Recommendations for Improved Infrastructure for Vaccine Distribution in Angola

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Abstract

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Angola is one of the poorest countries in the world. With a high infant mortality rate and 43% of the population under the age of 14, immunization practices will be key to Angola's future economic and social stability. This paper analyzes recent infectious disease outbreaks in Angola's history, relevant vaccines, sources of governmental and external funding for healthcare, and infrastructural and policy challenges tied to the distribution of vaccines, before recommending changes necessary for the improvement of vaccine coverage rates throughout all populations. Key policy changes include improved vital documentation, school-based immunization programs, and in-service training for healthcare workers, while the primary suggested infrastructural change is the use of controlled temperature chain storage rather than traditional cold chain storage during immunization activities.

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Background

Angola is a central African nation with a population of 19 million people. The life expectancy at birth is 55.29 years, and it has the eighth highest infant mortality rate in the world. In addition, the total fertility rate (TFR) is 5.54, the 11th highest in the world (Boslaugh). With nearly half of the population under the age of 14, implementing effective immunization activities will be key to Angola's future economic and social stability because a population that is heavily affected by communicable disease will not be an efficient workforce and cannot support economic growth in the country. Creating an environment in which immunization activities can be sustained might be more complicated than it seems on the surface, though, because as of 2009 there was only about one physician per 6,000 population, and as of 2005 less than one hospital bed available per 1,000 population. This means that there are already few healthcare providers and locations available to administer vaccines, and the few that do exist are primarily tasked with managing the heavy flow of infectious disease patients. Health expenditures make up 3.8% of GDP, one of the lowest rates in the world. As noted by Oliveira, et al., immunization is widely considered to be the most cost-effective way to handle the heavy communicable disease burden of the developing world, and in a country with severely limited infrastructure such as Angola, taking advantage of available preventive therapies is of even greater importance.

From 1961 to 1974, Angola fought a war of independence against Portugal and immediately after decolonization became embroiled in a civil war which lasted until 2002, destroying an estimated 70% of the country's public healthcare infrastructure (Central Intelligence Agency). Despite the 13 years that have elapsed since the end of the conflict, electricity, transportation, and water supply remain underdeveloped, and these structural problems in turn affect the ability of the few healthcare workers in the country to provide

effective care for their patients ("Angola Infrastructure Report"). Currently, Angola is ranked 149th out of 187 countries on the 2014 Human Development Index (HDI), a composite statistic including life expectancy, education, and income indicators that are used to rank countries into one of four levels of human development (Republic of Angola). In its current position, Angola is ranked in the lowest group, categorized as having low human development ("2014 Human Development"). As a developing country with a history of destructive conflict, it is also a hotbed for infectious diseases. In total, the WHO estimates that 79% of years of life lost (YLLs) in Angola are due to communicable diseases (Boslaugh). While not all of these YLLs are vaccine preventable, the majority of them are, and raising vaccine coverage rates would significantly impact life expectancy, particularly for children ≤5 years of age.

History of Vaccine Preventable Outbreaks in Angola

Cholera

Cholera is an acute infectious disease caused by the bacterium *Vibrio cholerae*, and mediated by cholera toxin. It only affects humans, causing severe watery diarrhea that can lead to dehydration and shock. Untreated cholera can lead to death in a matter of hours (Kabir). According to Davidson, cholera is not primarily transmitted person-to-person, but it usually appears in the form of epidemics due to large-scale contamination of water and food supplies. Countries that often suffer from natural disasters that impact water supplies (e.g., tsunamis or hurricanes) are at particular risk for cholera outbreaks. In the last two centuries, seven cholera pandemics have been recorded. Although it is treatable with oral and intravenous hydration therapy and antibiotics, many deaths from cholera occur in developing countries due to lack of access to vaccines or medical care ("Cholera Guidelines"). In 2010,

there were 317,534 cholera cases reported to the WHO. However, due to weaknesses in reporting mechanisms, the WHO estimates that there are actually three to five million cases and over 100,000 deaths related to cholera annually (Davidson). Despite the high incidence rate, there are currently three licensed oral cholera vaccines (OCVs). The two most common vaccines—Dukoral and Shanchol—have been accepted for purchase by the WHO for United Nations affiliated agencies, while the last—mORCVAX (or mORC-Vax)—is produced exclusively in Vietnam (Pape).

In Angola, there are on average over 1,800 reported cases of cholera annually, according to WHO data updated in 2011. In periods of epidemic, however, these numbers can skyrocket. According to the Global Task Force on Cholera Control, between 13 February and 9 May of 2011, Angola reported 82,204 cases of cholera and over 3,000 deaths. And, as stated in the Weekly Epidemiological Record from 26 May 2006, over 50% of these cases were centered around the country's capital and most populous city of Luanda. In late 2011, there was another outbreak in Lukapa District due to contaminated river water, which in two months caused 470 cases and nearly 80 deaths (Moreiera, et al). As of 2013, Angola had the second highest number of cholera cases in Africa after the Democratic Republic of Congo, and the seventh highest case fatality rate (CFR)—the percentage of deaths within a given set of cases—on the continent, at 3.7% (Cholera: Situation).

Meningococcal Disease

The only form of bacterial meningitis that is known to cause epidemics is meningococcal meningitis. The infection is caused by the bacterium *Neisseria meningitidis*. There are currently two major vaccines available: meningococcal conjugate vaccine (MCV4), also known as Menactra, and meningococcal polysaccharide vaccine (MPSV4), or

Menomune (Davidson). Even with therapy, there is a 10% fatality rate and 15% rate of central nervous system damage in cases of meningococcal meningitis, so vaccination is critical (Robbins). The majority of meningococcal meningitis outbreaks worldwide occur in the so-called "Meningitis Belt" of Africa, which stretches east to west from Mauritania to Ethiopia and south to the Democratic Republic of Congo. In recent decades, however, there seems to have been a spread of meningitis epidemics further outside of the belt and into other African countries, including Angola ("Meningococcal Meningitis"). From 1994-2001, there were six meningococcal meningitis outbreaks in Angola with over 8,400 documented cases. Although the outbreaks were dealt with quickly and effectively using mass vaccination campaigns, with the use of prophylactic vaccination these outbreaks could have been prevented altogether (Gaspar, 2001).

Paralytic Poliomyelitis

Poliomyelitis is an acute infection that affects the cells of the central nervous system, often causing paralysis as a result. In 1 in 200 cases of poliomyelitis, this paralysis is irreversible. Humans are the only known carriers of the infection, and it is typically transmitted orally, or via the oral-fecal route (Hoyle, "Poliomyelitis").

