Shallow Report on Fungal Diseases
October 2022
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Summary

Considering the expected benefits of eliminating fungal infections (i.e. fewer deaths, less morbidity and greater economic output) as well as the tractability of vaccine development, I find that the marginal expected value of vaccine development for fungal infections to be **1,104 DALYs per USD 100,000**, which is around 2x as cost-effective as giving to a GiveWell top charity.

Discussion:

- The estimates I rely upon potentially undercount fungal disease mortality and morbidity.
- There is considerable uncertainty over the rate at which the problem of fungal infections is getting better (or indeed, worse), unlike for better-examined diseases like malaria
- It would be valuable to get expert quantitative modelling on this matter.
- Health benefits drive the results, not the economic benefits, as is typical for many mainstream health ideas I've examined (e.g. tobacco taxation, road speed limits, alcohol taxation).
- Assumes lifetime coverage for the vaccine
- Expert advice on the whole theory of change for assessing tractability would be most clarifying
- High uncertainty over the marginal production costs of antifungal vaccines.
- The intervention requires massive amounts of money, and more than that, piecemeal contributions will not make a marginal difference, since pharmaceutical companies will not try to develop a vaccine without high upfront financial commitments that ensure they will profit in expectation. The corollary is that big funders like Open Philanthropy will potentially be more interested in such an area.

Expected Benefit: Averting Fungal Infection Deaths

The primary expected benefit of eliminating fungal disease is preventing death. This benefit is modelled in the following way.

Moral Weights: I take the value of averting one death to be **29.3 DALYs**. This is calculated as a function of (a) a human's full healthy life expectancy of 63.69, (b) a minor age-based philosophical discount, and (c) assuming we save someone of the median age in the relevant population. For more details, refer to CEARCH's evaluative framework.

Scale: I calculate the deaths from fungal infections per annum by looking at three separate sources. Per Brown et al, fungal infections kill one and a half million people every year (1.5 million deaths). Meanwhile, an estimate from the European Journal of Clinical Microbiology and Infectious Diseases suggests a slightly higher figure (1.6 million deaths) - an estimate that is corroborated by the Global Action for Fungal Infections (GAFFI) (1.6 million deaths). Overall, I take a weighted average (**1.595 million deaths**) that penalizes the Brown et al estimate somewhat – it may be less reliable than the more recent ones due to the lesser availability of studies pre-2013. That said, this does not seem like a significant issue either way, as figures converge, likely due to methodological similarities.

Persistence: If we managed to prevent fungal deaths, the per annum benefits would persist over time and would hence need to be summed up across various years, but there are a couple of important discounts that we need to implement.

Firstly, I discount for the probability of the solution not persisting; in this case, the specific solution we are assessing for this cause area is that of a vaccine, and hence the risk of the solution not persisting consists of a fall in vaccination rates. I model this by assuming a steady state in vaccine uptake of childhood vaccines of 85% (the rate having stagnated there for around a decade pre-COVID), and then calculating the per annum decline as a function of a once-in-a-century pandemic potentially occurring, and the drop in childhood vaccinations that results if said pandemic occurs (taking population-weighted average of the falls in vaccination rates for high-income countries and LMICs). I take that there will be no policy reversal (i.e. governments no longer mandating childhood vaccinations) given the steady state pre-COVID. Overall, the risk of the solution not persisting is **0.03%**.

Secondly, I discount for the probability of the problem being counterfactually solved (i.e. fungal infections declining due to the intervention of other actors or else due to structural changes).

On the one hand, fungal infections are actually likely to *increase* over time due to various factors outlined by Casadevall (e.g. more people becoming immunocompromised due to modern medical therapies involving suppressing the immune system, and climate change selecting for temperature-resistant fungi that can infect mammals like humans). I model this increase as a function of two factors. One, the expected rise in infections from more people becoming immunocompromised, which is in turn a function of the rise in organ transplants (seemingly the primary driver for increased demand in immunosuppression drugs) and the proportion of transplants that suffer infections. And two, the per annum expected increase in fungal infection due to climate change, which is in turn a function of the per annum chance of a new fungal infection like Candida Auris emerging due to climate change, and the number of Candida Auris cases as a percentage of total fungal infection cases, as extrapolated from US data.

