Exploring the broader economic benefits of prospective group A strep vaccination

Phase I: a cost-of-illness study of rheumatic heart disease in Fiji and New Caledonia, and invasive group A strep in the UK and US

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The World Health Organization

by the
Harvard School of Public Health
Boston, MA

in collaboration with the
Center for International Child Health,
University of Melbourne,
Melbourne, Australia
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EXECUTIVE SUMMARY

Group A strep (GAS) is a common infective agent that causes the widest range of clinical disease in humans of any bacterium. There are an estimated 18 million people currently suffering from a serious GAS disease – such as invasive GAS disease, acute rheumatic fever (ARF), and acute post-streptococcal glomerulonephritis (APSGN) – with over 1.7 million new serious cases per year and 500,000 deaths annually. The burden of serious GAS disease is found predominantly in developing countries and impoverished populations living in wealthy countries. There are currently two GAS vaccines in the pipeline: a 30-valent vaccine and the ‘J8’ vaccine that aims to target a conserved portion of all GAS strains. Both are in pre-clinical phases.

Despite the burden of GAS disease and the push for vaccine development, there exists a dearth of data on the economic impact of GAS disease or prospective vaccination. Insofar as policymakers rely on the results of economic evaluations to guide health-spending priorities, a lack of data on the economics of GAS vaccination could delay or limit the uptake of a licensed vaccine. Assembling data on the economic benefits of GAS vaccination now could help to strengthen the case for development and delivery of the vaccination going forward.

Recent literature suggests, however, that existing economic evaluations of vaccination have adopted a narrow perspective that fails to account for a host of vaccination-mediated productivity benefits. Studies by Professors Bloom, Canning, Bärnighausen and others at the Harvard School of Public Health (HSPH) have suggested a new framework that accounts for a broader set of vaccination-mediated gains, including increased schooling, greater cognitive and physical productivity, and a host of externalities such as herd effects and reduced antibiotic resistance.

Building on Bloom et al.’s work on the broader economic benefits of childhood vaccination, we herein propose to use primary and secondary research techniques to build the evidence on the economics of prospective GAS vaccination in four countries. Health economists from HSPH and GAS disease experts from the University of Melbourne will carry out these efforts.

The study will use primary data to investigate the cost-of-illness of two key GAS disease endpoints – rheumatic heart disease (RHD) and invasive GAS – in Fiji, New Caledonia, the UK, and the US. Data from Fiji and New Caledonia will be used to investigate the epidemiology and costs of RHD, while data from the UK and US will be used to investigate the epidemiology and costs of invasive GAS. The research team will also use secondary research techniques to model the potential impact of vaccination on the epidemiology and cost of RHD and invasive GAS in the four respective settings. Findings from this study will be shared through academic journals and a white paper for policymakers.

In addition to these outputs, the team will also prepare a proposal for further research on the benefits of GAS disease, which could involve partnering with GAS vaccine clinical trials to collect data on broader vaccination-mediated benefits such as school attendance and cognitive development. Finally, the team will assemble a manual or protocol to guide and encourage further work on the broader economic benefits of vaccination.
INTRODUCTION

Background on group A strep.
First discovered in 1879 by Louis Pasteur, the group A beta-haemolytic streptococcus (GAS) is a common infective agent that causes the widest range of clinical disease in humans of any bacterium (1). The most common infections caused by GAS are pharyngitis and impetigo, which occur primarily in children. Worldwide, there are over 100 million prevalent cases of impetigo and over 600 million new cases of GAS pharyngitis per year (2). These two clinical endpoints are considered ‘non-serious’ but can progress to ‘serious’ endpoints such as invasive GAS disease, acute rheumatic fever (ARF), and acute post-streptococcal glomerulonephritis (APSGN). There are an estimated 18 million people currently suffering from a serious GAS disease with over 1.7 million new cases per year and 500,000 related deaths per year (2). The burden of serious GAS disease is found predominantly in developing countries and impoverished populations living in wealthy countries.

Invasive disease refers to infections of GAS in normally sterile sites, such as the bloodstream, bone, or joints. There was an apparent resurgence of invasive infections in the US and Europe in the 1980’s, and today the incidence of invasive GAS disease in developed countries is approximately 3-5 per 100,000 population, with a case fatality rate of 10-15% (3-5). In the US these figures translate to over 10,000 cases with more than 1500 deaths annually (6). Data from developing countries suggest that incidence rates and mortality rates are three-fold higher compared to those in developed countries (7, 8).

