Published in final edited form as:
Med Mycol. 2009 ; 47(6): 592–600. doi:10.1080/13693780802326001.

Economic burden of mucormycosis in the United States: can a vaccine be cost-effective?

Ashraf S. Ibrahim, PhD[1,2,*], **John E. Edwards Jr., MD**[1,2], **Richard Bryant, MD**[2,3], and **Brad Spellberg, MD**[1,2]

[1]Division of Infectious Diseases, Harbor-University of California at Los Angeles Medical Center, and the Los Angeles Biomedical Research Institute, Torrance, California

[2]The David Geffen School of Medicine at UCLA, Los Angeles, California

[3]Department of Orbital and Ophthalmic Plastic Surgery, UCLA Medical Center, 10833 Le Conte Ave, Los Angeles, CA 90095

Abstract

Mucormycosis is a life-threatening infection which causes unacceptably high morbidity and mortality despite treatment. Therefore, a vaccine to prevent mucormycosis is desirable. A major barrier to developing an anti-mucormycosis vaccine is the perception that such a vaccine would not be cost-effective to deploy because the disease is rare. We used data from a recent retrospective study to calculate the annual cost to the US healthcare system caused by mucormycosis infections. We created a model to estimate the cost-efficacy of a niche, anti-mucormycosis vaccine deployed in a targeted manner to high-risk patients. We found that each case of mucormycosis results in an average direct cost to the US healthcare system of $97,743, for an overall cost of mucormycosis of $50 million per year. In the base case scenario, targeted deployment of an anti-mucormycosis vaccine would result in a net cost per quality adjusted life year saved (QUALY) of $17,249. Variations in the price of the vaccine, its market penetration, or the cost of infection could dramatically decrease the net cost, and could even result in net savings per QUALY. In conclusion, mucormycosis causes considerable cost to the US health care system. Targeted deployment of a niche vaccine could decrease infection rates and mortality from mucormycosis in a cost-effective manner.

Introduction

Mucormycosis is an infection caused by fungi belonging to the order *Mucorales* of the class *Zygomycetes* (1,2). Major risk factors for mucormycosis include diabetes mellitus, organ or hematopoeitic stem cell transplantation, neutropenia, and malignant hematological disorders. Recent data have demonstrated a striking increase in the number of reported cases of mucormycosis (2-6). The frequency of mucormycosis is expected to continue to rise due to increasing rates of diabetes, more aggressive cancer treatment in the aging global and US population, and increasing transplant procedures in the developed world.

Unfortunately, even with first-line antifungal therapy and aggressive surgical debridement, the mortality of mucormycosis exceeds 50% (2,5,7). In patients with prolonged neutropenia, and in those with disseminated disease mortality is 90-100%. The high morbidity and mortality of

*Correspondence: Division of Infectious Diseases, Harbor-UCLA Medical Center, 1124 W. Carson St., Torrance, CA 90502. USA. Phone: (310) 222-6424. Fax (310) 782-2016. ibrahim@labiomed.org.

Financial Disclosures: A.S.I., J.E.E., and B.S. own equity in NovaDigm Therapeutics, Inc., which is developing vaccine technologies. NovaDigm Therapeutics, Inc. provided no financial support for these studies.

mucormycosis despite treatment underscores the need to develop preventative strategies. Vaccination is one such promising strategy, and has been investigated for a variety of other invasive fungal infections (8). However, the relatively low incidence of mucormycosis has dampened enthusiasm for such a vaccine, because of the perceived high cost of vaccination relative to life years saved.

We recently conducted a retrospective investigation of forty-one cases of mucormycosis at two tertiary care medical centers (9). The results from that study enabled us to calculate the costs associated with mucormycosis infection. We therefore created a model to estimate the cost-efficacy of a potential vaccine for mucormycosis.

