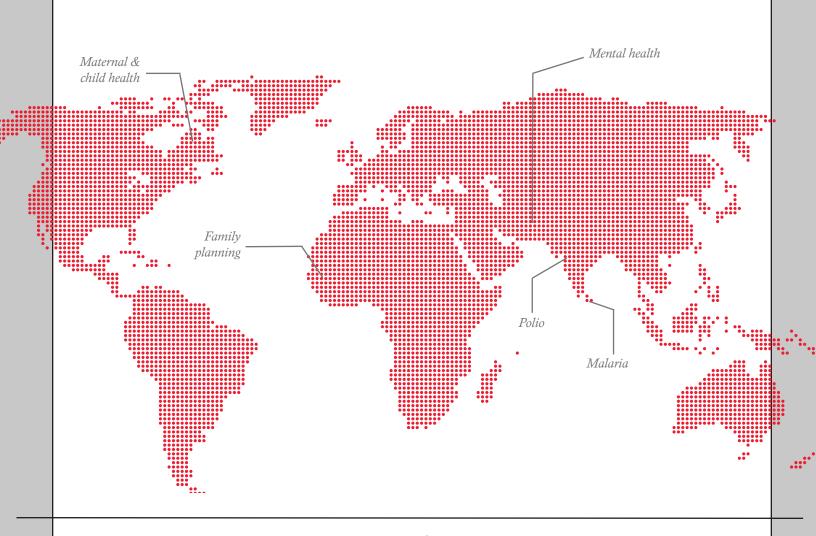
# Global Health Case Studies

A Compilation from PPHS 511 Fundamentals of Global Health







GLOBAL HEALTH PROGRAMS PROGRAMMES DE SANTÉ MONDIALE

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## Introduction

Case studies are a great way of teaching and learning, and they are now an integral part of global health training and practice. Case studies not only teach us about what has worked in global health, but also help shine a light on interventions that have failed, and lessons from such failures that we can use to design better interventions. Millions Saved is an excellent example of a compilation of global health case studies.

PPHS-511, Fundamentals of Global Health, is a relatively new course, first taught at McGill in 2015. This interactive 500-level survey course, now offered in both fall and winter terms, aims to give students the opportunity to broaden their understanding and knowledge of global health issues, including core topics such as history of global health, global health governance, global burden of disease, global health ethics, and global health diplomacy and advocacy. The course covers topics that span the unfinished agenda (e.g. infectious diseases, and maternal/child health), as well as the emerging agenda (e.g. global environmental health, and the emerging epidemic of non-communicable diseases). The highlight of the course, since its inception, is the case studies that student groups prepare, present in class, and often successfully publish.

This ebook is a compilation of case studies published by students in PPHS-511. Some have been published in a student-led journal called <u>The Prognosis</u>, published by <u>McGill Global Health Programs</u>, while others have been published in peer-reviewed journals. In addition to the case studies, this book also provides a template for developing case studies.

I am very grateful to McGill students for their enthusiasm for global health, and for PPHS-511 students for their excellent work on developing these case studies. Vaidehi Nafade and Sophie Huddart are alumni of this course and they have helped compile the case studies and develop the case study template. I am grateful for their superb work and commitment to global health.

I look forward to adding more published case studies to this online book in the coming years!

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TAMING THE TIDE:
STORIES
FROM INDIA

CLAIRE BENTLEY, VANESSA BROMBOSZ, SOFIANNE GABRIELLI, GA EUN LEE, VAIDEHI NAFADE, LINDSAY STEELE, MUHAMMAD WALI This paper examines an innovative sanitary pad manufacturing process in India that uses machines staffed by local women. In considering its financial viability, we assess whether the intervention -- based on a social entrepreneurship model -- adequately addresses the economic and social challenges of menstrual hygiene management in rural regions of the developing world.

## Background

The impact of poor menstrual hygiene management (MHM) on women's health, education, and economic participation has attracted attention only in recent years. The situation is particularly dire in India, where a national survey conducted in 2011 by the research agency AC Nielsen and Plan India found that 70 percent of women cannot afford sanitary napkins (SNs). Of the 355 million women of reproductive age, only 12 percent use SNs. In rural areas, home to 68 percent of the total population, (1) usage is even lower, at around 2 percent. (2) In comparison, 64 and 88 percent of women use SNs in China and Indonesia, respectively. (3)

The social and economic costs of inadequate menstrual protection are significant. A study of 1,033 women and 151 gynecologists found that, in addition to five missed days of school per month among adolescent girls (ages 12 to 18 years), around 23 percent drop out altogether after they begin menstruating. (4) It is estimated that providing women with more opportunities, including facilitating full participation in school and the workforce, could increase India's economic growth rate by 4.2 percent. (5)

Many girls in India begin menstruating with insufficient guidance and information about this important physiological change. (6) Studies have indicated that between 56 and 66 percent of girls have no information about menstruation prior to reaching menarche. (4,5) One study in Rajasthan found that 70 percent of girls believe that menstruation is unnatural. (7) This

lack of awareness is exacerbated by persistent cultural taboos that surround menstruation, which is often "associated with impurity, secrecy, and shame." (6) Based on a study of Delhi slums, adolescent girls who are menstruating are frequently restricted from engaging in certain activities, such as worship (92 percent) and household chores (70 percent). (8)

Rather than purchasing SNs, over 77 percent of Indian women depend on cloths or rags that are often reused, while 88 percent have resorted to other materials such as ashes, newspapers, dried leaves, corn husks, and sand. (9) Furthermore, 48 and 38 percent of girls in urban and rural areas of West Bengal, respectively, reported unsatisfactory cleaning practices. (10) Although there is little data to suggest a causal link between the use of makeshift materials and reproductive disease, poor menstrual hygiene is associated with a higher risk of vaginal infections and pregnancy-related complications.

#### Problem Statement

In consideration of cultural factors, lack of education, and economic constraints, improving MHM requires a multi-faceted approach. Along with the behavioral challenges associated with low literacy levels and menstrual hygiene awareness, the problem is also market-based. There is little incentive for multinational companies to penetrate rural areas given the high transportation costs, difficulties of marketing to diverse and rural consumers, and relatively low profit margins. With scarce resources, commercial SNs are unaffordable and consumer access is limited. Finally,

the cost of traditional machinery necessary to manufacture SNs is out of reach for entrepreneurs seeking market entry.

#### Intervention:

#### Technology

Arunachalam Muruganantham, a craftsman from rural Tamil Nadu, India, was shocked when he realized that his wife would use dirty rags during menstruation so as not to sacrifice part of the family's food budget to purchase SNs. He recognized that an innovative solution was needed to address the MHM needs of rural women. His goal was to design a cheaper alternative to commercial SNs, which cost 4 rupees (INR) at the local pharmacy, a price almost 40 times higher than the value of the raw materials. (12)

After identifying the composition of a typical SN (cellulose extracted from wood fibre), Muruganantham set out to design a simplified and cheaper version of the expensive machine used to convert the wood fibre into cellulose. (12) In four years, Muruganantham successfully designed a semi-automatic assembly line machine using skills he had learned while working in a welding shop. He obtained machine parts through his previous partnerships in exchange for a stake in his company. (13)

Each machine, powered by electricity and a foot pedal, can produce up to 1,000 SNs per day using four simple steps. (14) First, the tough wood fibre is crushed into soft cellulose. The cellulose is then compressed into the desired shape and sealed with non-woven polyethylene. The final step involves sterilization by UV light. Upon receiving a national innovation award by the Indian Institutes of Technology (IIT) and an Indian presidential award, Muruganantham's technology was patented in 2006. (15) In spite of his success,

Muruganantham has not commercialized his product, determined instead to employ a decentralized manufacturing strategy.

## Addressing the Need

Muruganantham established his company, Jayaashree Industries, with the following objectives: increase the usage of SNs, create a sustainable model by providing employment opportunities, and improve health by raising awareness about proper MHM. (16) Muruganantham sells the machines at an affordable price to women's self-help groups (SHGs) in rural communities who receive financing through bank loans or non-governmental organizations (NGOs). Muruganantham transports the machines and raw materials himself, thereby reducing the number of players in the supply chain. Since he is present for the setup of the new machinery, Muruganantham also trains the women to use the semi-automatic machine in the span of three hours. All sites are staffed and managed by an average of ten women per unit. (14)

The women can customize the products they produce by selecting the name and designing the packaging. (12) With over 867 local brands, the products are marketable within many different communities despite regional variances in language and culture. (16) Generally, elderly women in the community, called resident dealers, take on the task of distributing SNs to women while also promoting good MHM practices. Another reason this model is well-adapted to rural settings is that it allows community members to obtain SNs as packages or single units, either by direct purchase or through a barter system. (13)

## Infrastructure and Financing

Muruganantham sells the machine at a starting price of 75,000 INR (about 1,090 USD) with additional

costs for materials and setup. (13) The entrepreneur is expected to pay 10 percent of the initial investment, with bank loans or NGOs covering the remaining 90 percent. Loans may be obtained by members of SHGs, comprised of 10 to 20 women from the same low-resource village. This is done through the pooling of resources, generated by monthly or bimonthly contributions to a common fund, or from formal microfinance institutions and commercial banks that provide group loans. (17) The banks work closely with NGOs to help facilitate lending and educate women about income-based work. (17) Lending to SHGs is also profitable for banks, as the women are then more likely to open accounts and take out loans themselves, with a recovery rate of about 99 percent. (17) This grassroots model allows women to participate not only as consumers, but also as investors, manufacturers, and marketers.

## Evaluation of Impacts and Outcomes:

Investment Details

The Jayaashree Industries grassroots social entrepreneurship model provides women with low incomes the means to start their own businesses and recoup their initial investment in under four years. Becoming a napkin manufacturer requires an initial investment of 371,170 INR (Figure 1).

Estimated monthly expenses are 84,775 INR, which include raw materials, labor, and administrative ex-

penses. Estimated monthly revenues are 100,000 INR. This is based on the production of 5,000 packets per month (the quantity that one machine can produce) at 20 INR per packet (the recommended retail price). This means that manufacturers can expect to make a monthly net profit of 15,225 INR, a profit margin of 15 percent (Figure 2).

Expenses	Value (Rs.)
Raw Materials*	51,275
Labor*	30,000
Administrative Expenses*	3,500
Subtotal	84,775
Revenues	
Napkin Sales	100,000
Subtotal	100,000
Net Profit	15,225
Profit Margin	15%

Figure 2: Expected Monthly Expenses and Revenues Details. \*See Appendix B for additional cost details

Monthly sales and net profit may vary as the microenterprises set their own retail prices and may not follow the recommended pricing. With a 14 percent interest rate on the investment and 10 percent depreciation on machinery, the expected annual net profit is 106,485 INR (Figure 3). Based on these calculations, entrepreneurs can expect to recoup their initial investment of 371,170 INR in 3.5 years.

Details	Value (Rs.)
Working Place Advance	25,000
Machineries, Installation and Training Fees*	237,015
Other Accessories*	5,500
Running Capital for Two Months	98,875
SSI Registration and Other Administrative Expenses**	7,780
Total	371,170

Figure 1:
Total Initial Investment Details
\*See Appendix A for
additional cost details
\*\*SSI Registration
was calculated using
vakilsearch.com

Figure 3: Annual Net Profit Details

Annual Net Profit	Value (Rs.)
Annual Profit	182,700
14% Interest Rate on Investment	51,964
10% Depreciation of Machineries	24,252
Net Profit Per Year	106,485

Low Cost Product

Jayaashree Industries SNs are demonstrated to be lower cost than other popular products on the market in India (Figure 4). The marketplace is currently dominated by Procter & Gamble (P&G) and Johnson & Johnson (J&J).[18] Popular J&J products, the Stayfree Secure Cottony Soft and Carefree Regular, retail for 2.50 INR and 5.25 INR per SN, respectively, with an average per unit price of 3.88 INR. Popular P&G products, Whisper Choice and Whisper Ultra Soft XL Wings, retail for 4.00 INR and 11.14 INR per SN, respectively, with an average per unit price of 7.57 INR. On average, Jayaashree Industries SNs retail for 1.00 - 1.50 INR per unit, less than a third of the cost of commercial products. This range depends on the pricing

determined by the local women.

Employment for Women

Another positive impact of the intervention is the creation of jobs for local women. By 2014, there were over 2,000 machines spread across 887 taluks in India and 14 countries (Nepal, Bangladesh, Myanmar, Sri Lanka, Philippines, Mauritius, South Africa, Zambia, Ghana, Nigeria, Kenya, Malawi, Somalia and the USA), with each machine employing between 10 and 14 women. (16) Accordingly, there are over 20,000 women directly benefitting via employment from this model today. In India, these women make a monthly salary of 5,000 INR, or 200 INR per day for 25 working days per month. (18) These wages are competitive with rural wages in other sectors of India's economy. Based on Indian Labour Bureau data from 2014, average daily wages were 207 and 239 INR in the agricultural and non-agricultural sectors, respectively. (20) The model also offers indirect benefit to over one million "resident dealers" in communities across India. (16) From

Producer	Sanitary Napkins	Cost (Rs.)	Disposable			
Popular Brand in Market*						
Johnson & Johnson	Stayfree Secure Cottony Soft	2.50/ pad	yes			
Johnson & Johnson	Carefree Regular	5.25/ pad	yes			
Procter & Gamble	Whisper Choice	4.00/ pad	yes			
Procter & Gamble	Whisper Ultra Soft XL Wings	11.14/ pad	yes			
Alternatives (Non-Profit	t)					
Eco Femme	Eco Femme Day Pad	236.00/ pad (Available to rural women at subsidized cost)	Washable/Reusuable			
SEWA Rural	Falalin Cloth	10.00/ piece (Subsidized rate)	Washable/Reusuable			
Goonj	My Pad	2.00/ pay	Washable/Reusuable			
Alternatives (For- Profit)						
Jayaashree Industries	Pads	1.00/ pad	yes			
Aakaar Innovations	Anandi Pad	2.50/ pad	yes			
*Price per pad is approximate, calculated based on maximum retail price (MRP)						

Figure 4: Sanitary Napkin Market in India, Price Comparison

2008 to 2012, the number of direct beneficiaries grew from 155 to 5,000, the number of indirect beneficiaries from 45,000 to 1,000,000, and the number of municipalities marketed from 7 to 35. (16) (Figure 5). These numbers represent growth rates of 323, 2,222, and 500 percent, respectively, over the four-year period.

#### Uptake

In India, with sales of \$236 million in 2012 and projected sales of \$442 million by 2017, the market for feminine hygiene products is rapidly expanding at an annual rate of 3 to 5 percent (11,13). In comparison to their competitor Kimberly-Clark, P&G has pursued a more aggressive marketing strategy in emerging markets (22), and their Whisper brand accounts for nearly half of the Indian SN market. (23) While there is no data available on the SN market share of Jayaashree Industries, the rural SN consumer market is largely untapped and vast, and it is expected that their market presence will continue to expand. (13)

Limited data on the usage and acceptance of Jayaashree Industries products has made it difficult to evaluate the impact of the venture. One trial found that women who had previously used commercial SNs were "extremely satisfied" with Jayaashree Industries products. However, it is unclear whether this experience is widespread. (18) Additionally, there is no data about the lifespan of the machines. Given these statistical gaps, it is challenging to assess the uptake of the venture, and an impact evaluation is highly recommended.

### Sustainability

Muruganantham has helped SHGs arrange for bank loans and leveraged government schemes to cover the initial capital required. (13) However, the 99 percent loan repayment rate by SHGs is a positive indicator of its long-term viability. (17) It is unclear whether Muruganantham is gaining or losing money as there is no data available on Jayaashree Industries' net profits. While most of Jayaashree Industries' revenue is from machine sales, it is unclear whether the company also receives a portion of the profits generated by SN sales. Without more data, it is difficult to evaluate the sustainability of Jayaashree Industries with confidence.

#### Reflections:

## Strengths and Limitations

The greatest strength of Jayaashree Industries is its ability to respond to the unique needs of the rural market and spread throughout regions previously untouched by multinational corporations. Through a multi-pronged approach, Jayaashree Industries created a low-cost product as well as a business model. First, their innovation has enabled rural women to practice proper MHM and offers them the opportunity to run their own SN manufacturing businesses with high returns on investment. Second, Jayaashree Industries recognizes the importance of cultural sensitivity by allowing women to market and distribute SNs themselves in a manner that suits their communities. Third, as an intervention based on grassroots entrepreneurship, the model is more self-sustaining than an external intervention from other actors, such as the govern-

Beneficiaries	2008-2009	2009-2010	2010-2011	2011-2012
No. of primary/direct beneficiaries	155	875	1,200	5,000
No. of secondary/indirect beneficiaries	45,000	150,000	280,000	10 Lakhs
Total no. of municipalities marketed	7	16	25	35

Figure 5: Growth of Direct and Indirect Beneficiaries of Jayaashree Industries from 2008 - 2012.

\*Notes: 10 Lakhs = 1,000,000

ment or NGOs. Fourth, an emphasis on transparency has allowed social entrepreneurs in other countries to access the project details of Jayaashree Industries on public domain (individuals in 110 countries have already done so), permitting replication and expansion on a global scale.

Although the grassroots model offers numerous strengths, it also presents certain limitations. First, Muruganantham's resistance to commercialization in favor of protecting local SN manufacturing limits the ability to scale-up the project, while production and marketing costs continue to rise. It may also become increasingly challenging for Jayaashree Industries to compete with multinational corporations who have started to realize the untapped potential of the rural market. For example, there is already evidence that P&G and Kimberly-Clark are designing programs to educate school-age girls about MHM. (11) Second, the sustainability of the intervention may be adversely affected by variations in the ability of SHGs to secure and properly manage loans. Third, while the machines are designed to be simple to assemble and maintain, the operators may lack the skills necessary to do so. Finally, while Jayaashree Industries recognizes the importance of coupling knowledge-sharing with marketing, there does not appear to be a concrete and effective education strategy that could overcome MHM-related stigma.

#### Future Directions

Within India, Muruganantham's ultimate goal is to achieve 100 percent uptake of SNs and provide employment for one million women with the installation of 100,000 units. (24) He also plans to expand outside of India to 106 countries, including Kenya, the Philippines, and Bangladesh through a network of partnerships. (12) Given the logistical limitations of supplying

the machines himself, Muruganantham may need to outsource machine assembly and training to continue expansion on a national scale. He is also seeking to cultivate partnerships with NGOs, corporations, organizations, banks, and governments to facilitate financing schemes for rural women interested in participating as entrepreneurs. Finally, he hopes to expand the line of products offered to include customizable SNs that vary by size and level of absorbency, as well as other types of products, such as diapers for children and adults. Although Muruganantham is currently adamant in his opposition to commercialization, (25) whether his stance will endure remains to be seen.

#### Lessons Learned

The Jayaashree Industries model presents a useful case study to understand how social enterprises can help to address previously neglected health needs in rural settings. Muruganantham was able to fill a gap left by multinational corporations by harnessing his experience and understanding of the social and cultural context of his target population. Whether this grassroots microenterprise model proves to be sustainable will provide important lessons about the value of engaging local stakeholders, the obstacles to raising awareness about heavily stigmatized health topics, and the challenges of scale-up inherent in a country as large and culturally diverse as India.