According to the WHO, Angola experienced an outbreak of wild poliovirus type 1 (WPV1) as recently as 2010. The outbreak began in 2007, and over the next three years it spread into parts of Angola that had previously been declared polio-free, as well as reinfecting border provinces in the neighboring Democratic Republic of Congo. As of 2010, the Angolan poliomyelitis outbreak was the only outbreak in Africa that was geographically expanding, leading the WHO to name this region the greatest risk to poliomyelitis eradication on the continent ("Polio in Angola"). Angola had previously interrupted transmission and was

declared polio-free from 2002 to 2004, but WPV transmission was eventually reestablished from three distinct strains originating in India. WPV1 subsequently spread throughout central Africa, reversing much of the progress towards eradicating poliomyelitis on the continent (Kidd).

Rotavirus

Rotaviruses are found throughout the world, but are most prevalent in low-income countries where they are the primary cause of severe diarrheal disease in children under the age of five. The World Health Organization (WHO) estimates that over 500,000 children in this age group die each year from vaccine-preventable, but highly contagious, rotavirus.

There are currently two oral live attenuated vaccines, Rotarix and RotaTeq, which as of 2013 had been introduced into 52 countries, with a 14% global coverage rate. The WHO recommends the inclusion of a rotavirus vaccine in all national immunization programs, regardless of rotavirus prevalence, but particularly in countries where rotavirus related diarrhea causes ≥10% of mortality of children aged five and under.

In the 2008 study conducted by Naghipour and Nakagomi, 65% of all rotavirus related deaths appeared to have occurred in just 11 Asian and African countries; one of these countries was Angola. In fact, Angola had an under-five mortality rate of 389 per 100,000, the second highest in the entire group. That means that as of 2008 there were over 8,700 deaths annually of Angolan children under age five due to rotavirus. In addition, it is estimated that one-third of under-five hospitalizations in Angola due to diarrheal disease are caused by rotavirus infections ("Rotavirus Disease"). As of 2013, complications from rotavirus were still one of the most prominent health problems faced by Angolan children.

Tuberculosis (TB) and Multi-Drug Resistant Tuberculosis (MDR-TB)

As noted by the WHO's tuberculosis fact sheet, TB kills more people globally than any infectious agent save HIV/AIDS. HIV/AIDS patients are also 26-31 times more likely to develop TB than the non-infected people, and given that Angola is ranked 21st in the world in regards to the number of people living with HIV/AIDS (2.41% of the total population), and 20th in terms of deaths due to HIV/AIDS, widespread TB vaccination is critical for the public health situation in Angola. Additionally, there have been numerous studies showing co-morbidity of TB and both type 1 and type 2 diabetes. In 2008, Jeon and Murray conducted a meta-analysis of observational studies relating TB to diabetes and found there was a 3.11 increased risk of TB in diabetes patients, with a 95% confidence interval of 2.27-4.26, suggesting that diabetes prevalence is another important factor to consider when creating TB interventions. According to the International Diabetes Federation, nearly 200,000 Angolans between the ages of 20 and 79 suffer from diabetes (for a 2.2% national prevalence rate), emphasizing once again the importance of vaccinating for TB among the Angolan population.

In 2013, nine million people worldwide contracted the infection caused by *Mycobacterium tuberculosis*, leading to 1.5 million deaths. It is estimated that nearly 500,000 of these cases were MDR-TB. Over 95% of TB-related deaths occurred in low- and middle-income countries such as Angola, affecting primarily young adults. TB is a vaccine-preventable infection, but once infected it takes patients a minimum of six months of supervised drug treatment to recover. In cases of MDR-TB, which make up approximately 5% of all TB cases worldwide, patients do not respond to the two most powerful first-line therapies: isoniazid and rifampicin. While still treatable with second-line drugs, cases of MDR-TB can often require as much as two years of costly chemotherapy treatment. The WHO has observed MDR-TB cases in every country they surveyed for TB data, 100

countries in total. In addition, 9% of MDR-TB cases can also be classified as extensively drug-resistant TB, or XDR-TB. In cases of XDR-TB, patients do not respond to first- or second-line drugs, severely limiting the potential for successful treatment ("Multidrug-Resistant Tuberculosis"). This is part of why TB vaccinations are so imperative. The current standard vaccine for TB is called Bacille Calmette-Guérin, or BCG ("Tuberculosis (TB)").

In Angola, the 2013 incidence rate of TB - the number of new cases that year - was 320 per 100,000, leading to approximately 69,000 new cases. The prevalence rate - the total number of TB cases, old and new - was 423 per 100,000, affecting 91,000 people in total. Over 8,000 of these patients died ("Angola").

Current Vaccination Standards, Practices, and Coverage

Background on the National Immunization Program

The National Immunization Program (NIP) was founded in 1979 to provide free and universal vaccination for Angolan children. At its outset, the goals of the NIP were ≥ 90.0% vaccination coverage for TB and neonatal tetanus (TT); ≥ 95.0% vaccination coverage for diphtheria, tetanus, and pertussis (DTP), oral polio vaccine (OPV), hepatitis B (Hep B), Haemophilus influenzae type B (Hib), and measles, plus full coverage for yellow fever (YF) (Oliveira, et al).

1979 was also the year in which the WHO's Expanded Program on Immunization (EPI) first became active in Angola. As stated in the Ministry of Health's Immunization Multi-Year Plan, the goal of the EPI was to vaccinate all children under one year of age for Poliomyelitis, DPT, measles, and TB, as well as pregnant women for tetanus. In the 59 most populous municipalities, a strategy called "Reach Every District," or RED for short, was implemented. A critical part of immunization logistics involves something called the cold

chain, a temperature-controlled supply chain that allows officials to keep vaccines within a certain range of temperatures during transport and storage. In the municipalities that implemented RED, staff were trained in vaccination and cold chain procedures in an attempt to accelerate the process of routine immunization and to improve efficiency in vaccine administration.

Actual Coverage vs. Goal Coverage

Despite the presence of the NIP/EPI over the past thirty-six years, immunization coverage rates have still not reached goal levels. The NIP has come closest to reaching its goal of ≥ 90% coverage against TB with the BCG vaccine: currently, BCG coverage in Angola is at 83%. Other vaccine coverage rates have fallen far short of the goal, with HB and Hib vaccines only at 23% coverage as of Oliveira's 2009 data, which is 72 percentage points below goal coverage levels. DPT, measles, TT, and OPV fared a little better, with coverage rates at 73%, 77%, 78%, and 78%, respectively, with YF-17D falling far below the goal of full coverage at only 40%. Based on the 2015 report from the WHO's Global Monitoring System, rotavirus coverage is low at 18%, with MCV1 coverage much higher at 85%.

