lack of Best Practice Consensus

To minimize the risk of CMV infection and disease among those at high risk (D+/R-), current guidelines from the American Society of Transplant Infectious Diseases recommend 6 months of prophylaxis [7]. Various reports have indicated that extending prophylaxis beyond 6 months may be reasonable. One placebo-controlled RCT found that lifetime CMV risk (4 years after transplantation) was decreased when 12 months of prophylaxis were used [7]. A few other

single transplant centers have reported 12 months or longer of prophylaxis, but concerns regarding increased costs, risk of resistance, and toxicity remain [7]. Currently, there is no consensus regarding the optimal duration of CMV prophylaxis following lung transplantation [10]. This lack of consensus surrounding best practices lends itself to a CEA focused on the ideal length of prophylaxis for CMV.

3.0 Hypothesis or Expected Outcomes

Generally, the results from a CEA can take a few forms. One strategy may be more effective and less costly. When this occurs, the recommendation is to choose that strategy, as there is no downside – they are considered to be economically dominant [12]. Conversely, a strategy may be less effective and more costly. In this situation, that strategy would not be recommended, as it is worse in terms of costs and benefits – this is considered to be economically dominated [12]. Often, however, a strategy will be more effective but also more costly. When this occurs, the strategy is compared against a cost-effectiveness threshold – essentially, the amount of money considered to be acceptable to expend to gain one QALY [12]. Historically, that threshold was set at \$50,000/QALY in the US, which originated from the 1970s and is related to the cost of dialysis for patients with end-stage renal failure at that time [12]. Current recommendations suggest the use of not one single threshold, but rather multiple thresholds of \$50,000, \$100,000, and \$200,000/QALY [18]. Decision makers could then assess results based on those thresholds and decide which threshold is most appropriate for them specifically, based on the available resources and possible alternate uses of those resources [18].

When looking to the question of prophylaxis duration following lung transplantation, it is likely that our result will fall into this last category, increased effectiveness at some increased cost. Increasing the length of time a patient is receiving prophylaxis will certainly come with an increased cost, as will the cost of treating resistant CMV strains that may be more likely to be present. While it is possible that increasing the duration of prophylaxis could result in a decrease of effectiveness due to the toxicity of treatment for resistant CMV, this is not likely, as studies thus far have shown the opposite. In the case of prophylaxis duration following lung transplantation,

the most likely outcome is that increased duration will see increased benefits along with increased costs, and the decision to implement a longer prophylactic regimen will depend on the cost-effectiveness threshold chosen.

4.0 Design, Methodology, and Data

4.1 Rationale for Choosing A CEA

As stated above, performing a cost-effectiveness analysis on prophylaxis duration after lung transplantation will allow us to compare different lengths of prophylaxis on both high risk (D+/R- “mismatch”) patients and non-mismatch patients. A CEA allows us to take into account different costs and benefits for both types of patient cohorts, and for different prophylaxis durations. Additionally, sensitivity analyses can be performed, where each of the model parameters can be varied to capture the effects of any uncertainties.

When using a CEA, we can model hypothetical cohorts of simulated patients. A hypothetical cohort creates simulated patients, with characteristics, probabilities, and utility values that come from previously published literature. This hypothetical cohort is then used to populate the model – specifically, in this case, used to create the simulated patients that are given differing lengths of prophylaxis. Modeling in this way allows for the use of retrospective data found in published literature to compare differing prophylaxis durations on simulated, rather than real, patients.

The CEA will model the trajectories of these simulated patients, following them through cycles of infection, disease, and recovery, and capturing the costs and health benefits that they receive, or lose, as they pass through these health states. Specifically, the model chosen is a Markov state transition model. Markov models are most useful when examining sequential decisions made over time, because they operate in cycles. At the end of each cycle, the simulated patient may transitioned to a new health state, based on a probability of that transition occurring found in the

literature; they also accumulate QALYs according to the health state that they are in and the amount of time spent in it [19, 20].

4.2 Details of the Model and Patient Trajectories

This specific Markov model was built using TreeAge Pro 2017 (TreeAge Software, Williamstown MA). Both mismatch and non-mismatch patients are included in the model, just as they would be in actual clinical practice. The model uses month-long cycles, meaning that simulated patients can move between health states each month, and has a 5-year time horizon. The model also utilizes a healthcare system perspective, in which costs considered are direct medical costs incurred to the healthcare system, rather than societal, which also considers costs like missed wages due to illness. Future costs and effectiveness are discounted at 3% per year.

Health states of no CMV, viremia and disease due to sensitive and resistant CMV, and death are included in the model. Each state also accounts for episodes of acute cellular rejection (ACR). These health states are the states that simulated patients move between while moving throughout the model – the possible health states that they can experience. When comparing the durations of prophylaxis, different strategies were compared using the ICER (difference in costs between strategies divided by the difference in effectiveness). The effectiveness was measured both in QALYs and in life-years gained.