Methods

The Model

To estimate the cost-efficacy of a vaccine deployed in patients at risk for mucormycosis, we developed a model to calculate: 1) the annual direct cost of mucormycosis infections to the US health care system; 2) the annual cost of deploying a niche vaccine targeted to patients at risk for mucormycosis; and 3) the cost per quality adjusted life-years (QUALY) saved by the vaccine. Our model used a societal perspective (10) when considering costs, and contained several key assumptions (Table 1). The first assumption was that the primary costs of infection would be due to a combination of hospital costs, surgical costs, and antifungal costs (Table 2). Antifungal costs were separately calculated from hospital costs, because these costs are known to be particularly high for mucormycosis due to the high doses and prolonged course of expensive, lipid preparations of amphotericin that are most commonly used to treat the disease (2).

We assumed only a fraction of the overall at-risk population would receive vaccination (i.e. the market penetration was less than 100%). Therefore, the number of infections in the setting of vaccination was calculated as the sum of: the number of infections occurring in patients who were not vaccinated plus the number of breakthrough infections occurring in patients who were vaccinated.

Base Case Estimates (Table 2)

The number of at-risk patients was calculated by summing the annual incidence in the US of diabetic ketoacidosis, hematopoeitic stem cell transplantation, solid organ transplantation, and neutropenia. While only half of diabetic patients with mucormycosis are in ketoacidosis on presentation (5,9), diabetic patients with ketoacidosis have a higher attack rate of mucormycosis than diabetic patients not in ketoacidosis. For example, it is estimated that only 1-10% of diabetics in the US develop ketoacidosis per year (11,12), yet ~50% of diabetics with mucormycosis are in ketoacidosis on presentation (5,9). Furthermore, ketoacidosis is also a marker of poorly controlled diabetes. Hence, we focused on diabetics in ketoacidosis as a subset of the overall diabetic population that is at high risk for mucormycosis.

Vaccine efficacy was assumed to be 50% in the base case (i.e. the attack rate of breakthrough infections in vaccinated patients was assumed to be 50% compared to the attack rate of infection in unvaccinated patients). In the base case, the cost of a single dose of vaccine was assumed to be $150, and the cost reduction for breakthrough infections was assumed to be reduced by 33% versus the cost of infections in unvaccinated patients, due to a partially ameliorated course of disease during breakthrough infection.

The mortality rate for breakthrough infections in vaccinated patients was assumed to be 40% in the base case, reflecting a 20% relative reduction compared to the 50% mortality in unvaccinated subjects (2-6,9). There are no published data on average number of life years in

patients after cure of mucormycosis, nor for quality of life during those years. Therefore, we used data from studies of patients with severe sepsis/septic shock or acute respiratory distress syndrome, which are also severe infections with high morbidity and mortality (13-16), to provide a base case and range for sensitivity testing.

Cost Estimates for Mucormycosis Infection

The PubMed database was searched for title word/abstract "cost" and title/abstract "mucor*" OR "zygomycosis" (search completed 3/17/08). This search identified 13 abstracts. Both authors reviewed the abstracts and manuscripts and found no description of cost of infection, cost of hospitalization, total dose of antifungal administered, or number of surgeries received in any of the articles. Furthermore, previous case series of mucormycosis not identified by the cost-focused Pubmed search were evaluated for the same parameters, but again no cost information was identified in these series (3-6,17).

To collect information related to cost of mucormycosis, we used a database from a recent, retrospective review of 41 cases of rhinocerebral mucormycosis seen over a 12 year period (1994-2006) at two tertiary care medical centers, Harbor-UCLA Medical Center (HUMC, a tertiary care, public, teaching hospital) and the UCLA Center for the Health Sciences (CHS, a tertiary care, private, teaching hospital) (9). As described previously, cases were identified at both medical centers by searching hospital databases for ICD9 117.7 (zygomycosis/ mucormycosis) from 1994 to 2006. Charts were abstracted with a standard form to gather data on demographics, clinical history, medications, and outcomes. The study was approved by Institutional Review Boards at both medical centers.