On the other hand, fungal infections can also be expected to decrease as economic growth brings improved sanitation, nutrition and health care. Using the difference in fungal disease

prevalence rates between rich countries and LMICs, as well as how long it will take LMICs to catch up to the prevailing wealth of rich countries, I calculate the expected decline in the fungal infection rate over time. Meanwhile, in terms of culture – the other big area of potential structural change we have to consider – there does not seem to be any reason to think this will affect infection rates one way or the other.

Moving beyond structural factors, various agents (i.e. governments, charities, businesses) do not seem to be committing much resources to fungal infections: (a) fungal infections are seemingly neglected by health authorities per Kainz et al; (b) of the big charitable foundations, Wellcome does fund some antifungal research, but it does not appear to be especially significant; and (c) biotech companies seem not to have committed much resources or made much progress on antifungal drugs over the last 20 years. The role of agents in actively solving this problem seems very minor, and I subjectively rate this as having 0.001 the impact of the structural decline.

Overall, I take the rate of counterfactual solution to be the negative epidemiological trend less the positive economic and agentic trends, which sums to **0.41%**.

Thirdly, I discount for the probability of the world being destroyed anyway (i.e. general existential risk discount). Here, I factor in the probability of total nuclear annihilation, since the benefits of saving people from fungal disease in one year is nullified if they had already died in a previous year. For the exact risk of total nuclear annihilation, I take it to be one magnitude lower than the risk of nuclear war itself, since nuclear war may not kill everyone. For the probability of nuclear war, I use the various estimates on the probability of nuclear war per annum collated by Luisa, but with accidental nuclear war factored in, and then calculate a weighted average that significantly favours the superforecasters. The reason for this is that (a) the estimate of the probability of intentional nuclear war based on historical frequency is likely biased upwards due to historical use being in a MAD-free context; (b) the probability of accidental nuclear war based on historical close calls is highly uncertain due to the difficulty of translating close calls to actual probabilities of eventual launch; and (c) experts are notoriously bad at long-range forecasts, relative to superforecasters. Meanwhile, I do not take into account other existential risks like supervolcano eruption and asteroid impact, since the chances of those occurring at all is very marginal per Denkenberger & Pearce, let alone the chances of such events killing everyone and not just most people. Overall, therefore, I treat the general existential risk discount to be just the risk of nuclear war but adjusted a magnitude down (i.e. **0.07%**)

Fourthly, I apply a broad uncertainty discount of **0.1%** to take into account the fact that there is a non-zero chance that in the future, the benefits or costs do not persist for factors we do not and cannot identify in the present (e.g. actors directing resources to solve the problem when none are currently doing so).

Value of Outcome: Overall, the raw perpetual value of eliminating fungal infection deaths is **$7.77 * 10^9$ DALYs**.

Probability of Occurrence: Unlike longtermist problems, there is no uncertainty that this is an actual problem -- fungal diseases cause considerable morbidity and mortality globally. Hence, I just assign a **100% chance** to fungal infection being an actual problem that harms people.

Expected Value: Overall, the expected value of eliminating fungal infection deaths is just **7.77 * 10^9 DALYs**.

Expected Benefit: Eliminating Fungal Infection Morbidity

Even when not fatal, fungal infections can cause disability and suffering, and I model the benefit of eliminating such morbidity in the following way.

Moral Weights: I take the value of averting fungal infection morbidity to be equivalent to **0.051 DALYs** – this employs the disability weight for infectious disease (acute episode, moderate).