National Immunization Schedule for Children (2012-2015)	
Age	**Recommended Vaccines**
Birth	BCG Polio (1)
2 Months	Pentavalent (DTP + HB + Hib) (1) Polio (2) Pneumonia (1) Rotavirus (1)
4 Months	Pentavalent (DTP + HB + Hib) (2) Polio (3) Pneumonia (2) Rotavirus (2)

National Immunization Schedule for Children (2012-2015)	
Age	**Recommended Vaccines**
6 Months	Pentavalent (DTP + HB + Hib) (3) Polio (4) Pneumonia (3) Vitamin A (1)
9 Months	Yellow Fever Measles Vitamin A (2)

Fig. 1

(Source: Immunization Multi-Year Plan 2011-2015)

NIP/EPI Initiatives

In the thirty or so years since 1979, the NIP and the EPI have established a number of initiatives to improve vaccine coverage rates and to interrupt transmission of infectious diseases. According to information found in the Ministry of Health's Immunization Multi-Year Plan, the government has worked in conjunction with the Global Polio Eradication Initiative to hold 45 National Immunization Days, which provide two to six rounds of supplementary immunizations per year. Since 1999, Local Immunization Days have been held sporadically as well. However, in both of these cases, effectiveness has been limited by the quality of the campaigns, which regularly miss 5% of un-vaccinated children. In addition, one study estimates that as many as 25% of all children are routinely missed by healthcare providers, even during supplementary immunization activities (SIAs) that are intended to provide vaccine coverage to members of the population who do not have access to routine immunizations (Polio in Angola). After collaboration with several organizations — the WHO Regional Office for Africa (WHO AFRO), the U. S. Centers for Disease Control (CDC), and the Angolan Armed Forces, to name a few — structured epidemiological surveillance for

acute flaccid paralysis (AFP) was initiated in Angola in 1994 and strengthened after a 1999 polio epidemic.

In 2003, a so-called "Attack Campaign" was held nationally to vaccinate children between the ages of nine months and fifteen years against measles. A first follow-up campaign was held in 2006, and a second follow-up in 2009, both targeting children ≤ five years. Other national immunization campaigns target children between the ages of nine months and five years every two to three years in an attempt to raise coverage against measles.

The data related to TT in Angola is limited and not always reliable due to the large number of births that occur outside of the public health system and the lack of reporting mechanisms. In response, the NIP has created campaigns targeting pregnant women and women of childbearing age in order to raise coverage, and in many municipalities up to 80% of women in these groups have been vaccinated.

State of Infrastructure and the Public Health System

Organization of the Public Health System

According to the Angolan Ministry of Health, the National Health Service in Angola is divided into three levels of care. The primary level is comprised of health centers and health posts, the secondary level is made up of networks of municipal and provincial hospitals, and the tertiary level includes central hospitals with expanded services. As of 2009, there were 2,200 health centers and health posts, 200 municipal and general hospitals, and 9 central hospitals. The distribution of these healthcare providers is uneven, with an estimated 60% of inhabitants having physical access to some type of healthcare. The quality of primary

care varies greatly by region, though, and there is no effective way to communicate and refer patients between the different levels of care.

The management of the National Health Service is similarly divided into four categories. The core of the healthcare system is the Ministry of Health. At the provincial level, operational and technical support is provided by the Ministry of Health to the provincial government. At the municipal level, healthcare management is more executive in nature and is dependent on a municipal health team for administration. Finally, local health units are put in place that are dependent on the municipal administration for leadership.

Within the Ministry of Health, the Immunization Section of the Department of Hygiene and Epidemiology oversees the NIP/EPI. The Immunization Section is broken down into three main departments: the surveillance section, which maintains two technicians; the vaccination section, with three technicians; and the logistics and cold chain section, also with three technicians (see Appendix A). Additionally, there is one EPI supervisor and one technician provided in each municipality, three technicians provided to each province, and one to two clinicians at every health facility who are nominated to complete epidemiological surveillance activities.

Medical Personnel

Angola has a critical shortage of healthcare workers. As of 2009, there were less than 3,000 doctors in the entire country, meaning there was less than one doctor for every 6,000 inhabitants (Republic of Angola). At all levels of service, nurses represent the primary workforce. However, based on a small survey of nurses at a hospital in Luanda that was published in the *International Nursing Review*, this workforce may not be as efficient or

knowledgeable as one might hope. Among the sample of nurses taken at the hospital, 24% considered their education "deficient and believed they were unqualified to take up the function to which they were designated." Over half stated a desire to practice a different profession, and nearly 70% were practicing a different job than they had originally been hired to do. While the majority expressed a wish to continue their education and to become more specialized within their field, economic challenges, physical distance from schools, familial responsibilities, and lack of educational opportunities were all listed as factors preventing further education and training.

This shortage of qualified healthcare workers has created a vacuum in which unqualified medical practitioners have a huge potential market. In one article written by China's Xinhua News Agency, it is revealed that in just eight months in 2004, the Angolan police arrested 200 fake doctors and 140 fake pharmacists in the poor areas surrounding the capital of Luanda. When considering the short time frame and limited geographical area in which these arrests took place, the number of potential fraudulent healthcare workers who likely exist throughout the country becomes a major issue.

Government Funding for Social Welfare

According to *Business Monitor International's* Angolan Infrastructure Reports from the first and second quarters of 2015 (Q1 and Q2, respectively), the Angolan government dedicated one-third of its $55 billion spending plan to social welfare projects, including healthcare, education, and housing. Traditionally, the Angolan government has prioritized economic development over social welfare, but in the 2013-2017 National Development Plan that targets social infrastructure, healthcare expansion will be prioritized after water and electricity access.

One primary challenge for the Angolan economy is its reliance on oil exports to support its social welfare programs and infrastructural development. Seventy percent of government revenues and 90% of export revenues come from oil production, so with the Q2 collapse of crude oil prices and lowered production due to poor oil field maintenance, Angola had to borrow over $1 billion from the World Bank, and President dos Santos cut $14 billion out of the annual budget, thereby dropping social welfare spending by approximately $5 billion for the year. In its Q2 report, *Business Monitor International* predicts that the greatest impact of the suspension of development and transportation projects will not be felt until late 2015 or early 2016.