The cost of antifungal therapy, hospitalization, and surgery was calculated from the existing database from our prior retrospective study of mucormycosis patients (9). We multiplied the total dose received by each patient in milligrams of polyenes (amphotericin B deoxycholate (AmB), liposomal amphotericin B (LAmB), or amphotericin B lipid complex (ABLC)) by the drug acquisition costs for each respective polyene to calculate the cost of antifungal per patient. Drug acquisition costs for AmB, LAmB, and ABLC were assumed to be $0.1/mg, $1/mg, and $0.425/mg, respectively, based on wholesale costs at our institution. Nonpolyene antifungal costs were not included in the best case estimate, as they constituted a minority of treatment, and because polyenes are the only drugs licensed by the US Food and Drug Administration (FDA) for the treatment of mucormycosis. Because combination therapy with polyenes plus either posaconazole or echinocandins is increasingly frequent, we modeled such costs in sensitivity analyses.

Costs of hospitalization were assumed to be $1100/day for ward beds and $2400/day for ICU beds (18). Because numerous different types of surgeries were performed on the patients with mucormycosis, ranging from total orbital exenteration to surgical reconstruction of the orbit to endoscopy with biopsy and debridement, no single estimate of surgical cost was sufficient. Medicare reimbursement for related Head and Neck surgeries ("orbital procedures", "major head and neck procedures", "sinus and mastoid procedures") range from $10,000 to $30,500 (in 2007 dollars) (19). Covered charges (included those not reimbursed by Medicare, for those procedures are even higher, ranging from $36,000 to $99,000 (19). Based on these data, we used a conservative estimate of an average cost of $10,000 per surgery.

Sensitivity testing for average life years gained was based on our mucormycosis case series dataset (9). Specifically, only 39% of the patients with mucormycosis in our series had cancer or were status post transplantation (16/41 patients). Of the remaining patients, 23 were diabetic, 1 was on corticosteroids, and 1 had no obvious risk factors other than underlying structural sinus abnormalities and chronic sinusitis. Of those 25 patients, the average age was 50 years old. Even if the 16 cancer/transplant patients lived for 0 days after their cure from

mucormycosis, if the remaining 25 patients lived an average of only 8 years, as we set as our base case scenario, the overall population would have lived slightly less than 5 years. Thus, we set the lower limit of life years gained in our sensitivity analysis to 4 years.

Sensitivity testing for costs of adjunctive antifungals was based on a wholesale, daily cost of approximately $100 for posaconazole or echinocandins. We assumed that adjunctive therapy would be administered for a maximum of 100 days, resulting in a maximum cost of adjunctive antifungal therapy of $10,000 per case.

All costs were adjusted to 2007 dollars utilizing the Consumer Price Index inflation calculator established by the U.S. Department of Labor, Bureau of Labor Statistics (20). Variations from base case estimates were analyzed in sensitivity analyses (Table 3).

Results

Economic impact of mucormycosis

From our retrospective study of 41 cases of mucormycosis, the average length of stay of patients in hospital was 35 days, with a range of 4 to 120 days. Half of the hospital days were spent in ward beds and half in ICU beds. The average (range) cost of hospitalization (hospital days * cost per day) was $61,463, with a range of $7,000 to $210,000. These costs do not include costs of post-discharge care in nursing homes, or home intravenous antibiotic or home hospice care. Nor do the costs include external health facility costs for four surviving patients who were transferred back to their original health care facilities after they had stabilized (9). We also did not include indirect costs (e.g. costs of lost economic productivity, lost wages, etc.) in the analysis.

Every patient was treated with a polyene antifungal agent throughout the duration of their mucormycosis treatment. Seventeen patients were treated with AmB at an average total dose of 1,100 mg of AmB. Thirty patients were treated with ABLC at an average total dose of 10,700 mg. Thirteen patients were treated with LAmB at an average total dose of 22,700 mg. The average total polyene cost per patient was $14,085, with a range of $295 to $88,000. Several patients received adjunctive therapy with echinocandins, posaconazole, hyperbaric oxygen, or cytokines such as GM-CSF. The costs of the adjunctive therapies were not included in the overall analysis.

Every patient received surgical treatment for their mucormycosis. The average number of surgeries received was 2.2 (range 1 to 5). The average calculated surgical cost per patient was $22,195 with a range of $10,000 to $50,000.

Summing the costs of hospitalization, polyene therapy, and surgeries, the average total cost per patient was $97,743, with a range of $17,835 to $348,000.