All patients begin in the no CMV health state and, based on clinical estimates, we model 20% as mismatch patients. From the no CMV state, simulated patients move throughout the model as shown in **Figure 1**. Patients can either continue to remain CMV-free or can progress to CMV viremia. Patients with viremia can progress to viremia due to resistant virus, disease due to

sensitive virus, remain the same, or improve and return to the no CMV state. Likewise, patients with sensitive disease can progress to disease due to resistant virus, remain the same, or improve and return to the no CMV state. As patients continue to move through the model, we assume that a worsening patient either moves from viremia to disease, or from a sensitive to resistant virus. Similarly, patients who improve are assumed to return to the no CMV state. From this point, patients can again remain CMV-free, or can progress once more to a CMV state, simulating the recurrence of CMV that is seen clinically. Patients can also remain the same – spend multiple cycles in the same health state – which simulates the needs for additional rounds of treatment. Each of these states also includes the risk of developing acute cellular rejection concurrently. Death can occur from any state in the model.

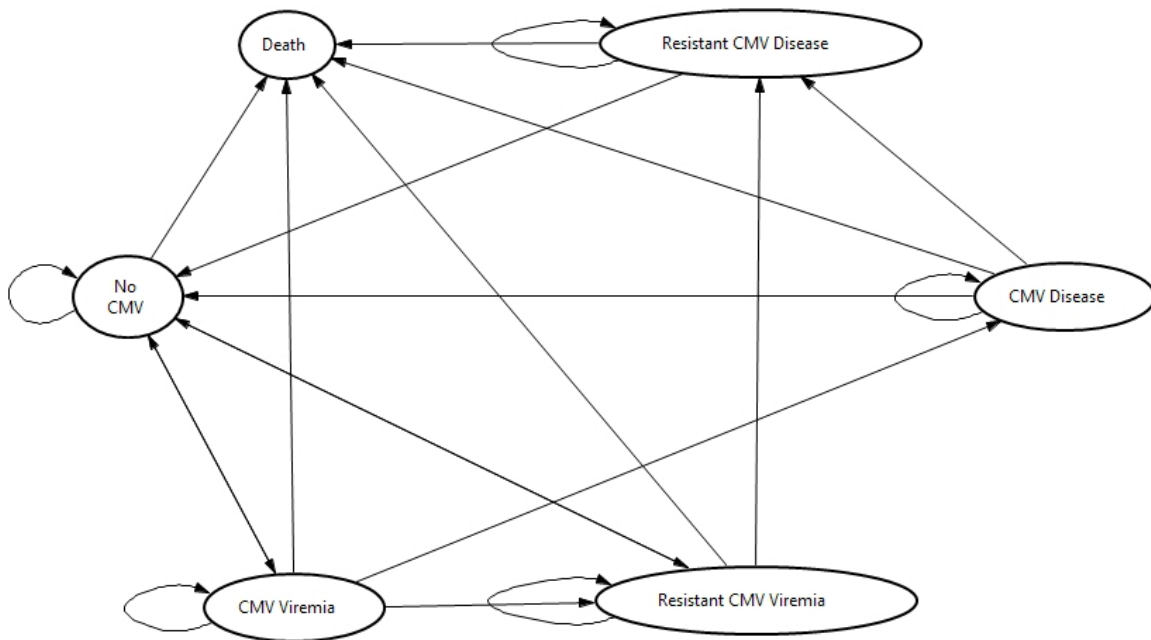


Figure 1. Markov State Transition Diagram of Possible States and Transitions in the Model

Non-mismatch patients receive 6 months of prophylaxis in the model, which is the standard length of prophylaxis for these patients in clinical practice. Mismatch patients receive either 1 year of prophylaxis, as is standard clinically, or they receive an extended prophylaxis duration of 2 years. Prophylaxis consists of 900 mg of valganciclovir and CMV PCR testing. Episodes of sensitive CMV viremia are treated with IV ganciclovir for 3 weeks, followed by valganciclovir prophylaxis for 3 months, and weekly CMV PCR tests for 3 months. Resistant CMV viremia is first treated as an inpatient, and then on an outpatient basis with 3 months of Foscarnet, a weekly CMV PCR, laboratory surveillance 3 times a week, intravenous (IV) replenishment of fluids, potassium, and magnesium. Of the patients receiving Foscarnet, 10% are assumed to develop renal failure which requires hemodialysis. Acute cellular rejection (ACR) is assumed to be treated in the hospital as well.