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Appendix A Total Initial Investment - Additional Details

Machineries and Other Accessories

Machineries, Installation and Training	Qty	Rate	Total (Rs.)
De-fiberation Machine	1	26,800	26,800
Soft Touch Sealing Machine	2	28,000	56,000
Belt Napkin Making Machine Length Sealing	1	20,500	20,500
Belt Napkin Making Machine Side Sealing	1	17,500	17,500
Pneumatic Core Forming Machine	1	65,000	65,500
Pneumatic Core Dies	2	1,875	3,750
U V Treat Unit	1	10,400	10,400
VAT 14.5%			29,065
Packing and Handling Charges			2,500
Installation and Training Fees			5,000
Subtotal			237,015
Other Accessories			
Weighing Scale (to Weigh Wood Pulp)	1		3,000
Work Table	2		2,000
Plastic Buckets and Trays	5		500
Subtotal			5,500
Total			242,515

Appendix B

## Expected Monthly Expenses and Revenues - Additional Details

Raw Materials

Daily Requirements	Qty	Value (Rs.)
Wood Pulp	12.8 Kgs	742
Top Layer	400Mts	672
Back Layer	750 Grams	187
Gum	1.5 Kg	225
Packing Covers	150 Nos	225
Subtotal		2,051
<b>Total Monthly Requirements</b>	25 days	51,275

## Labour

Semi Skilled Workers	Qty	Rate (Rs.)	Salary (Rs.)
Daily	6 workers	200	1,200
Monthly	25 days		30,000

## Administrative Expenses

Monthly Expenses	Value (Rs.)
Rent	1,000
Electricity Bill	1,500
General Administrative Expenses	1,000
Total	3,500

RECLAIMING CHILDBIRTH:

THE INUULITSIVIK
ABORIGINAL

MIDWIFERY PROGRAM

MCGILL UNIVERSITY

PATRICK BIDULKA, ROSEMARY CHUANG, RAMLA BARISE, MIN GI CHO, KEDAR MATE



The Inuulitsivik Midwifery Program was created in response to the inefficient evacuation policy implemented by the Government of Canada in the 1950s. Under this evacuation program, pregnant women from the Nunavik region would be sent to deliver in southern Canadian hospitals, in an effort to decrease the high perinatal mortality rate in this region. Maternal and child health disparities persisted, with Inuit women and their babies continuing to suffer worse health outcomes than the rest of the Canadian population. The Inuulitsivik Midwifery Program, implemented in 1986, is designed to bring birth back to the isolated Nunavik communities. The program is currently based in three main birthing centres located in Puvirnituq, Inukjuak, and Salluit, Quebec. Implementation of the program saw a major decrease in the evacuation of pregnant Inuit women to southern hospitals in Canada. The program is correlated with a decrease in perinatal mortality rates, and increased patient satisfaction. Canada's brutal history of residential schools and attempts at a "cultural genocide" of Indigenous peoples (encompassing First Nations, Metis, and Inuit) have resulted in vast economic and health disparities that are rooted in a multitude of factors. For this case study, the focus will be on Inuit communities in Northern Quebec. A critical evaluation of the Inuulitsivik Midwifery Program, a community-based initiative in response to the Evacuation Policy of the 1970s, will be conducted, followed by concluding recommendations. It is believed that midwifery programs may act as a potential solution to address several relevant Sustainable Development Goals proposed by the United Nations: good health and well-being, reduced inequalities, and sustainable cities and communities (2). This case study examines the impact of culturally sensitive interventions in assisting Canada's most marginalized population.

## Background:

Inuit Communities

The Inuit people have much lower life expectancy relative to other Canadians; Inuit men are at a gap of 10 years in Nunavik compared to non-Indigenous men. The birth rate in Inuit communities is twice that of the Canadian average, which led to a 12% increase in the Inuit population between 2006 and 2011. Within such demographics, it is noteworthy that 25% of all

first-time mothers are under the age of 20 at the time of their first pregnancy (3). The rapid growth of these communities combined with stark health disparities, exemplify major public and global health concerns. It is important to note that data on Indigenous health is widely regarded as inadequate and incomplete; there are several limitations to this case study as there has not been enough meaningful research and data collection performed in these communities (4).

## So What?

From this case study we learn about the importance of having global health solutions that are tailored to the specific needs and context of the communities being served. The Inuulitsivik Midwifery program was established by members of the Inuit community who saw a significant lacking in the way pregnancy and birthing services were administered. The vital take away, that can be applied in many global health contexts, is the significant impact associated with listening to communities, and providing them with platforms through which they can voice their needs and proposed solutions.

Inuit in Canada live in 53 remote isolated communities across regions of Arctic Canada. Health care in these areas consists of limited nursing stations, as well as doctors, dentists and specialists who visit two to three times annually. Nunavik patients in need of urgent and emergency care must be transported by air approximately 1000 km (a four to eight-hour flight) to Montreal, Quebec or Moose Factory, Ontario (5). This is particularly problematic for Inuit women who experience higher rates of complications during pregnancy and have infant mortality rates more than four times the national average (3). As Professor Yves Bergevin, Senior Maternal Health Advisor to the United Na-

tions Population Fund argued, the scaling up of quality services and the targeting of the vulnerable allows us to address poverty and inequity (6).

#### Evacuation Plan

Due to difficulties in recruiting medical professionals to rural Inuit communities, the Evacuation Policy was implemented in the 1970s by the Canadian government. Pregnant First Nations and Inuit women were routinely sent to the south and other regional centres, typically at 36 weeks' gestation, to complete their pregnancies in a medical facility. Women who rejected this evacuation were often deemed uneducated, selfish, and guilty of putting the health of their families at risk. This evacuation policy has resulted largely in "needless isolation, duress and distress for Aboriginal women forced to give birth apart from their partners and families". This situation would indeed be regarded as unacceptable to any other Canadian population (7).

The evacuation plan was partly successful in decreasing stillbirth and perinatal death rates among Indigenous populations; however, by its end, perinatal mortality rates among the Inuit were still two and a half times the Canadian average (8). Women who were separated from the support of family and friends experienced low social support and high stress during the perinatal period, which may increase the risk for many maternal and newborn complications, including premature and small for gestational age infants, and postpartum depression (9, 10). The most significant negative impact is psychological, as demonstrated by mothers who mentioned to researchers that "only their first children were real Inuit, not [those delivered outside the community]" (11). The cultural identity of those born outside Inuit communities is compromised by the evacuation policy, as these Inuit children are denied traditional ceremonies and rites of passage integral to Indigenous upbringing.

#### Before the Evacuation Plan:

Traditional Birthing Practices

Beliefs and traditions based on pregnancy and childbirth vary among Aboriginal communities, and reflect unique views and needs. The Indigenous way of life interweaves medicine and spirituality, representing an interconnection between mind, body, spirit, and emotions - all of which are viewed as essential to optimal health (12). The birth of a child signifies new life and balance between the spiritual and physical worlds (13). Aboriginal birthing practices are an art form that has been passed down through generations, preparing girls to grow into mothers. Extended family members, especially grandmothers, play an important role in the traditionally natural approach to pregnancy and childbirth, as they guide women through the entire pregnancy and childbirth experience. Pregnancy is viewed as a gift from the creator; a woman's ability to give life and raise children is deemed sacred, bestowing upon them authority and respect within Aboriginal cultures (14,15,16).

During pregnancy, Inuit women increase their intake of caribou, muktuk, and seal, while limiting their consumption of berries and aged food based on the sage advice of the elderly women in the community (17). Although their avoidance of berries is based on anecdotal evidence, it coincides with scientific findings suggesting that berries may contain small amounts of alcohol due to natural fermentation, which is harmful to the developing fetus (18). A woman-centred process (19), childbirth is an event eagerly anticipated by the local community. Following birth, ceremonies are conducted to establish familial relationships and strengthen communities (20). The baby is kept in constant contact with the mother, either in the hood of her parka, or nestled in the front of the parka feeding (21).

## Traditional Midwifery

Prior to implementation of the evacuation policy, traditional Aboriginal births were assisted by older, experienced women from the community (21). Because of the cultural familiarity of the Aboriginal midwife, she was able to incorporate various traditional elements

involving spiritual, mental, physical, and emotional health in the community services she provided. Aboriginal midwives were charged with passing moral and ethical values from one generation to the next, in addition to guiding the birthing process (21). In contrast, Westernized evidence-based medicine is based on the biopsychosocial model which views health and disease as an independent entity from other aspects of well-being. An extensive comparison between modern methods of medicine and Indigenous practice was reported by Durie et. al. (2004) which noted that Indigenous knowledge is often discredited on the premise of scientific evaluation, which disregards anything that cannot be supported by empirical evidence. It considers Aboriginal knowledge of social, physical, spiritual, and mental health as inferior, subordinate or irrational superstitions (22). Modern medicine has institutionalized the birthing process, prioritizing birth outcomes and leaving little room for the Aboriginals' spiritual understanding of childbirth (22,23).

## Loss of birth, loss of spiritual life

The evacuation policy, officially implemented in the early 1970s, sought to improve perinatal and maternal health outcomes, using modern science as a supposedly superior knowledge system. The policy was unsuccessful, with large disparities persisting between Aboriginal communities and the rest of Canada (24). Furthermore, the evacuation policy has been reported to have profound spiritual and cultural consequences on Aboriginal communities (25,26). Health Canada, public health officials, and many Aboriginal organizations are now beginning to acknowledge the pivotal role loss of culture has played in shaping the health conditions of Aboriginal Peoples, and have recognized the possible benefits of Indigenous knowledge, language and spirituality in health services for the population (27). The Society of Obstetricians and Gynecologists of Canada (SOGC) also concluded in 2007 that improving prenatal and birth experiences for Aboriginal women should involve "expanding health centres and providing training for Aboriginal midwives within [their] communities" (10). These parallel lines of thought have contributed to the marriage of traditional Aboriginal values with evidence-based medicine, in order to create modern Aboriginal midwifery programs better suited to serving this high-risk population.

## Post-evacuation policy:

The re-birth of Aboriginal Midwifery

The Inuulitsivik Aboriginal Midwifery program began as a result of activism for Inuit cultural revival and self-government, with the opening of a birthing centre in Puvirnituq in 1986. The main objective: to bring birth back to the community. Following the opening of the birthing centre in Puvirnituq, similar centres were created in Inukjuak in 1998, and in Salluit in 2004. These three birthing centres provide intrapartum care to 75% of the Hudson coast. The remaining 25% live outside these three communities and need to "leave home"; however, unlike with the evacuation policy, they still receive care in their own region, language and culture (28).

As mentioned, midwifery has always been a part of traditional Aboriginal birthing culture. Respecting the importance of Aboriginal traditions, the current midwifery program integrates Western medicine with traditional knowledge. The midwives in Nunavik are the lead caregivers for maternal and newborn care. The midwives lead a weekly meeting with a perinatal review committee - an interdisciplinary team consisting of midwives, student midwives, nurses and doctors. During these meetings, they agree on a plan of care, including site of delivery, for each individual patient. At this time, the midwives begin weekly follow-ups with the pregnant mother until birth. Two midwives are normally present at parturition, with nurses or an on-call doctor in Puvirnituq ready to assist if needed. Following delivery, the mother and baby are seen daily for one week. Subsequent follow-up visits then occur once per week for up to 6 weeks post-partum. These midwives also provide care outside of pregnancy, from adolescence to menopause, such as contraception education, STI prevention, and uterine and cancer screening (28).

Program Implementation: Training and Selection Process

A critical component to the success of this program is the competence of the midwives. Midwifery students are chosen from the community; both the health care providers and community members base the selection on applications and interviews. Selecting the students from amongst the community guarantees culture and language proficiency, as well as sustainability of the program. These students are trained for day-to-day clinical situations in the community, in conjunction with structured learning modules. Training on-site avoids reviving the nightmare of residential schools, and equips trainees with important skills to cope with the settings and situations that are frequently seen in Nunavik. The return of childbirth facilitated by the midwives provides a sense of empowerment and autonomy to the community (28).

Teaching and evaluation are facilitated by two groups: Inuit mentors and non-Inuit mentors. The non-Inuit mentors are asked to recognize their role as teachers, not as leaders, respecting the Inuit culture and tradition. The teaching method follows the Inuit pedagogy, which emphasizes "being shown rather than told", mentorship, storytelling, and other traditional oral methods (28).

By the time the students graduate, they are expected to have acquired emergency skills, well-women/baby care, and community health experience at a comparable, if not more extensive, level as the rest of Canadian midwives. Requirements for graduation include completion of 1240 supervised clinical hours, follow-up of 60 perinatal cases up to 6 weeks postpartum, and attendance of 40 births as a second attendant, where the student takes responsibility for the immediate care of the newborn (28).

## Program Evaluation:

A major limitation of the evacuation policy, which governed Nunavik maternal health until the implementation of the Inuulitsivik Midwifery program in 1986, was the cost of transporting pregnant mothers. Transportation costs for the region of Nunavik are

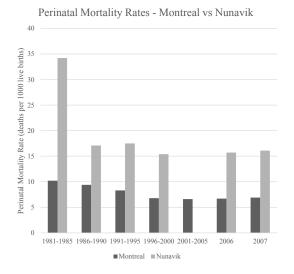
undocumented, however we examine Nunavut's transportation costs, as both regions are similar in terms of geography and population demographics (29). Of the \$100 million transferred from the federal government to Nunavut health care between the years 1996-2006, over \$50 million was used for transportation (30). This figure highlights the burden of transportation on health care expenses when relying on evacuation to southern hospitals as primary modes of treatment for Aboriginal communities. In addition to the high cost of transportation, Inuit women report greater dissatisfaction with treatment in southern hospitals. Although difficult to quantify, this dissatisfaction certainly adds to the monetary costs of the evacuation program, jeopardizing its efficiency. Dr. Gary Pekeles, director of the Northern and Native Child Health Program at the McGill University Health Centre, estimates a cost of \$20,000 to evacuate a single pregnant mother from Nunavik (31). Using this figure, it was estimated that the Inuulitsivik Midwifery program avoided a total of approximately \$2,900,000 in transportation costs between 2000-2007 by overseeing 1,184 births in Nunavik (86.3% of all births in that time frame) (32).

## Perinatal Mortality Rates

Perinatal mortality rates are used as a primary evaluative indicator of the Inuulitsivik Midwifery program, as it is "arguably the most important indicator of the quality of perinatal and maternity care" (33). Between 1981 and 1985, under the final years of the evacuation policy implemented by the federal government, the perinatal mortality rate (per 1000 live births) in Nunavik was a staggering 34.2, compared to 10.2 in Montreal. Nunavik's perinatal mortality rate decreased from 34.2 to 17.1, recorded between 1986-1990, and was as low as 15.4 between 1996-2000, compared to 6.8 in Montreal the same year (23) (see Figure 1). These decreases in perinatal mortality observed in Nunavik since 1986 are coincident with the implementation of the Inuulitsivik Midwifery program (1986), pointing to a correlation between the implementation of the midwifery program and lower perinatal mortality.

The persisting disparity between Montreal and Nun-

avik perinatal death rates cannot be blamed on ineptitude of the Aboriginal midwifery program, as there are many upstream contributing factors to the higher perinatal mortality rates in the Nunavik population. Namely, most pregnancies in Nunavik are considered high risk due to the harsh realities of Aboriginal health, including high risk of mental illness, alcohol abuse, smoking, food insecurity (9), and a greater likelihood of developing certain gestational complications (32).



## Transfer Rates

The main objective of the Inuulitsivik Midwifery program was to return childbirth to the Inuit communities of Nunavik, and reclaim its cultural significance. Thus, transfer rates may be analysed as a processing indicator of this program. Under the previous Evacuation Plan, 91% of pregnant women in Nunavik were transferred to medical facilities outside of the region, mainly in Montreal and Moose Factory Ontario (32). With the implementation of the midwifery program, this percentage decreased dramatically: 13.7% of pregnant women were transferred outside of Nunavik between 2000-2007, with 86.3% of Inuit women giving birth at one of the three Inuulitsivik health centres. Moreover, Inuit midwives made up 72.8% of the birth attendants in the same time period, with the remain-

ing 27.2% consisting of non-Inuit midwives and physicians (32)

## Hudson Coast and Ungava Bay - A Comparison

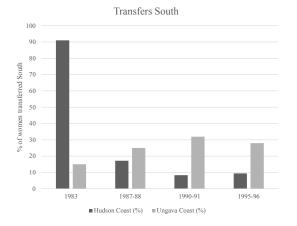
The Ungava Tulattavik Health Centre is another health centre in Nunavik, located on the Ungava Bay. This health centre is staffed mainly by non-Inuit physicians, and existed before the creation of the Inuulitsivik Midwifery Program in 1986. This created a kind of natural experiment, to observe any differences the Inuulitsivik Midwifery program would have on important outcome measurements such as perinatal mortality (34).

When comparing perinatal birth outcomes on the Hudson Coast, where births are led by Aboriginal midwives of the Inuulitsivik Health Centre, to the Ungava Coast, where births are led by trained physicians stationed at the Ungava Tulattavik Health Centre, it was found that there was no statistically significant difference in perinatal death rates between the two communities (33). As such, measures such as episiotomy intervention rates between the two delivery programs are studied as a proxy for unnecessary interventions. There is a stark contrast between episiotomy intervention rates between the Hudson Coast and the Ungava Bay, with rates almost six times higher on the Ungava Bay from 1990-1991 (33). Additionally, there was a higher rate of evacuations to hospitals in the south on the Ungava Coast, despite the dominant presence of professionally trained medical doctors at the Ungava Tulattavik Health Centre (see Figure 2). A possible explanation is that there is a high turnover of doctors on the Ungava Coast, which perpetuates the constant presence of less experienced medical professionals on site (33). This hypothesis illustrates an important strength of the Inuulitsivik Aboriginal midwifery program, being that local Inuit are trained to oversee the low-risk births, reducing the turnover rate and increasing the collective knowledge and experience shared among the midwives.

## Reflections and Recommendations:

The implementation of the Inuulitsivik Midwifery program is novel in that it accommodates the culture

of the Inuit communities of Nunavik, while providing modern medical treatment and care to delivering mothers. This program veers from the colonial oppression, marginalization, and forceful integration policies of the past which prevented Aboriginal communities from developing in accordance with their own needs and interests (35). It is important to note that Indigenous communities have higher health disparities compared to the rest of Canada, with Aboriginal women carrying an even more disproportionate burden of disease as well as poorer social outcomes (36). Thus, it is paramount that policies targeted to serve this population be stringently evaluated and revised, as was the case with the Evacuation Policy. This policy was catered towards the Western ideal of medical practice, and failed to acknowledge the cultural significance of Aboriginal ways of healing.



A major accomplishment of the midwifery program is the nature through which it was established. Members of the Hudson Bay Inuit community who had personally experienced the shortcomings of the Evacuation Policy created the Inuulitsivik Health Centre Midwifery initiative. Furthermore, the program achieves the integration of modern, evidence-based medicine with traditional Aboriginal practices to deliver more suitable care to the Inuit women of Nunavik (16). Finally, continuity and stability of the program is accomplished through the integrated midwifery educational system. The Inuulitsivik midwives are long term staff

that deliver culturally relevant care to their fellow community members. This eliminates the problem of the high staff turnover rates seen in non-Inuit managed health centres (10).

It is immensely important, however, to keep in mind that the establishment of this program should not bring an end to the discussion surrounding the provision of permanent services that would enable all mothers to deliver their children within their own region. This program is only feasible when it comes to delivering low-risk births – high-risk births still need to be evacuated south (32). This study concludes that efforts to establish resources and facilities catered to the delivery of high risk births in the community should be undertaken. This may help reduce the stagnant perinatal death rates of the Nunavik population observed in the most recent data (Fig. 1). Aboriginal women should not have to choose between their culture and their safety.

This case study is wary of declaring the Inuulitsivik Midwifery program a success, as there is crucial data missing from this analysis. Firstly, the cost analysis is incomplete, as there are discrepancies in the financial reporting between different organizations (37,38), and full audit reports are not publically available for the Inuulitsivik Health Centre. Costs specific to the Midwifery program are also unavailable. A full cost-benefit analysis is also missing from our report, as it is difficult to represent qualitative successes in a way that can be compared to costs in dollars. In a program such as this, total social costs and benefits must be included when evaluating the overall efficiency of the program. This case study calls for further data collection from the midwifery program, including qualitative measures that can evaluate community development, cohesiveness, gender inequalities, and overall satisfaction. Furthermore, a lack of comprehensive quantitative data (with sufficient statistical power) such as a complete history of perinatal mortality rates with the Evacuation Policy vs. the midwifery program, interrupt the complete evaluation of the intervention. It is paramount to the long-term success of the Aboriginal midwifery program that more research is done to evaluate the impact of this program and all other First Nations health care initiatives. A comprehensive monitoring and evaluative system must be integrated into the Inuulitsivik midwifery program in order to allow local and provincial policy makers to address and improve critical areas of weakness.