Coinciding with the apparent resurgence of invasive GAS disease in the developed world, ARF also re-appeared in middle class areas of the United States (9). Roughly 60-80% of ARF cases lead to rheumatic heart disease (RHD), a chronic cardiac valvular illness. RHD is a major cause of acquired cardiac disease worldwide, with an estimated 15 million prevalent cases. It leads to premature mortality, with an estimated 250,000 deaths per year due to the disease (2).

Control of GAS disease, particularly RHD, is difficult. With this in mind, and with the large burden of disease, there have been renewed calls for a vaccine to prevent GAS disease (10). Vaccines against GAS have been in development since early last century (11). Modern vaccines show great promise in pre-clinical studies and can be categorized into two groups: those that focus on the M protein (the major GAS virulence determinant) and those that focus on non-M protein antigens. Although non-M-protein vaccines such as streptococcal C5a peptidase, GAS carbohydrate, and fibronectin binding proteins have progressed well in preclinical studies, none has progressed to clinical trials.

The most advanced vaccine candidate is a multivalent vaccine based on the aminoterminus region of the M protein. It has undergone phase I and II clinical trials in adults, with good evidence of safety and immunogenicity (12). It is estimated that this 26-valent vaccine will provide protection against 80-90% of invasive GAS and pharyngitis isolates in North America (13). However, there are many circulating types of GAS in developing countries that would not be covered by this vaccine, as described in a recent review (14). Reformulation of this vaccine into a 30-valent vaccine may circumvent these problems. A second M protein vaccine (the “J8” vaccine), based on the
conserved region of the M protein, may potentially provide protection against all GAS strains (15, 16). Clinical trials of this candidate are currently in preparation.

Problem statement.
Despite the burden of GAS disease, there is a lack of data on its economic consequences. Insofar as policymakers rely on economic data when setting health spending priorities, a lack of robust economic information on GAS could delay or limit the vaccine’s introduction into national immunization programs. Thus, building an understanding of the costs and benefits of GAS vaccination now could help to encourage development and delivery of a successfully licensed vaccine in the future.

A broader framework for assessing the economic benefits of vaccination.
Economists and health specialists have long believed that a strong economy is an important foundation of a healthy population. Recently, this wealth-to-health relationship has been viewed in reverse, with many researchers noting that the health of a population is an important ingredient underlying a strong economy. A healthy population can, in theory, work more, longer, and harder; typically has lower fertility and a correspondingly reduced burden of youth dependency; tends to be more and better educated; saves and invests more for the long term because of longer life expectancy; and attracts more foreign direct investment. Recent empirical evidence provides strong support for the view that economies tend to grow significantly faster if their constituent populations are not subject to high levels of morbidity and mortality.

Understanding the health-to-wealth connection is key to economic evaluations of health interventions. In the case of immunizations, existing economic evaluations have usually taken a narrow perspective on vaccination-mediated benefits, focusing on the direct effects of a vaccination on health, avoided medical expenditures, and avoided loss of parental income. Based on recent studies, however, we believe that certain childhood vaccinations can lead to gains in cognitive and physical capacities (17-20). These increases encourage greater educational attainment and enhanced earning capacity later in life. Accounting for these additional benefits is likely to show that some vaccinations have yielded high returns on investment – returns that may be on par with, if not exceeding, returns to spending on primary and secondary education, which is commonly regarded as a highly worthwhile investment. Figure 1 presents a general conceptual framework accounting fully for the benefits of childhood immunization.
As Figure 1 shows, ‘outcome-related productivity gains’ such as increased educational attainment are just one example of the broader set of vaccination-mediated benefits. In addition, improved child health and survival due to vaccination programs may also lead to changes in parents’ decisions (e.g., increasing investment in a child’s education and health) that can improve the long-term economic development prospects of a country. Finally, vaccinations may yield considerable additional external benefits, such as protecting unvaccinated members of a community against the vaccine-preventable disease or preventing the development of resistance to antibiotics used to treat vaccine-preventable diseases.