4.3 Data Sources

4.3.1 Probabilities

The probabilities used to populate the model for CMV-related risks and rejection occurrence were obtained from national estimates for mismatch and non-mismatch patients, and clinical assumptions where no national estimates exist. The use of national estimates, rather than clinic-specific probabilities, allow for broad generalization and application of the model, and account for regional differences that may exist. From published literature, probabilities for developing CMV viremia and disease, probability of infection due to valganciclovir-sensitive or

resistant CMV, mortality risk from CMV, ACR risk, and other probabilities for moving between states in the model were obtained, as shown in **Table 1**.

Table 1. Model Probability Parameters

Probabilities	Base Case		Range		Reference
	Nonmismatch	Mismatch	Nonmismatch	Mismatch	
Develop CMV on prophylaxis	10	10	0-30	0-30	[21]
Develop CMV off prophylaxis	30	50	25-86	25-86	[9, 11]
Progress to CMV Disease	20	20	15-30	15-30	Assumed
Progress to resistant viremia	5	15	3-9	9-27	[11, 22]
Progress to resistant disease	5	15	3-9	9-27	[11, 22]
Episode of ACR	21	33	18-25	27-39	[21]; Assumed
Death without CMV	10	8	8-12	6-10	[23]
Death from viremia	5	5	0-10	0-10	[11]
Death from disease	20	20	10-30	10-30	[8]

While on prophylaxis, patients have a 10% chance of developing CMV (considered “breakthrough” CMV); once off prophylaxis, mismatch patients have a 50% chance of developing CMV, and non-mismatch patients have a 30% chance of developing CMV. Resistant strains of CMV are estimated to occur in 5% of non-mismatch patients, and in 15% of mismatch patients

(cite Limaye). Episodes of ACR are estimated to occur at different rates not based on mismatch status, but rather on CMV status – ACR is estimated to occur among 21% of patients in the no CMV state, and among 32% of patients in any of the CMV states, due to the association between CMV and ACR [21]. For use in the model, these yearly probabilities are converted into monthly probabilities.

4.3.2 Costs

As mentioned, the model takes a healthcare system perspective, so costs included in the model include the prophylaxis regimen for mismatch and non-mismatch patients, CMV PCR testing, treatment of sensitive and resistant CMV viremia and disease, and treatment of ACR, as seen in **Table 2**. When including the costs of treatment for CMV, the possibility of additional rounds of treatment is also considered. When considering treatment of resistant strains, the costs considered are inpatient costs, the outpatient treatment costs that follow, and the cost of testing for resistance.

Table 2. Model Cost and Utility Parameters

Parameters	Base Case	Range	Reference
<i>Costs</i>			
Acute Rejection	\$16,019	\$12,815-\$19,222	[24]
Monthly Prophylaxis	\$2,498	\$1,998-\$2,997	[25]
CMV Viremia	\$16,414	\$13,131-\$19,696	[25, 26]
Resistant CMV Viremia	\$53,938	\$43,150-\$64,725	[25-27]
CMV Disease	\$26,663	\$21,330-\$31,996	[25, 26]
Resistant CMV Disease	\$60,866	\$48,693-\$73,039	[25-27]
<i>Utilities</i>			
No CMV	0.70	0.50-0.90	[28]
CMV viremia	0.65	0.45-0.85	[29]
Resistant CMV viremia	0.65	0.45-0.85	[29]
CMV disease	0.50	0.30-0.70	[29]
Resistant CMV disease	0.50	0.30-0.70	[29]
Episode of ACR	0.50	0.30-0.70	[29]

Monthly prophylaxis, while patients are receiving it, costs \$2,498, which includes the cost of valganciclovir plus the cost of filgrastim for a portion of the patients. Each cycle of treatment of viremia costs \$16,413, which includes ganciclovir treatment and the PCR testing to ensure that the viremia has been successfully treated. Treating CMV disease costs \$26,663, which again includes the costs of ganciclovir for treatment, PCR testing, and filgrastim for 6% of patients. Treatment of resistant viremia is \$53,938, and resistant disease is \$60,866 – treatment of resistant cases comprise both an inpatient and outpatient cost, where the outpatient cost includes labs for

electrolyte levels, fluid, potassium, and magnesium replacement, and hemodialysis for 10% of patients. Episodes of ACR, which occur concurrently with costs of CMV, are treated as an inpatient cost of \$16,019.

4.3.3 Utilities

All utility values for health states are estimated from published literature, and can be found in **Table 2**. Patients without CMV have a utility value of 0.70, patients with sensitive or resistant viremia have a utility value of 0.65, and patients with sensitive or resistant disease have a utility value of 0.50. Episodes of ACR have a utility of 0.50. For ACR, the utility of rejection and CMV are both considered, with the combined utility being calculated by multiplication (e.g. utility of an episode of ACR combined with sensitive CMV disease = $0.5 * 0.5 = 0.25$).