## **Concluding Remarks:**

The Inuulitsivik Midwifery program is recognized by numerous organizations, including the International Confederation of Midwives, the World Health Organization, and the Canadian Society of Obstetricians and Gynecologists (39). As the first midwifery program of its kind in Canada, it has been used as a model for the implementation of other midwifery programs in the country, serving Aboriginal populations outside of Nunavik (17). Potential scalability in other countries with marginalized Indigenous populations is questionable, and must be considered on a case-by-case basis. Currently, the midwifery-led health centres are unable to manage high-risk deliveries, and must resort to evacuating these pregnant women to deliver in a hospital setting. This solution may not work, for example, in a country whose government cannot or will not afford the transportation costs of high-risk pregnancies.

Contemporary global health trends focus on increasing the proportion of physician-led deliveries in established medical facilities worldwide – a concept at odds with the Inuulitsivik Midwifery program. It is important to understand that global health is an extremely nuanced field, with no such thing as a one-size-fits-all solution. This leads to more tailored global health interventions, best-suited to the population being served. In the case of the Nunavik population, deliveries in hospital required the isolation of the Inuit mother from her family, her language, and her culture. A more suitable approach, tailored to the Inuit population of Nunavik, was achieved through the collaboration of the Inuit, physicians, and health experts alike.

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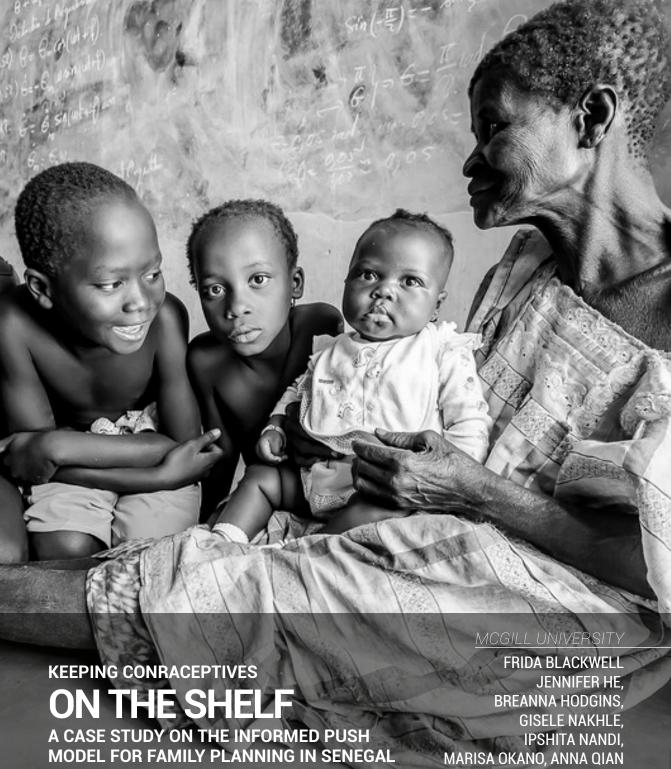
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IPSHITA NANDI, MARISA OKANO, ANNA QIAN In 2011 the Informed Push Model (IPM) was designed by Intrahealth International and its partners to address the issue of contraceptive unavailability in urban areas of Senegal. The IPM is a supply chain intervention system that brings the source of supply closer to the source of demand and alleviates local health facilities from directly placing and picking up product orders. A pilot study was conducted over a 6 month period in a district of Dakar and stockouts were completely eliminated at all 14 public health facilities. The project then expanded to include all 140 public facilities in the Dakar region with continued success and is currently undergoing further scale-up to the national level.

Editorial Note: A lack of consistently reliable access to contraception is one of a multitude of factors hindering family planning efforts by women in many low- and middle-income countries. When contraceptive products are out-of-stock at the point of purchase ("stockouts"), women's contraceptive choices are affected. It should be noted that stockouts are one of many determinants of contraceptive choice, and the authors are not positioning that stockouts are the only consideration in this matter. The following article describes efforts to implement the Informed Push Model, a supply chain intervention, in an attempt to increase Senegalese women's access to preferred contraceptive devices, by preventing stock-outs.

"Deciding about pregnancy should be by choices, not by chance. Having the information and means to do so is a basic human right. Family planning is one of the best investments that we can make for women's empowerment, gender equality, sustainable development and creating the future we want."

- Dr. Babatunde Osotimhehin Executive Director, UNFPA

## So What?

Stockouts of contraceptives at health facilities are one of the main reasons that women in low-income countries simply cannot access the family planning products they desire. The Informed Push Model is Senegal's attempt at addressing this issue by providing women with choice and availability, and thereby giving them more control over their reproductive health.

#### Introduction

Family planning has a strong influence on the socioeconomic development of a country; it empowers women, enabling them and their partners to decide if and when they want to have children. Programs that encourage the use of contraceptives prevent unintended pregnancies and unsafe abortions, and are key to economic growth in countries with high fertility rates. In Senegal, as in many West African countries, the lack of consistent access to contraceptives prevents many women from reliable family planning.

Frequently, gaps in the supply chain lead to contraceptive products being out-of-stock in pharmacies and health clinics. Supply chain limitations also mean that many locations only offer one or two types of contraceptives, making it difficult for women to find a method that fits their family planning needs. The prevalence of family planning can be described by the modern contraceptive prevalence rate (mCPR), which is a measure of the percentage of women of reproductive age who are using a contraceptive method. In Senegal, the mCPR was only 13% from 2008-2012 (1), which contributed to the nation's high fertility rate: about 5 births per woman from 2010-2013 according to the World Health Organization (WHO). Senegal also has rapid population growth (2.6% in 2015), as well as high maternal and child mortality rates (390 maternal deaths/100,000 live births reported in 2008-2012, and 60 child deaths/1000 live births in 2012).(1) The WHO also reported that the median age in Senegal was 18 years in 2012; therefore, a large proportion of the population today falls into the young child-bearing age category, and family planning and contraceptive use continue to be fundamental for the overall health of the country.

## Background

Over the last 3-4 decades, the government of Senegal has implemented several initiatives involving family planning (FP) as a key strategy to improve the health of women and infants (2). In 1980, contraception was made legal for the first time in the country, and in 1988 the government adopted an official policy to reduce the population growth rate and the number of children per woman. The National Family Planning Program (PNFP) was launched in 1990 and resulted in a moderate increase in the use of modern methods of contraceptives by 0.7% each year from 1992-1997 (3). However, in 1998 the FP program was integrated into the Division of Reproductive Health within the Department of Primary Health Care. This led to a reduced focus on FP as priorities were instead placed on other health issues of the country (3). In 1995 and again in 2005, Senegal's population policy was updated to align with the international agenda as per the Millennium Development Goals (MDGs), whose objectives were to reduce the worldwide maternal mortality ratio by 75%, and to achieve universal access to reproductive health by 2015. These efforts have led to important gains in the nation's maternal and child health; for example, the total fertility rate (TFR) decreased from 7.2 to 5.3, a decline of almost two lifetime births per woman between 1978 and 2005 (1). However, progress has been slower since 2005: the TFR has remained relatively constant over the past ten years and the mCPR increased by only 1.9% from 1997-2011 (5).

In February 2011, eight representatives from West African nations met at a conference in Ouagadougou where they formed a unified commitment to boost reproductive health programs in the region. Following this partnership, Senegal's government put forth the

National Action Plan for Family Planning for the period 2012-2015. Its goal was to increase the rate of contraceptive use in women of childbearing age to 27% by the end of 2015 (4). As part of this action plan, the government of Senegal identified 5 key challenges that impact the progress of family planning in the country (4):

- Demand creation
- 2. Availability of products
- 3. Access to services
- 4. Political and financial engagement
- 5. Coordination between stakeholders

Therefore, in 2012, the Informed Push Model was implemented as a supply chain delivery system intervention to address the second identified challenge of product availability.

#### Problem Statement

A baseline evaluation of the contraceptive supply chain from 2010-2011 in two districts of Senegal revealed that stockouts of FP products in the public sector caused over 80% of female users to be unable to acquire the contraceptive method they wanted (15). 55% of the women experiencing a stockout switched between products, rendering the contraceptive method less effective, and the remaining 45% discontinued use or went to a private pharmacy to purchase their desired product at a higher price (8). This problem of supply and demand was a major cause of low client satisfaction, and in 2011 it was reported that 29% of women in Senegal had an unmet need for FP (7). Therefore, an intervention in the supply chain system was necessary to address the issue of contraceptive product stockouts at local public health facilities.

## **Project Intervention**

Initially, the system to distribute contraceptives from central warehouses to local facilities used a "pull" model based on customer demand (2). The system was managed as follows:

- Local health facilities known as service delivery points (SDPs) sent their orders to the district depots
- The district aggregated these orders and sent a collective order to the Pharmacies Régionales d'Approvisionnement (PRA)
- The regional facility transmitted the orders from all its districts to the Pharmacie Nationale d'Approvisionnement (PNA)

In this system, each operational level was responsible for planning their commodity needs and placing orders four times a year. The PNA then delivered products based on the quarterly inventory records. Although this system ensured effective integration of FP products in the PNA system, a drawback was the problem of storing enough products since the PNA, PRAs, and districts had to stock large quantities of different contraceptive products at one time. Moreover, delays were often noted in the ordering of contraceptives by the SDPs because profits from the sales of contraceptives were first used to pay for the SDP's operating costs. Furthermore, the local staff of medical practitioners and midwives often did not have the resources or the expertise to maintain an adequate stock of supplies. The inefficiencies in this system resulted in major stockouts at the SDPs even when contraceptives were available at the national or regional levels.

## Fixing the supply chain:

The "push" model of delivery is based on forecasted demand of products as opposed to actual or consumed demand (Figure 1) (8). The IPM brings the source of supply closer to the source of demand by employing dedicated professional logisticians to deliver the contraceptive products through loaded trucks directly to the health facilities. These logisticians project demand for contraceptives and are therefore directly "informed" on the needs of each SDP. Based on these forecasts, contraceptives are delivered to the SDPs on a monthly basis, which relieves health facilities from

the task of placing orders and spending time picking up the products (8).

Key features of the IPM intervention include task shifting, public-private partnerships, payment based on consumption, and aligning incentives, as described below:

## Task shifting

By using specialized logistics professionals based at a regional level to carry out tasks such as quantification, data collection, and distribution, the logistics performance of the delivery system is improved, and health workers are thus freed to focus on their specialties in providing health services. The logistics professionals come from the private sector and utilize a practice called vendor-managed inventory, whereby they take responsibility for actively resupplying SDPs rather than the SDPs requisitioning products. Additionally, by distributing products directly from the regional level to the SDPs, the district is no longer required to maintain a physical inventory, thereby streamlining the supply chain. The district's role shifts from physical supply chain operations to management of SDPs and service provision. Task shifting also allows for leveraging of the limited supply chain management expertise by using a small number of trained professionals to serve a large number of SDPs.

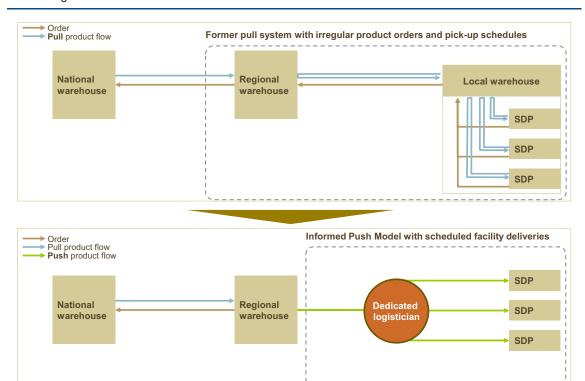
## Public-private partnerships

The IPM uses private operators, or third-party logistics providers, to store and distribute the family planning products to public health facilities. The third-party logistics providers are experienced logistics companies with previous experience in the health sector, and are managed with performance-based pay contracts to ensure results.

## Payment based on consumption

Before the IPM, SDPs were required to pay for family planning products at the time of order, which resulted

FIGURE 1. Informed Push Model Streamlines Deliveries and Eliminates Orders Between Service Delivery Points (SDPs) and the Regional Warehouse



in major cash flow problems. With the IPM, the products are delivered and consumption data recorded. The SDPs are then charged based on these consumption rates. This re-established the cost-recovery system and eliminated the cycle of stockouts at SDPs.

## Aligning incentives

The IPM aligns the incentives of all parties involved in making sure that family planning products reach SDPs and the community.

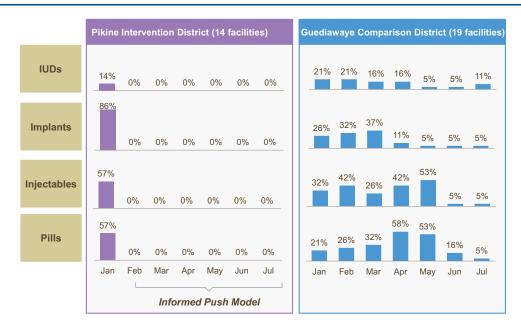
## Implementation

To assess the efficiency of the IPM in reducing stockouts as well as its feasibility and sustainability, a pilot project was undertaken in the Pikine district of Senegal over a 6-month period from February 2012 to July 2012. The neighbouring district of Guediawaye, where the IPM was not implemented and the original "pull" delivery system was maintained, was used as a control for the pilot study (8).

#### Evaluation

The IPM is evaluated using several different indicators. The immediate process indicators of the IPM are measured through changes in contraceptive stockouts rates and mCPR. The downstream, long-term outcomes of the IPM are measured by Senegal's fertility rates and maternal mortality rates. The results of the IPM through these indicators are discussed below.

**FIGURE 2.** Percentage of Facilities Experiencing a Stockout in 2 Comparison Districts, Dakar, Senegal, January–July 2012



#### Process indicators:

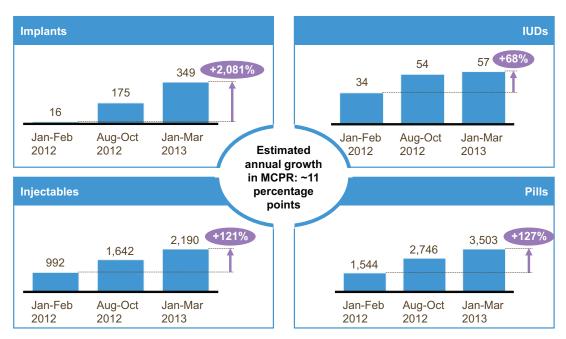
The results of the pilot study in the Pikine district were dramatic. Before the IPM was implemented, Pikine experienced high levels of stockouts, such as a 43% stockout rate for the injectable contraceptive Depo Provera, and an 82% stockout rate for the contraceptive implant Jadelle (15). This translates to the products only being available to consumers about 17 and 5 days out of each month, respectively. However, after just one month of the IPM's implementation, stockouts of oral contraceptive pills, injectables, implants, and intrauterine devices (IUDs) were completely eliminated in all 14 public health facilities in Pikine (Figure 2) (8). In the Guediawaye district stockout rates persisted at an average of 23%. The immediate success of the pilot study led to the expansion of the IPM delivery system to include all 140 public health facilities in the entire Dakar region, and within another six months the stockout rates dropped to less than 2% throughout the city (8).

In addition, the elimination of stockouts led to an increase in contraceptive use. After one year of the IPM's service delivery improvements, the mCPR in Pikine rose by 11% (Figure 3) (8). The types of contraceptive methods used also changed. Women started taking advantage of the newly available choices, such as the long-acting contraceptive implants, whose consumption increased by 2,081% in just one year (8).

#### Downstream outcomes:

Apart from the immediate results of the IPM, the sustained outcome of this intervention would be a reduction in fertility rates and maternal mortality rates. However, it is currently not possible to conclusively evaluate the long-term effect of the IPM pilot study as these data are only collected at a national level, and the IPM is still undergoing scale up to include the entire

**FIGURE 3.** Average Monthly Consumption of Contraceptives in Pikine District, Dakar, Senegal, Before and 1 Year After IPM Implementation



country. Furthermore, such data is only available up to the year 2013, and according to the World Health Organization, the fertility rate in Senegal dropped only slightly from 4.98 to 4.93 births per woman from 2012 to 2013. Therefore, a decline in fertility rates when the IPM is functioning at a national level is necessary in order to deem the IPM project a success. Furthermore, Senegal will hopefully experience a decrease in maternal mortality rate as the IPM continues to operate throughout the country. In 2013, the maternal mortality rate was about 350 deaths per 100,000 live births, and 16.4% of deaths among women of reproductive age were due to maternal causes (13). In the future this number must decline in order to deem Senegal's IPM a success for maternal and child health.

## Funding and Cost Analysis

Funding for the IPM relies on private donors. In 2012

the Bill and Melinda Gates Foundation partnered with the international NGO Intrahealth as well as Senegal's Ministry of Health to implement the pilot study. About 160,000 USD was spent on the progressive expansion of the IPM in 2012 (4). After the success of the pilot, the Bill & Melinda Gates Foundation and Merck & Co. Inc., through its Merck for Mothers initiative, announced a \$9 million partnership to provide financial and technical support for the national expansion of the IPM (12). Senegal's Ministry of Health, Senegal's National Pharmacy (the PNA), and the private software company Dimagi, are working in partnership with Intrahealth as the lead implementing partner (9).

The total annual operating cost for family planning when the project reaches a national scale in Senegal is estimated to be 500,000 USD, which is equivalent to about 11% of the national annual spending on con-

traceptives (8). The IPM functions under a cost recovery model, in which revenue is not recognized until the seller's costs have been recovered in sale transactions. Preliminary analysis has therefore suggested that the total costs recovered at a national scale will be 1,050,000 USD annually (8). This represents a level of sales that would support a national mCPR of 25% to 30%. It is also expected that 50% of the cost recovery (525,000 USD) will go to IPM logistics costs, such as hiring of trained logisticians (10).

In Senegal, private-sector pharmacies and health clinics may charge 3 to 9 times the price for a health product compared to a public facility (8). Before the IPM was implemented, the price of one month's supply of oral contraceptive pills from a private pharmacy in Senegal was about \$3.10 (USD). Due to the decrease in stockouts at local public clinics, oral contraceptives have been made available to women at a price of about 20 cents US per month (11). To date, about 2.3 million USD has been spent on the expansion of the IPM from 2012-2015 (4).

## **Project Challenges:**

Further cost-effectiveness analysis is critical for a complete evaluation of the IPM. For example, the cost of PNA management and the cost of integrating other products into the IPM supply chain are unknown. To ensure project sustainability and self-sufficiency without relying on outside sources of funding, the IPM must transition to being fully managed by the PNA and its 11 regional PRAs. Currently, the PNA is reluctant to ensure their sustained involvement in the project. The target of having the PNA managing the IPM in 6 regions of the country by July 2015 was not reached. Intrahealth is therefore working with consultants from McKinsey to present a sound transition plan of the IPM that will include the proposed operational system and a financial balance showing how PNA can break even or possibly even make profit (M. Dicko, personal communication, October 23, 2015). There is also

the intention to request a consultant to undertake a high-level advocacy plan with the Ministry of Health, private partners supporting health in Senegal, and the PNA. As such, the IPM design will remain flexible to respond to the most cost-effective and politically viable option. At this point it is not clear what the PNA's role will be in continuing the IPM and therefore Intrahealth is currently in discussions with the PNA and with the Ministry of Health on this issue (15).

Furthermore, to ensure the project is sustainable at the final national scale up stage, there must be integration of the IPM system with other health products so that delivery costs remain feasible. The IPM is currently distributing 11 family planning products, however this must be increased to 118 health products in total (M. Dicko, personal communication, October 23, 2015). Therefore, in-depth product segmentation analysis is needed to guide the inclusion of additional health products, and a comparative analysis of the cost per unit of product delivered through alternative distribution models is also necessary.