In addition, not all of the money that is earmarked for social welfare arrives at its intended destination. The Angolan government suffers from a notable lack of transparency across all sectors, and there is very little social accountability holding public officials responsible for their actions within the government. As a result, Angola has faced a long-term struggle with corruption and has had difficulties attaining and maintaining foreign or domestic investment. Budgetary execution is often poor, lowering the growth estimates for the 2014-2018 period by an average of 4%. Widespread inefficiencies within government institutions are one of the primary causes of budgetary problems, despite continued financial support from outside investors, including significant investments from China and Brazil. As the CIA World Factbook notes, healthcare expenditures by the Angolan government only come to 3.8% of GDP, putting it 172nd out of 191 countries listed. Considering the already limited funding provided to this sector, these losses due to corruption and inefficiency create a major stumbling block for improved access to healthcare.

External Funding/Resources for Social Welfare (e.g., GAVI funds)

While in the long term it is hoped that the government of Angola will be able to create and manage a sustainable immunization program without outside aid, many of the vaccines that are currently being distributed in Angola are funded by external organizations, including international governmental organizations (IGOs) (e.g., the United Nations Children's Fund, the WHO), and international nonprofits or non-governmental aid organizations (NGOs) (e.g., PATH, Médecins Sans Frontières).

One of the primary international organizations that supports vaccine distribution throughout the developing world is the GAVI Alliance (also known as the Global Alliance for Vaccines and Immunisation). GAVI partners with both governmental and non-governmental organizations, including the United Nations Children's Fund (UNICEF), WHO, the World Bank, and the Bill and Melinda Gates foundation to provide affordable and sustainable vaccines to populations living in poverty (Gavi). According to the 2013 Annual Progress Report submitted to GAVI by the Angolan government, GAVI funded nearly 14% of Angola's immunization activities that year. The $7.3 million provided by GAVI in 2013 went towards new and underused vaccines (e.g., Rotavirus vaccine), cold chain equipment, personnel, injection supplies (including auto-disable (AD) syringes that eliminate the spread of infection due to re-used needles) and campaign funding.

Based on information reported in the same document, a further $319,665 was provided by UNICEF to supplement campaign activities, and $1.19 million provided by the WHO for routine immunization costs, personnel, and other campaign costs. In total, 2013 government expenditures on immunization, including donated funds, were $53.53 million. Approximately $44.69 million in healthcare funding was paid out by the government itself, and $16.16 million by external donors.

Necessary Conditions for Vaccine Storage and Transport

Live Attenuated Vaccines

Live attenuated vaccines make use of disease-causing viral or bacterial pathogens that have been weakened to the point where they will cause no or minimal disease. These vaccines tend to be more effective than killed whole cell bacterial vaccines, and often stimulate immunogenic responses similar to infection by the wild-type pathogen. Attenuated pathogens are also capable of replicating within host cells in cases where cell-mediated immunity is the desired immune response, and live microorganisms allow for memory cell production due to the continual antigenic stimulation they provide.

But, although live attenuated vaccines are the most effective method of protecting against disease, they also have several suitability issues. Firstly, for patients who have weakened or compromised immune systems (e.g., HIV-infected patients or patients who require chemotherapy), even the weakened pathogens may prove too strong and cause disease rather than the desired immune response. Even in healthy patients, there are rare cases of infection or complications resulting from live attenuated vaccines, the most prominent examples of which are vaccine-associated paralytic poliomyelitis (VAPP) and vaccine-derived poliovirus (VDPV) as a result of OPV use, fatal disseminated TB infection from BCG, febrile seizures from measles vaccine, and vaccine-associated neurotropic disease (encephalitis) from YF-17D. These are all found in less than 0.3% of cases, and some in even smaller quantities. In addition, live vaccines have the potential for being contaminated by outside viruses. Although there is no strong evidence for fetal damage and/or birth defects as a result of immunization with live attenuated vaccines, there is a tendency to avoid immunizing pregnant women with live attenuated vaccines as a precaution against increased risk of fetal damage.

Outside of the limitations on the populations to which live attenuated vaccines can be administered, there are also issues of stability. Because they contain living microorganisms, live attenuated vaccines require careful maintenance of the cold chain and attention to temperature during both transport and storage. Without proper cold chain procedures, the vaccines can become inactive or lose their potency. There are inexpensive vaccine vial monitors (VVMs), produced by PATH in collaboration with the Temptime Corporation, that allow healthcare workers to easily identify vaccines that have been heat damaged. Today, the dime-sized stickers that change color when exposed to certain temperatures are required on all UNICEF and WHO vaccine purchases. While VVMs are useful in preventing the administration of damaged vaccines and the loss of undamaged vaccines and result in an estimated savings of $14 million each year to the global health community, they cannot reactivate the vaccines once they are damaged ("World's Smartest Sticker"). For this reason, live attenuated vaccines can still pose a problem in countries such as Angola where the cold chain is limited and electricity is not consistently available.

Despite these difficulties, live attenuated vaccines are ideal where the infrastructure can support them, and as a result the WHO includes five live attenuated vaccines in its immunization recommendations. The five live attenuated vaccines that should be included in any national immunization program are BCG, OPV, measles, rotavirus, and YF. The Angolan National Immunization Plan currently includes all five of these vaccinations in its immunization schedule for children aged nine months and under (see fig. 1 for full recommended immunization schedule).

Killed (Inactive) Vaccines

Inactivated or killed vaccines are composed of viral or bacterial microorganisms that have been killed prior to use in the vaccine. While inactivated vaccines are incapable of causing disease, they also may not cause sufficient response to create immunity, or the immunity may be short-lived, thus requiring regular boosters. In some cases, inactivated vaccines require several doses to instigate an immunologic response in a patient, which is not an ideal situation in communities where even single-dose vaccine coverage rates are sub-standard. However, because they pose no risk to patients, inactive vaccines are considered safer and can be more widely used than live attenuated vaccines, even in vulnerable populations (e.g., immunocompromised patients). Although there may be minor adverse reactions to inactive vaccines such as redness or swelling at the injection site, serious complications are far more rare than those associated with live attenuated vaccines. Today, many high-income countries are choosing to use inactive vaccines where possible. Inactivated polio vaccine (IPV), for instance, has become far more prevalent in developed countries in recent years, as it counteracts the risk of VAPP and VDPV that is posed by OPV usage. However, IPV is more expensive than OPV, meaning that low- and middle-income countries almost exclusively rely on OPV for their childhood immunizations.