A 2008 study by Bloom et al. applied and tailored this conceptual framework to sites in four countries, each of which offered comprehensive coverage data on a range of vaccinations as well as other datasets related to outcomes of interest (i.e., educational attainment, cognitive function scores, etc.). The four study sites are Bangladesh, Canada, Mexico, and South Africa. Results show that in both Bangladesh and South Africa, vaccination against measles is correlated with greater educational attainment (21, 22); data from Mexico suggest that vaccination with the pneumococcal conjugate vaccine yields short-term gains in cognition. Both of these findings are likely due to

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reductions in disease-specific sequelae. Results from Canada demonstrate strong household-level herd effects, which could further guide and inform spending decisions in resource-poor settings. All of these findings support the idea that the benefits of immunization extend far beyond reductions in morbidity and mortality and associated medical care costs. Indeed, vaccinations have considerable potential to facilitate income growth and economic development.

**Objectives of proposed research.**
Building on Bloom’s earlier work on childhood vaccinations, we herein propose to begin exploring the broad set of economic benefits related to prospective GAS vaccination. We propose a study with the following aims:

1. Tailor the Bärnighausen et al. conceptual framework to the GAS scenario, and take stock of the existing literature on the economics of GAS disease and vaccination;

2. Use primary research techniques to demonstrate the cost-of-illness of RHD in Fiji and New Caledonia, and invasive group A strep in the US and UK (addresses categories 2 and 3 in figure 1);

3. Use secondary research techniques to model the impact of two prospective GAS vaccinations on GAS epidemiology and the subsequent (reduced) cost-of-illness of RHD and invasive GAS in the four respective sites, to assess the savings that can result following vaccine introduction;

4. Draft a proposal for future research on the benefits and costs of prospective GAS vaccination (e.g. categories 4-6 in figure 1); and

5. Document processes required to build an understanding of the broader economic benefits of vaccination, to guide and encourage further research in this domain.

**Significance of research.**
While the forthcoming GAS vaccine is intended to prevent GAS-related disease and death, too high a price tag could limit uptake, especially in developing countries where the majority of people who would benefit most from the vaccination reside. An understanding of the full value of the GAS vaccination could therefore serve as an important and potentially decisive input for policymakers as they review costs and decide whether to introduce the vaccine into routine national immunization schedules.
METHODS

The proposed study will draw on data from the four countries for use in two exercises: a modeling exercise that examines the impact of potential GAS vaccination on the epidemiology of RHD in Fiji and New Caledonia, and invasive GAS in the UK and US; and a cost-of-illness study of RHD in Fiji and New Caledonia, and invasive GAS in the UK and US, in pre- and post-vaccination scenarios. See Figure 2 for a schematic of methods and processes.

Constructing the benefits framework and conducting a systematic literature review. The study will begin by tailoring the Bärnighausen et al. framework to GAS disease (17, 18). The framework will be a highly detailed document that distills the universal set of benefits related to GAS vaccination, including its impact on endpoints not included as part of this study. Disease experts included as part of this study will play a critical role in this stage. The final product will demonstrate the broad set of benefits attributable to prospective GAS vaccination, thereby elucidating the vaccination’s full comprehensive value. No such framework or roadmap for research on prospective GAS vaccination currently exists.

Next, researchers will take stock of the existing literature on the economics of GAS disease and vaccination. Researchers will design and run robust search algorithms in several key databases, including Pubmed, Embase, and Web of Science; algorithms will use both controlled vocabulary (e.g. MeSH) and free-text options. Following review and adherence to pre-designed inclusion and exclusion criteria, researchers will identify articles for full-text review. Key metrics will be extracted from the selected articles, including data on specific inputs to epidemiological or economic models of GAS disease or vaccination. Drawing on the benefits framework for GAS, researchers will draw conclusions regarding the scope and depth of existing economic evaluations of GAS disease.

The entire systematic literature review will be reported on in adherence to PRISMA guidelines (23).

Study populations and data sets for analyses. The analyses will draw on datasets from two Pacific Island countries, Fiji and New Caledonia, to investigate the epidemiology and economics of RHD. Both countries offer electronic health records that detail information on RHD incidence, hospitalization, and related spending. See Appendix 1 for more information on study populations and datasets related to RHD.