#### Reflection

Although the IPM is viewed as a success story for Senegal's family planning initiative, the scale up of the project to a national level is encountering several challenges. The bigger the operation and the more extensive the geographical reach, the more supplies and manpower necessary to sustain the project. As the model expands into regions that are less populated and potentially have more difficult road conditions, modifications are necessary to ensure optimal delivery systems. The government of Senegal is therefore working on establishing standard operating procedures, issuing and managing contracts with private logisticians, and supporting data use and performance management to advance the IPM nationally (8). It is also necessary to train providers in contraceptive technology and to intensify demand-creation and advocacy activities focused around family planning.

This supply chain intervention case study highlights the complexity of system implementation, evaluation, and scale up of programs targeted towards urban districts to more remote areas with limited resources. Improved maternal health is a global initiative, and the IPM reflects an important first step in achieving this goal for a country with traditionally limited access to reproductive health services. Given that the project is still in progress, substantial conclusions cannot yet be drawn. However, the program was largely successful in eliminating contraceptive stockouts in the country's most populated region, a key issue to be addressed. Future consideration of geographical delivery barriers, information sharing, and health promotion programs would be highly beneficial in ensuring the continued success and uptake of the program. Hopefully, the IPM can serve as a model for other countries with high maternal mortality rates and low contraceptive availability to continue making progress in achieving health equity throughout the world.

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IMPROVING
MENTAL HEALTH
CARE IN POST-WAR
AFGHANISTAN

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MONICA BAHOSHY, LAUREN CHUN, LEILA FARAHDEL, RYAN HARTLEY, ADRIANNA MODAFFERI, ARYAN SHEKARABI Mental disorders act as a leading cause of disability world wide, especially in war and disaster torn regions. The effects of mental conditions are especially high in women living in "fragile states" such as Afghanistan, where resources to appropriate mental health care are extremely scarce. HealthNet TPO, a Dutch NGO has made an attempt to fill this fundamental health care gap through a three-tiered intervention. This case study critically evaluates HealthNet TPO's efforts in Afghanistan based on the intervention's scope, performance, and sustainability. The findings of this case analysis conclude that HealthNet TPO has been successful in sustainably expanding mental health resources; however, it remains unclear if the performance level is satisfactory to meet the elevated needs of the Afghan population.

#### The Global Burden of Mental Health

Mental disorders are one of the leading causes of illness and disability worldwide, with depressive conditions acting as the fourth leading cause of the global burden of disease. Approximately 1 in 4 individuals will suffer from a mental illness at some point in their lives. (1, 2) Both the rates and severity of depression are exacerbated in individuals living in war and disaster-torn conditions. Furthermore, depressive disorders are twice as common among women due to additional social factors such as gender discrimination, poverty, sexual, and domestic violence. (3) Some treatments are available, yet approximately two-thirds of individuals suffering from these conditions fail to seek help from a health care professional, partially due to the stigma and discrimination that surrounds mental illness. (2) Globally, there is great imbalance in the distribution of mental health resources. In low and middle incom-

# So What?

Mental health is an important aspect of health that is negatively affected in areas of war and destruction. The war in Afghanistan strained the health-care system, leaving its most vulnerable population – women – with no access to resources. Quality mental healthcare services in low-resource areas must be addressed through the expansion of existing services, collaboration with the government, and the implementation of evidence-based practices.

ecountries especially, the lack of approporately educated health care professionals acts as a central barrier in obtaining appropriate psychosocial treatment. (1) More than 40% of countries worldwide have no mental health policies, while 30% offer no mental health programmes for their distressed populations. (2) Moreover, war and disasters have a major impact on psychosocial well-being, doubling the rate of mental disorders amoung the population. (1) In addition, approximately 80% of people affected by wars, violent conflicts, and displacement from their homes are women and children. (3) Since mothers are the primary caregivers for their families, changes to their health status may impact their child care abilities, and by extension, the health of their children. As such, the lack of access to appropriate treatment within these nations make mental disorders that much more devastating and debilitating. The objective of our case study is to analyze and evaluate a mental health intervention in Afghanistan. Also, we will present recommendations based on our analysis of the services provided, which we hope will inform future mental health interventions in developing regions.

# Afghanistan's Need for Mental Health Services

After the fall of the Taliban regime in 2001, the Afghan health care system was completely demolished, with the mental health sector disproportionately affected. There were severe shortages in staff, supplies, orga-

nization, and infrastructure. Mental health services were limited to a few regional hospitals and the only psychiatric hospital was destroyed. (4) There were no qualified psychiatric nurses or clinical psychologists and only two practicing psychiatrists to treat a population where approximately 60% suffered from mental illness. (4) With these characteristics, Afghanistan was classified as a "fragile state", as its government lacked the capacity to provide the basic services and necessary security measures for its population. (4) Without a department of Mental Health in the Ministry of Public Health (MoPH) in Afghanistan, it was difficult to categorize the needs of the population.

In the late 1990's, the World Health Organization (WHO) Regional Office for the Eastern Mediterranean attempted to organize a comprehensive 3-month diploma to train 20 doctors in psychiatry, but it failed due to the high levels of violence found within these regions. (4) Later, with the help of the WHO, the Basic Package of Health Services (BPHS) was created to provide a standardized package of basic essential services and promote the redistribution of health resources to this underserved Afghan population. (4, 14) At the time, there was a strong need to develop tangible and long-term improvements to the health care system as a whole. Given that the nation had been in a constant state of war for decades, addressing mental health issues associated with the stress and uncertainty of living in these conditions became imperative. (4) When the BPHS failed to accurately describe the targeted mental health interventions, donors doubted the feasibility of integrating them into the basic services and ultimately neglected this crucial health care sector. Therefore, devising a solution now relied on external organizations to develop their own methods and tools. (4) The MoPH realized the necessity for a sustainable mental health program and restructuring of the health care system. An estimated 13 million Afghans suffered from mental health problems, and even more struggled with varying degrees of stress disorders. (5) A survey conducted in Nangarhar Province in 2003 confirmed that the rates of depression and anxiety are high, particularly amongst women. It revealed that 58.4% of all women in the province had depressive symptoms, 78.2% had anxiety symptoms, and 31.9% had PTSD symptoms. (5)

#### HealthNet TPO's Global Presence

HealthNet TPO is a Dutch non-governmental organization, established in 1992 by Médecins Sans Frontières to bridge the gap between emergency aid and structure development. HealthNet TPO works to improve health care in war- and disaster-torn areas with an overall mission to "reach accessible health care for all". (6) To date, HealthNet TPO has implemented projects in 27 different countries, with a long-term presence in several fragile states, including Afghanistan, where they have been active since 1993. (4) In early 2002, HeathNet TPO attempted to begin addressing the mental health needs in Afghanistan. Using the WHO Mental Health Gap Program as a guideline for services and interventions, they designed and implemented a project that aimed to provide comprehensive and diverse training programs for mental health care practitioners in the Nangarhar province (population 1.38 million). (7) After conducting a needs assessment in Nangarhar, they discovered that this population was devoid of any mental health care, and therefore designed a three-tiered, sustainable scheme to enable the existing health care system to address this pressing issue. (4)

#### The Three-Tiered Intervention

The first goal was to integrate mental health care into basic health services. (4) HealthNet TPO approached

this objective by training health care workers in the identification and management of mental health conditions at each of the three levels of the health care system: health posts, basic and comprehensive health centers, and district hospitals. At the basic and comprehensive health centers, health care workers were trained in the identification and treatment of priority disorders. Physicians received additional comprehensive psychotropic training, and nurses and midwives were trained on psychosocial interventions and psycho-education. (4) District hospital mental health services were expanded to include both outpatient and inpatient services. Each hospital was assigned a fulltime physician who had been trained in mental health care at the psychiatric department of a teaching hospital in Pakistan, and a psychosocial worker trained to provide support groups and psycho-education. (4) Training sessions were initially conducted in English and translated into Pashto by Afghan doctors on the HealthNet TPO team. The training sessions involved videos, role-play, group discussion, and patient-doctor simulations. (4) To integrate this program throughout the entire province, a multistep approach was taken. First, the population was assessed through focus group discussions to explore the local concept of mental illness, and classified these disorders as either epilepsy, common (such as depression and anxiety), or severe (such as psychosis) mental disorders. Next, materials and methodology were developed and training began in six rural districts, called the Shinwar cluster. The training programs and the provision of psychotropic drugs were then expanded throughout the entire province and integrated within the general health budgets. (4)

The second goal was to strengthen community care and resilience through psycho-education on mental health issues, psychosocial distress, and coping mechanisms. (4) Community health workers now offer support groups and workshops on a variety of topics such as grief, drug use, and domestic violence. They also implemented individual case management through supportive counseling. The final goal was to achieve policy support and integration for mental health. HealthNet TPO was able to reach this goal by initiating the establishment of the Mental Health Department within the MoPH in 2005 by providing financial support and acting as an active partner within the Afghan MoPH. (4)

#### Analysis of HealthNet TPO's Intervention

In order to evaluate HealthNet TPO's intervention in Afghanistan, we conducted a 3-factor analysis. By evaluating HealthNet TPO's efforts in the Nangarhar region based on their scope, performance, and sustainability, we can analyze both the strengths and weaknesses of the intervention in order to evaluate and adapt the program for future improvements and expansions.

#### Scope

To appropriately determine whether HealthNet TPO's intervention in Afghanistan was of adequate scope, we applied the framework proposed by the WHO in the WHO MIND project. (8) In this outline, the WHO describes the various types of mental health interventions that should be included, along with the resources and availability that should be allocated to each, in order to execute an effective mental health intervention. This framework is illustrated by a pyramid of health care: the peak represents interventions that require more resources and infrastructure, while the base of the pyramid describes more community-based and self-care oriented initiatives (Figure 1). (8) The key takeaway from this WHO framework is that lower income countries looking to develop their mental health services should focus less on costly resources that often meet a lower demand, such as in-patient mental institutions, but rather should focus efforts on establishing and expanding the use of less costly interventions, such as mass community mental health services, as well as promoting and educating on self-care. Another key point highlighted by the WHO report is that, in order to have the greatest impact, mental health services should be integrated with primary health care, via incorporation within general health facilities.



Figure 17: Optimal Mix of Mental Health Services - WHO Pyramid Framework | This framework demonstrates that greater resources should be allocated to low cost, high demand services, and lesser to high cost, low demand facilities when attempting to integrate novel healthcare services.

When the state of affairs was compared pre and post HealthNet TPO's intervention, it was clear that these methods covered a wide scope of mental health services. Before the intervention was implemented, Afghanistan's population of more than 21 million lacked basic mental health care, with only two practicing psychiatrists and no other health care professionals with any mental health training. (4) There was also no mental health care representation in the MoPH of Afghanistan. The intervention tackled these issues by providing appropriate training for health care workers at several levels of the health care system. (4) Overall, HealthNet TPO's intervention led to the addition of 931 community health care workers, 275 nurses, and 334 physicians trained in mental health care. (4) A

comparison with pre-intervention is described in Table 1. The data also show that the intervention focuses mainly on community mental health care initiatives and self-help/support groups, which is in congruence with the Optimal Mix of Mental Health Services proposed in the WHO pyramid framework. (8) Based on this, it can be concluded that the scope of HealthNet TPO's intervention in Afghanistan was successful in expanding at levels of the health care system to better serve the needs of the population.

Table 1: Comparison table between prior and post intervention

Pre-intervention (2001)	Post-intervention
2 psychiatrists	931 CHWs, 275 nurses, and 334 physicians trained in MH
No mental health care representation in MoPH	MH in first tier BPHS and representation in MoPH
	Basic/comprehensive health centers
	District hospitals with specialists
	Community health care with volunteers and CHWs

#### Performance

To evaluate the performance of HealthNet TPO's intervention, the "Triangle of Health Care", described in Dr. William Kissick's book titled Medicine's Dilemmas: Infinite Needs Versus Finite Resources has been used as a framework. Dr. Kissick proposed that health care is constrained by three competing, yet equally important factors: access, cost, and quality. He argues that when one of these factors is changed, it inherently affects the others. For example, if one were to increase the quality of health care, it would subsequently increase the cost of the care offered. To take this further, within an area where medicine is not socialized, an increase in cost would cause a decrease in access to services.

Based on the data reported by HealthNet TPO, overall access to mental health services had increased when comparing the number of consultations for mental health disorders before and after intervention implementation. (4) In 2002, before the intervention was employed, the absolute number of consultations for mental health disorders totaled to 659. (4) This number increased to over 3,000 by 2004 and, finally, over 20,000 consultations in 2005 when the intervention was expanded to the entire province (Figure 2). (4) Therefore, consultations in mental health increased by over 3000% in the province of Nangarhar, and it can be concluded that access did indeed increase, likely as a result of the expanded scope of mental health services.

# Number of consultations for MNS disorders in Shinwar Cluster

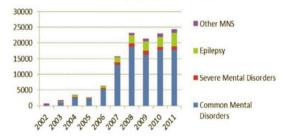


Figure 23: Number of Consultations for Mental Health Services Between 2002 and 2011 | HealthNet TPO development began in 2002, and was scaled up between 2005 and 2008 to the six regions of the Shinwar Cluster. This data demonstrates the increased access after implementation of the intervention.

As mentioned previously, HealthNet TPO had been contracted by the Afghan government to rebuild the health care infrastructure in Afghanistan. Based on HealthNet TPO's 2009 financial report, the total health care spending in Afghanistan summed to €55 213 726, whereas funds dedicated to their mental health and psychosocial services totaled €993 718. (9) Based on these figures, mental health care expenditures represented 1.8% of HealthNet TPO's total health care spending in the 2009 fiscal year. In order to extract any concluding information from this figure, we used

the WHO Mental Health Atlas 2011(10) (the 2006-2010 publication were unavailable) as a guideline to compare this value to other nations. In this report, Afghanistan falls into two categories based on its geographical location (Eastern Mediterranean Region) and its World Bank income level (Low). (10) Other countries in these two categories are listed in Figure 3. Based on this data, mental health care spending represented, on-average, 3.75% of total health care spending for countries in the same geographical region as Afghanistan. (10) Comparatively, countries that fall into the same income level as Afghanistan spent 0.53% of their health care budget on mental health services. (10) Therefore, two conclusions can be made when comparing Afghanistan's mental health care expenditure with geographically or financially similar countries. First, Afghanistan spent less on mental health services in relation to its total health care expenditures compared with other countries in the region, and second, Afghanistan spent more on mental health services than other countries who have similar income levels. It should be noted, however, that this data cannot be used to make a definitive conclusion on whether this expenditure is adequate to support the needs of the country or not.

Eastern Mediterranean Region	Low World Bank Income Level
Afghanistan	Afghanistan
Egypt	Dem. Rep. of Congo
Morocco	Burkina Faso
Qatar	Burundi
Saudi Arabia	Cambodia
United Arab Emirates	Bangladesh
Lebanon	Guinea

Figure 39: Classification of Countries – WHO Mental Health Atlas | Afghanistan's mental health expenditures are higher than the average of the countries of similar income level, but lower than the countries in similar geographical regions.

In order to bring together the other two factors in our analysis of the intervention's performance, we would need to analyze the quality of HealthNet TPO's intervention. This analysis could have looked at a number indicators, such as suicide rates, self-reported symptoms, DALYs attributed to mental health disease. Unfortunately, despite numerous attempts to obtain data from HealthNet TPO and the Dutch government, these values were inaccessible. This represents an enormous gap in the quality analysis, as it cannot be determined whether the resources directed towards mental health services in Afghanistan produced effective results.

#### Sustainability

The sustainability analysis of a global health intervention should consider various factors related to project design, quality, integration, and the community of interest. (11) The Cochrane Handbook for Systematic Reviews of Interventions recommends the model developed by Shediac-Rizkallah as a useful framework for determining sustainability in public health. (11, 12) This model contains three aspects of sustainability that can be used to evaluate the mental health services implemented by HealthNet TPO.

First, HealthNet TPO's intervention does not appear to be able to maintain or sustain any health benefits achieved through the program. The increased health service coverage in Afghanistan was associated with less time spent with each patient, which in turn potentially lowers the quality of each consultation. (4, 13) Shorter consultation times may largely affect women because they experience higher levels of anxiety and depression than men. (5) With the subordination of women in social life within Afghanistan, these appointments may serve as one of the few opportunities to address their mental health issues. Furthermore, the

program may be unable to continue delivering substantial benefits if financial and administrative assistance terminates. There was no projected plan for the program to be financially self-sufficient in the future. The program is currently funded by external sources, with the Global Fund as the primary donor, contributing to 49% of total funding (Figure 4). (9) The increased prioritization of mental health services in the BPHS may lead to more government financial assistance in the future but this is purely speculative. (14) In the short term, the program is sustainable due to the continual external funding by numerous organizations.

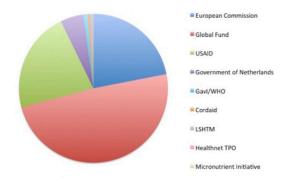


Figure 48: HealthNet TPO Project Funding Structure | The program is currently being funded by nine differed external donors. The Global Fund acts as the primary donor, contributing to 49% of the projects total financial support.

For the second aspect of sustainability, HealthNet TPO was indeed successful in institutionalizing mental health services, allowing activities to continue as part of the general health care system. Mental health services were successfully integrated by educating existing staff at each level of the health care system, while HealthNet TPO continues to provide further and updated mental health training. (15) As such, long-term viability of mental health services is possible because of its incorporation into primary care, but it is questionable whether these services could continue without the

administrative support of HealthNet TPO. The improved access to services, based on the increased number of mental, neurological, and substance use (MNS) consultations is a further indication of success from this perspective of sustainability.

Lastly, the program also achieved sustainability from a capacity-building perspective. There is an increased capacity in the Nangarhar community to appropriately treat mental health issues, as the activities of the program can be maintained and continued at the connumity level. HealthNet TPO strongly emphasizes community involvement to address mental health problems through educational workshops and support groups. Increased access to information helps foster a sense of empowerment within the community, or "community resilience", because local individuals learn the skills necessary to identify and address mental health problems. (5) It is implied that the trained community members are now able to educate others on mental health and sustain these support groups, should HealthNet TPO remove its services.

In summary, the program, based on its methodology, shows signs of sustainability. However, HealthNet TPO does not provide a clear plan for how mental health services are to be sustained if the NGO's support and external financial assistance were withdrawn in the future. Furthermore, the evaluation of this program would have benefitted and been further enhanced by statistics and data describing its success at the community and patient level.

# Conclusions on Mental Health Care in Afghanistan, Post-Intervention

In summary, the involvement of HealthNet TPO in Afghanistan has lead to the establishment of a mental health department within the government, as well

as the integration of mental health care services into the existing health care framework. The lack of program evaluation is the fundamental shortcoming of this case study. While the main goal of the intervention to improve access to mental health services was accomplished, no definitive conclusions can be made regarding its efficacy, particularly due to lack of data on clinical outcomes. The published evaluations are purely quantitative measures of the number of patients passing through the system, with little impact evaluation of the care they are receiving. In terms of clinical outcomes, HealthNet TPO posited that the shortened appointment times due to the increased demand may negatively impact the quality of care, as physicians may turn to favoring psychotropic interventions over the more time-consuming psychosocial alternatives. (4) However, there is no published analytical evaluation of mental health care at the individual patient level. There are indications that women are less likely to make use of social resources for mental health problems. (5) Understanding that women represent a vulnerable group in Afghanistan, it would have been interesting to measure gender differences in uptake of access to care for mental health. This data is integral to health care policy reform as it provides vital information for future improvements and developments.

In order to build an accurate and comprehensive evaluation on HealthNet TPO's overall impact on mental health care in Afghanistan, it is necessary to investigate how these implemented health care policies translate to clinical practices. Since this information has not been made available to the public, it is assumed that no evaluation was performed. The following are suggested evaluation methods. Patient follow-up is crucial to provide direct feedback and allow for the improvements at the level of the patient. (16) Efficiency is a key factor in health care, and as such, a database

containing patient records and medical history would provide for better organization and access to information by the administration and health care professionals. (17) Finally, a specialized task force charged with evaluating mental health practices would provide an overall perspective on how the policy is translated to the clinic and community posts.