There are two other sub-categories of inactive vaccines other than whole-cell vaccines. Subunit vaccines and toxoid vaccines both contain different portions of the pathogen, but like whole cell vaccines, neither is capable of causing disease. Subunit vaccines, which can be further divided into protein based, polysaccharide, and conjugate vaccines, are much more precise than whole-cell vaccines, containing only the antigenic portion of the pathogen that is necessary to create an immunogenic response. However, it is much more difficult to determine which combinations of pathogens will cause the proper

immune response, and in some cases the elicited response does not prove effective in creating memory cells for future protection against the pathogen. Some commonly used subunit vaccines include Acellular pertussis vaccine (aP), which is usually found as part of the DTaP combination; Hep B; Hib; vaccines for the A, C, W135, and Y strains of meningococcal disease; and pneumococcal conjugate (PCV-7, PCV-10, and PCV-13).

Toxoid vaccines are based on the toxins that are produced by bacteria and cause the majority of disease symptoms. A toxoid is a protein-based version of the toxin that is used as the antigen in toxoid vaccines. They are harmless to humans and cannot cause the disease, making them safe for immunocompromised individuals. The toxoid is usually adsorbed to either aluminum or calcium salts in an effort to increase the immunogenic response. TT and diphtheria toxoid (DT) are both commonly used toxoid vaccines. Like other inactive vaccines, toxoid vaccines are fairly stable when exposed to changes in temperature, humidity, and light.

Inactive vaccines generally have a much better stability profile than live attenuated vaccines because there are no live components to the vaccines. They do not have the same temperature and cold chain requirements as their live counterparts, making inactive vaccines more practical and suitable for use in the developing world where the infrastructure to maintain the stability and potency of a live attenuated vaccine does not always exist.

Rotarix/RotaTeq

Rotarix is an oral, live attenuated vaccine that is produced by GlaxoSmithKline. It is a monovalent vaccine, containing only one human derived strain of the G1P[8] serotype. However, in addition to the G1 and P[8] specificities, Rotarix also contains two neutralizing

viral proteins, VP4 and VP7, a protease-dependent protein and a glycoprotein, respectively. Rotarix has been on the market since 2004 and based on clinical efficacy studies conducted on several continents the vaccine has rates of IgA seroconversion as high as 96% and was nonreactogenic after two doses.

GlaxoSmithKline is the primary supplier of vaccines to UNICEF, and a private partner of GAVI. The company has committed 132 million doses of Rotarix to GAVI over the 2012-2016 period — enough to protect 60 million children from rotavirus-induced gastroenteritis — in addition to promising a price freeze for all developing countries graduating from GAVI alliance support for the next five years (GAVI Alliance). Angola is within the group of countries that could potentially receive benefits from GlaxoSmithKline as part of its participation with GAVI.

RotaTeq is the sole alternative to Rotarix, and is also oral, live attenuated, and pre-qualified by the WHO for use within National Immunization Programs. Unlike Rotarix, it was developed from a bovine strain of rotavirus: WP3, a G6P[5] serotype. RotaTeq also provides protection against the G9P[8] serotype and has been shown to have 74% efficacy against any rotavirus disease. However, it requires three doses and has lower success against rotavirus-associated hospitalizations than Rotarix (O'Ryan, Linhares).

Dukoral/Shanchol

Both Shanchol and Dukoral are oral vaccines containing killed cholera bacteria. Shanchol is a bivalent vaccine containing Vibrio cholerae O1 and O139 cells, while Dukoral is monovalent, comprised of Vibrio cholerae O1 cells in combination with the recombinant B subunit of cholera toxin. Although there are over 200 known serogroups of *V. Cholerae,* the O1 and O139 serogroups secrete similar cholera toxins and are responsible for the majority of

cholera cases worldwide. Currently, Shanchol is the preferred vaccine, but due to compositional issues, both Shanchol and Dukoral have often been considered unsuitable for use in low-resource situations (Kabir).

Shanchol is favored over Dukoral for two reasons: firstly, the long-term protective efficacy of Dukoral has not been clearly established; secondly, Dukoral has not been approved for use in children under 2 years of age who make up many cholera cases in the developing world. Additionally, Dukoral requires boosters every six months for children ≤ five years, and every two years for the rest of the population while Shanchol only requires three year boosters. As of July 2015, the DOVE Project (Delivering Oral Vaccine Effectively) at StopCholera lists the public sector price for Dukoral at $5 per dose, and the price for Shanchol at $1.85 per dose, making Shanchol a more cost-effective vaccine as well ("Comparison").

Oral Polio Vaccine

The live attenuated OPV has been routinely mass-administered since 1961. As of 2011, OPV was the most unstable of the vaccines recommended by the EPI. Ideal cold chain conditions are -20°C, but if maintenance of the ideal cold chain is impossible, it has been determined that OPV can be stored between 2°C and 8°C for a maximum of six months without losing potency (Zipursky, et al.).

Systematic OPV administration throughout the world in combination with AFP surveillance implemented by the World Health Assembly's Global Polio Eradication Initiative helped cut the number of countries in which poliomyelitis is endemic from 125 in 1988 to just seven in 2000. Although there are some risks associated with OPV administration,

primarily VAPP and VDPV, both are rare. Currently, OPV use is necessary to interrupt WPV transmission (Dowdle, et al.).

There is a killed alternative to OPV called IPV. Now common in the developed world, IPV is often too expensive for use in low- and middle-income countries like Angola. However, the WHO recommends that even countries that choose to use OPV for their zero dose (given at birth) and primary series (consisting of the three subsequent doses) include at least one IPV dose in the schedule, co-administered with an OPV dose given at 14 weeks of age (Poliomyelitis).

Pentavalent Vaccine

Pentavalent vaccine is a 5-in-1 shot that protects infants against some of the most prevalent infectious diseases in the developing world: one injection includes the vaccines for DTP, Hep B, and Hib. Currently, Janssen Biotech, Inc., a subsidiary of Johnson & Johnson, is providing the leading pentavalent vaccine, Quinvaxem, to GAVI-eligible countries throughout the developing world. Since 2006, Janssen has supplied over 270 million doses of Quinvaxem at discounted UNICEF prices to developing countries, including Angola (GAVI Alliance).

As noted in Oliveira's article analyzing factors associated with vaccine coverage levels, single dose vaccines typically have far higher coverage rates than multiple dose vaccines, either due to delays in meeting the vaccination schedule, or to difficulties in gaining sufficient access to the healthcare system. In this way, having a pentavalent vaccine is an ideal way to increase coverage rates. However, combining vaccines does come at a cost.