Scale: As with how I approach estimating the deaths from fungal infections, for morbidity I consult three separate sources – Brown et al (2.08 million cases of severe fungal infections per annum); the European Journal of Clinical Microbiology and Infectious Diseases (300 million cases); and GAFFI (13.5 million cases). However, I apply different weights. Beyond penalizing the Brown et al estimate for the lesser availability of studies pre-2013, I also penalize both the Brown et al and GAFFI estimates since they focus on just the most significant fungal infections – which makes them potentially a significant undercount., and is accordingly given less weight. Overall, this translates to around **272 million** cases of severe fungal infections per annum.

Persistence: The same discounts discussed in the section on fungal infection deaths are applied here.

Value of Outcome: Overall, the raw perpetual value of eliminating fungal infection morbidity is **2.3 * 10^9 DALYs.**

Probability of Occurrence: The same probability discussed in the previous section – for fungal infection being an actual problem that harms people – is applied here.

Expected Value: All in all, the expected value of eliminating fungal infections is **2.3 * 10^9 DALYs.**

Expected Benefit: Increased Economic Output

Beyond the health benefits, there are also economic benefits to eliminating fungal infections, which I incorporate into the model in the following manner.

Moral Weights: I take the value of doubling consumption for one person for one year to be **0.21 DALYs**. This is calculated as a function of (a) the value of consumption relative to life from GiveWell's IDinsight survey of the community perspective, as adjusted for social desirability bias, and (b) CEARCH's estimate of the value of a full, healthy life in DALY terms. For more details, refer to CEARCH's evaluative framework.

Scale: I start by calculating the economic burden of fungal infections relative to annual income, per infection sufferer. I look at three separate estimates, and take a weighted average.

The first estimate is Benedict, Whitham & Jackson's. From this estimate of the total economic burden of fungal infections in the US (including direct medical costs, productivity loss from absenteeism, and output loss from premature deaths, but not the economic value of life, as that has already been accounted for), I calculate the economic burden of fungal infections relative to annual income per infection sufferer, by taking cost per infection sufferer and dividing by GDP per capita. Cost per infection sufferer is itself a weighted average of the cost for treatment-seekers (who suffer the direct medical costs) vs non-treatment seekers (who do not). For the calculation of line item costs, I look at the direct medical costs vs productivity loss from fungal infections, and divide through with the relevant population.

The second estimate is Drgona et al's. From this estimate of the per-patient economic burden of Aspergillus and Candida in Europe on a direct medical cost basis, I calculate the economic burden of fungal infections relative to annual income per infection sufferer, by taking cost per infection sufferer in euros, converting it to USD, and dividing by GDP per capita in USD. Cost per infection sufferer is again a weighted average of the cost for treatment-seekers (who suffer the direct medical costs) vs non-treatment seekers (who do not), calculated using the Benedict, Whitham & Jackson US data on the split. For the calculation of line item costs, I look at the direct medical costs provided, but do not model the productivity costs due to the lack of data.

The third and final estimate is Jian et al's. From this estimate of the per-patient economic burden of mucormycosis in China (inclusive of the direct medical cost, direct non-medical cost and indirect cost) in yuan, I calculate the economic burden of fungal infections relative to annual income per infection sufferer, by taking cost per infection sufferer in yuan, converting it to USD, and dividing by GDP per capita in USD. Once more, cost per infection sufferer is a weighted average of the cost for treatment-seekers (who suffer the direct medical costs) vs non-treatment seekers (who do not), calculated using the Benedict, Whitham & Jackson US data on the split. For the calculation of line item costs, I look at the breakdown of direct and indirect medical costs vs total costs inclusive of productivity losses.