As Afghanistan has been in a state of war for over 35 years, the population of this nation has suffered tremendously in terms of their safety, health, and psychosocial well-being. As financial resources allocated towards health care services are often lacking, mental health, especially in fragile states, is often an afterthought. It is important for mental health initiatives to be integrated into basic health services for all nations worldwide, as mental illness is one of the leading causes of global disability. Mental health care must also incorporate evidence-based practices that account for the particularities of women's mental health, their role in society, and the gender-based issues, discrimination, and biases they face. These mental health initiatives within Afghanistan should not end with HealthNet TPO, as there are still improvements to be made. Additional efforts need to be implemented in order to assess and improve the quality of care, increase access, and promote further education on the topic of mental health in order to reduce the stigma and discrimination surrounding mental illness.

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# The Doha Declaration in Action: An Examination of Patent Law Flexibilities in the South African Acquired Immunodeficiency Syndrome Epidemic

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# **Abstract**

Patent law flexibilities outlined in the Trade-related Aspects of Intellectual Property Rights agreement make it possible for low-income nations to provide affordable essential medicine during health crises. During the rise of the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic in South Africa, multinational pharmaceutical companies challenged the implementation of these flexibilities. In response to this lawsuit, the World Trade Organization enacted the Doha Declaration, an affirmation of the right of low-income nations to import and produce generic versions of patented essential medicines. This case study assesses the Doha Declaration's impact on access to HIV/AIDS treatment in South Africa by examining drug pricing, antiretroviral treatment coverage and drug licensing fees. The declaration ultimately contributed to the decrease in HIV/AIDS treatment costs and the subsequent increase in availability and affordability of life-saving drug regimens.

**Key words:** Drug accessibility, global health, human immunodeficiency virus/acquired immunodeficiency syndrome, patent law, South Africa

#### INTRODUCTION

Much of public health focusses on technical advancement: Better drugs, improved diagnostics and the development of new vaccines. These technologies undoubtedly play an indispensable role in ensuring health for all, but medicines, vaccines and assays cannot result in a positive impact unless the most vulnerable populations gain access to such treatments.

This case study focusses on an often overlooked factor of getting drugs through the 'last mile:' Patent law. In order for companies to risk investing in new technologies, they must be assured that they will make a profit from their investment, yet the resultant pricing may hinder the accessibility of such products to the most vulnerable populations. Here, we analyse how life-saving pharmaceuticals were made accessible to a population in desperate need through patent law flexibilities. Specifically, we will examine the increase in accessibility of antiretroviral (ARV) drugs in South Africa. We will link this improved accessibility to the patent flexibilities laid out in the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement and subsequent Doha Declaration.



We begin with a description of the relevant legal documents outlining patent flexibility and the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) crisis in South Africa. The intervention of interest in this case study, the Doha Declaration, is then described followed by a quantitative and qualitative assessment of its impact.

#### BACKGROUND

# Trade-Related Aspects of Intellectual Property Rights and its flexibilities

Broadly speaking, intellectual property rights seek to protect inventors by giving them exclusive control over intangible 'creations of the mind'. Intellectual property issues have played a significant role on the international stage vis-à-vis

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the TRIPS agreement. The agreement entered into force for members of the World Trade Organization (WTO) in 1995.<sup>[1]</sup> This agreement outlines the minimum standards for intellectual property rights protection for the WTO members.

The intent of the TRIPS agreement is to increase global incentives in research and development. [2] The TRIPS agreement compels all member countries to abide by a minimum level of intellectual property protection in all fields, with respect to both the processes and the products. Non-compliance is subject to the WTOs dispute settlement mechanism, which may lead to a variety of trade sanctions. [3]

The critical feature of the TRIPS agreement with respect to this topic is its provision of a degree of flexibility for certain member countries. These flexibilities are designed to 'allow developing countries and least developed countries (LDCs) to adopt measures necessary to protect public health and nutrition, and to promote public interest in sectors of vital importance to their socioeconomic and technological development'. [4] Thus, in the development of their national intellectual property laws, developing countries and LDCs are empowered to focus on promoting the public interest without being impeded by the stringency of the TRIPS obligations.

The TRIPS flexibilities that are of particular interest for our purposes include: [3]

- Transition periods: LDCs were not obliged to implement the provisions of the TRIPS agreement on pharmaceutical products until January 1<sup>st</sup> 2016. LDCs were eligible for extensions of this transition period if they had not built a viable technological base by that deadline
- Compulsory licensing: The government can authorise a third party to produce a patented invention without the consent of the patent holder. This flexibility requires that the holder of the compulsory license produce strictly for the domestic market
- Parallel importation: Parallel importation grants governments the right to import drugs, without the authorisation of the patent holder, from countries where the cost is lower
- The Bolar provision: The Bolar provision allows competitors (often, generic manufacturers) to prepare production and regulatory procedures before patents expire.

Cumulatively, these TRIPS flexibilities attempt to address the unique needs of low resource settings by offsetting the harshness of the TRIPS obligations themselves.

One way to apply these flexibilities was for a developing country to demonstrate that it was in the midst of a public health emergency. By the late 1990s, no one could deny that the HIV/AIDS epidemic in South Africa had reached catastrophic proportions.

# Human immunodeficiency virus, acquired immunodeficiency syndrome in South Africa

As the world came to realise the dangers posed by HIV, South Africa was the epicentre of the epidemic with an estimated 5

million people infected by the year 2000. This amounted to about one in nine South Africans.<sup>[5]</sup>

While ARV treatment was becoming readily available in industrialised countries throughout the 1990s, South Africa, where the burden of disease was highest, still had limited access to these medicines.<sup>[6]</sup>

Since 1994, the country's healthcare system had been functionally two-tiered. Close to 20% of the population, predominately white, were covered by private healthcare, whereas the remaining population relied on the public system. The existing public healthcare was characterised by 'irrational use of resources, poor working conditions and inadequate infrastructure'. [7] Many South Africans simply could not afford to buy these essential drugs from the private system. Three-drug ARV therapy combinations cost 10,000–15,000 USD per person per year, whereas 11% of South Africans were living on <1 USD a day and 34% were living on <2 USD a day. [8]

The first antiretroviral treatment (ART) approved for HIV infection, zidovudine, became available in 1987. [9] However, since zidovudine cost about 1000 USD per month, most individuals in South Africa could not afford the regimen. [7,10] As a result, in 1996, the South African government began a healthcare reform, the aim of which was to increase the access and affordability of essential medicines. Part of this reform was the implementation of the National Drug Policy, which included a set of objectives to improve the public health system including reducing drug prices, developing a local pharmaceutical industry for the production of drugs and increasing the number of prescriptions of generic drugs in both private and public sectors. [7,10]

#### The medicine act amendment

In 1999, South Africa took legislative action to amend the South African Medicines and Related Substances Control Act to add Section 15C, known as the Amendment Act. This act created the legal framework to relax domestic patent laws and enable access to affordable medicines, thereby allowing the South African government to use the generic substitutions of off-patent drugs and to permit parallel importation of patented drugs.[7] While the right to take this action had been outlined in the TRIPS agreement, it had not yet been exercised on a national scale. In response, fifty pharmaceutical companies sought to prevent the enactment of the Amendment Act and subsequently took the South African government to court, claiming that the amendment was unconstitutional and violated the TRIPS agreement, which South Africa had signed. The European Commission and the US government were lobbied by the Pharmaceutical Researchers and Manufacturers of America to apply pressure on the South African government to withdraw the Amendment Act. The US Trade Representatives (USTR) placed South Africa on a special 301 'watch list', and in March 1998, the USTR withheld trading of South African products and threatened to apply further trade sanctions.<sup>[7]</sup>

The lawsuit brought the fight against HIV in South Africa to the forefront of global media and exposed the measures that the pharmaceutical companies, supported by the US government, were prepared to take to protect their intellectual property.[11] The activism of several HIV advocacy groups played an essential role in pressuring the US government to modify its policies with regard to intellectual property rights. [6] The South African Treatment Action Campaign (TAC) called for international protests around the world against 'drug profiteering'.[7] HIV activists generated negative publicity targeting presidential candidate Al Gore regarding his role as co-chairman of the US/South African Bi-national Commission. Nongovernmental organisations (NGOs) including Consumer Project International, Health Protect International and Doctors without Borders (Médecins sans Frontières, MSF) united to organise a conference in opposition to the WTO ministerial session. Known as the Amsterdam Conference, the aim was to interpret the provisions of the TRIPS agreement with public health in mind and to better understand how the WTO agreements affect resource-poor countries. The conference was attended by 350 participants representing 50 countries and their success overshadowed the Seattle WTO conference, which was bombarded with demonstrations. The coordinated efforts of the NGOs and activists caused the US government to distance itself from the litigation. By late 2000, the pharmaceutical companies could no longer rely on their governments for support, and in April 2001, the lawsuit was dropped. [6,7]

#### **The Doha Declaration**

While the lawsuit was ultimately dropped, the question remained: would developing countries actually be allowed to use the flexibilities outlined in the TRIPS agreement or would each attempt be met with lengthy and expensive legal action?

WTO members met in Doha, Qatar, to resolve this issue and in November 2001, the WTO adopted the Doha Declaration on the TRIPS agreement and public health. The declaration sought to reaffirm the right of governments to employ TRIPS flexibilities to protect public health. This document clarified that each WTO member had the freedom to determine what constitutes a national emergency, assess the need for and grant compulsory licensing and utilise parallel importation. <sup>[7]</sup> The Doha Declaration marked a pivotal change in global policy with regard to Trade-related Intellectual Property law by unequivocally stating that developing countries could and should take advantage of the flexibilities outlined in the TRIPS agreement. The ultimate goal of this document was to enable greater access to much needed essential medicines such as ART. <sup>[6,11]</sup>

#### **Political opposition**

Unfortunately, while the Doha Declaration upheld the right to use patent law flexibilities to improve access to life-saving ARV drugs, the newly elected President of South Africa opposed the use of ARVs entirely.

At the beginning of 2000, President Mbeki sent a letter to his international counterparts expressing his skepticism that HIV was truly the root cause of AIDS. He argued that other factors, such as socioeconomic status, may be the origin of AIDS.[5] In addition, President Mbeki, together with the Minister of Health, Dr. Manto Tshabalala-Msimang, claimed zidovudine was poisonous and publicly advocated for the use of alternative treatments and nutritional interventions to treat AIDS. Despite the extensively documented clinical benefit of zidovudine, the government refused to implement the ART treatment.[12] In 2001, the government even declined Boehringer Ingelheim (BI) offers to donate the necessary medicines for a treatment programme for HIV-infected pregnant women, claiming that the drug's efficacy and side effects had not been sufficiently studied by the South African government.[13] The government's mistrust towards Western medicine was due in part to the historically present racial segregation and oppression of the black population during the colonial regime. As a result, some black South Africans feared further marginalisation and harm through various methods such as the distribution of poisonous medications.<sup>[5]</sup> It is estimated that by withholding available ART, the government contributed to approximately 30,000 AIDS-related deaths and the infection of 35,000 babies with HIV by denying ART treatment to the South African population.<sup>[14]</sup> In the 2000s, the Treatment Action Campaign played a pivotal role in stopping the anti-ART campaign. The TAC successfully promoted the implementation of ART therapy for the prevention of mother-to-child transmission by suing the government over its inaction.[12] Based on these advocacy efforts, the issue of ART access gained momentum at the local and international levels. In 2003, the Mbeki government responded to national and international pressure by approving a programme of national access to ART and prevention of mother-to-child transmission programmes.[15]

This protracted opposition to ART occurred simultaneously with the efforts of NGOs and generic pharmaceutical companies who were working tirelessly to increase the availability and use of ARV drugs. While the effect of the political opposition to ART is not the central question of interest for this case study, it undoubtedly hampered the uptake and use of ARVs. It is likely that without President Mbeki's opposition, the effects of the Doha Declaration may have been even more dramatic.

# **Impact evaluation**

The goal of this case study was to evaluate whether the Doha Declaration was successful in reducing the price of and increasing access to ARV drugs. To evaluate its effectiveness, we will examine:

- Legal proceedings that cited the Doha Declaration
- Drug prices pre- and post-Doha Declaration
- ARV coverage rates pre- and post-Doha Declaration
- Licensing fees pre- and post-Doha Declaration

#### **Direct applications**

In 2003, the TAC filed a complaint with the South African Competition Commission (a government body designed to ensure equality and efficiency in the South African economy) against two major pharmaceutical companies, GlaxoSmithKline (GSK) and BI. The TAC alleged that the companies were overpricing essential ARV drugs and blocking access to generic production. The suit was ultimately settled. The settlement documents directly cited the Doha Declaration as evidence that GSK and BI were legally bound to allow generic licensing.<sup>[16]</sup>

The Doha Declaration's support for TRIPS flexibilities also spurred the South African pharmaceutical company, Aspen Pharmacare, to begin requesting voluntary licenses to manufacture generic ARV drugs. In 2007, it held eleven licenses to produce generic AIDS drugs and remains one of the largest generic producers in South Africa.<sup>[17]</sup>

Without the Doha Declaration, pharmaceutical companies would have little to no incentive to grant generic licenses without large royalty fees. Forcing companies to give compulsory licenses encourages companies such as Aspen to produce generic drugs. Furthermore, competition between multiple generic manufacturers can contribute significantly to reducing drug prices.

Drug pricing, ARV coverage and licensing fees are indirect measures of the Doha Declaration and it is important to remember that these measures are likely to be affected by multiple factors in addition to patent law including political will, advocacy, improvements to manufacturing and foreign aid. However, the Doha Declaration is fundamental to many of these measures. Without the clarity provided in the Doha Declaration, generic licenses would be unlikely to be granted without a lawsuit, drug prices would not fall until patents fully expired and licensing fees would remain high. Thus, while we cannot fully attribute these changes to the Doha Declaration, we remain confident that this document is a major driver of the following observed phenomenon.

# **Drug pricing**

Table 1 shows the prices of several ARV drugs sold in South Africa immediately before the TAC complaint against GSK and BI and the reduced prices for the same drugs using the parallel importation clause in the TRIPS agreement to import these medicines from generic drug manufacturers outside of South Africa. The right to exercise parallel importation for essential generic drugs was not exercised before the Doha Declaration.<sup>[18]</sup>

Table 1: A comparison of antiretroviral drug prices in 2003 in South Africa and prices available through parallel importation of generics

Drug	Price per month (USD)		
	Price in South Africa in 2003 (\$)	Price with parallel importation (\$)	
Zidovudine	37	6	
Lamivudine	40	3	
Zidovudine/lamivudine	50	9	
Nevirapine	23	5	

While parallel importation rights affirmed in the Doha Declaration dramatically reduced the price of ART, cost is not the only barrier to treatment. Patent flexibilities can result in lower prices, but unless there is government support and adequate health infrastructure, even low-cost drugs can fail to reach the patient.

# **Antiretroviral coverage**

After 2001, ARV coverage began to rise rapidly [grey line, 8 Figure 1] began to increase throughout Sub-Saharan Africa.<sup>[19,20]</sup> A multitude of factors contributed this upward trend including advocacy, education, international aid and most importantly, the advent of generic drugs.

While ART use has increased in South Africa, coverage remains far from universal. The ultimate goal of the Doha Declaration is to provide access to life-saving medicines for the world's most marginalised populations. Despite the progress in ARV coverage rates, failing to reach even 50% of the affected population in need indicates that, along with weaknesses in the general health system, the licensing systems supported by the Doha Declaration are not being utilised to their full extent.

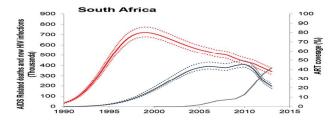
# **Drug licensing**

Immediately after the Doha Declaration, the proportion of purchased ARVs that were generic began to increase throughout Sub-Saharan Africa.

Before the Doha Declaration and the settlement set by the Competition Commission, Aspen Pharmacare had only been able to license generics from GSK and BI for a 30% and 15% royalty fee, respectively. In the settlement between the TAC, GSK and BI, the companies agreed to license drugs with a 5% maximum royalty fee.<sup>[18]</sup>

# CONCLUSION

In sum, the Doha Declaration has made a meaningful impact on several aspects of ART availability and accessibility in South Africa. Government bodies ordering pharmaceutical companies to grant generic licenses directly cited the declaration. Pharmaceutical companies also cited it as a motivator to diversify into generic drug production. The downstream effects of the declaration also include reduced drug pricing, increased generic licensing and increased coverage. While the gain in accessibility and use of ART drugs in South Africa is not



**Figure 1:** Grey line shows the percentage of the South African human immunodeficiency virus-positive population estimated to be using antiretroviral treatment between 1990 and 2013. The red and blue lines show the number of human immunodeficiency virus infections and deaths, respectively.

solely caused by the Doha Declaration's support of the TRIPS flexibilities, it is likely that without it, many of the public health advancements would not have occurred as quickly. As such, the authors believe that the Doha Declaration was successful in its aim to promote access to essential medicines.

There are, however, limitations to its effect. The TRIPS flexibilities apply only to essential medicines in developing countries who have declared health emergencies.<sup>[3]</sup> This narrow definition means that second-line therapies are often barred from the same patent law flexibilities that first-line ART drugs benefit from. In fact, second-line ART drug pricing has remained largely stagnant over the last decade.<sup>[21]</sup> There is, however, a benefit to the high prices of these second-line therapies. The profit margins for these newer drugs are not threatened by TRIPS maintain the incentive for pharmaceutical companies to continue researching new drugs.

In closing, the Doha Declaration affirmed that pharmaceutical companies should not profit at the cost of the world's most vulnerable populations. Born out of a South African lawsuit, it produced real and hopefully long-lasting impacts on the availability and use of ART in the AIDS epidemic.

#### **Looking forward**

The patent flexibilities outlined in the TRIPS agreement are under threat whenever a new international trade agreement is brokered. In October 2015, the Trans-Pacific Partnership (TPP) was signed. According to the US Manager and Legal Policy Adviser for the MSF Access Campaign, Judit Rius Sanjuan, the TPP will 'go down in history as the worst trade agreement for access to medicines in developing countries, which will be forced to change their laws to incorporate abusive intellectual property protections for pharmaceutical companies'. [22] Unfortunately, the full impact of the Doha Declaration may be revealed when its flexibilities are reversed.

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# A Case Study of Gavi's Human Papillomavirus Vaccine Support Programme

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# **Abstract**

Human papillomavirus (HPV), a sexually transmitted DNA virus that can lead to cervical cancer, is the most common cancer among women in developing regions. More than 270,000 women die per year from cervical cancer globally, and 85% of those deaths occur in developing countries. In the past, many low- and middle-income countries (LMICs) have been unable to afford the implementation of HPV vaccination programmes, resulting in high cervical cancer mortality rates. Gavi, an organisation created to improve worldwide access to vaccines, undertook an initiative that had the goal of decreasing the price of an HPV vaccine to under \$5 and increasing access for adolescent girl populations in LMICs. This was done through market shaping, co-financing and implementation support. This case study will present and evaluate Gavi's intervention by assessing targets, investigating cost-effectiveness and identifying strategic challenges.

Key words: Cervical cancer, Gavi, global health, human papillomavirus, immunisation

# Introduction

Human papillomavirus (HPV) is a sexually transmitted DNA virus that infects the skin and mucous membranes. Worldwide, the prevalence of HPV is ~11.7%. The frequency of HPV cases is much higher in developing regions, with Eastern Africa (33.6%) and the Caribbean (35.4%) having the highest prevalence. [1] Although approximately 90% of HPV infections regress to a subclinical state within 2 years, a persistent infection may lead to cancer. Many of the 100+ HPV strains are oncogenic with variants 16 and 18 alone causing roughly 70% of cervical cancer cases.<sup>[2]</sup> Cervical cancer is the most common cancer among women in developing regions. With a 52% mortality rate, more than 270,000 women die per year from cervical cancer globally, and 85% of those deaths occur in developing countries. Effective screening, vaccination and treatment programmes can reduce the high mortality rate, but these programmes are not readily available in developing regions.[2]

There are currently several HPV vaccines available: Cervarix® produced by GlaxoSmithKline (GSK), Gardasil® (Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant), and Gardasil®9 (Human Papillomavirus 9-valent

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Vaccine, Recombinant) which are both produced by Merck and Co. These products are virus-like particle (VLP) vaccines containing complex protein structures. By 2016, national HPV vaccination programmes were active in many regions including North America, Australia, most of South America, the majority of Europe and a handful of African countries. These vaccine programmes target children between 9 and 13 years of age and are typically administered in three doses over 6 months. Recently, however, the World Health Organization (WHO) has suggested that two doses of the HPV vaccine may be effective.

