Invasive Pneumococcal Disease and Child Mortality

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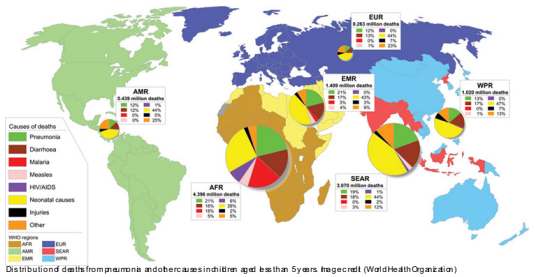
Introduction

Invasive pneumococcal disease (IPD) is the leading cause of vaccine-preventable death in children younger than five throughout the world, and over 90% of the deaths occur in developing countries.[1] It is important to understand the biological mechanisms behind IPD, the components of pneumococcal vaccine development, and the other determinants of child health in order to determine which types of interventions can lower child mortality. Possible interventions include vaccination programs, as well as cultural, economic, and social changes that would improve female status, maternal health, and thus child health. In my thesis, I draw on theories and empirical methods in the fields of health economics, chemistry and public health to analyze the relationship between invasive pneumococcal serotypes, child mortality and female status. The specific aims of my thesis are:

(1) Analyze the relationship between invasive pneumococcal serotypes, pneumococcal vaccines and child mortality using organic synthesis and translational science methods.
(2) Analyze the association between child mortality, invasive pneumococcal serotypes and female status in developing countries using the OLS regression method.



Distribution of deaths from pneumonia and other causes in children aged less than 5 years. Image credit (World Health Organization)

Chapter 1: Organic Synthesis

Beginning as early as 1900, *S. pneumoniae* infections were treated with penicillin, which remained effective until the 1960s due to the development of resistant bacteria. In 1983, the first pneumococcal vaccine, Pneumovax-23, was released and was shown to be effective against nearly 90% of pneumococcal infections; however, this vaccine was only recommended for healthy adults and children over the age of two. In 2000, Pfizer introduced Prevnar-7, and then in 2010 Prevnar 13 was introduced marking the first commercially available conjugate vaccines effective for children under the age of two. These vaccines have been shown to be highly effective against infections caused by *S. pneumoniae* in the United States and other developed countries. However, significant work remains in the development of vaccines against invasive pneumococcal disease (IPD). There are several issues with pneumococcal vaccines. Currently, the vaccines are developed by the growing of harmful bacteria, require lengthy extraction and purification processes, account for only 23/90 possible serotypes, and target serotypes predominately found in developed countries. In this section, I provided background on the pneumococcal vaccines, the chemically synthesized of the constructs of *SPn* serotype 8, and performed a cost analysis on the synthesis of conjugated *SPn* serotype 8 vaccines on a 1.00-gram scale.

Chapter 2: Quantitative Analysis

Little is known about the underlying country-level characteristics that could mitigate the negative effect of invasive *SPn* serotypes on health in developing countries.

This project aimed to analyze:

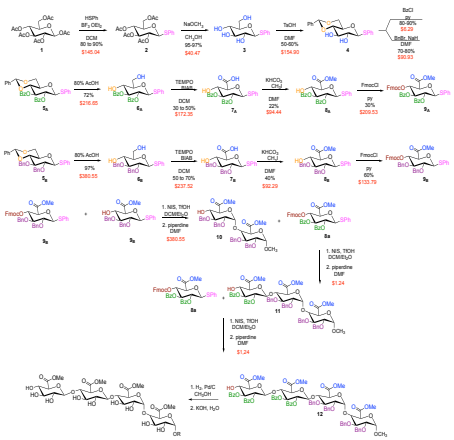
(1) the relationship between invasive *SPn* serotypes and child-mortality rates in developing countries
(2) the impact of gender inequalities on mitigating the serotype's effect on child mortality rates,
(3) the role of pneumococcal vaccines on mitigating the serotype's effect on child mortality rates, and
(4) other economic, political and cultural characteristics that diminish the serotype's effect on child mortality rates.

Methods and Results

i. Invasive *SPn* serotype index and C_{50} SPn were constructed based on a comprehensive literature review. I then merged the invasive serotype data from multiple data sources with country characteristics from the World Bank, World Health Organization, United Nations Human Development Report, Macro Data Guide, and Transparency International.
ii. The presence of invasive pneumococcal serotypes in the country was associated with higher child mortality rate of 20.6 children per 1000 live births ($p = 0.028$) in the baseline model without controls.
iii. When controlling for Gender Inequality Index (GII) and other social, economic, and political characteristics, the invasive serotype coefficient was associated with higher child mortality rate of 7.968 children per 1000 live births ($p = 0.051$).
iv. Using total fertility and female literacy, I found that 1% increase in female literacy ($p < 0.000$) leads to a decrease of 1.2 child deaths per 1000 live births. Additionally, I found a positive relationship between total fertility ($c = 3.962$, $p = 0.075$) and child mortality at a 10% confidence level. Other country characteristics found to have a statistically significant relationship with child mortality were culture fragmentation, political atmosphere, and income.

PS8 Synthesis

The PS8 tetrasaccharide is synthesized from two glucuronic acid building blocks created from readily available glucose and linked together using standard glycosylation procedures. The building blocks required for our study were generated through a benzylidene precursor.



Cost Analysis

I back calculated the amount of materials used to synthesize the 1.00-gram product using the reaction synthesis and theoretical yields adapted from my Experimental Procedure, conducted/extrapolated from the Summer of 2015.