In some cases, vaccines with a high degree of stability of potency, such as those containing diphtheria and tetanus toxoids, are combined with inherently unstable

components, such as pertussis toxin and filamentous hemagglutinin. This combination, which creates the DTP vaccine, is in turn a large component of Quinvaxem and other pentavalent vaccines. Due to differences in thermal stability between components, as well as the interaction of components in the liquid state, these combined vaccines can prove especially difficult to stabilize (Corbel). The challenges that come with vaccine storage and transport for unstable vaccines are multiplied when considering the case of a developing country such as Angola that has limited cold chain infrastructure and trained personnel.

Policies for Improving Vaccine Coverage

Public education

With only 60% of the Angolan population having physical access to a healthcare provider at any level of service, providing effective health education is a major challenge. However, lack of parental knowledge of vaccinations and poor communication with medical personnel are two of the four primary factors which can reduce the effectiveness of otherwise strong immunization campaigns, making education possibly the single most important factor in increasing vaccine coverage rates.

Because of the limited access that many rural or impoverished Angolan families have to healthcare providers, creating clinic-based educational initiatives that involve citizens getting healthcare information directly from doctors in a hospital setting would have an equally limited impact on coverage rates. Instead, community-based educational initiatives should be implemented and targeted particularly towards marginalized (impoverished, rural, and minority) communities. The implementation of community-based initiatives would vary based on the community, but the ideal would be to have educational opportunities available in

a community gathering place. One common example would be a school, because by implementing public health education in a school setting, children and parents from across income levels and professions could be reached. Although educational access is also limited in these communities, the average school life expectancy for children in Angola is still nine years for females, and fourteen years for males. Since the most important age group to vaccinate is children ≤ five years of age, and the average woman in Angola has between five and six children (the TFR is at 5.37), even school-based education campaigns that only reach one child in a given family could disseminate the knowledge necessary to get immunizations to several other children within the same family. Where applicable, it is also possible to create site-specific educational initiatives in community areas outside of the school setting, or in clinical settings when available (in Luanda province, for example). With approximately $10.36 million in expenditures towards health campaign costs each year, of which nearly $800,000 is donated by the WHO and UNICEF, financing should be readily available, even when oil prices and/or production drop, negatively impacting the government's social welfare budget.

Improved Documentation

One of the major challenges both in conducting proper epidemiological surveillance activities and in ensuring the availability of immunizations and immunization activities to the entire population, regardless of urbanization or poverty level, is proper documentation at birth. The majority of children in Angola are born at home, outside of the public health system, and as a result may not have any vital records maintained by the government and/or public health system (birth certificates, medical records, etc.). As they get older, this lack of documentation can prevent them from accessing many government services, including proper

healthcare. By giving lay or traditional healthcare providers (e.g., local midwives) the resources to create this documentation, just as if the child had been born in a clinical setting, the availability of vital records could be vastly increased within a generation. In cases where records already exist, they will ideally be kept either in on-site safes that are temperature-, weather-, and impact-resistant in case of disaster, or at an off-site location that is similarly protected from damage.

In addition to ensuring proper documentation of home births, client-held medical records have been shown to improve vaccine coverage rates in some studies (others have shown this intervention to have little statistical significance, but none have shown any negative impact). Based on the research conducted by Oliveira, et al., 52% of children in Angola had no immunization records whatsoever, so providing those records to parents as the child is immunized could be an effective method of increasing the accuracy of epidemiological knowledge for the government and external NGOs or IGOs, and of verifying that children receive all necessary doses of vaccines on the proper schedule without relying on a reporting system that is known to be weak and unreliable.

Client-held medical records are also an extremely cost-effective solution that would have little impact on the healthcare budget, and there are already similar interventions in place on a global scale for specific vaccinations. When receiving the YF-17D vaccine, for instance, patients in most countries receive an International Certificate of Vaccination that was standardized by the WHO in Annex 6 of its 2005 International Health Regulations and is internationally recognized. Similar prophylactic certificates are available for other vaccines as well, although they are not as commonly distributed to patients in countries that have strong epidemiological surveillance within the public health system. However, these papers only require a stamp or a few handwritten pieces of relevant information that can be easily

filled in by any healthcare provider (vaccine given, date of immunization, vaccine manufacturer, batch number, etc.). With access to these simple records, patients are able to verify their immunization status to healthcare providers, even during SIAs or other activities that take place outside of the normal clinical environment or with healthcare providers other than their normal doctor/nurse. Even for patients who are uneducated on vaccination procedures or are not literate themselves (only 60.7% of the female population is literate, and the total over-15 literacy rate is at 71.1%), ownership of these prophylactic cards/certificates can prevent many of the errors that currently occur during immunization activities due to lack of knowledge of a patient's immunization history. The standards provided for International Certificates of Vaccination in the International Health Regulations would make this a straightforward intervention to implement, requiring very few resources, whether human or otherwise.

School-based immunizations

There are two primary types of immunization interventions involving schools: firstly, the government can mandate certain vaccinations as a pre-requisite for childcare or school attendance. Although minimum immunization requirements for school enrollment have been proven to be effective in increasing vaccine coverage rates in relevant populations, there are some concerns about mandating vaccine coverage in a country that already has low rates of educational enrollment. In Angola, using school attendance as an opportunity to provide health education and access would be the preferred method of intervention over restricting school attendance based on immunization history.

The second method of immunization interventions in schools is more applicable to the Angolan situation. School- or childcare-based immunization programs are multicomponent interventions that combine public health education with vaccine administration. Although bringing members of an already limited population of healthcare providers to schools and childcare centers may seem like a resource-intensive method of improving vaccine coverage, especially in rural areas that do not have health centers nearby, it can be an incredibly effective way of reaching children of all ages and ensuring the administration of necessary vaccine boosters on the proper schedule.

Since the majority of infectious disease cases occur in children, it makes sense to prioritize vaccination to this segment of the population, along with pregnant women who can pass certain diseases such as Hep B to fetuses. Ideally, immunization programs would first be implemented in childcare centers, to provide early vaccination to children ≤ 5 years of age. However, since childcare centers are rarer in Angola than in the developing world, implementation in primary schools would be an important step to provide further access to older children and adolescents.

Training for healthcare workers

As referenced above, training and educational opportunities are extremely limited in Angola due to a number of factors. There is a dearth of educational institutions, and even when available, higher education can be expensive in a system where the majority of nursing team members only earn an average of $171 per month, and even the far more qualified registered nurses, who have at minimum a full undergraduate education, barely earn $1100 per month.