When the first HPV vaccine, Gardasil, was released in 2006, it cost between \$100 and \$233 per dose in developed countries and between \$30 and \$100 per dose in developing countries. [6] This pricing left the vaccine beyond the means of many low- and middle-income countries (LMICs); hence, in 2011, the Pan American Health Organization negotiated a price of \$14 per dose for its member countries. [6] Despite this

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decrease in price, it is still too expensive for many LMICs. In comparison, the HPV vaccine would need to be offered at \$2 per dose to be comparable in cost-effectiveness to the vaccines against *Haemophilus influenzae* type B and hepatitis B, which have achieved high uptake in African countries.<sup>[7]</sup>

#### **Problem statement**

HPV infection leads to over 70% of cervical cancer cases, which in turn causes more than 270,000 deaths of women every year, mostly in the developing world. Although effective and safe vaccinations are available to prevent HPV infection, many of the countries most burdened by HPV and cervical cancer have been unable to afford the implementation of HPV vaccination programmes. Innovative and cost-effective strategies are therefore needed to lower the price of HPV vaccines and ensure that they reach those who need them most.

# The intervention: Gavi's human papillomavirus vaccine support programme

# Gavi's background

Gavi, the vaccine alliance, is a global health alliance whose goal is to improve worldwide access to vaccines. Gavi was founded upon a variety of public-private partnerships between national governments, UN agencies, private sector and nongovernmental organisations and foundations. The Alliance received initial funding of \$750 million from the Bill and Melinda Gates Foundation and is now funded by governments (77%), corporations and foundations (22%), and private individuals (1%).<sup>[8]</sup>

#### Gavi's human papillomavirus vaccine targets

In 2011, Gavi announced that it would offer HPV vaccine procurement and implementation support to qualified countries. [9] To achieve Gavi's goal of making HPV vaccines affordable and accessible to the world's poorest, the organisation set three primary targets:

- Negotiate with HPV vaccine manufacturers to reduce the price of the vaccine from \$30 to \$100 per dose range to a more affordable price of under \$5 per dose. While Gavi has not commented directly on the origin of this price target, it corresponds with cost-effectiveness benchmarks suggested by the WHO and other studies<sup>[5,7,10]</sup>
- Increase access to the vaccine. Gavi's targets were to immunise one million girls against HPV by 2015 and to immunize 33 million girls by 2020.<sup>[11]</sup> To promote this target, Gavi set an additional target to implement its first HPV vaccination programme in 2013
- Collaborate with other pharmaceutical producers to encourage the development of more HPV vaccines by 2018.<sup>[9]</sup>

#### Gavi's strategy

What makes Gavi's intervention notable is its three-pronged business model of market shaping, co-financing and implementation support. Furthermore, Gavi's HPV vaccination support programme focuses on a hard-to-reach population (adolescent girls) in nations with an annual per capita gross national income (GNI) below or equal to its eligibility

threshold. Gavi defines a country as eligible if its GNI per capita over the past 3 years is equal to or below \$1,500.<sup>[12]</sup> Gavi aims to ensure the sustainability of HPV vaccination programmes through shifting the terms on which vaccines are supplied: Moving from the whims of charity to the profit and marketing motives that strongly resonate within pharmaceutical companies. Thus, countries working with Gavi do not receive vaccines for free but must account for their real cost.

#### Market shaping

Market shaping is a strategy whereby both the demand and, therefore, the supply of a product (the vaccine) are intentionally altered to make a large number of cheap units be as, if not more, profitable than a small number of expensive units. This is achieved when a number of countries pool and guarantee their demand. This gives pharmaceutical companies leeway to provide the vaccine at a lower price.

Gavi's strategy requires influencing "pull factors" to change the demand for the drug. To do this, Gavi must ensure that participant countries include the HPV vaccine on their policy agendas so that funding from both countries and Gavi's donors for vaccine procurement is predictable and stable. Measures to strengthen healthcare delivery systems must also be put in place. [13]

Gavi's market-shaping strategy also involves influencing the "push factors" to change the supply of the vaccine. This is done by pooling the demand of many countries to gain bargaining power in negotiations with pharmaceutical companies. Other supply-side interventions include leveraging existing capacities to improve vaccine delivery, guaranteeing stable and accurate demand forecasts and providing incentives to new manufacturers to work with this model. Using this model, pharmaceutical companies can go from a low-volume-high-cost strategy to a high-volume-low-cost strategy, thus creating a market where more individuals can pay for the drug and the company is able to sell more.

#### Co-financing

To ensure the financial sustainability of their model, Gavi establishes a co-financing model with each country that it supports. The co-financing model requires governments of participating countries to contribute towards the cost of the vaccines. [14] Co-payments for the HPV vaccine are calculated according to the country's economic status: Countries that are classified as low-income will be required to contribute less than stronger situated countries. A country's ability to co-finance is determined at the application stage. As a country's GNI increases, the proportion of the vaccination costs paid directly by its government will increase. Once the country's GNI reaches the upper threshold for Gavi support, the country graduates from Gavi funding. [12]

#### **Implementation support**

Gavi has created two paths by which a country can gain its support in implementing HPV vaccination programmes. To receive funding, a country must demonstrate its capacity to immunise >50% of adolescent girls (ages 9 - 13) in an

average-sized district. If this is demonstrated, Gavi will begin working with the country to implement a national scale HPV vaccination programme.[15] If a country cannot demonstrate this capacity, Gavi will assist the country in running a demonstration programme. Gavi's board established three purposes of a demonstration programme. First, it is meant to assess the delivery strategy coverage, feasibility, acceptability and cost in order to create evidence supporting a national scale Gavi-supported intervention. Second, a programme is meant to examine how HPV vaccine delivery can be integrated with other adolescent health interventions already in place in the country. Third, the demonstration programme is an opportunity to encourage the integration of HPV vaccination into a national cervical cancer prevention and control strategy. [16] After 1 year of running a demonstration programme, the country must be able to show that the extant programme can be successfully scaled up to receive Gavi support for the introduction of a national-level programme.

## **Evaluating Gavi's intervention**

# **Progress towards targets**

Lower vaccine price

Gavi negotiated the supply and costing with two pharmaceutical companies: Merck and Co and GSK. By doing so, the price of the HPV vaccine was reduced to \$4.50/dose from Merck and \$4.60/dose from GSK.<sup>[17]</sup>

#### Increase access to the vaccine

Gavi's demonstration programme strategy reached its target to implement the first programme in 2013 with Kenya. Since then, Gavi-supported programmes have vaccinated one million girls reaching its second target. Gavi's targets, however, should be evaluated beyond individual countries given that its market sharing strategy hinges on pooling the demand from many countries participating in the programme.

Gavi forecasted that by 2015, 21 countries would conduct demonstration projects and 8 countries would launch national HPV vaccination programmes. As of October 2015, 22 countries had implemented demonstration projects, in line with the forecast. Only three countries, however, had been approved for national-level vaccination programmes: Rwanda and Uganda, who launched their national programmes in 2014 and 2015, respectively, and Uzbekistan, who will launch its programme in 2017.<sup>[11]</sup>

#### Encourage new producers

Data regarding the third target, to work with more pharmaceutical companies by 2018 to produce a cheaper vaccine, were unavailable.

#### Human papillomavirus prevention and cost-effectiveness

Several studies have concluded that HPV vaccination of pre-adolescent girls is cost-effective for a large majority of Sub-Saharan African countries when the cost per vaccinated girl is less than US\$25.<sup>[5,7,10]</sup> This represents the cost of 3 doses at \$5 per dose and estimates for vaccine wastage, transportation, administration, immunisation support and other programmatic costs. This is in line with the prices

offered to countries through Gavi. These studies also note the importance of various methods of screening in preventing cervical cancer. Many of these alternatives have proven to be difficult if not impossible to implement in resource-poor settings.<sup>[7]</sup> In addition, screening requires a bolstering of healthcare infrastructure on a larger scale than that of a primary prevention vaccination programme.

Due to the lack of data, the best proxy available for effectiveness is the number of girls vaccinated to date. As it has been shown that the HPV vaccine prevents infection with the most cancer-related and death-associated HPV types (16 and 18), it can be anticipated that high vaccination coverage will reduce the mortality of cervical and related cancers. [10,19] A full cost-effectiveness evaluation of Gavi's HPV programmes could be furthered by comparing the cost and number of deaths averted in this intervention to results from other related interventions (such as expanding pap smear access and cervical cancer treatment). Unfortunately, there are no data directly comparing the results of Gavi-supported programs with other programs addressing HPV and cervical cancer in the same regions. While all available data indicate that Gavi-supported vaccination programmes are cost-effective, the true impact of Gavi's intervention on health outcomes will only become clear after several decades of implementation and monitoring. In addition, these data do not paint a full picture of the opportunity cost of choosing HPV vaccination over other interventions.

# Strategic challenges

Many new vaccine programs face implementation difficulties, in part due to anti-vaccination organisations' campaigns. [20] Still, due to its higher cost, older target population and connection to sexual behaviours, the HPV vaccine likely faces more implementation challenges than most.

# **Delivery challenges**

An HPV vaccination programme requires a new vaccination delivery platform for adolescents since the vast majority of vaccination programmes in developing countries are targeted at infants.[20] Creating a platform for the HPV vaccine that targets older girls contributes to the HPV vaccine's higher cost. Yet, vaccinating a large number of adolescents is needed for developing countries' populations to benefit from herd immunity.[20] Reaching marginalised adolescent girls makes widespread HPV vaccination in Gavi-supported countries difficult.<sup>[21]</sup> As a protein-based injectable drug that is temperature and time sensitive, the vaccine itself is also unsuited for delivery in many LMIC climates.[22] Edible vaccines (as opposed to injections by healthcare workers) are being considered for the second-generation HPV vaccine developments. [22] Perhaps, Gavi's future procurement negotiations (Target 3) should include manufacturers researching these more practical options.

#### **Moral considerations**

HPV vaccination initiatives also face ethical challenges: Considering that HPV can affect both boys and girls (although girls face the worst effects and bear the burden of cervical cancer), is it fair that only girls are being targeted for vaccination? Kane *et al.*, explained that many men will not be protected from HPV for years (i.e., until heterosexual herd immunity results), and men who have sex with men will continue to face HPV contraction risks. Furthermore, considering that HPV is spread through sexual activity, vaccinating boys could contribute to further herd immunity, especially if the female target population only achieves lower coverage levels.<sup>[20,23]</sup>

Negative attitudes towards the vaccine may also be an obstacle to programme implementation. Anti-immunisation groups have already targeted the HPV vaccine, claiming that HPV vaccines have had deadly results.<sup>[20]</sup> The HPV vaccine's connection to sexual behaviour can pose a problem in sexually conservative cultures.<sup>[20]</sup> One strategy that can help adjust countries' attitudes towards the vaccine is a marketing campaign. Kane *et al.*, found that programme marketing which focused on the drug's ability to prevent cervical cancer, rather than on how HPV is transmitted, was more successful.<sup>[20]</sup>

#### **Demonstration projects**

Gavi-supported HPV demonstration programmes may prove to be a structural weakness in the initiative. The demonstration projects are meant to be used as learning opportunities for countries to determine their capacity to scale up vaccinations programmes to a national level. However, Gavi itself has admitted that there is "a degree of misalignment between the demonstration project's learning objective and the requirement for countries to have a demonstrated ability to qualify for support for national introduction".[24] This incentivises countries to choose target sites for demonstration projects that will provide the easiest access to and strongest uptake by the target population. High-coverage resulting from choosing easier target sites signifies that countries are more likely to be deemed eligible for Gavi support. [24] However, these results from locations most amenable to a vaccine programme could suggest an inflated portrayal of the country's actual capabilities in creating HPV vaccination programmes that would reach adolescent girls on a national scale.

#### Changing policies and reduced demand

Finally, vaccine policy changes have challenged Gavi's market-shaping abilities. For its market-shaping strategy, Gavi forecasted the demand for the HPV vaccine based on the recommended course of three doses per individual. Soon after the demand was calculated, the WHO suggested that a two-dose schedule might be sufficient. The UNICEF, which procures the vaccine for Gavi-eligible countries, reported that 4 million doses were bought as of May 2015, which is less than was forecasted. [15] The WHO recommendation could, in theory, cause the demand for vaccine doses to decrease, which in turn could reduce Gavi's negotiating power with pharmaceutical companies. This indicates that seemingly beneficial policy changes could negatively affect Gavi's strategy.

# **Cost of vaccine**

Ultimately, just under \$5 per dose is still a high price for LMICs, especially from the perspective of long-term,

independent sustainability. Padmanabhan *et al.*, believe that in low-income countries, doses should cost under \$2 for the vaccine to be broadly adopted in the long-term. <sup>[3]</sup> The high costs of new vaccines have played a factor in Gavi's decision to drop 16 LMICs, such as Honduras and the Democratic Republic of the Congo, from Gavi support. <sup>[25]</sup> Numerous factors contribute to vaccines' high costs, including the vaccine's demand, as well as the length of time the vaccine has been on the market. <sup>[25]</sup>

One of the biggest challenges that mass HPV vaccination campaigns face is overcoming its cost as a new vaccine. Médecins Sans Frontières has noted that in only 10 years, the cost of a recommended set of vaccines to protect a child has risen 25 times to nearly \$40, in part due to newer vaccines being more expensive. [26] With limited budgets, developing countries must prioritise their spending and have to ask whether vaccinating against HPV (one relatively expensive treatment) is worth the opportunity cost of other treatments that could have been provided with that money. [20] Older vaccines cost as low as \$0.19 per dose so even at \$4.50 per dose the HPV vaccine is still relatively costly. [25] Countries might feel that the HPV vaccine does not offer enough "bang for its buck," especially once countries graduate from receiving Gavi support and must pay for each dose themselves.

#### Lack of competition

As target 3 implies, the lack of HPV vaccine competitors is a weakness in Gavi's current strategy. After all, they have negotiated a long-term deal with two companies (Merck and GSK) at once, and these are the only two companies that currently have approved HPV vaccines on the market. This Gavi agreement is not the first time that Merck and GSK have shared resources on an HPV vaccine project: To avoid lawsuits from each other and to get both of their HPV vaccines to market in a timely fashion, GSK and Merck cross-licensed their technologies to each other.<sup>[27]</sup>

Gavi is determined to bring HPV vaccines to LMICs as soon as possible; it is not waiting for cheaper vaccines to be produced (even though HPV vaccines have only been around for ten years). In Gavi's 2012 procurement strategy, it planned to negotiate deals with Merck and GSK for the period lasting from 2013 through 2017. Gavi's procurement strategy noted that it did not expect any new HPV vaccine to be available before 2018. HPV vaccines at least for now, is to sustainably support the development of national HPV vaccination programmes in LMICs when there are no cheaper alternatives available in the near future. Gavi and its countries (via co-payments) must pay for large amounts of trade-named (although admittedly lower-priced) vaccines to vaccinate enough girls.

#### Patent and resource capacity issues

In 2006, Merck's Gardasil was the first HPV vaccine introduced to the market. [28] Since a key patent for GSK's Cervarix technology was filed and approved in 2006 [29] and Merck's Gardasil's was issued in 1998 [30] and patents tend to last about twenty years, patent-related issues surrounding

research and generic production of these vaccines will probably not be overcome for several more years. [27] However, according to research on HPV vaccine patents, patents probably will not be the main inhibitor of cheaper HPV vaccine manufacturing. After studying the patents involved in Cervarix and Gardasil, Padmanabhan *et al.*, found that Indian manufacturers can probably manufacture a bivalent HPV vaccine very similar to the current vaccines as long as the combination of VLP proteins in the new product is not identical to Gardasil's or Cervarix's. [3]

It might not be patent issues, but knowledge and resource capacity issues, which prevent the development of affordable HPV vaccines. As large, complex biological molecules produced using cell lines, the active agents in HPV vaccines are considered "biologics" rather than "small molecule drugs" (such as aspirin). [28] It is very challenging to prove that two biologics are the exact same (as opposed to proving that two small molecule drugs are the same) because biologics are so much larger and more complicated than small molecule drugs. [28] Identical small molecule drugs might be produced using several different pathways; therefore, patents protect small molecule drugs as much (if not more than) knowledge of the production process. However, with complex biologics, the production process determines the final product; the same product can probably not be reproduced using alternative pathways.<sup>[28]</sup> The process is not typically patented. It is a fiercely defended corporate secret protected even further by the fact that since it is unpatented, generic drug manufacturers cannot search the patent literature for production ideas. [28] Therefore, (unlike for small molecule drugs) even once the patents on the active ingredients in Cervarix and Gardasil end; unless detailed knowledge of the cell lines, the molecules themselves, and the exact processes used to produce these vaccines become known; generic production of these specific HPV L1-VLPs will probably not be possible.

Interestingly, public universities actually developed many of the procedures critical to the downstream development of the currently available HPV vaccines. However, the universities offered the licenses for many of these critical technologies exclusively to pharmaceutical corporations. [28] If these universities had instead offered their licenses and expertise to cheaper drug companies (for example, Indian generic drug manufacturers), as the second-generation HPV vaccine researchers are now doing, the first-generation HPV vaccines might have been more affordable. [3] Perhaps, Gavi should be supporting these university-LMIC research partnerships as part of its target three goals instead of funding Merck-GSK's through negotiations.

# CONCLUSION

Gavi's strategy is significant because it provides a way for LMICs to implement sustainable national-level HPV vaccination programmes targeting an adolescent population using market forces to its advantage. Gavi managed to achieve its first two major goals as it successfully lowered the negotiated vaccine prices down to under \$5 per dose and vaccinated 1 million girls by 2015. It has also managed to increase accessibility to adolescent populations in these countries as shown in its ability to implement 24 demonstration projects (its original target was 21 demonstration projects by 2015).

It is too early to determine whether Gavi's strategy will succeed or not; after all, 24 demonstration projects are still in the works. However, Gavi's results so far have been modest at best. Only two countries (Rwanda and Uganda) had implemented a national strategy when Gavi's goal was to have eight countries with national strategies by 2015. Gavi's third target (to collaborate with more pharmaceutical companies to produce cheaper vaccines) has no indication of success thus far. Gavi's strategy has faced delivery challenges, potentially inflated demonstration project results and the threat of reduced demand. However, most critical to the HPV vaccine's adoption in LMIC's is the cost of the vaccine, which many still consider to be too high relative to other treatments for countries with finite health spending resources to justify. Without competition from cheaper HPV vaccines, this cost problem will not likely resolve itself soon. Overall, while vaccines can certainly be cost-effective (especially in regions where HPV screening services are unavailable), Gavi's strategy might have had a better chance of long-term success if it waited for cheaper vaccine alternatives to be developed or focused on promoting their development. As it stands, countries may drop out of the Gavi programme if they cannot meet their co-payments (or once they graduate, their full payments); or, they may opt-out of the programme entirely. If costs were lower, countries would have a better chance of developing sustainable national HPV vaccination strategies. Gavi may be able to implement demonstration projects but to claim that those projects are likely to produce the multitude of sustainable national strategies that Gavi wants remains unconvincing.

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Nil.