5.0 Findings and Results

When conducting the base-case analysis, the ICER was calculated between strategies of differing duration lengths as a ratio of the difference between the costs relative to the difference in the effectiveness, measured in both life-years gained and quality-adjusted life-years. In addition to the base-case analysis, one-way sensitivity analyses were performed – all parameters were varied individually over reasonable ranges. Furthermore, a Monte Carlo probabilistic analysis was performed, where all model parameters were varied simultaneously over their distributions as listed in **Tables 1 and 2**. For probability and utility values, the distributions fitted were β distributions, which have a possible range of 0 – 1. The cost variables were fitted with γ distributions, which have possible values of ≥ 0 .

5.1 Base Case Analysis

For the base case analysis, the model is run with the base case values for probabilities, costs, and utility values, for both outcomes of QALYs and life-years gained. In the base case, one year of prophylaxis costs \$61,130, and increasing the duration to two years costs \$63,453 – an increase of \$2,323 for the additional year of prophylaxis. Effectiveness in terms of life-years gained is 3.375 for one year of prophylaxis, and increases to 3.396 for a two year duration. Similarly, effectiveness in terms of quality-adjusted life-years is 2.351 and 2.396 for one and two years of prophylaxis, respectively. Thus, as duration of prophylaxis increases, both costs and

effectiveness also increase. This results in an ICER of \$110,510/life-year gained, and \$150,280/QALY when considering the base-case scenario, as seen in **Table 3**.

Table 3. Base-case Results

Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	ICER
<i>Life-years gained</i>					
1 year prophylaxis	\$61,131	--	3.375	--	--
2 years prophylaxis	\$63,453	\$2,323	3.396	0.021	110,510
<i>QALYs gained</i>					
1 year prophylaxis	\$61,131	--	2.350	--	--
2 years prophylaxis	\$63,453	\$2,323	2.366	0.015	150,280

As mentioned, an ICER of \$50,000/QALY was used historically, but is now considered to be outdated. Instead, the ICER can be considered against the previously-suggested thresholds of \$50,000, \$100,000, and \$200,000 per QALY. When using these recommendations, the base case result of \$150,280/QALY falls under the upper threshold of \$200,000 per QALY.

5.2 One-Way Sensitivity Analyses

When conducting one-way sensitivity analysis, each individual parameter in the model is varied over a reasonable range, and the ICER is calculated again under these ranges of values. One-way sensitivity analyses were performed for each variable, and found that only the probability of CMV while on prophylaxis being varied led to one year of prophylaxis being preferred over the longer, two year prophylactic regimen. If a \$200,000/QALY threshold is selected, one year of prophylaxis becomes preferred when the risk of CMV while on prophylaxis increases to 22%, from the base-case risk of 10%, as seen in **Figure 2**.