In order to improve clinical care, the WHO has created several different training packages, including in-service training for healthcare professionals that is specifically focused on increasing the standard of care given to critically ill children and newborns in low- and middle-income countries. This package was adapted from in-service training used in high-income countries and can be used to provide healthcare workers with basic or advanced modules in neonatal and pediatric emergency health care; trauma care; emergency triage, assessment, and treatment; control of diarrheal diseases; and management of acute respiratory infections. These modules include notes and references, case studies, self-evaluation tools, manuals, and guidelines assembled by professionals from over 15 countries, several NGOs, and the International Pediatric Association (IPA). Analysis of two randomized controlled trials by Kawaguchi and Mori found overall improvement in healthcare practices, including statistically significant reductions in the frequency of inappropriate and potentially harmful practices per resuscitation in the group that underwent in-service training. However, due to the limited data available, in-service training modules as described above are only recommended in cases where they can be implemented in a cost-effective manner. The WHO modules, which were funded by the US EPA Office of Children's Health Protection, are free of charge, can be adapted to last from as little as one day to as long as 40 hours, and are available in English, Spanish, French, and Russian. Training just a few healthcare workers in each hospital or clinic would be a virtually free way to ensure improved standards of healthcare throughout the municipality or province, particularly for children and newborns.

Methods for Improving Infrastructure as it Relates to Vaccine Distribution

Cold chain

The cold chain is one of four primary areas of immunization logistics (the other three being transport, vaccine supply and quality, and immunization safety). It is also arguably the most difficult of the four to maintain the quality of, particularly during SIAs or other immunization campaigns. There are, however, some fairly inexpensive methods of temporarily extending the cold chain both for use in rural areas and for SIAs. Companies including AOV International, CIP Industries, and Termo-Kont Limited produce small and large, short-range and long-range vaccine cold boxes, some of which are available for as little as $3.60 per box, and can keep vaccines within cold chain standards ranging from as little as 14 hours for the short-range boxes to as much as 134 hours for the long-range boxes.

Controlled Temperature Chain

Although the vast majority of vaccines currently recommended by the WHO have only been approved for storage in temperatures between 2°C and 8°C at the highest, there have been a number of studies in recent years testing the potency of vaccines after exposure to temperatures higher than 8°C. This new potential method for allowing vaccines to be transported outside of the traditional 2°C to 8°C temperature range is called the controlled temperature chain (CTC), and has been studied by the WHO alongside other global health organizations such as PATH. In these new CTC environments, vaccines must be carefully monitored during storage and transport, but are generally allowed to reach up to 40°C for as long as four days immediately preceding administration, greatly widening the potential for use in developing countries that lack ready access to ice pack or refrigerated storage.

In 2012, a study was conducted during a vaccination campaign in Benin using MenAfriVac (a meningococcal A conjugate vaccine) in a CTC environment. The pre-qualification by the WHO marked the first time that a vaccine was granted a label variation and authorization for use at ambient temperature in a developing country. In addition to VVMs, a peak threshold indicator that changed color immediately upon reaching 40°C (as opposed to the gradual change of VVM stickers) was placed inside each vaccine carrier to prevent the use of overexposed vaccines. At the end of each day, unused vials were marked with a line to indicate one day of CTC exposure, and then stored at ambient temperatures overnight. During the campaign, 15,570 vials of MenAfriVac were administered to 155,000 patients, with only 18 vials being discarded due to too much time spent in the CTC and none reaching the 40°C temperatures that would set off the indicators. Out of the 21 supervisors and 77 vaccinators surveyed after the campaign, 52.4% of supervisors and 54.1% of vaccinators felt that the CTC posed no risk, and 98.7% of supervisors and 100% of vaccinators indicated that they would prefer CTC to the traditional cold chain during any future immunization campaigns (Zipursky, et al.).

Using a CTC during campaigns as opposed to the traditional cold chain would greatly expand the opportunities for effective SIAs in rural areas. In the case of the traditional cold chain, healthcare workers are often forced to return to urban areas each night to maintain the proper vial temperature, severely limiting their ability to reach rural areas in regions where transportation infrastructure is underdeveloped. The use of CTC instead allows vaccinators to travel with vaccines for days at a time without having to be concerned about returning to an area with refrigeration to maintain the potency of the vials. The Zipursky studies demonstrated at field-level that as long as the WHO's flexible cold chain guidelines are followed, the OPV vaccine (specifically mOPV3), one of the most unstable vaccines

currently in use, is able to be safely transported in extreme and unstable temperatures without a loss of potency more than 0.5log CCID50/dose (the maximum drop in potency allowed by OPV specifications). Similarly, MeniAfriVac was used in a mass immunization campaign outside of the traditional 2-8°C cold chain without adverse reactions. As in the MeniAfriVac study, supervisors and vaccinators widely stated that they were comfortable using OPVs stored in a CTC, assuming they were marked with VVMs. A similar study completed by Juan-Giner, et al., using TT vaccines, demonstrated a ≥95% seroconversion rate in women aged 14-49 with a 95% confidence interval of 5.6%, meaning that CTC storage is also a viable alternative for toxoid vaccines. Most notably, all three of these studies were conducted during SIAs in developing sub-Saharan African countries with infrastructural challenges similar to those found in Angola (two in Chad and one in Benin), demonstrating the feasibility of holding similarly-planned SIAs in Angola.

Conclusions

Decades of internal conflict, lack of transparency within the Angolan government, and high poverty rates have created a situation in which there is suboptimal vaccine coverage throughout most of the Republic of Angola. There is a severe shortage of qualified healthcare workers, government expenditures on healthcare are some of the lowest in the world, and 79% of YLLs are directly attributable to communicable diseases.

There are a number of factors that have prevented higher rates of vaccine coverage, despite the end of conflict and slowly increasing government expenditures on social welfare. These factors include lack of access to primary care providers, weaknesses within the cold chain, lack of vital documentation, poor public health education, and lack of educational opportunities for healthcare providers.

Having considered all of the challenges and limitations of increasing vaccine coverage rates throughout all populations, but with specific focus on marginalized communities in poor and/or rural areas, there are a few interventions that I believe have the ability to significantly impact vaccine coverage rates without a major redistribution of financial resources: use of CTC rather than traditional cold chain storage, implementation of inactive vaccines where possible (e.g., IPV rather than OPV), the employment of client-held medical records and multicomponent school-based immunization programs, and the increase in in-service training for current healthcare workers. All of these methods have the potential to significantly raise vaccine coverage rates throughout all populations in a matter of a few months to a few years. With the exception of multicomponent school-based immunizations, any one of these interventions could be implemented independent of the others, allowing for flexibility within the budget based on oil prices and production. Despite the challenges that have prevented meeting immunization standards to this point, it is possible to begin implementing these interventions within already existing programs and structures, and to do so without requiring any drastic or unrealistic changes to the economy or social welfare budget. When considering that 43% of the population is under the age of 14—almost 8.5 million children—many of whom are currently at risk of death from vaccine-preventable diseases, it is impossible not to consider these solutions as a critical part of any public health program moving forward.