#### **Conflicts of interest**

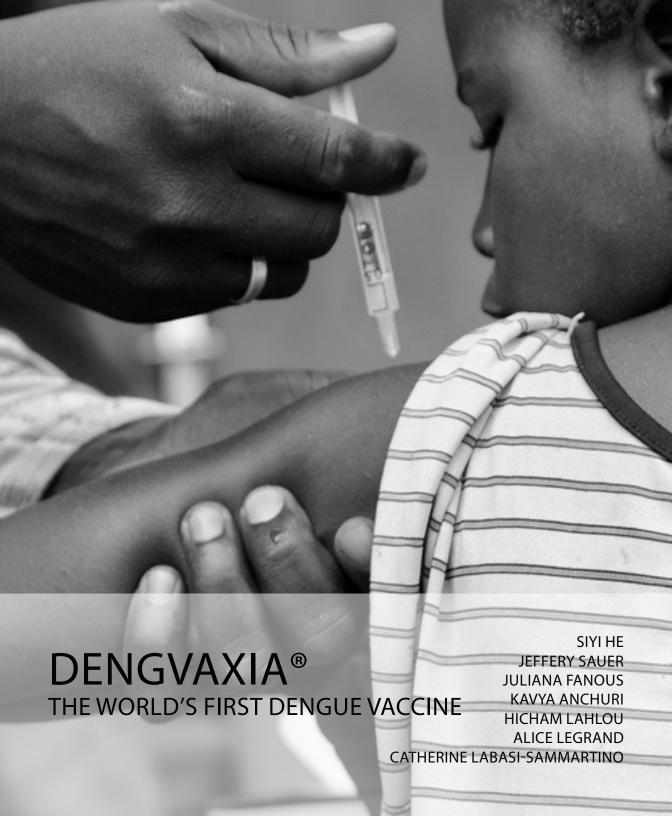
There are no conflicts of interest.

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Dengue fever is considered a Neglected Tropical Disease (NTD), as it both affects predominantly resource-limited countries and highlights the need for increased research and development (R&D) (1). The situation has become critical given that transmission of dengue has increased in both frequency and magnitude, and has expanded to new areas. However, over the last two decades, dengue R&D has grown extensively, particularly in the vaccine division of the pharmaceutical company Sanofi, which has led to the development of the world's first dengue vaccine: Dengvaxia®. Concerns have now surfaced regarding the vaccine's efficiency, specifically amongst children younger than 9 years of age, and in low-transmission areas. Therefore, the creation of Dengvaxia® is not the final step towards the eradication of dengue. R&D must not only continuously seek an improved version of Dengvaxia®, but should also consider other dengue vaccine candidates, and improve distribution of the vaccine in all affected countries.

## Background

Dengue fever is a viral disease, transmitted predominantly by the Aedes aegypti mosquito vector. It is characterized by a multitude of clinical manifestations, including symptoms such as headache, muscle/joint pain, nausea, sore throat, and rash (2). While dengue fever is self-limiting in the majority of cases, secondary infections can lead to more severe presentations, notably dengue hemorrhagic fever (DHF) (3). There are four distinct strains (or 'serotypes') of the dengue virus, all members of the Flaviviridae virus family: DENV-1, DENV-2, DENV-3, and DENV-4, each capable of giving rise to an epidemic. Regions labeled as 'hyperendemic' show infection from multiple strains, while 'hypoendemic' areas only show infection from one strain (4).

Descriptions of symptoms consistent with dengue fever have been found in a Chinese medical encyclopedia dating back to 265-420 AD, while epidemics of dengue in what is now considered the West Indies and Central America were reported in the 17th century. The A. aegypti mosquito had spread to urban coastal areas worldwide by 1800 due to rapid industrialization and increased far-range

transportation. By the end of World War II, hyperendemicity and DHF had emerged in Southeast Asia. Following decades of mosquito control efforts attempting to suppress A. aegypti in the Americas, many eradication programs initiated by the Pan-American Health Organization (PAHO) were discontinued in the 1970s (3). By 1995, dengue incidence had reverted to pre-intervention levels in the Americas and Pacific regions. Global incidence of dengue has since increased rapidly, particularly in the last fifty years (3).

Efforts to estimate global disease incidence yield a figure of 50-200 million clinically observable infections per year worldwide, though the risk of contracting dengue is greatest in the Americas and Asia (5). The year 2015 saw outbreaks of dengue worldwide, most notably in Brazil, Malaysia, the Philippines, India, Hawaii, and the Pacific Islands. Approximately 500,000 people are thought to require hospitalization due to DHF each year, of which approximately 20,000 cases are fatal (3). Together, both fatal and non-fatal presentations of dengue account for 1.14 million disability-adjusted life-years (DALYs) lost in 2013 (6).

Stanaway et al. (2016) show the percent increase in DALYs lost due to dengue from 1990-2013 in various regions of the world, demonstrating a robust, progressive escalation of the global burden of dengue (6). However, the true incidence of dengue may be larger than reported, as 3.9 billion people across 128 countries are thought to be at risk of dengue infection (2).

From a biomedical standpoint, there are several obstacles to the development of a successful dengue vaccine. Firstly, the most challenging obstacle to recognize is that secretion of neutralizing antibodies in response to a weakened dose of dengue does not alone signify acquired immunity from natural infection or the next encounter with the dengue virus (13). As vaccine trials which assess the efficacy of a vaccine usually rely on the host's seroprevalence of antibodies mounted against the pathogen in question, this particular obstacle renders such an approach unviable. Rather, longitudinal studies of vaccine efficacy need to be performed in the field --in regions where dengue is endemic --with long-term follow-up of vaccine recipients to observe their resistance (or lack thereof) to subsequent exposure to dengue. As a result, any new vaccine to be developed for dengue prevention will be far more expensive in the R&D stages than for other diseases for which a simpler, more rapid marker of acquired immunity exists.

Secondly, non-human primates do not develop overt dengue fever, which poses a challenge for testing potential treatments in non-human models. Thirdly, each of the four dengue virus strains is antigenically distinct, such that the immunological response mounted by an infected patient is different against each strain. The lifelong immunity conferred via infection by one serotype does not protect from the other three serotypes, leaving the patient susceptible to secondary infection. Thus, an effective vaccine would have to be multivalent, providing immunity against all four serotypes, in order to prevent both primary and subsequent infections. However, multivalent live vaccines can cause interference between serotypes (7), meaning that the vaccine recipient will only mount a robust immune response to one or two of the serotypes. Fourthly, there is a risk that dengue vaccination could result in antibody-dependent enhancement (ADE). ADE occurs when non-neutralising antiviral proteins facilitate virus entry into host cells, leading to increased infectivity in the cells. It is an important risk to take into consideration because a partially effective vaccine as Dengvaxia® may increase the severity of natural infections, as secondary infections are more severe in some cases. Finally, the dengue vaccine, when co-administered with previously established vaccines, should not have undesirable effects. This is a complicated issue to consider, given that different countries have diverse immunization programs and schedules (8).

Before 1970, only nine low-and-middle-income countries (LMICs) had experienced severe dengue epidemics (3). Yet, while low-income countries (LICs) were financially incapable of investing in a vaccine, high-income countries (HICs) did not support the project because dengue neither affected their populations nor threatened their security. However, the burden of disease has shifted geographically, as the disease is now endemic in more than 100 countries and cases have been identified in France (in 2010) and in Florida (in 2013), among others. In fact, "threat of a possible outbreak of Dengue fever now exists in Europe" (2). In HICs, dengue and the mosquito vector accompany travelers returning from dengue-endemic countries.

Furthermore, endemic areas of the mosquito vector are expanding as the range of suitable environmental conditions for its reproduction is increasing due to climate change (10). Indeed, Monaghan et al. posit that by 2061-2080, A. aegypti habitat "would increase by 8% under moderate emissions pathways" (11). Evidently, the spread of the disease has prompted a call for intervention.

#### The Call for Intervention

Despite efforts to control dengue, based primarily on vector control and case-management, both the costs and burden of disease have continued to grow. Prevention of dengue by vaccination has become necessary to cope with these concerns (12). Historically, the development of a safe and effective dengue vaccine has faced many challenges (13, 14). In the last decade, vaccine development efforts have increased dramatically due to a heightened awareness of the dengue pandemic (15). Sanofi Pasteur, the vaccines division of Sanofi, has developed a recombinant, live-attenuated tetravalent dengue vaccine. A live-attenuated viral vaccine actively replicates in the host, resulting in an array of wild virus-like antigens, which could potentially provoke a response similar to natural immunity (16). CYD-TDV, branded Dengvaxia®, was licensed in 2015 as the first dengue vaccine. To date, eleven countries have approved the vaccine (17). In April 2016, the World Health Organization (WHO) recommended that dengue-endemic countries consider using Sanofi Pasteur's Dengvaxia® "to immunize populations with high levels of dengue endemicity, aged between 9 and 45 years old" (18).

# Vaccine Development and Implementation

**Phase I clinical trials**: small-scale trials conducted to assess vaccine safety in humans.

Phase II clinical trials: larger trials that mainly assess the efficacy of the vaccine against artificial infection and clinical disease. Vaccine safety and side-effects are also studied.

Phase III clinical trials: conducted in a large pool of subjects across several sites to evaluate efficacy under natural disease conditions. If the vaccine retains safety and efficacy over a defined period, the manufacturer can request the regulatory authorities for a license to market the product for human use.

#### Results of Clinical Trials: Phases I, II, III

Ten years of Dengvaxia® clinical trials were conducted prior to the successful completion of Phases I-III in 2014, involving 25 clinical studies in 15 countries worldwide. More than 40,000 volunteers were enrolled in the clinical studies, and 29,000 of them received Dengvaxia®. The vaccine demonstrated protection of 67% of these participants against dengue (15).

A Phase Ilb study (CYD23) – observer-masked, randomized trials – was conducted in healthy Thai schoolchildren aged 4–11 years. In Ratchaburi, Thailand, 2669 children were randomly assigned to receive three injections of CYD-TDV, and 1333 were assigned control injections, consisting of the rabies vaccine or placebo. Overall, 3673 participants were included in the primary analysis (vaccine, n = 2452; control, n = 1221). The vaccine efficacy was 30.2% (95% Confidence Interval [CI]: –13.4 to 56.6), but differed by serotype. In the intent-to-treat population (all children who were enrolled and randomly allocated to treatment), the efficacy observed for

for DENV-1 was 61.2% [95% CI: 17.4–82.1], for DENV- 3 was 81.9% [95% CI: 38.8–95.8], and 90.0% [95% CI: 10.6–99.8] for DENV-4 (15). However, for DENV-2, which is the predominant serotype, efficacy was only 3.5% (95%CI: –59.8 to 40.5). The lack of observed efficacy against DENV-2 occurred again in phase III studies.

Two pivotal phase III studies, CYD14 and CYD15, were respectively carried out in children aged 2-14 years in Asia, and in children and adolescents aged 9-16 years in Central and South America. Each of the studies included five endemic countries, consisting of 11 sites in Asia and 22 sites in Latin America. Both trials (CYD14&CYD15) successfully met their primary end-point. During the active phase of the disease, both trials showed higher efficacy against severe disease and hospitalization for dengue (in CYD14, 56.5% overall efficacy against dengue disease vs. 67.2% against hospitalization; in CYD15, 60.8% overall efficacy against dengue disease vs. 80.3% against hospitalization) (15). Secondary analyses showed that all four dengue serotypes contributed to the overall efficacy, although the efficacy against serotype 2 was inconclusive, which is considered a weak point of Dengvaxia® and is still under research.

In total, six vaccines are in clinical development, but to date only Dengvaxia® has completed phase III trials (48). Dengvaxia® has a three-dose schedule, each six months apart, with its durability not yet established. The vaccine was well tolerated, with no safety signals after 2 years of active follow-up after the first dose. In both trials, there were no marked differences in the rates of adverse events (49), which is a key to Dengvaxia®'s success since other dengue vaccine candidates failed to avoid adverse events. Moreover, no cases of acute viscerotropic

or neurotropic diseases were recorded, and no vaccine-related deaths were reported (15). In addition to the surveillance during clinical trials, there is a four-year long follow-up phase called LTFU, which is in line with the WHO guidelines. During the first year of LFTU, there were no significant differences in symptoms and signs between vaccine and control groups. These results, which include data from 10 countries with different populations in age and ethnicity, have demonstrated the efficacy and safety of Dengvaxia®.

Moreover, Dengvaxia® also takes the risk of resulting in antibody-dependent-enhancement (ADE) into consideration. No, or only minimal, ADE activity in vitro was observed. In particular, there was no in vitro ADE in the presence of broad neutralizing responses against all four DENV serotypes (50). More research is ongoing and will continue to be addressed by long-term follow-up and future post-licensure studies.

So far, the vaccine is approved in eleven countries: Mexico, The Philippines, Brazil, El Salvador, Costa Rica, Paraguay, Guatemala, Peru, Indonesia, Thailand, and Singapore, and the distribution process differs in each (19). Dengvaxia® is now available in certain private healthcare clinics in Costa Rica, Mexico and the Philippines for immunization of individuals 9 to 45 years of age. In El Salvador, the vaccine is now considered the first public dengue prevention, and can be administered by healthcare professionals. In Brazil, Paraná State has launched the first public dengue immunization program in the Americas, targeting vaccination of 500,000 of the state's residents this year. The first public denque immunization program has also begun in the Philippines, where the country planned to give one million public school children their first dose

by June 2016. For many of these implementations, Dengvaxia® has received endorsements from key medical societies at national and regional levels.

#### **Reasons for Success**

During the last century, the dengue virus rapidly expanded from its tropical origins to subtropical and temperate climates. In the early 2000s, both the WHO and the U.S. military classified dengue as "the most important and rapidly spreading mosquito-borne viral disease in the world", which resulted in the classification of the disease as a major international concern (20). One of the key events prompting the successful development of Sanofi's dengue vaccine was the emergence of the Dengue Vaccine Initiative (DVI) in 2010 (47), a non-profit organization that seeks to promote further awareness of the urgent need to support both the development and use of the dengue vaccine (17). To assist this initiative, the International Vaccine Institute (IVI) advocated for international research and partnerships, as well as knowledge-sharing between the WHO, the Sabin Vaccine Institute, and the International Vaccine Access Center through the John Hopkins School of Public Health (47). This resulted in the formation of a Global Product Development Partnership wherein multinational partners could contribute expertise in vaccine development and production, demand forecasting, budget impact planning, economic aspects analysis, as well as vaccine advocacy (47).

Since the development of the vaccine, Sanofi Pasteur, the current manufacturer of Dengvaxia®, has partnered with several international institutions. For instance, the vaccine division has partnered with the University of Mahidol in Bangkok, where a previous version of the vaccine had been researched, as well as the Pediatric Dengue Vaccine

Initiative (PDVI) in 2006 to accelerate R&D for a dengue vaccine (22). Finally, Sanofi conducted its R&D in nations with robust R&D infrastructure (USA, France), which led to accelerated testing and manufacturing of the vaccine.

The DVI has managed to attract massive sources of financing since the emergence of the Global Product Development Partnership. In 2011, the DVI received grants from vaccine developers to facilitate discussion between the major stakeholders in order to ensure the vaccine is widely available in countries where dengue is prevalent (21). The Bill & Melinda Gates Foundation committed to a US\$55 million grant in 2003 to the International Vaccine Institute to accelerate the development of a safe and protective dengue vaccine (32). In 2011, the foundation allocated an additional US\$6.9 million grant to further promote this agenda (23). Since then, it has continued to support DVI (21).

# Assessing the Evidence

Sanofi Pasteur has alleged that developing the vaccine required nearly 20 years of research and approximately US\$1.7 billion in investment (24). Although early agreements between Sanofi and other players extend from 1994, the previously mentioned global health funds accounted for the sustained financial commitment that enabled the vaccine's development. Western news outlets have reported on the large market for Dengvaxia®, suggesting that the rapid approval of the vaccine in different countries could lead to a US\$1.4 billion market by 2020 (25). Sanofi Pasteur increased sales by 15% to US\$5.1 billion (from 2015) and has seen consistent growth in recent years despite the er revenue streams, such as Sanofi's diabetes franchise (26).

Pricing for Dengvaxia® is likely to change over time. Early pricing reports from the government-subsidized school children vaccination plan in the Philippines reported that Dengvaxia® would cost the government around US\$70 per child (3,500 Philippine Pesos), although other early immunization campaigns in the Philippines were reported to cost approximately US\$22 per injection (27). Early estimates from Brazil place the cost of the vaccine between US\$46-55 (29), which make it much more expensive than other mosquito-borne infectious disease medications; for example, the price of chloroquine tablets to treat malaria, depending on the place of procurement and available subsidies, can be as low as US\$0.10 (51).

# Challenges for the Future

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) met in April of 2016 to make recommendations based on mathematical modelling evaluations. These evaluations demonstrated that in high-transmission settings, the introduction of routine Dengvaxia® vaccinations in early adolescence could reduce dengue hospitalizations by 10-30% over a period of 30 years. Accordingly, the SAGE suggested that countries consider introducing Dengvaxia® "only in geographic settings [with a] seroprevalence of approximately 70% or greater in the age group targeted for vaccination [and stated that Dengvaxia®] is not recommended for use in children under 9 years of age, consistent with current labelling" (30).

The primary limitation of Dengvaxia® is mixed vaccine efficacy in specific subpopulations. A modeling study found that in high-transmission areas, vaccination is associated with a 20 to 30% reduction in both symptomatic disease and hospitalization (31). There is evidence that Dengvaxia® can

produce infection-enhancing antibodies in vaccinated seronegative individuals (32), leading to higher hospital admission rates, notably among children younger than 9 years (33). A potential solution to this issue would be immunological screening before vaccination in order to identify seropositive individuals, such that they would be the only group to receive the vaccine. However, this would significantly reduce the prospective vaccination population (34).

Moreover, recent evidence suggests that dengue virus antibodies can significantly increase the Zika outbreak peak, speed up the Zika outbreak peak timing and therefore enhance the Zika virus infection by driving greater Zika replication. Using a selection of human monoclonal antibodies, researchers have demonstrated that plasma immune to the dengue virus produced antibody-dependent enhancement (ADE) of a Zika virus infection (35, 36). Although the sequence of the envelope protein for each virus differs by 41-46%, the dengue virus antibodies, rather than neutralizing it, bind to the Zika virus and promote ADE (35). The Zika virus could potentially be considered an additional member of the dengue serocomplex (35). Overall, the enhancement of Zika by dengue antibodies could lead to particularly devastating outcomes since the highest prevalence of Zika occurs in areas where dengue is currently endemic. Further investigations are thus necessary to better understand these processes that must be considered in the development of an effective dengue or Zika vaccine (36).

A fifth serotype of the dengue virus, dubbed DENV-5, was discovered after genome sequencing of a viral sample from a patient in the Sarawak region of Malaysia during an outbreak in 2007, though the

infection was initially attributed to DEN-4 (37). Primates infected with the isolated DENV-5 strainmounted distinct immune responses from those elicited by either of the first four viral strains, indicating that the fifth serotype was indeed a distinct pathogen (38).

The public health consequences of this new serotype remain to be seen, though most cases in the Sarawak outbreak —some of which, presumably, can be attributed to DENV-5— were deemed mild (38). However, the discovery of a new viral strain further complicates the multivalent vaccine-development process, as a fully effective dengue vaccine must address all existing dengue serotypes in order to prevent a more severe secondary infection.

## **Keys to Lasting Success**

Funding for the development of Dengvaxia<sup>®</sup> is attributed to corporate, philanthropic, and governmental benefactors, namely, Sanofi Pasteur, the Bill & Melinda Gates Foundation, and the Australian government. This multilateral financial support was a pivotal factor in the completion of the clinical trials, exemplifying the importance of global cooperation and the coordination of private and public partnerships. Furthermore, the vaccine's approval by the WHO provided all member-states with a trusted certification of Dengvaxia® safety and effectiveness. There are three key principles to ensure Dengvaxia's success going forward: (1) advanced trials leading to full WHO approval, (2) a commitment by Sanofi Pasteur to prioritize better health over increased profits, and (3) continued innovation in product development, and implementation of global partnerships.