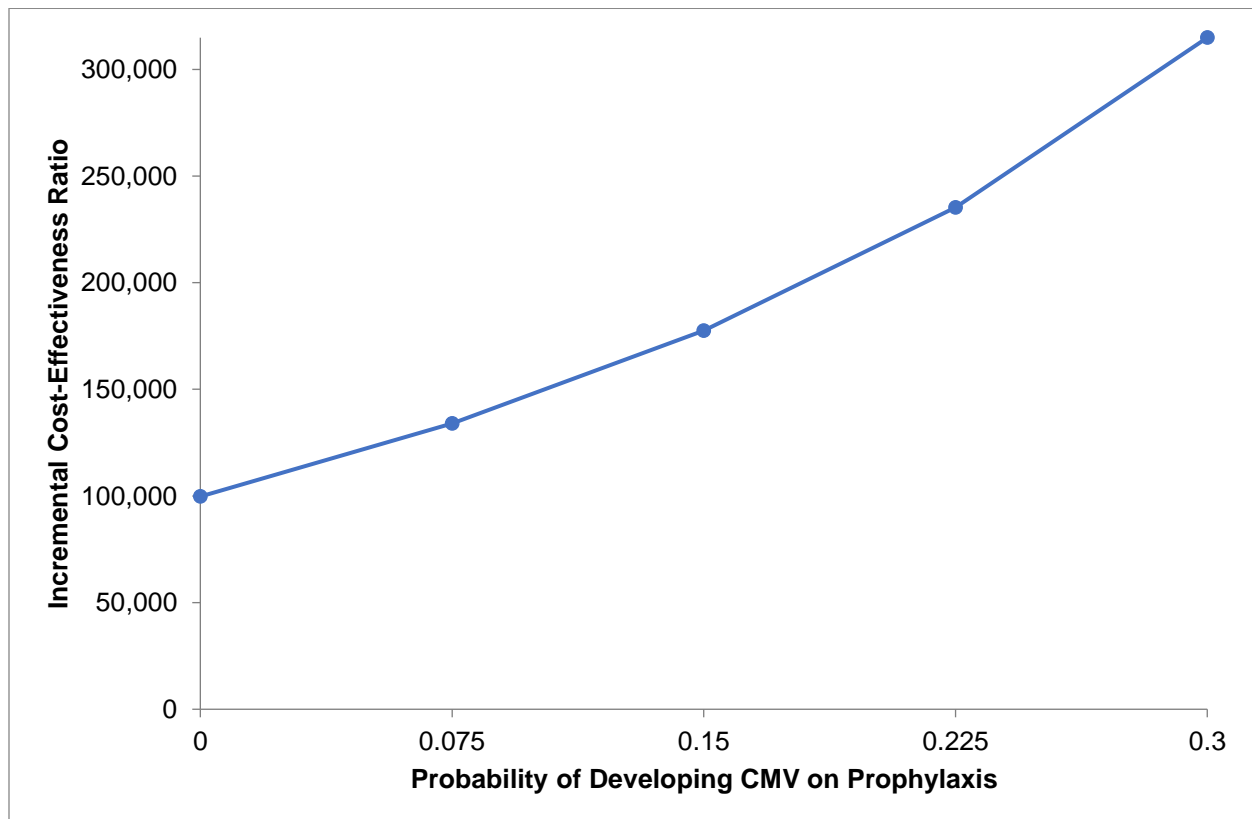


Figure 2. Change in Incremental Cost-effectiveness Ratio (ICER) with Varying Risk of Breakthrough CMV While on Prophylaxis

In the base-case scenario, the probability of being a mismatch patient is 20%, which mirrors lung transplant patients on a national level. Of course, it is possible that a particular region, city, or transplant clinic location may have a lower or higher than average percentage of CMV mismatch patients. When the probability of mismatch is varied in a one-way sensitivity analysis, as the probability increases, so does the average cost of treatment, as seen in **Figure 3**. However, since the probability of mismatch affects both the one-year and two-year prophylaxis arms equally, the differences in costs and effectiveness between strategies are proportionate to each other, and thus the incremental cost-effectiveness of the 2-year strategy remained unchanged with variation of mismatch likelihood.

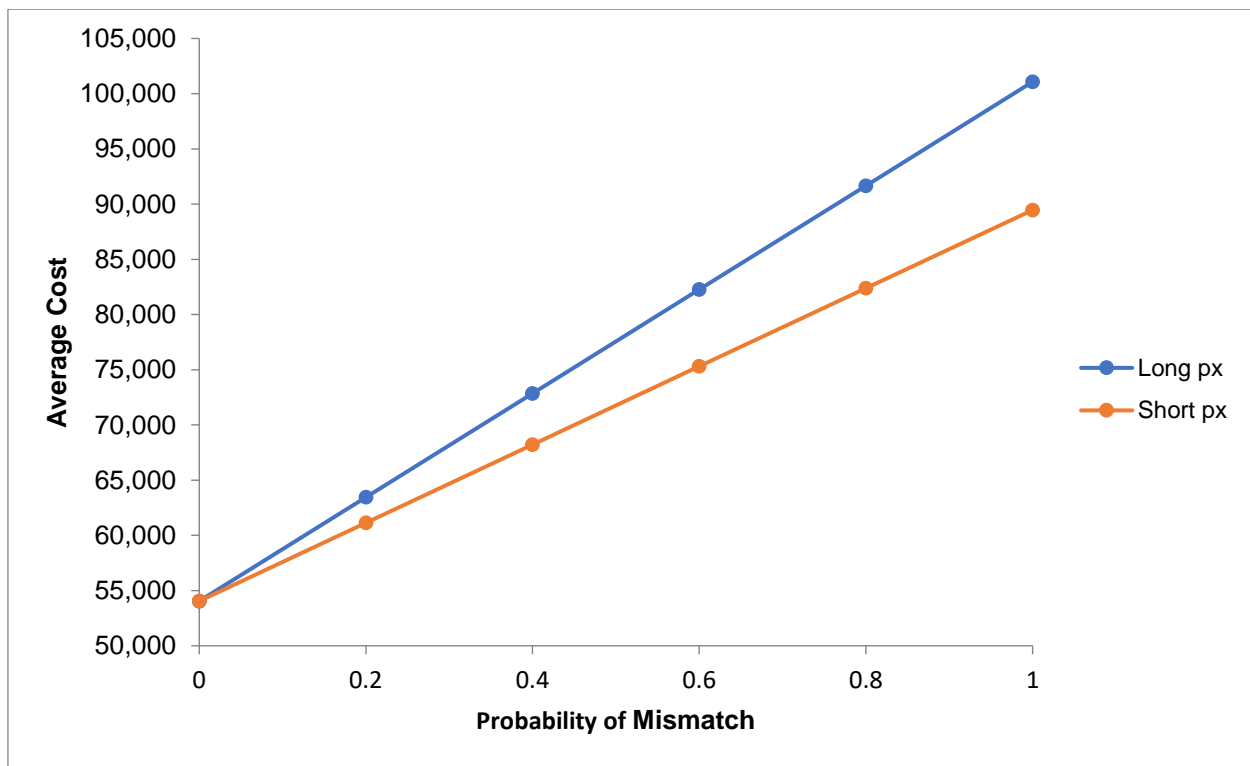


Figure 3. Change in Average Cost with Varying Probability of Mismatch Status

While the base-case compares the clinically standard one year of prophylaxis with a longer duration of two years, prophylactic regimens of longer than two years can also be compared. If the