In terms of how these three estimates are weighed, three sets of penalties are applied. Firstly, Drgona et al are penalized for not considering productivity costs. Secondly, Drgona et al and Jian et al are penalized for focusing only on specific fungal infections rather than fungal infections in general. And thirdly, the Benedict, Whitham & Jackson and Drgona et al estimates are penalized for being more relevant to the rich world when fungal infections disproportionately hurt LMICs. Overall, therefore Benedict, Whitham & Jackson and Jian et al are much more strongly weighed relative to Drgona et al. The resultant weighted average indicates the degree of consumption doubling per infection sufferer if their fungal infection is treated, and from this we can calculate the total number of equivalent consumption doublings (i.e. **13.1 million doublings**).

Persistence: Same discounts as before are applied.

Value of Outcome: Overall, the raw perpetual value of increased economic output is **$4.57 * 10^8$ DALYs**.

Probability of Occurrence: Same probability as before is applied

Expected Value: All in all, the expected value of increased economic output is **$4.57 * 10^8$ DALYs**.

Tractability

To solve the problem of fungal disease, I consider the potential solution of vaccine development, which I break down into four distinct steps:

- Step 1: Advance market commitment triggering attempts by pharmaceutical companies to develop antifungal vaccines, whether general purpose (i.e. for all fungal infections) or specific to a major fungal disease (i.e. cryptococcal meningitis, pneumocystis pneumonia, disseminated histoplasmosis, aspergillosis, candidiasis, or SAFS)
- Step 2: These attempts at vaccine development succeeding
- Step 3: Countries adopting antifungal vaccines as part of childhood vaccination schedules.
- Step 4: Antifungal vaccines reducing disease burden.

Step 1: To estimate the probability of an advanced market commitment triggering attempts to develop antifungal vaccines, I take both an outside and inside view.

For the outside view, I consult three reference classes. The first is the original AMC for a pneumococcal vaccine. This was a success, and companies did try to develop a vaccine. The second is the AMC for COVID vaccine. This too was successful, and companies did of course attempt vaccine development. Still, attribution here is tricky – presumably, the

pharmaceutical companies would attempt to develop vaccines anyway even without an explicit AMC, though it is also important to note that this would be under the implicit understanding that governments don't want their citizens to die from COVID and hence will buy such vaccines in the future (i.e. an effective AMC, albeit implicit). The third reference class is the ongoing AMC for carbon removal technology. For the February 2022 call for proposals, there were 75 expressions of interest, of which 26 were invited to make a formal application, and of which a final six were selected for purchase – clearly, companies are responding to the promised funding. Overall (while this is immaterial in a context of all reference frames converging on 100% success) I create a weighted average to calculate the chances of success; I penalize the carbon AMC reference frame for being of weaker relevance to the epidemiological context – yielding an estimated probability of 100% for an advanced market commitment triggering attempts to develop a vaccine.

For the inside view, I reason that given the profit motive (but also the technical feasibility concerns that the pharmaceutical companies will have), there will be perhaps a 83% chance of an attempt to initiate vaccine development.

For the aggregate view – the outside view adjusted by the inside view – I give more weight to the former than the latter, given that the inside view is subject to the usual worries about inferential uncertainty, yielding an overall estimate of 98% probability.

Step 2: Remember that there are two kinds of vaccines we are considering here – general (i.e. for all fungal infections) or specific to a major fungal disease (i.e. cryptococcal meningitis, pneumocystis pneumonia, disseminated histoplasmosis, aspergillosis, candidiasis, or SAFS). The general vaccine is possible – per Cassone & Torosantucci, a vaccine made up by an algal beta-glucan (laminarin), conjugated with a protein component, protects against infections by different fungi and induces antibodies capable of inhibiting fungal growth.

And to assess the probability of these attempts at vaccine development actually succeeding – whether for the general or specific antifungal vaccines – I take a purely outside view. I do not believe an inside view is useful here, given my lack of understanding of the scientific and technical background of fungal infections and vaccines that would allow an accurate deduction of outcomes.