For investigations involving invasive GAS, the study will draw on data from the US and UK. Both countries have sophisticated bacterial surveillance systems in place, which can isolate and identify the incidence and effect of invasive GAS. Cost data are unavailable through the database but will be derived from other sources (e.g. hospital records, the literature, other). See Appendix 1 for more information on study populations and datasets related to invasive GAS.

Modeling the impact of prospective GAS vaccination on the epidemiology of RHD and invasive GAS.
At present, there is no licensed vaccine to protect against GAS disease. Thus any discussion of vaccine performance must rely on modeled, not measured, data. This study proposes to model the impact of prospective GAS vaccination on the epidemiology of RHD in Fiji and New Caledonia and invasive GAS in the US and UK (24). The team will use preliminary data on vaccine performance from the literature to develop or modify an existing static model to explore the impact of a vaccine on disease. Categories of model inputs are included in Appendix II, which will be decided as part of the study.

Computing cost-of-illness of RHD and invasive GAS, in pre- and post-vaccination scenarios.
Cost-of-illness studies measure the economic burden of a disease and estimate the maximum amount that could potentially be saved or gained if a disease were to be eradicated. Although only one part of a broader cost analysis, cost-of-illness studies provide important inputs to cost-benefit analyses.

As per standard cost-of-illness studies (25, 26), we will collect data on both direct (medical and non-medical) and indirect costs related to RHD in Fiji and New Caledonia, and invasive group A strep in the UK and US. A list of preliminary cost categories appears in Appendix III. The study perspective, discounting rates, and variables used for sensitivity analysis will be decided as part of the study.

Limitations and challenges to the research plan.
Both disease endpoints present challenges to the analysis phase. For RHD, baseline epidemiologic data in New Caledonia may be less reliable than in Fiji, which is considered highly robust. However, a French cardiologist and researcher will be reviewing the New Caledonia register in detail in 2012 (personal communication, M Mirabel, Bichat Hospital, France). Admission data is also available at the main hospitals in both countries, although admission data at smaller health centers may be less reliable.

Regarding invasive GAS, robust data regarding incidence and mortality rate of invasive GAS disease in the US and UK are available through prospective surveillance programs (ABC and StrepEuro respectively). However, cost data are not available through these databases, and therefore extrapolation from other sources will be required. One potential solution, at least for the US data, would be to seek more detailed cost data from a selected group of sentinel sites (personal communication, C Van Beneden, CDC, USA).

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While the research team aspires to create the most robust and comprehensive model possible, the actual constructs of the model will be heavily influenced by data availability.)
Figure 2. Study plan for examining RHD in Fiji and New Caledonia, and invasive GAS in the UK and US.

<table>
<thead>
<tr>
<th>Framework development</th>
<th>Data collection from in-country sites</th>
<th>Cost-of-illness study (COI), pre-vaccination</th>
<th>Develop and/or apply epi model</th>
<th>Cost-of-illness study (COI), post-vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Develop framework that distills the universe of benefits related to prospective GAS vaccination.</td>
<td>Collect epi and econ data from select databases; clean datasets.</td>
<td>Conduct COI studies in pre-vaccination scenario; the COI will operationalize some of the benefits categories listed in the framework.</td>
<td>Develop and/or apply modified epi model to select countries to examine impact on disease.</td>
<td>Conduct COI studies in post-vaccination scenario to gauge cost reductions; the COI will operationalize some of the benefits categories listed in the framework.</td>
</tr>
<tr>
<td>- RHD data from Fiji and New Caledonia</td>
<td>- Invasive GAS data from UK and US</td>
<td>- COI of RHD in Fiji and New Caledonia</td>
<td>- COI of invasive GAS in UK and US</td>
<td>- COI of RHD in Fiji and New Caledonia</td>
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</tbody>
</table>
DELIVERABLES

To satisfy the core objectives of this study and to reach a wide variety of outlets and audiences, the research team envisions the following eight deliverables:

1. **Bärnighausen et al. framework (2008) tailored to the case of GAS disease.** This framework will outline the narrow and broad set of benefits associated with GAS vaccination and also provides a lens through which to review and classify the existing literature on the economics of GAS disease and immunization. The framework will be highly detailed and speak to a universal set of benefits related to multiple GAS endpoints. No framework of this kind currently exists.

2. **Systematic literature review of existing economic evaluations of GAS disease.** This review will assess the scope of existing economic evaluations of GAS, and may also provide critical inputs to the modeling exercises (e.g. expected efficacy, coverage, or duration of protection of vaccination).