Vaccine market size, market penetration, and infection incidence

An estimate of the market size for an anti-mucormycosis vaccine targeting at-risk populations can be generated by summing the incidences of diabetic ketoacidosis, recipients of hematopoeitic stem cell or solid organ transplantation, leukemia, and neutropenic patients. Estimates of the population-based incidence of diabetic ketoacidosis vary from 10 to 20 per 100,000 population (11,12,21,22). Given a population of ~300 million in the US, the total number of cases of diabetic ketoacidosis is approximately 45,000 (range 30,000-60,000) per year in the US. There are approximately 20,000 hematopoeitic and 30,000 solid organ transplants per year in the US and approximately 45,000 patients with leukemia and 60,000 patients with neutropenia per year in the US (23-25). Hence the total at-risk population for the base case scenario was 200,000 per year in the US (Table 2).

Market penetration of individual vaccines varies depending on severity of target illness and statutory requirements for vaccination (26). For mucormycosis, the target disease is extremely deadly and the vaccine would be focused to individuals at specific risk for infection. In the base case, we assumed market penetration to be 50%, which is in the middle range of nonmandatory vaccines (26). We also assumed that 50% of vaccinated patients would receive a booster dose.

A population-based estimate of the incidence of mucormycosis, published in 1998, indicated that approximately 500 cases per year occurred in the US (27). Patients with prolonged neutropenia, leukemia, or hematopoeitic stem cell transplantation have been reported to have a risk of mucormycosis of 1-8% (28-30). Risks in diabetic patients are likely lower, although specific data are not available. Given an at-risk population of 200,000, an overall attack rate of 0.25% would result in 500 infections per year, which is equivalent to the population based estimate from 10 years ago. Such an overall attack rate would reflect a ~0.3% attack rate in 145,000 leukemic, neutropenic, and transplant patients, and a ~0.1% attack rate in 45,000 diabetics in ketoacidosis per year.

Vaccination of 50% of the at-risk population would leave approximately 100,000 unvaccinated, at-risk patients per year with a 0.25% attack rate of infection, resulting in 250 infections in unvaccinated patients per year. Assuming the vaccine was 50% effective at preventing mucormycosis infection, the breakthrough infection attack rate would be 0.125% in the remaining 100,000 vaccinated patients, resulting in an additional 125 infections. Hence, the base case estimate of infections after deployment of the vaccine is 375 infections per year, reflecting a 25% reduction in overall number of infections (from 500 to 375) due to use of the vaccine.

Vaccine reductions in mortality and cost

Given an overall 50% mortality from mucormycosis (1-5,9), we estimate approximately 250 deaths per year in the US from the 500 cases of infection in the at-risk populations in question. After deploying a vaccine, a 50% mortality rate would occur in the 250 unvaccinated patients who developed infection, resulting in 125 deaths. Assuming that the vaccine reduced the mortality of breakthrough infections by 20% relative to the mortality in unvaccinated patients, the mortality rate of breakthrough infections would be 40%. Hence, approximately 50 deaths would occur per year from the 125 breakthrough infections in vaccinated patients. The total deaths in the setting of vaccination, including in unvaccinated and vaccinated patients, would be therefore 175, reflecting a total of 75 lives saved per year by deploying the vaccine.

The total cost of mucormycosis per year in the US is estimated to be $48.9 million (500 infections * $97,743 per infection). In the setting of vaccination, the cost would be $24.4 million in the 250 unvaccinated patients who developed infection (250 * $97,743 per infection) plus $8.2 million for the 125 patients who developed breakthrough infections (125 * $97,743 * 66.7%, to reflect a 33% reduction in cost of breakthrough infections). The total cost of mucormycosis in the setting of vaccination would therefore be $32.6 million per year, reflecting an absolute savings of $16.3 million.

Assuming a cost per vaccine dose of $150, a 50% market penetration, and 50% booster rate, the total cost of vaccination would be $22.5 million (200,000 at-risk * 50% vaccination rate * $150 per dose * 1.5 for booster). The net cost of vaccination (i.e. cost of vaccination minus infection cost reduction) would be $6.2 million ($22.5 million - $16.3 million). The net cost per life saved would be $82,793 ($6.3 million / 75 lives per year).