Chapter 2: Quantitative Analysis

Outcome Variable:	Mean	Std. Dev	Definition
Under 5 Mortality Rate	39.27	28.57	Number of children per 1000 live births that die before the age of 5
Explanatory Variables:	**%**		**Definition**
Invasive Streptococcus (ISpn)	0.53		Equals 1 if the prevalent serotype in country is 1,5, and/or 7
C_{50}Spn	0.60		Equals 1 if the top 5 prevalent serotypes in country are found in PCV10
	Mean	**Std. Dev**	
Gross Domestic Product per capita (US$)	6900.25	9429.24	Gross domestic product per capita.
GINI	42.27	6.91	0 complete equality - 100 complete inequality
Corruption Perception Index (CPI)	36.47	13.79	100 highly clean - 0 highly corrupt
Democracy Index	5.71	3.25	0 complete autocracy - 10 complete democracy
Gender Inequality Index (GII)	4.6	0.13	0 complete equality - 10 complete inequality
Female Literacy	74.46	23.50	Total percentage of the female population age +15 that can read and write
Total Fertility Rate	3.08	1.48	Number of children who would be born per woman
Culture	1.4	0.18	0 complete homogeneity, 10 complete fragmentation
Public health spending per capita (US$)	386.86	494.86	Amount of public health spending per capita
Physician per pop	1.08	1.09	Number of doctors per country population
DTP3	86.63	11.23	% of infants <1 vaccinated for DTP3

Empirical Models

(1) Base Model:
Eq (1): $Hi = \beta_0 + \beta_1 * ISPn_i + \epsilon_i$
where ϵ_i is an error term

(2) Political Economic Factors Model:
Eq (2): $Hi = \beta_0 + \beta_1 * ISPn_i + \beta_2 * GII_i + X_{ik}\gamma + \epsilon_i$

where X_i is a vector of political/econ indicators: log GDP per capita (US$), GINI, CPI, Democracy, Culture

(3) Vaccine Model:
Eq (3): $Hi = \beta_0 + \beta_1 * ISPn_i + \beta_2 * GII_i + X_{ik}\gamma + Z_{ik}\mu + \epsilon_i$

where Z_{ik} are vaccine characteristics: C_{50} SPn, DTP3

(4) Exploration of GII Model:
Eq (4): $Hi = \beta_0 + \beta_1 * ISPn_i + \beta_2 * FemLit_i + \beta_3 * TotalFert_i + X_{ik}\gamma + Z_{ik}\mu + \epsilon_i$

where FemLit and TotalFert are individual GII characteristics: Female Literacy, Total Fertility Rate

(5) Healthcare Extension Model:
Eq (5): $Hi = \beta_0 + \beta_1 * ISPn_i + X_{ik}\gamma + Z_{ik}\mu + K_{ik}\kappa + \epsilon_i$

where K_{ik} are health system characteristics: Health Expenditure per capita (US$) and log Physicians (per 1000 pop)

Results

	(1) Base Model		(2) Political and Economic Factors		(3) Vaccine Model		(4) Exploration of GII Model		(5) Healthcare Extension Model	
	Adjusted R^2 : 0.103		**Adjusted R^2 : 0.864**		**Adjusted R^2 : 0.891**		**Adjusted R^2 : 0.888**		**Adjusted R^2 : 0.883**	
	N=38		**N-36**		**N=36**		**N=36**		**N=36**	
	Coefficient	p Value	Coefficient	p Value	Coefficient	p Value	Coefficient	p value	Coefficient	p Value
ISPn	20.556***	0.028	7.968**	0.051	10.624***	0.007	7.900**	0.050	10.552**	0.014
Gender Inequality Index (value)			17.816***	0.000	16.377***	0.000			17.092***	0.000
Female Literacy							-0.806***	0.000		
Total Fertility Rate							3.962*	0.075		
log GDP per capita (US$)			-0.216	0.971	4.986	0.374	15.799**	0.021	4.963	0.458
GINI (with in last 15 years)			-0.854**	0.014	-0.903***	0.006	-0.190	0.549	-0.899**	0.013
CPI			0.401**	0.045	0.371**	0.045	-0.151	0.386	0.421	0.125
Democracy			-1.614**	0.016	-1.582***	0.010	0.101	0.866	-1.655**	0.018
Culture			4.197***	0.001	3.374***	0.004	**0.243****	0.049	3.508*8	0.014
Health expenditure per capita (current US$)									-0.002	0.851
log Physicians (per 1000 population)									2.142	0.738
C_{50} Spn (DTP3) immunization coverage among 1-year olds (%)					-9.404**	0.035	-15.736***	0.001	-8.976*	0.066
					-0.273	0.134	-0.198	0.284	-0.274	0.153

Conclusions and Future Work

Using organic synthesis and translational science methods, I found that synthesizing pneumococcal serotype for vaccine development is lengthy and expensive. Using empirical methods utilized by health economists, I found a positive association between invasive pneumococcal serotypes and child mortality, and that an increased female status, especially female literacy, mitigates the impact of invasive pneumococcal disease on child mortality. Using translational science and health economic methods, I found that pneumococcal vaccines can alleviate the burden of invasive pneumococcal disease on child mortality.

My findings demonstrate the need for a combination of interventions improving women's status in developing countries and investments in PCV10 child immunization programs to reduce child mortality. I would like to expand my research by: (1) Analyzing the current utilization of PCV10 and price per country, (2) Exploring current country level child immunization policies' effects on child mortality rates over time, and (3) Exploring current country level female rights based policies' effects on child mortality rates over time.

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