3. **An epidemiological model of the impact of prospective GAS vaccination on: a) the burden of rheumatic heart disease in two Pacific Island countries (Fiji and New Caledonia); and b) invasive group A strep in the US and UK.** This model will forecast the impact of two vaccine products on RHD in Fiji and New Caledonia, and invasive GAS in the UK and US, respectively. (NB: While the research team aspires to create the most robust and comprehensive model possible, the actual constructs of the model will be heavily influenced by data availability.)

4. **Cost-of-illness study of rheumatic heart disease in Fiji and New Caledonia, in pre- and post-vaccination scenarios.** This study will compute the direct (medical and non-medical) and indirect costs associated with RHD in Fiji and New Caledonia. These estimates will be calculated in pre- and post-vaccination scenarios and will address two key categories from Figure 1: ‘health care cost savings’ and ‘care-related productivity gains’.

5. **Cost-of-illness study of invasive group A strep in the US and UK, in pre- and post-vaccination scenarios.** This study will compute the direct (medical and non-medical) and indirect costs associated with invasive GAS in the US and UK. These estimates will be calculated in pre- and post-vaccination scenarios and will address two key categories from Figure 1: ‘health care cost savings’ and ‘care-related productivity gains’.

6. **A series of publications to disseminate findings, including:**
   
   i. **A manuscript for the academic community.** The manuscript will include the systematic review and the conceptual framework, as applied to GAS vaccination. The intention of this paper is to present the framework to the wider scientific community to inform a new conversation about more comprehensive economic evaluations of vaccines, in a manner that is broader and more comprehensive than previous publications.

   ii. **White paper for the policy-making community.** The white paper will be aimed at an audience of policymakers in countries that would benefit from GAS vaccination.
introducing them to the study concepts in a language and manner that is understandable and relevant to their needs and concerns. The paper will present the conceptual framework, discuss the potential costs and benefits of GAS vaccination, explain how to measure/quantify such costs and benefits, and comment on issues or challenges in doing so.

7. **A proposal for future research on the broader benefits of GAS.** The proposal will include methods for building an understanding of the remaining four Bärnighausen et al. categories and may involve a collaboration with the GAS RCT team(s).

8. **Manuals and protocols guiding research on the broader economic benefits of vaccination.** The research team will leverage current and past experiences to construct a variety of documents to encourage and guide further research on the broader economic benefits of vaccination.
**TIMELINE**

We request a 10-month timeframe to complete project activities and deliverables. Specific timelines and deadlines are outlined below:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Deadline</th>
<th>Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compile and clean datasets</td>
<td>2/29/12</td>
<td></td>
</tr>
<tr>
<td>Tailor the Bärnighausen et al. framework to GAS disease</td>
<td>2/29/12</td>
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<tr>
<td>Conduct a systematic literature review of the economics of GAS vaccination</td>
<td>3/31/12</td>
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<tr>
<td>Analyze and synthesize finding from literature review</td>
<td>3/31/12</td>
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<td>Team meeting in Melbourne</td>
<td>3/31/12</td>
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<tr>
<td>Conduct cost-of-illness studies of RHD, pre-vaccination</td>
<td>6/30/12</td>
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<tr>
<td>Conduct cost-of-illness studies of invasive GAS, pre-vaccination</td>
<td>6/30/12</td>
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<tr>
<td>Model the impact of prospective GAS vaccination on RHD and invasive GAS</td>
<td>7/31/12</td>
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<tr>
<td>Conduct cost-of-illness studies of RHD, post-vaccination</td>
<td>8/31/12</td>
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<tr>
<td>Conduct cost-of-illness studies of invasive GAS, post-vaccination</td>
<td>8/31/12</td>
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<tr>
<td>Prepare white paper for policymakers; manuscript for academic community; etc.</td>
<td>10/31/12</td>
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<tr>
<td>Prepare proposal for further work on the economics of GAS vaccination</td>
<td>10/31/12</td>
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<tr>
<td>Draft protocols and manuals for building the evidence on the broader economic benefits of vaccination</td>
<td>10/31/12</td>
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REFERENCES


APPENDICES

Appendix I. Study sites and data sources.