prophylaxis duration is increased to the entirety of the five-year time horizon that the model simulates, the ICER increases to just over \$200,000/QALY, as seen in **Figure 4**.

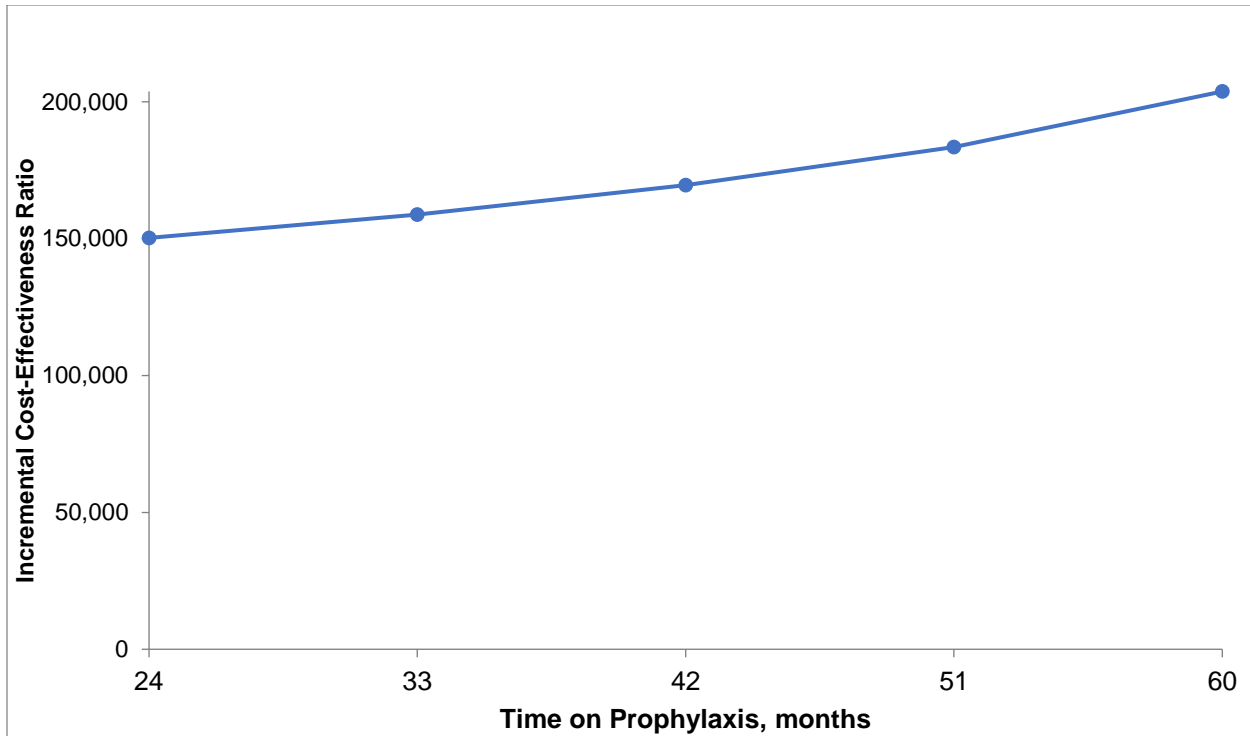


Figure 4. Change in Incremental Cost-effectiveness Ratio (ICER) with Varying Time on Prophylaxis

5.3 Probabilistic Sensitivity Analysis

In addition to varying all parameters in the model through one-way sensitivity analyses, a probabilistic sensitivity analysis can be performed. In a probabilistic analysis, all variables are varied simultaneously, and different values are selected from each parameter’s distribution for each of the 1,000 runs of the model that are performed, generating acceptability curves. An acceptability curve indicates how often a specific strategy is favored at specific willingness-to-pay (WTP) thresholds. A WTP threshold is a cost-per-QALY threshold – below the threshold, the cost-

per-QALY is considered acceptable; above the WTP threshold, the cost-per-QALY is no longer deemed to be acceptable.