Reflections

As an International Studies major, my background is primarily in the fields of politics and policy. However, I will be completing my graduate work in global health at the University of Edinburgh, and I wanted my research topic to reflect my intended graduate

study. Although the field of global health is very broad, working on expanding access to prophylactic vaccinations in the developing world seemed like an obvious choice to me. Vaccines are a cost-effective way to handle communicable disease, and developing countries carry by far the heaviest burden of such diseases.

There are many countries that could be used in this type of research. The vast majority of regions in the world contain at least one country that suffers from a high communicable disease burden, and even developed countries are starting to see rising rates of infectious disease due to parents opting not to vaccinate their children. In the United States, for example, measles had been completely eliminated by 2000. But, from January to May 2014, 288 cases of measles were reported to the CDC. In total, there have been fifteen outbreaks in the U. S. since measles was eliminated, almost exclusively affecting unvaccinated persons (Gastanaduy, et al.). However, Africa is of personal interest to me, as I spent over five months of last year living and studying in Morocco, and saw firsthand some of the problems faced by people living in poverty there.

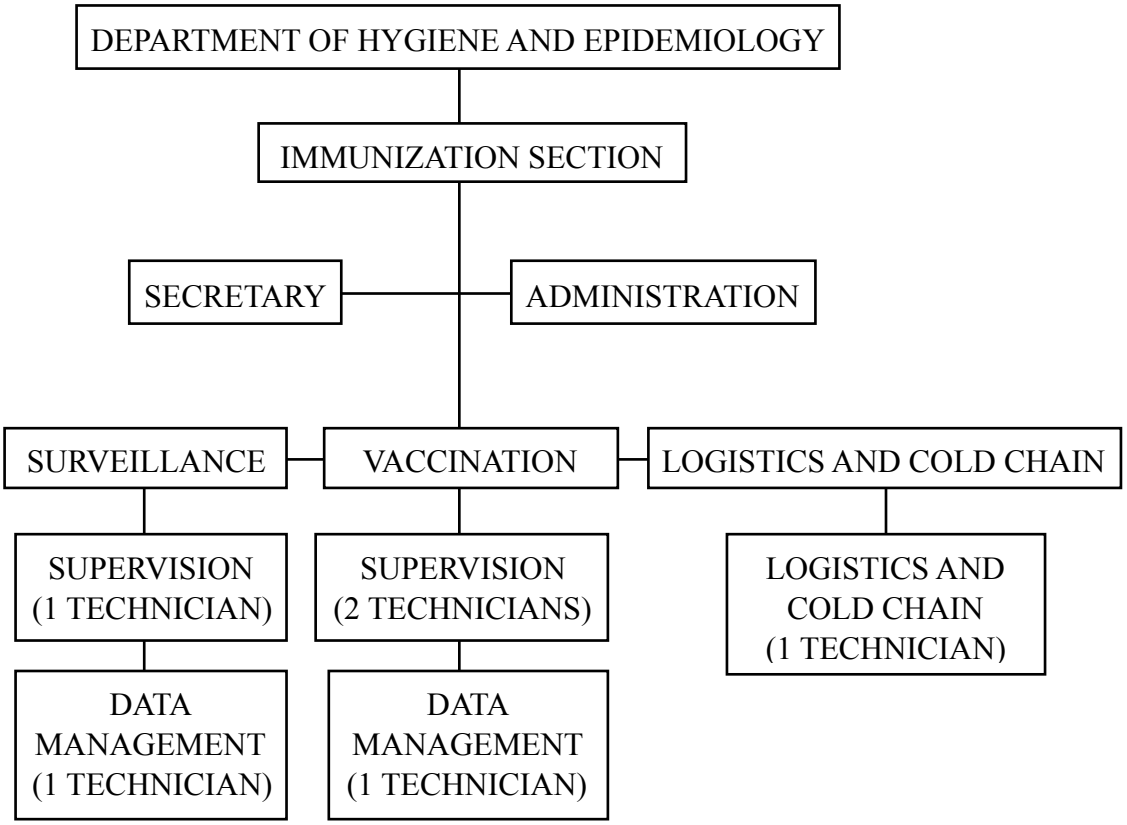
When I started looking through the WHO's Global Health Data Observatory to find the country that would best fit my needs, Angola immediately jumped out to me as a potential option. Not only does it have an extremely high communicable disease burden, but a large number of the diseases that affect the Angolan population have licensed vaccinations available, which was key to what I planned to study. In addition, I knew there would be enough data available via the WHO, UNICEF, and other various NGOs and IGOs to be able to create realistic and implementable recommendations for improvement.

Although there were certainly challenges involved in researching a topic so far removed from my academic background, I do not regret my choice at all. Because Missouri Southern State University does not have a public health school, I opted for a faculty mentor

within the Biology department, and a second reader who is a respiratory therapist. These choices were critical to my success, as I was able to get detailed scientific information on vaccines from a professor of immunology, pathogenic bacteriology, and virology, and a medical perspective on the diseases that I was writing about from a professional who works in a hospital setting.

While the process was incredibly challenging, I am also very grateful to have had this experience. Looking forward towards my graduate program, I know that I will have to write a dissertation, and I am sure that I will be able to use the lessons that I learned from writing this paper in that setting as well. Whether or not I will choose to expand on this exact topic is yet to be determined, but there are certainly many directions that I could choose to go within this topic. In addition to expanding on policy implementation within Angola, I could also apply my research to other countries facing similar difficulties, altering the policy initiatives I listed above to fit into a different cultural and economic situation. It would also be possible to take on this same topic of raising vaccine coverage rates from a different perspective, focusing on raising global coverage rates of a single vaccine, instead of focusing on raising all vaccine coverage rates in a single country. Whether or not I decide to utilize those particular topics during my postgraduate studies, I certainly plan to use my education to expand healthcare access to citizens of developing countries, and I know that increasing rates of vaccine coverage will be a major part of that work.

Appendix A: The EPI Structure



(Source: Immunization Multi-Year Plan 2011-2015)

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