<table>
<thead>
<tr>
<th>GAS endpoint</th>
<th>Possible study site</th>
<th>Disease burden</th>
<th>Available data source(s)</th>
<th>Types of data available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic heart disease</td>
<td>Fiji</td>
<td>• Estimated prevalence (based on echocardiography screening):</td>
<td>• Electronic health information system (“PATIS”)</td>
<td>• ICD-10 coded disease data;</td>
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<td></td>
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<td>• 8.4 cases per 1,000 population</td>
<td>• Rheumatic heart disease register</td>
<td>• Length of hospital stay</td>
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<td>• Unit cost per stay</td>
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<td></td>
<td>• Prescription usage</td>
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<td></td>
<td></td>
<td></td>
<td>• Surgical costs – both in-country and cases sent overseas</td>
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<td></td>
<td>• Secondary prophylaxis program costs</td>
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<td></td>
<td></td>
<td></td>
<td>• Mortality per admission</td>
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<tr>
<td>Rheumatic heart disease</td>
<td>New Caledonia</td>
<td>• Disease burden unknown but anecdotal evidence suggests high burden</td>
<td>• Electronic health information system</td>
<td>• Length of hospital stay</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Rheumatic heart disease register</td>
<td>• Unit cost per stay</td>
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<td>• Prescription usage</td>
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<td>• Secondary prophylaxis program costs</td>
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<td>• Mortality per admission</td>
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<tr>
<td>Invasive group A strep</td>
<td>United States</td>
<td>• Estimated incidence:</td>
<td>• Active Bacterial Core Surveillance (ABC) at the Center for Disease Control and Prevention, Atlanta, USA</td>
<td>• Length of hospital stay</td>
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<td></td>
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<td>• 8,950–11,500 cases annually</td>
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<td>• Length of ICU stay</td>
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<td></td>
<td></td>
<td>• Estimated mortality:</td>
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<td>• Prescription usage</td>
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<td></td>
<td>• 1,050–1,850 deaths per year</td>
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<td>including intravenous immunoglobulin</td>
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<td>• Acute surgical procedures</td>
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<td></td>
<td>• Laboratory tests performed</td>
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<td>• Length of rehabilitation</td>
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<td></td>
<td>• Mortality per admission</td>
</tr>
<tr>
<td>Invasive group A strep</td>
<td>United Kingdom</td>
<td>• Estimated incidence:</td>
<td>• StrepEURO and the Health Protection Agency of the United Kingdom</td>
<td>• Length of hospital stay</td>
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<tr>
<td></td>
<td></td>
<td>• 625 cases (2010)</td>
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<td>• Length of ICU stay</td>
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<td>• Prescription usage</td>
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<td></td>
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<td>• Mortality per admission</td>
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Appendix II. General inputs to epidemiological models of vaccination.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Disease endpoints</td>
<td>Clinical endpoints targeted by vaccine and considered by the analysis.</td>
</tr>
<tr>
<td>Vaccine efficacy</td>
<td>Reduction in incidence of disease among people who have received a vaccine, compared to the incidence in unvaccinated people. The efficacy of a new vaccine is measured in phase II or phase III clinical trials.</td>
</tr>
<tr>
<td>Duration of protection</td>
<td>Length of time for which a vaccine protects against disease (assuming the vaccine was administered appropriately)</td>
</tr>
<tr>
<td>Immunization schedule</td>
<td>Number and timing of vaccine doses required to fully immunize an individual.</td>
</tr>
<tr>
<td>Vaccine coverage rates</td>
<td>Percent of vaccine-eligible population that actually receives the vaccine.</td>
</tr>
</tbody>
</table>
Appendix III. General inputs to cost-of-illness studies.

<table>
<thead>
<tr>
<th></th>
<th>Direct</th>
<th>Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>Non-medical</td>
<td>----</td>
</tr>
<tr>
<td>In-patient care</td>
<td>Transportation⁴</td>
<td>Lost wages</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Within country</td>
<td>Work disability</td>
</tr>
<tr>
<td>Surgery</td>
<td>Outside country</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Relocation expenses</td>
<td></td>
</tr>
<tr>
<td>Out-patient care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

³ Note that some nations are unable to provide care for RHD in country, and must instead transport patients to nearby countries with the appropriate facilities.
APPLICANT PROFILE

Harvard School of Public Health (HSPH).