The acceptability curves for the probabilistic analysis of the model can be seen in **Figure 5**. When a WTP threshold of \$150,000/QALY or higher is chosen, the two-year prophylactic duration is favored. At a \$200,000/QALY WTP threshold, two years of prophylaxis is favored in 61.9% of model iterations. This means that, for 61.9% of the model's 1,000 runs with values randomly selected from each variable's distribution, two years of prophylaxis was the preferred strategy based on the ICER.

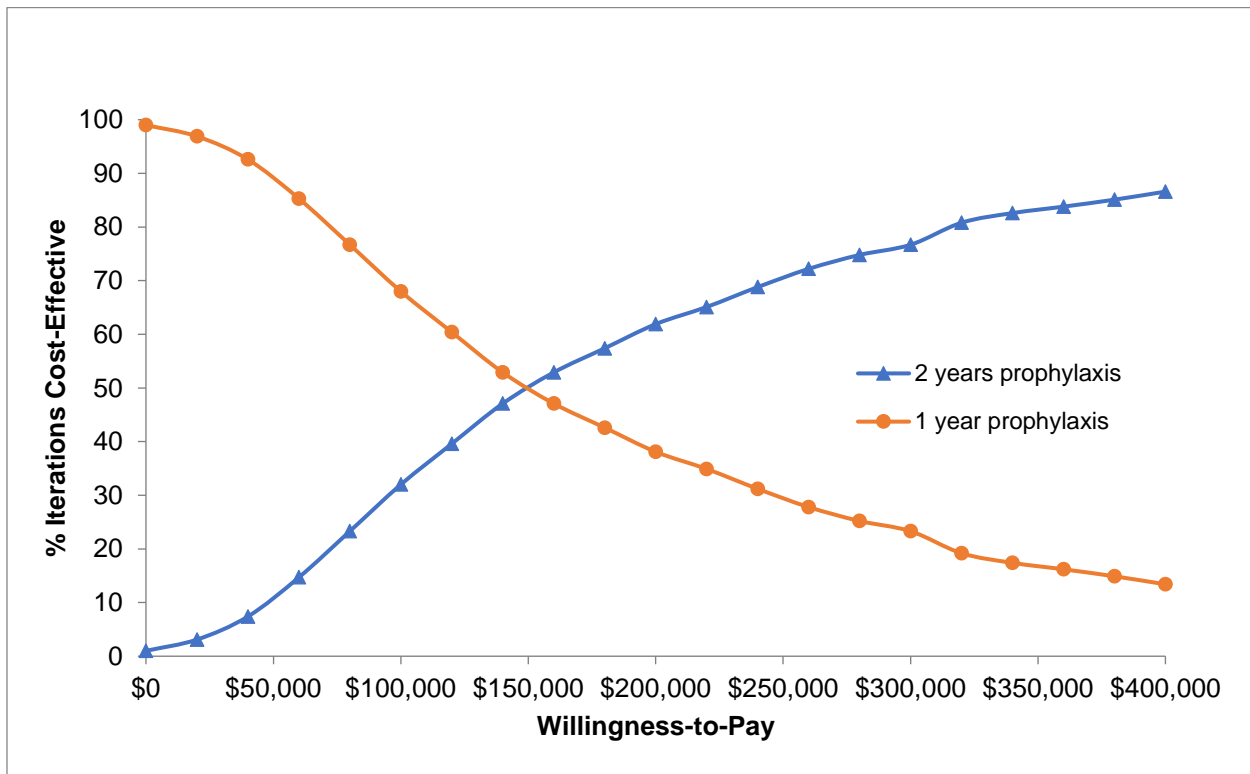


Figure 5. Probabilistic Analysis Results Showing the Favored Strategy Across a Range of Costs per QALY

6.0 Analysis

The ICER results, both in terms of life-years gained and QALYs, fall under the upper threshold of \$200,000, indicate that extending prophylaxis duration to at least two years is economically reasonable. Sensitivity analyses confirm that extending even beyond that two-year duration may continue to be economically reasonable, dependent upon which cost-effectiveness threshold is selected. These results account for the possibility of increased resistant strain emergence that could accompany increased prophylaxis duration, and the toxicity of treatment for these resistant CMV strains. The favorability of increased prophylaxis duration confirms previous center-specific studies that found benefit in extending prophylaxis. Findings of this simulation model are strengthened by the use of national data, rather than data from a single center.

The model does have some limitations. In using national data to estimate mortality following lung transplantation, these estimates do not distinguish between deaths attributable to CMV and deaths from other causes, including other opportunistic infections triggered by uncontrollable CMV infections. Thus mortality risk estimates of patients without CMV could be over-estimated, as continued prophylaxis would likely decrease mortality for CMV mismatch patients. This would, in turn, lower the ICER and result in a more cost-effective result. Furthermore, rejection episodes are thought to be associated with CMV in some way, though it is not yet known if the relationship is causal, or merely an association. In this model, however, rejection is treated as an independent event.