To form my outside view, I consult three reference classes. The first is the base probability that any vaccine candidate from the pre-clinical development phase reaches market entry. The second is the base probability that a new antifungal drug is developed, which I calculate by taking the number of new antifungals developed (1) and dividing over the number of years (30) since the last new antifungal was developed. The third is the base probability that any new drug entering clinical trials is ultimately approved by the FDA. When I aggregate the three reference classes, I weighed the base rate of success of vaccines more heavily, relative to the other two. Using the base rate of success for antifungals may be problematic insofar as it was calculated based on historical rates of antifungal development, which is a function not just of how hard the process scientifically is, but also of market demand – which is of course

ex hypothesi altered here. Meanwhile, the base rate of success for drugs in general is just less representative as a reference class than the base rate of success for vaccines or anti-fungal medication in particular, since anti-fungal vaccines are what we are interested in here. Overall, we thus have around a 6% chance of success – which I use for the development of both general and specific antifungal vaccines.

Step 3: Even after a vaccine is developed, it will have to be deployed, and countries may not necessarily do so. I assume the best way of deploying an antifungal vaccine is to add it to the list of childhood immunizations, and proceed to take a combined outside and inside view to assess the likelihood of governments doing this.

For the outside view, I look at three reference classes again. The first is simply the adoption rates of various vaccines. For this, I calculate the average uptake rate for 194 countries across the following vaccines – aP (acellular pertussis) vaccine; Hepatitis A vaccine; Hepatitis B vaccine; HepB birth dose; Hib (Haemophilus influenzae type B) vaccine; HPV (Human Papillomavirus) vaccine; IPV (Inactivated polio vaccine); IPV (Inactivated polio vaccine) 2nd dose; Japanese Encephalitis; Measles-containing vaccine 2nd dose; Meningococcal meningitis vaccines (all strains); Mumps vaccine; PCV (Pneumococcal conjugate vaccine); PPV (Pneumococcal polysaccharide vaccine); Rotavirus vaccine; Rubella vaccine; Seasonal Influenza vaccine; Varicella vaccine; and YF (Yellow fever) vaccine. The second reference class, meanwhile, is public support for vaccines, as indicated by the percentage of people in the world that think vaccines are important for children to have. The third reference class is economic ability to deploy a new vaccine, as indicated by the percentage of countries in the world above mean global GDP. In aggregating these reference classes to form an aggregate outside view, I give far higher weight given to the vaccine adoption rates, as it is simply a more direct and relevant figure for estimating the future willingness of countries to adopt antifungal vaccines – yielding a probability of adoption of 59.5%.

Balancing this out is an inside view of the matter, wherein I rate the probability of convincing the WHO to recommend antifungal vaccines for childhood immunization schedules at around 67%, on the basis that the WHO is generally supportive of health interventions (though subject to the constraint of bureaucratic inertia). Moreover, I rate the probability of governments as a whole implementing the WHO recommendation at 33%, on the basis that governments only imperfectly follow WHO guidelines, albeit not to too bad an extent on a matter as uncontroversial as childhood vaccinations. Overall, this yields a probability of adoption of 0.22%.

The combined outside-inside view is formed by giving significantly more weight to the former, again because the latter is subject to worries about inferential uncertainty. In all, therefore, the probability that countries will adopt antifungal vaccines as part of childhood immunization schedules is estimated to be 59.1%.

Step 4: Even after the vaccine(s) are successfully developed and deployed, the disease will not be fully eliminated, since (a) vaccines do not necessarily provide 100% immunity; (b)

uptake isn't perfect (as COVID has surely demonstrated beyond a shadow of a doubt); and (c) the vaccine that we manage to successfully develop might not be the general antifungal vaccine that works against all fungal diseases, but rather one of the specific ones that works only against one of the six major fungal diseases.

To assess disease reduction, I take a purely outside view, again on the basis of lacking the technical expertise needed to make an informed inside view.