Assuming an average of 8 life years gained per life saved (14,15), the vaccine would result in a net cost per life year saved of $10,349. Assuming an average quality of life per year of 0.6

(1 = normal, 0.5 = comatose) (13,15,31), the net cost per quality of life years saved in the base case would be $17,249.

Sensitivity Analyses (Table 3)

Sensitivity analyses were performed to model the impact of changes in the variables from the base-case model. Variations in the following parameters had little impact on the net cost per QUALY: number of at-risk patients per year, vaccine mediated reductions in the cost of breakthrough infections, the mortality rate for breakthrough infection in vaccinated patients, and the quality of life per year. Variations in vaccine efficacy (i.e. relative reduction in infection in vaccinated patients), mortality rate from infection, cost of adjunctive anti-fungal therapies, life years gained for survivors, and number of patients receiving booster doses had linear impacts on cost per QUALY (i.e. 2-fold changes in the variable resulted in approximately 2-fold changes in the cost per QUALY value).

The variables that had dramatic impact on net cost per QUALY were: vaccine market penetration, infection attack rate in at-risk patients, the cost of a dose of vaccine, and the cost of each case of infection. Of note, two of these parameters are under partial or complete control of the manufacturer of a vaccine: market penetration and cost of dose. Increasing the vaccine coverage from 50 to 75% of at-risk patients resulted in a 20-fold reduction in cost per QUALY (Table 3). Decreasing the cost of vaccine dose from $150 to $75 made the vaccine actually save $14,001 per QUALY as opposed to costing $17,249 per QUALY in the base case. Similarly if the infection attack rate in the target population was 0.5%, the vaccine would save $14,001 per QUALY. In contrast, if the attack rate was 0.125%, the vaccine would cost $79,749 per QUALY. If the cost of infection were increased to $196,000, the vaccine would save $28,241 per QUALY.

Discussion

Our analysis of the potential cost-efficacy of a vaccine targeting mucormycosis revealed several factors critical to development of such a vaccine. First, mucormycosis imparts considerable cost on the health care system in the US even though the disease is rare. Second, because of this high cost of infection, in the base case scenario, a niche vaccine priced at $150 would be considered cost-effective by the generally accepted standard of ≤$50,000 per QUALY (32). Third, two of the most critical parameters for making the vaccine remain cost-effective are under the control of the manufacturer: cost of the vaccine and market penetration. Even small changes in cost of the vaccine result in dramatic improvements in cost-efficacy. Furthermore, improvement in market penetration also dramatically improved cost-efficacy. Hence, there is considerable robustness in the current analysis, as unfavorable variations in other parameters could be offset by improving vaccine coverage or altering the price of a vaccine by small amounts. Finally, the upper limit of the cost per dose for a mucormycosis vaccine is likely to be approximately $300 for the vaccine to remain cost-effective, unless future studies determine that elements of our sensitivity analysis should be changed.

We employed conservative assumptions in the model. For several reasons, the cost of mucormycosis is likely to be dramatically higher than we estimated. First, we did not include indirect costs, such as lost productivity/wages of infected patients in the analysis. Nor did we consider cost of continued supportive care for survivors after hospital discharge (e.g. nursing home, rehabilitation, future reconstructive surgery, hospice care, etc.). Several patients received additional in-patient care after being transferred back to their originating, outside facilities, and those costs were not included. Nor were costs of adjunctive therapies, such as cytokine or antifungal therapies aside from polyenes, included in the analysis. We also used highly conservative surgical cost estimates, given the complexities of the surgeries required for debriding mucormycosis, as well as facial reconstructive surgery for survivors. As

mentioned above, any increase in cost of infection would dramatically improve the cost-efficacy of the vaccine.