The use of national data to estimate utility values, used in the calculation of QALYs, presents another limitation. The utility values used to calculate the QALYs, and the resulting ICER, are relatively low. Utilities range from 0 (dead) to 1 (perfect health); utilities in this model

range from 0.25 – 0.70. Using published literature estimates, there is no differentiation between utility values of sensitive and resistant strains of CMV, though it is likely that they are different. When these utilities were varied over plausible ranges during sensitivity analyses, the results were not substantially changed, indicating that even with more accurate utility values, two years of prophylaxis remained the preferred strategy.

7.0 Discussion

CMV viremia and disease are one of the most common infections following lung transplant, and CMV mismatch patients are at an increased risk for developing CMV [6-8]. The optimal prophylaxis duration with valganciclovir following transplantation, especially for mismatch patients, remains unknown, and different centers have varying protocols ranging from six months to over a year. Limited, site-specific studies have indicated that prophylaxis for longer than a year may be beneficial, but this contention has not yet been studied on a large scale [7]. Generally, along with extended periods of prophylaxis come concerns about increased risk of resistant CMV strains and about Foscarnet toxicity effects while treating those resistant strains.

Understanding the correct duration of prophylaxis is important because of the association between CMV, BOS, episodes of acute rejection, and graft failure. Though the link is not fully understood yet, some association between CMV and episodes of acute rejection, potentially leading to graft failure, is noted [8, 11]. CMV is also associated with BOS, a progressive condition that limits survival following lung transplantation [7, 9, 11]. If prophylaxis is successful in decreasing or delaying CMV infection and disease, it would follow that BOS and graft failure could also be decreased or delayed.

Model results do indicate that extending prophylaxis duration to two years does provide added benefit in the form of life-years gained and QALYs, and that extending even past those two years continue to provide extra benefit, even when taking into account the increased risk of resistance and associated toxicity of treatment. Further research could be performed to assess if increasing prophylactic duration does, in turn, decrease or delay the appearance of BOS and graft failure, both of which play major roles in post-transplant mortality.

One important point of discussion, when considering these results, is the use of QALYs as a measure of effectiveness. Currently, QALYs are the most frequently used measure of effectiveness for cost-effectiveness studies, but they are not without controversy. The largest concern with QALYs is that they are not seen to be “patient-centric” [30, 31]. This means that they do not necessarily account for an individual patient’s wishes or preferences. Perhaps a patient has a major life milestone of a family member (wedding, graduation) that is very important to them, and that they want to make sure they’re present at – QALYs do not take this into account. It’s also possible that a patient does not place much value on losing a particular aspect of their health – for example, they do not mind being in pain, they are willing to lose some mobility – and QALYs are not able to account for this. Additionally, QALYs are based on a mathematical calculation, so the value of two years at “perfect health” (utility = 1) and four years at a lesser health (utility = 0.5) come out to the same QALY value, but may not be valued equally by the patient. These issues continue to be present when considering the instruments and tools used to elicit the utility values used in the QALY calculation. The individual methods referenced earlier (standard gamble, time trade-off, visual analog scale) are time intensive and individualized, and therefore not used frequently in favor of the use of standardized questionnaires. These questionnaires, however, do not account for individualized difference between patients [30]. There is also the larger issue on placing a value on a patient’s life or health, and making decisions based upon the various thresholds mentioned above [30]. When using a cost-effectiveness analysis to guide decision making, these factors need to be considered.

8.0 Conclusions, Recommendations, and Public Health Implications

Based on the results of the model, extending prophylaxis duration to two years for CMV mismatch patients provides extra benefit, both in terms of life-years gained and QALYs, and is economically feasible. Both the base-case results and the subsequent sensitivity analyses support this conclusion. Given the lack of a single recommended strategy for prophylaxis for this particular group of patients, these results should be useful for lung transplant centers reviewing their prophylaxis strategy.

This recommendation is especially important given the limited life expectancy following lung transplantation when compared to other solid organ transplants. Given the potential impact the increasing prophylactic duration to two years, or longer, has on the decrease on appearance of BOS and episodes of acute and chronic rejection, it is even more important that lung transplant centers consider these findings and begin implementing an extended prophylaxis regimen.

The public health implications, too, are clearly evident. Given that there are a limited number of organs available for transplantation, and that the demand outweighs the supply and is only continuing to grow, it follows that implementing the proper duration of prophylaxis will allow these organs to be used to their maximal benefit. The potential to decrease mortality of transplanted patients is pivotal, and the potential for reducing graft failure could also decrease or delay the need for re-transplants, again ensuring that donated organs are used to the greatest benefit on the population level. Increasing prophylaxis duration will improve outcomes overall.

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