To develop the outside view for disease reduction from a general antifungal vaccine, I consult three different reference classes. The first is the average protection rates of various current vaccines. I calculate this indicator of expected vaccine protection, from the average of the following vaccines – chickenpox, dengue, diptheria, flu, hepatitis A, hepatitis B, Hib, HPV, measles, meningococcal, mumps, pneumococcal, polio, rotavirus, rubella, shingles, tetanus, whooping cough, anthrax, Japanese encephalitis, rabies, smallpox, tuberculosis, typhoid fever and yellow fever) – and then modify it by the expected number of people covered (estimated through current childhood vaccination coverage). The second reference class is the rate at which current antifungal drugs prevent infection. I calculate this indicator of expected vaccine protection, from the effectiveness of antifungal drugs for the prevention and treatment of oral candidiasis, and then again modify it by the expected number of people covered (estimated through current childhood vaccination coverage).The third reference class is the rate at which anti-infection drugs in general successfully fight off disease. I calculate this indicator of expected vaccine protection from the effectiveness of antibiotics, antiretroviral drugs and antihelminthics, and then once more modify it by the expected number of people covered (estimated through current childhood vaccination coverage). In aggregating these three reference classes, I give much higher weight to the vaccine and antifungal reference classes, as the success of anti-infection drugs in general is just less representative as a reference class for antifungal vaccines, which are what we're interested in. That said, the rates don't vary that much, which makes sense – they wouldn't have been approved for general use if their effectiveness were outside the range of what's conventionally considered sufficiently effective. In any case, the aggregate outside view estimate of disease reduction from a general antifungal vaccine is 63%.

For disease reduction for each of the potential specific vaccines (i.e. cryptococcal meningitis, pneumocystis pneumonia, disseminated histoplasmosis, aspergillosis, candidiasis & SAFS), I simply take the headline proportion of disease reduction for the general antifungal vaccine, and then adjust downwards based on the fraction of fungal infections that are that specific disease. This yields the result that a cryptococcal meningitis vaccine will achieve 7% overall diseases reduction; a pneumocystis pneumonia vaccine will achieve 10%; a disseminated histoplasmosis vaccine will achieve 3%; an aspergillosis vaccine will achieve 37%; a candidiasis vaccine will achieve 14%; and a SAFS vaccine will achieve 8%.

Putting the estimates across all four steps in the theory of change together (i.e. probability of an AMC triggering attempts to develop both general and specific antifungal vaccines, the probability of successful vaccine development, the probability that countries will adopt

antifungal vaccines as part of childhood immunization schedules, and the disease reduction from vaccine deployment), we see that the expected proportion of disease reduction from an advance market commitment to both general and specific antifungal vaccines is 5%.

As for the cost of the AMC – I calculate this total cost to be the sum of (1) total baseline dose cost and (2) total deployment costs. For total baseline costs, I calculate that as a function of (a) individual baseline dose cost, as estimated from the original pneumococcal AMC dose cost (i.e. pricing at marginal cost of $3.5 save for the first 20% of doses, which are priced at $7 to provide additional subsidies, presumably as an incentive for development and manufacturing); (b) total doses required, which a sum of the initial dose required, as a function of current vaccination rate and global population, plus additional doses required per year, as a function of initial dose required, total population turnover every 73.4 years, and the appropriate time discounts; and (c) the probability that a successful vaccine is even developed. Meanwhile, total deployment costs is calculated as a function of (d) individual delivery costs, as estimated from COVID figures, which are around $1.66 per dose; (e) total doses required, as calculated in the manner already described; and (f) the probability of countries deploying the successful vaccine. Total costs are estimated to be 48.5 billion USD. Note that this is the cost in expectation – actual costs (and actual benefits) will turn out to be very different depending on whether the vaccines are successfully developed and deployed.

Consequently, the proportion of the problem solved per additional USD 100,000 spent is around **0.0000001**.

Marginal Expected Value of Vaccine Development for Fungal Infections

Combining everything, the marginal expected value of vaccine development for fungal infections is **1,104 DALYs per USD 100,000 spent**, making this 2x as cost-effective as a GiveWell top charity.