We also assumed no additional efficacy benefit of the booster dose, but charged additional cost of the booster dose against the cost-benefit of the vaccine. It is likely that patients receiving booster doses would have some additional efficacy benefit. Since that efficacy benefit is difficult to predict, we chose not to include it in the model, which would have led to a further decline in infection and mortality rates, and therefore a further cost-efficacy benefit. Finally, the estimate of 500 cases of mucormycosis infections per year in the US is likely low. A population-based study from 1998 estimated 500 cases per year in the US at that time (27). As mentioned, mucormycosis has been dramatically rising in incidence since the early to mid-1990s. Therefore, the actual incidence of disease in the US is likely considerably higher. If so, the vaccine would save additional lives and therefore result in more favorable cost-benefit ratio.

The primary limitation of our analysis is the limited datasets available to provide estimates of the variables in the model. For example, our cost estimates are based on analysis of a dataset evaluating costs of caring for rhinocerebral mucormycosis. However, it is likely that costs of caring for pulmonary, gastrointestinal, disseminated, or other forms of mucormycosis are similar. Furthermore, we are unaware of any other studies evaluating issues such as cost of mucormycosis infections or years of life post-infection for survivors of mucormycosis.

Another limitation of the study is the imprecision in estimate of the attack rate of infection. Additional research in these areas is warranted, and would improve the accuracy of the model. Nevertheless, sensitivity analyses revealed which variables most critically impact the cost-efficacy of the vaccine, and supported the notion that a vaccine could be deployed for this disease in a cost-effective manner. Finally, our model does not take into consideration the cost of developing the vaccine. If vaccine development were paid for using public resources (e.g. public health service grant funding), these societal development costs would diminish the cost-benefit of the vaccine, and are not accounted for in our model. However, if vaccine development was paid for by a private company or using funds not derived from public sources, such costs would not impact the societal cost-benefit of vaccine deployment.

Deployment of the vaccine could be expanded to include diabetics with poorly controlled diabetes, rather than limiting use of the vaccine in patients with diabetic ketoacidosis. However, the attack rate for mucormycosis is not currently known in such patients, so it is difficult to predict what effect this expansion of use would have on cost-efficacy of a mucor vaccine. Another limitation of our analysis is that approximately half of diabetics who present with mucormycosis are newly diagnosed with their diabetes upon their presentation with mucormycosis (5,9). Obviously such patients would not be considered for vaccination prior to their infection. However, in our study, we found that most such patients had developed their diabetes due to treatment with high dose corticosteroids (9). Targeting use of the vaccine in diabetic recipients of high dose corticosteroids would also be reasonable from a clinical perspective, and would help capture such patients prior to their mucormycosis infections. Because data are not available estimating the annual incidence of treatment with “high dose” corticosteroids in the US, nor are data available on the attack rate of infection in such patients, we did not include corticosteroid-related diabetes in our cost-efficacy model.

In summary, while mucormycosis is a relatively rare disease, it imparts considerable costs on the US health care system. Targeted use of a niche vaccine, focusing on at-risk populations, could be a cost-effective tool to reduce morbidity, mortality, and health care costs in the US caused by mucormycosis.

Acknowledgments

Financial Support: This work was supported by Public Health Service grants R01 AI063503 and R21 AI064716 to A.S.I and K08 AI060641 and R01 AI072052 to B.S. B.S. is supported by American Heart Association Beginning Grant-in-Aid 0665154Y and the LA Biomedical Research Institute Liu Young Investigator Award. A.S.I. is also supported by a Burroughs Wellcome New Investigator Award in Molecular Pathogenic Mycology.