We are confident that HSPH has the resources, materials, and personnel required to execute this study. Below please find a summary of HSPH’s institutional capacity, followed by a summary of the research team.

a. Institutional capacity

Computer
Harvard School of Public Health (HSPH) staff/faculty PCs have a T1 connection to the internet thus facilitating rapid transfer of files from remote locations. All faculty members in the School of Public Health have access to software and hardware support from the HSPH help desk.

The Department of Information Technology at Harvard School of Public Health operates the Instructional Computing Facility (ICF), which exists to serve the academic computing needs of faculty, fellows and students of the School. ICF provides user assistance and operational support for the computer systems and applications required for all courses and thesis work.

In addition faculty members have access via the at ICF’s Micro Lab to the latest versions of statistical software packages (SAS, GLIM, STATA), advanced graphics and slide production facilities, high speed Laser printers, and pen plotters. Additional software available at the Micro Lab include EpiInfo, Epimap, S- and SPlus. Other data management tools include Paradox 3.4, Lotus, Minitab, Glim, SPSS, DBMS/Copy.

Office
GHP administrative support staff are located in the central office area of the Department. The Department’s facilities are currently undergoing a complete renovation, including work spaces, common areas and a state of the art conference room. There is a centrally located fax machine as well as a high-speed copy machine.

Library facilities
All faculty, students and staff have unrestricted access to the entire Harvard University Library system with over 8 million acquisitions and a full complement of hard copy journals, and electronic databases. Countway Library, the largest medical/health library in the world is physically in the next building.
b. Research team

**Principle Investigator and Project Director**

**Professor David Bloom** is Clarence James Gamble Professor of Economics and Demography and Chair of the Department of Global Health and Population at the Harvard School of Public Health (HSPH). His current research focuses on the interplay among demography, population health, and economic well-being. His 2005 publication (with David Canning and Mark Weston), “The Value of Vaccination”, shed light on a broader series of benefits resulting from childhood immunization; these include, among others, gains in productivity and herd effects for the unvaccinated (19). In 2008 he undertook a successful GAVI-supported study on the value of vaccination using data from Bangladesh, Canada, Mexico, and South Africa. In 2011 he coauthored a comprehensive review of the Hib vaccine in *Vaccine*, entitled ‘Rethinking the benefits and costs of childhood vaccination: The example of the *Haemophilus influenzae* type b (Hib) vaccine’ (17). This review demonstrates how neglected benefits and overestimated costs of the pentavalent form of the Hib vaccine have resulted in an underestimation of its health and economic value. Bloom is currently leading studies that examine the full range of benefits and costs related to HPV vaccination and prospective dengue vaccination.

**Additional Personnel**

**Professor Till Bärnighausen** is a Family Physician and Assistant Professor of Global Health and Population at HSPH. His research focuses on HIV epidemiology, health systems, childhood vaccinations in developing countries, and population health. Along with Bloom and others, he published a 2008 paper on the full range of benefits of the pneumococcal conjugate vaccine (PCV) in South Africa. This conceptual model focuses on the interplay between pneumococcal disease and HIV, thereby highlighting additional health benefits that could result from PCV vaccination. In 2008 he worked with Bloom and others on the South Africa portion of a GAVI-funded study of the value of vaccination; his analyses show that childhood vaccination for measles results in significantly increased educational attainment in primary school-aged children in rural South Africa. The gains in educational attainment will be translated into income data in a subsequent wave of the study. In related studies, he has investigated the role of health workers in ensuring vaccination coverage in developing countries (27), and the impact of a mother’s HIV status on her children’s vaccination status (28). Bärnighausen also served as a co-author of the 2011 *Vaccine* article (17) and contributes to Bloom’s HPV vaccination and prospective dengue vaccination studies.

**Ms. Jennifer O’Brien** is a research consultant to HSPH. Her current research focuses on the economics of vaccination and urban health, and she has previous experience working with EMD Serono, Inc and Bioscale, Inc. She was a key

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4 Contact details for PI:
David E. Bloom
665 Huntington Ave
Boston, MA 02115
Dbloom@hsph.harvard.edu
contributor to Bloom’s 2008 GAVI study and has co-authored publications on the value of vaccination with Bärnighausen and Bloom (18), including the 2011 *Vaccine* article (17). Jennifer has also chronicled the development of key vaccines and components for *iDrugs* and *Expert Review of Vaccines* (29-32). She is currently a consultant to Bloom’s HPV vaccination and prospective dengue vaccination studies.
Center for International Child Health, University of Melbourne.