References

1. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev 2000;13 (2):236–301. [PubMed: 10756000]
2. Spellberg B, Edwards J Jr. Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 2005;18(3):556–69. [PubMed: 16020690]
3. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 2002;34(7):909–17. [PubMed: 11880955]
4. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis 2000;30(6):851–6. [PubMed: 10852735]
5. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005;41(5):634–53. [PubMed: 16080086]
6. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis 2005;191(8):1350–60. [PubMed: 15776383]
7. Kwon-Chung, KJ.; Bennett, JE. Medical Mycology. Lea & Febiger; Philadelphia: 1992. Mucormycosis; p. 524-559.
8. Spellberg B. Prospects for and barriers to a fungal vaccine. Expert Opin Biol Ther 2007;7(12):1785–8. [PubMed: 18034644]
9. Reed C, Bryant R, Ibrahim AS, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis. 2008In Press
10. Gold, MR.; Siegel, JE.; Russell, LB.; Weinstein, MC., editors. Cost-Effectiveness in Health and Medicine. Oxford University Press; New York, NY: 1996.
11. Dunger DB, Sperling MA, Acerini CL, et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child 2004;89(2):188–94. [PubMed: 14736641]
12. Eledrisi MS, Alshanti MS, Shah MF, Brolosy B, Jaha N. Overview of the diagnosis and management of diabetic ketoacidosis. Am J Med Sci 2006;331(5):243–51. [PubMed: 16702793]
13. Heyland DK, Hopman W, Coo H, Tranmer J, McColl MA. Long-term health-related quality of life in survivors of sepsis. Short Form 36: a valid and reliable measure of health-related quality of life. Crit Care Med 2000;28(11):3599–605. [PubMed: 11098960]
14. Quartin AA, Schein RM, Kett DH, Peduzzi PN. Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. Jama 1997;277(13):1058–63. [PubMed: 9091694]
15. Manns BJ, Lee H, Doig CJ, Johnson D, Donaldson C. An economic evaluation of activated protein C treatment for severe sepsis. N Engl J Med 2002;347(13):993–1000. [PubMed: 12324556]
16. Davidson TA, Caldwell ES, Curtis JR, Hudson LD, Steinberg KP. Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. Jama 1999;281 (4):354–60. [PubMed: 9929089]
17. Gleissner B, Schilling A, Anagnostopolous I, Siehl I, Thiel E. Improved outcome of zygomycosis in patients with hematological diseases? Leuk Lymphoma 2004;45(7):1351–60. [PubMed: 15359632]
18. Candrilli, SD.; Mauskopf, J. How much does a hospital day cost?. 11th Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); 2006; Philadelphia, PA. 2006;
19. Short Stay Inpatient Diagnosis Related Groups. Centers for Medicare and Medicaid Services; 2006. 100% MEDPAR Inpatient Hospital National Data for Fiscal Year 2005 6/06 Update.
20. Consumer Price Indexes Inflation Calculator. U.S. Department of Labor, Bureau of Labor Statistics;

21. Alaghehbandan R, Collins KD, Newhook LA, MacDonald D. Childhood type 1 diabetes mellitus in Newfoundland and Labrador, Canada. Diabetes Res Clin Pract 2006;74(1):82–9. [PubMed: 16621109]
22. Henriksen OM, Roder ME, Prahl JB, Svendsen OL. Diabetic ketoacidosis in Denmark Incidence and mortality estimated from public health registries. Diabetes Res Clin Pract 2007;76(1):51–6. [PubMed: 16959363]
23. Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble WT. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. Cancer 2005;103(9):1916–24. [PubMed: 15751024]
24. Loberiza FR Jr. Serna DS, Horowitz MM, Rizzo JD. Transplant center characteristics and clinical outcomes after hematopoietic stem cell transplantation: what do we know? Bone Marrow Transplant 2003;31(6):417–21. [PubMed: 12665834]
25. Fast Facts About Transplant, January 1, 2006 - December 31, 2007. Scientific Registry of Transplant Recipients; 2008.
26. Ellis RW. Product development plan for new vaccine technologies. Vaccine 2001;19(1314):1559–66. [PubMed: 11166875]
27. Rees JR, Pinner RW, Hajjeh RA, Brandt ME, Reingold AL. The epidemiological features of invasive mycotic infections in the San Francisco Bay area, 1992-1993: results of population-based laboratory active surveillance. Clinical Infectious Diseases 1998;27(5):1138–47. [PubMed: 9827260][see comments]
28. Maertens J, Demuynck H, Verbeken EK, et al. Mucormycosis in allogeneic bone marrow transplant recipients: report of five cases and review of the role of iron overload in the pathogenesis. Bone Marrow Transplantation 1999;24(3):307–12. [PubMed: 10455371]
29. Marty FM, Cosimi LA, Baden LR. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. N Engl J Med 2004;350(9):950–2. [PubMed: 14985500]
30. Greenberg RN, Scott LJ, Vaughn HH, Ribes JA. Zygomycosis (mucormycosis): emerging clinical importance and new treatments. Curr Opin Infect Dis 2004;17(6):517–25. [PubMed: 15640705]
31. Angus DC, Musthafa AA, Clermont G, et al. Quality-adjusted survival in the first year after the acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;163(6):1389–94. [PubMed: 11371406]
32. Evans C, Tavakoli M, Crawford B. Use of quality adjusted life years and life years gained as benchmarks in economic evaluations: a critical appraisal. Health Care Manag Sci 2004;7(1):43–9. [PubMed: 14977093]

Table 1

Base-Case Variables and Assumptions

Factor	Calculation
Cost of Hospitalization	Days of hospitalization * per day hospital costs
Cost of Infection	Cost of Hospitalization + surgical costs + antifungal cost (see Table 2)
Total at risk population	Annual incidence in US of diabetic ketoacidosis, hematopoeitic stem cell transplants, solid organ transplants, leukemic and neutropenic patients
Cost of Vaccine	#vaccinated * cost of dose * (1 + fraction receiving booster dose)
Vaccine Savings	Cost of Infection without vaccine − Cost of Infection with vaccine
Net Cost	Cost of Vaccine − Vaccine Savings
Cost Per Life Saved	Net Cost / (Deaths from Infection without vaccine − Deaths from Infection with vaccine)
Cost Per QUALY*	Cost Per Life Saved / (life years gained * quality of life)

	Base Case Without Vaccine	Base Case With Vaccine
Number of Infections	Number of patients at risk * infection rate	Number of infections in unvaccinated patients + number of breakthrough infections in vaccinated patients
Deaths from Infection	Number of Infections * mortality rate	(Number of Infections * mortality rate for unvaccinated) + (Number of Infections * mortality rate for breakthrough infections in vaccinated patients)

Table 2

Base-Case Estimates and Ranges

Factor	Base Case Estimate	Range	Reference
Number of patients at risk per year	200,000	100,000-400,000	(11,12,21, 22) (23-25)
Market penetration	50%	30-70%	(26)
Fraction receiving booster dose	50%	30-70%	(26)
Infection rate for unvaccinated at-risk patients	0.25%	0.1%-2%	†
Vaccine efficacy (i.e. relative reduction of infection in vaccinated patients)	50%	25%-75%	N/A
Cost of vaccine dose	$150	$75-300	N/A
Cost reduction for breakthrough infection	33%	15%-50%	N/A
Mortality rate for infection	50%	25-90%	(1-5,9)
Mortality rate for breakthrough infection	40%	25-90%	N/A
Life years gained	8	4-16	(14,15)
Quality of Life per year	0.6	0.5-0.8	(13,15,31)
Number of patients receiving booster dose	50%	30-70%	(26)

† See text for discussion

Table 3

Sensitivity Analyses

Variable	Range	Lives Saved Per Year	Cost Per QUALY*
Number of At-Risk Patients Per Year	100,000-400,000	38 - 150	$17,249
Vaccine Market Penetration	25-75%	38 - 113	$100,582 - (−$10,529)*
Infection Attack Rate	0.125%-0.5%	38 - 150	$79,749 - (−$14,001)*
Vaccine Efficacy (i.e. relative reduction in infection)	25 to 75%	50 - 100	$42,842 - $4,452
Cost of Dose	$75 - $300	75	(−$14,001) - $79,749*
Cost of Infection	$49,000 - $196,000	75	$39,815 - (−$28,241)*
Cost Reduction for Breakthrough Infection	15% - 50%	75	$23,471 - $11,592
Mortality Rate	40 - 80%	50 - 150	$25,783 - $8,624
Mortality Rate for Breakthrough Infection	30% - 50%	88 - 63	$14,785 - $20,698
Life Years Gained	4 - 16	75	$34,497 - $8,624
Quality of Life Per Year	0.5 - 0.8	75	$20,698 - $12,936
Number of Patients Receiving Booster Dose	25% - 75%	75	$6,832 - $27,665

* QUALY = quality adjusted life year saved; negative values indicate net savings per quality life year