We are confident that the University of Melbourne has the resources, materials, and personnel required to execute this study. Below please find a summary of University’s institutional capacity, followed by a summary of the research team.

a. Institutional capacity

Computer
Centre for International Child Health (CICH) staff use faculty computers that have high-speed broadband connection to the internet thus facilitating rapid transfer of files from all locations. CICH is physically located within the Royal Children’s Hospital (RCH), one of the world’s premier children’s hospitals. All staff members in the CICH have access to software and hardware support from the RCH help desk.

In addition, staff at the CICH has access to information technology support from the University of Melbourne. Staff at the University of Melbourne provides assistance and operational support for computer systems and applications required for all courses and thesis work conducted at CICH.

Further, staff at CICH have access to epidemiologic and statistical expertise via the Clinical Epidemiology and Biostatistics Unit (CEBU), part of the Murdoch Children’s Research Institute. CEBU is located on campus at the RCH. Through CEBU, staff at CICH has access to the most recent issues of statistical software packages including STATA.

Office
CICH is located on the RCH campus, within the University of Melbourne Department of Paediatrics. As of November 2011, the RCH campus will move to an entire new site, and CICH will be housed within a state-of-the-art office complex. CICH administrative staff sit in a central part of the CICH office space. There is a centrally located fax machine as well as a high-speed copy machine.

Library facilities
All faculty, students and staff have unrestricted access to the entire University of Melbourne Library system which has a full complement of hard copy journals and electronic databases.

b. Research team

**Principle Investigator**
Andrew Steer is a Senior Research Fellow at the Center for International Child Health in the Department of Paediatrics, University of Melbourne. He is a paediatrician and paediatric infectious diseases physician at the Royal Children’s Hospital Melbourne. He also holds honorary research fellow positions at the Murdoch Children’s Research Institute (Melbourne, Australia) and Menzies School of Health Research (Darwin, Australia). He undertook a large US NIH
funded epidemiologic study of group A streptococcal disease in Fiji 2005-2008, considered to be the most comprehensive epidemiologic assessment of group A streptococcal disease in the world to date. He has published widely in journal articles and books on clinical and epidemiologic aspects of group A streptococcal disease, and writes guidelines on the management of rheumatic fever and streptococcal pharyngitis for US, Canadian, UK and Australian authorities. He is currently involved in a global collaboration to advance development of group A streptococcal vaccines.

**Additional personnel**

**Jonathan Carapetis** is Director of the Menzies School of Health Research in Darwin, Australia, which is Australia’s leading indigenous health research center. Professor Carapetis was previously chair of the World Heart Federation Rheumatic Heart Disease Technical Advisor Group 2007-9, and is chair of the Rheumatic Heart Disease working group for the Global Burden of Disease study.

**James Dale** is Gene H. Stollerman Professor of Medicine and Chief of the Division of Infectious Diseases at the University of Tennessee Health Science Center in Memphis, Tennessee, and is the developer of the 26- and 30-valent M protein vaccines.

**Samantha Colquhoun** is a Research Fellow at the University of Melbourne and has worked extensively in the Pacific, particularly Fiji, on rheumatic heart disease epidemiology and control.

**Chris Van Beneden** is staff epidemiologist with the Respiratory Diseases Branch of the Centers for Disease Control and Prevention (CDC) in Atlanta, USA, and heads up the Active Bacterial Core Surveillance program that includes invasive GAS surveillance at the CDC.

**Theresa Lamagni** is Senior Epidemiologist at the Healthcare Associated Infection & Antimicrobial Resistance Department of the Health Protection Agency of the United Kingdom, and is responsible for surveillance of invasive GAS surveillance in the UK.

**Bernard Rouchon** is Director, Agence Sanitaire et Sociale of New Caledonia and is responsible for rheumatic heart disease surveillance and control activities in New Caledonia.

**Mariana Mirabel** is a pediatric cardiologist the Bichat Hospital in Paris, France, who has expertise in rheumatic heart disease echocardiography and who will be assisting Dr Rouchon in rheumatic heart disease control in New Caledonia.