A key challenge will be recognizing heterogeneity across the different countries affected by dengue,

in regards to each nation's unique supply constraints, potential vaccine demand, and existing health policy. Country-to-country differences have complicated Dengvaxia® rollout strategies. International Vaccine Access Center researchers have identified key differences, including unequal availability of resources, constrained national budgets, insufficient health care coverage and policies, and diverse political priorities (39).

# Implications for Global Heath

While Dengvaxia® offers a promising model for vaccine development, perhaps equally important are other initiatives such as DVI. Dr. In-Kyu Yoon, the director of the DVI, has stated that "there is a need for more than one vaccine and more than one vaccine manufacturer" (41). Currently there are five dengue vaccine candidates in clinical development. The two most advanced candidates, now in Phase II trials, were respectively developed by the U.S. National Institutes of Health (NIH) and the Japanese pharmaceutical company Takeda (WHO, 2016). T003 from the US NIH is based on wild-type strains with specific mutations to weaken the virus. It has been licensed to several manufacturers, such as Butantan, who estimate Phase 3 trial completion by May 2018 (42). Another potential competitor to Sanofi Pasteur is Takeda. They have recently announced their investment of over 100 million euros in a dengue vaccination manufacturing plant in Germany (43).

In the past, Sanofi US decreased the price of a tuberculosis drug, rifapentine, in response to the actions of health equity advocates demanding support for US public health programs (44). This reduction in price demonstrates a willingness from Sanofi to engage with activists; a similar interaction may be important in the future of Dengvaxia®.

Moreover, Sanofi Pasteur purports a long-standing commitment to community involvement: "each year, the Sanofi family of companies [...] - [including] Sanofi Pasteur - strives to maintain and expand a strong Corporate Social Responsibility program by investing in youth, innovation and the community" (45). Shepard et al. (2016) predict Dengvaxia® will participate in the reduction of the current global economic dengue burden of US \$8.9 billion, 60% of which is due to productivity loss (46). However, the impact of these vaccines on the market and Sanofi's claim on Dengvaxia® as intellectual property has yet to be fully observed or quantified. Dengvaxia®'s development offers a hopeful example of how a product with decades of dedicated research, sufficient funding, and innovative multinational collaboration can improve the wellbeing of people around the globe.

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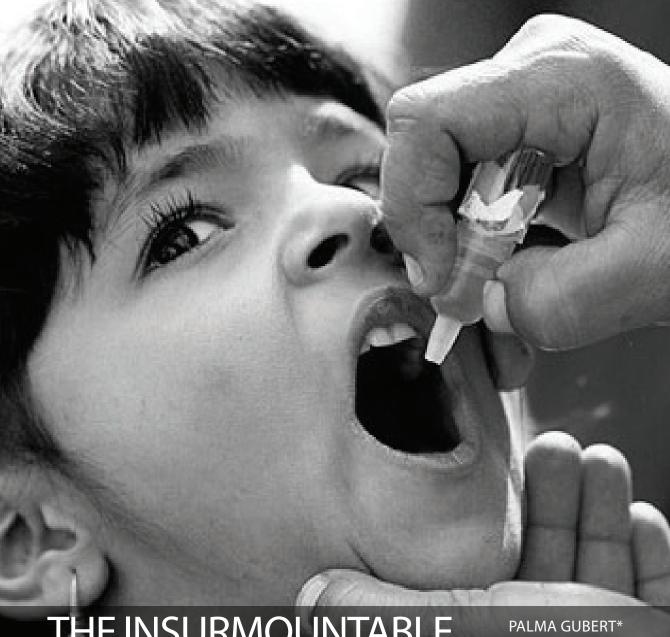
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THE INSURMOUNTABLE **FRONTIER** HOW INDIA ELIMINATED POLIO

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This case study evaluates India's efforts to eliminate all poliovirus strains in the country. This was done through massive immunization campaigns that targeted specific and marginalized groups, public awareness campaigns, and an emphasis on nation-wide surveillance. Ultimately, polio was successfully eliminated in India and the country averted 1.48 billion disability-adjusted life years. The number of cases declined from 200,000 in the 1970s to 400,000 in the 1980s, and finally to zero cases in 2012. This case owes its success to political will, coordinated inter-sectoral collaboration, significant funding (over US\$2.4 billion from multiple contributors), and persistent efforts to immunize all children.

#### Background

Poliomyelitis ("polio") is an infectious virus that can lead to paralysis or death. There are three serotypes of the wild poliovirus (WPV): WPV1, WPV2, and WPV3. Although polio is incurable, vaccines have helped to eliminate the virus in most countries around the world. In 1953, when 35,000 children per year in the United States were being disabled by polio, Jonas Salk developed the inactivated poliovirus vaccine (IPV). As a result, incidence of polio in the United States fell by 85 to 90% between 1955 and 1957. In 1962, another breakthrough occurred when Albert Sabin produced the oral poliovirus vaccine (OPV), which was less expensive and logistically easier to administer (1).

The global success of polio vaccination quickly became evident. By 1988, polio had disappeared from the United States, the United Kingdom, Australia and much of Europe, but remained prevalent in more than 125 countries. The World Health Organization (WHO) certified Latin America polio free in 1994, the Western Pacific region (including China) by 1997, and all of Europe by 2002 (2). India officially eliminated polio in 2014. As of 2016, Nigeria, Pakistan and Afghanistan are the only remaining countries that are not polio-free (3).

Eliminating polio in India was once seen as an insurmountable challenge due to its large and mobile population, extreme poverty, and poor sanitation, among other impediments (4). The elimination of polio was considered of secondary importance to that of other diseases such as malaria, leprosy, tuberculosis, and visceral leishmaniasis (kala azar). This further hindered efforts to stop its transmission (5). Once the Indian government prioritized polio, it provoked multilateral collaboration from non-governmental organizations and public and private parties from within and beyond the country. Ultimately, in 2011, India detected its last case of polio (6).

# The Strategy: Pre-2000

In 1974, the WHO launched the Expanded Programme on Immunization (EPI) with the aim of reaching all children with necessary vaccines. In 1978, the EPI was adopted by India, which accounted for at least 50% of the world's polio burden at the time (4, 7).

In 1979, the trivalent oral poliovirus vaccine (tOPV) was introduced in India (7). The tOPV protects against all three serotypes of poliovirus, and is administered orally, without the need for trained health professionals, sterile settings, or syringes (8).

Between 1978 and 1982, 104 million children were immunized with DPT (a combination vaccine against diphtheria, tetanus, and polio), and 4.1 million with three doses of tOPV. Despite these efforts, in 1981 India experienced a nationwide polio epidemic (7). From the 1970s and into the early 1990s, polio was still hyper-endemic in India, with 200 to 400,000 cases annually. In 1985, Rotary International introduced tOPV as part of its Universal Immunization Programme with the aim of reaching all Indian districts (5). Due to the low immunogenic efficacy of tOPV during the 1970s and 1980s, the number of polio cases reported in vaccinated children skyrocketed (7).

By 1988, polio was finally on the decline in India, which John and Vashishtha, in a 2013 study, attribute to increasing vaccine coverage and growing herd immunity (7). That same year, the World Health Assembly resolved to target polio for global eradication by the year 2000, a decision which India supported. The WHO promoted four strategic components to accomplish this task: achieve and maintain high OPV coverage, augment regular immunization with supplementary doses of OPV (Supplementary Immunization Activities, or SIAs), increase systematic polio surveillance with support from virology laboratories, and use local OPV campaigns to interrupt any remaining clusters of WPV transmission (7).

In 1995, the Global Polio Eradication Initiative (GPEI), together with the WHO, UNICEF, the Centers for Disease Control USA (CDC), and Rotary International, designed the National Polio Surveillance Project (NPSP), a joint initiative by the WHO and the government of India (7). NPSP supported the Indian government by providing technical assistance and monitoring for routine OPV immuniza-

tion, acute flaccid paralysis (caused by polio) surveillance, and SIAs (9). At the time, roughly 50,000 individuals were still contracting polio each year in India (6).

In the same year, Pulse Polio Immunization (or PPI, formerly SIAs) was launched by the Indian government. The program consists of two annual National Immunization Days (NIDs) on which children were vaccinated at fixed booths (10). There were over 700,000 vaccination booths in each campaign, staffed by 2.5 million vaccinators (11). Approximately 172 million children received vaccinations on each NID (12). Local community mobilizers encouraged members of the community to immunize their children on NIDs, and the program was publicly supported by religious leaders and celebrities. By 1991, 53% of Indian babies had received OPV, and 73% by 1997 (5). By 1999, after nationwide PPI campaigns, WPV2 was eliminated from India, but WPV1 and WPV3 continued to circulate (10).

#### Post-2000

Since the objective of eradicating polio before the turn of the century was not met, efforts in India began to intensify in the year 2000. Four rounds of PPI took place nationally in the fall and winter, with two additional rounds occurring sub-nationally in eight states with low EPI coverage. In the same year, the WHO and NPSP strengthened virology laboratories to intensify virological surveillance of WPV transmission (10). WPV transmission could not be interrupted in the states Uttar Pradesh (UP) and Bihar, despite PPI campaigns reaching 94-95% of targeted children (7). As a result, PPI began house-to-house vaccinations in addition to booth immunization. By 2001, WPV transmission exclusively took place in these high-risk states (10).

To combat lack of access to tOPV, the 'under-served' strategy was launched in 2003 to target specific marginalized communities in UP, including Muslims, migrants, and other socioeconomically disadvantaged groups who were often missed in routine tOPV immunization campaigns and National Immunization Days (NIDs) (5). It became clear in 2004 that the migrant population that travelled for seasonal work needed to be prioritized, and thus the 'transit vaccination' strategy was implemented, with vaccination teams working out of bus stands, railway stations, markets, and other points of transit (7).

In 2005, the monovalent OPVs type 1 and 3 (mOPV1 and mOPV3) were licensed in India. These monovalent vaccines only confer immunity to their respective virus serotype and demonstrate increased efficacy compared to tOPV (7). Uttar Pradesh and Bihar began to use mOPV1 and mOPV3 later that year, and continued to invest in the under-served and transit vaccination strategies (13). After 2005, PPI campaigns were increased to ten times per year to compensate for low routine coverage. The quality of polio surveillance was also bolstered such that poliovirus transmission could be quickly detected anywhere in India (7).

In 2006, the inactivated poliovirus vaccine (IPV), which provides immunity against all three polio strains, was licensed in India. The India Expert Advisory Group (IEAG) began limited use of supplemental IPV dosing in Uttar Pradesh, in addition to mOPV1 and mOPV3, and focused efforts began to specifically eliminate WPV1 (7, 9).

In 2009, the IEAG announced their 107-block plan to focus on high-risk areas of Uttar Pradesh and

Bihar (9). The IEAG recommended combining mOPV1 and mOPV3 to create the bivalent oral poliovirus vaccine (bOPV). By the end of 2009, WPV1 had nearly disappeared and thus WPV3 elimination was prioritized (10). In January 2010, bOPV was added to PPI campaigns. In 2010, 42 cases of WPV were detected, and in 2011, only one case was detected. In 2011, the average rate of unvaccinated children under two years old was 1.8% in Uttar Pradesh and 0.3% in Bihar (6).

Since its initiation in India in 1995, through collaboration with the government-run PPI and the WHO, the National Polio Surveillance Project provided 12.1 billion doses of OPV to India (11). In 2012, no WPV was detected and India was deemed polio-free. The WHO declared that India had successfully eliminated polio in March of 2014 (6).

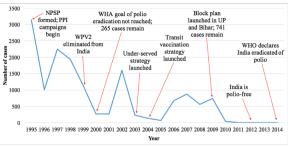


Figure 1. Total number of wild poliovirus cases in India, 1995 to 2014 (7, 14-16).

### **Health Impact**

A study by Nandi et al. analyzed India's elimination initiative from 1982 to 2012 by calculating the variation in paralytic polio cases, polio-related deaths, and disability-adjusted life years (DALYs) (12). The authors chose 1982 as a start date for their analysis, as OPV was only introduced in India sporadically between 1978 and 1982. They created a hypothetical counterfactual model in which the polio campaign did not occur, through which

it was determined that the polio campaign prevented 3.94 million paralytic polio cases, 394,000 deaths, and 1.48 billion DALYs from 1982 to 2012.

Furthermore, as a consequence of the polio elimination campaign, improvement of routine immunization (RI) and primary healthcare have been observed in India. India's 107-block plan concentrated its efforts on upgrading RI, decreasing rheal rates, increasing breastfeeding, and improving sanitation. Encompassed in this strategy was an attempt to attack multiple issues rather than solely focusing on polio vaccination. A mass education campaign took place to spread information about the aforementioned issues, and this multifaceted approach was a contributor to the success of the eradication initiative. The campaign effected change in multiple areas of health by strengthening several programs, and ultimately enhanced routine immunization and primary healthcare while simultaneously helping to eradicate polio (17).

### Financing & Cost-Effectiveness

As the possibility of worldwide polio eradication increases, the list of polio-endemic countries shrinks; polio eradication is no longer a region-specific issue, but rather a global fight. Most countries and organizations that have contributed funds to fighting polio have done so towards the global eradication effort as opposed to funding specific countries, creating difficulty in determining India-specific polio funding. Additionally, the timeline of funding is not straightforward due to the length of the polio eradication campaign. However, a general, though not absolute, understanding of the stakeholders in this initiative may be deduced from the existing literature.

Several donors have contributed specifically to India to combat polio, including the Global Alliance for Vaccines and Immunization (GAVI), Rotary International, Germany (via the GPEI), and the government of India. According to the WHO, the Indian government is one of the biggest contributors to the polio campaign. India's initiative was mostly self-funded; as of 2013 the Indian government had contributed US\$2 billion towards polio elimination (18). GAVI, the public-private partnership devoted to increasing vaccination rates in developing countries, provided US\$16,531,545 to India for IPV support between 2000 and 2016 (19). In addition, in 1985, Rotary International, an international service organization, introduced their PolioPlus program with the goal of immunizing all children against polio. Since its inception, PolioPlus has contributed US\$176.5 million towards polio efforts in India (D. Green, December 8, 2016). Germany has provided approximately \$275 to \$314 million to India since 2005 (20-26).

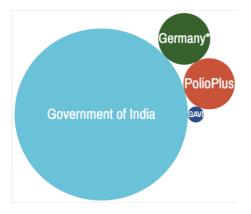


Figure 2. Approximate proportional spending by the government of India, Germany, PolioPlus, and GAVI towards polio elimination in India up to 2016.

\*This is an estimated value because Germany's donations towards polio in 2007 and 2008 were split between India and Nigeria. It is not stated how much each country received from the donations. We estimated the funds were split evenly between the two countries.

Nandi et al. estimated the overall growth in productivity in India as a result of the polio campaign at US\$1.71 trillion from 1982 to 2012 (12). If polio is eradicated globally, it is predicted that the net benefits will range from US\$40 to 50 billion in the twenty years post-eradication, almost 85% of which will directly accrue to low-income countries (27). Although these benefits in productivity and health are profound, they must be evaluated in the context of the costs of vaccination. Prinja et al. determined the cost of vaccination for polio as US\$28 per child (28).

#### **Challenges & Reasons for Success**

The GPEI accurately anticipated that India would be one of the most difficult countries in the world in which to eliminate polio. India faced several challenges such as a weak civic infrastructure for distributing vaccines, an inadequate public healthcare system, and a large mobile population prone to missing routine immunizations. In a nation with a population of more than 1.2 billion, a sizeable portion of India's inhabitants live in remote mountainous areas that are difficult to reach for vaccination. Poor sanitation and endemic diarrhea in Uttar Pradesh and Bihar, the two most populous northern states, intensified WPV transmission (10). Further exacerbating the problem, tOPV did not provide adequate immunity, leading to a rise in polio cases among already-vaccinated children throughout the late 1970s and early 1980s (7). Many communities also resisted immunization out of fear that vaccines were a covert sterilization effort from the Indian government, among other misconceptions (10). A feasible approach to elimination in India had to address each of these challenges.

Ultimately, the commitment of the Indian government toward its goal of eliminating polio was the key to success for this initiative. India's government was highly involved in the elimination process, taking ownership of the effort throughout. This included direct supervision and regular review of the GPEI program by the Prime Minister's office, as well as chief ministers taking control of elimination in their own endemic states (10).

However, the Indian government did not achieve polio elimination on its own. Collaboration between the government, non-governmental organizations, the public and private health sectors, and the general public was paramount to India's success. Organizations such as Rotary International, WHO, UNICEF, CDC USA, and the Bill and Melinda Gates Foundation contributed to the finances and labour that allowed for the realization of this enormous goal (29).

The polio elimination campaign relied on involvement of leaders from various societal spheres. Academic bodies, including the Indian Academy of Pediatrics, helped build community awareness by debunking the misconceptions surrounding polio vaccination (10). The use of religious leaders, iconic film personalities like Amitabh Bachchan, cricket players, and radio and television to support polio vaccination influenced the public to have their children immunized on NIDs (30). These combined efforts helped communicate the campaign to the public.

To address the shortage of healthcare workers needed to immunize all targeted children, the Indian government recruited more public health nurses and social workers. They also trained volunteers from all backgrounds - mothers, students, community leaders, and religious clerics - to work at vaccination booths and speak to families about upcoming immunization dates. Schoolchildren also organized and participated in large rallies to raise awareness about polio immunization (30).

There were two pervasive myths hindering the polio elimination effort. The first was the belief among certain Muslim communities that the polio vaccine was part of the Indian government's effort to sterilize Muslims again just as it had in 1975-1977 (36). The second was a misconception that a previously immunized child did not require further dosage. In fact, many parents believed that more than one dose was harmful to the child. To address the first myth, the Indian government enlisted the help of the Ulema, a council of Muslim clerics, who led public campaigns to dispel fears about sterilization. They made announcements at mosques and distributed signed letters ensuring the safety of the vaccines. To counter misinformation regarding the safety of additional vaccinations, the anti-polio campaign produced public service announcements on television educating parents as to why supplemental doses of the polio vaccine were not harmful, and were in fact essential for full immunity. The government also trained volunteer immunizers on how to persuade reluctant parents to vaccinate their children (30).

With an enormous population and lack of comprehensive health surveillance infrastructure, efficient management of the campaign was essential. Through the house-to-house strategy, for example,

health workers used a house-marking system to indicate the vaccination status of each residence (30). Simple innovations, such as tracking newborns and mapping missed children, also helped facilitate widespread OPV delivery. (10).

#### **Future Directions**

Although India has eliminated wild poliovirus, the threat of vaccine-derived poliovirus (VDPV) remains. This can occur in the rare instance when the attenuated form of the virus from OPV mutates into a virulent strain. Poor sewage and contaminated water sources facilitate transmission of VDPV (31). To avoid a large VDPV outbreak, India should transition towards IPV while simultaneously strengthening its health and sewage infrastructure.

IPV, which avoids the risk of VDPV, is also more efficacious compared to OPV, though it must be injected rather than administered orally. GPEI and GAVI have been working to introduce IPV into routine immunization in India since November 2015. However, a full switch from the OPV to the IPV has not yet taken place due to shortage of supplies and difficulties with storing IPV which requires coldchain management (32). Today, India's vaccination of infants against polio involves either a single dose of intramuscular IPV at fourteen weeks of age, or two fractional doses of intradermal IPV at six and fourteen weeks of age. Primarily as a result of cost restraints, no IPV will be given to children above this age group (A.S. Bandyopadhyay, December 10, 2016).

Furthermore, given that India shares a border with Pakistan, a nation which still has active polio cases, there is concern regarding the possible reintroduction of polio into India. The Indian government has thus mandated polio vaccine requirements for

travelers moving to and from polio-endemic countries in order to mitigate this threat (33). India continues to utilize the NPSP, a system which Dr. Nata Menabde, WHO Representative to India, claims "surpasses all quality performance indicators and standards that are recommended globally for such a system" (34). Such a program could be adapted to track the elimination of other communicable diseases, like malaria and visceral leishmaniasis.

The NPSP is the hallmark of India's current prevention strategy. It was set up by the WHO in 1997 to help support the government with early detection. As part of this large initiative, the program enrolled more than 40,000 health facilities from the private, public and informal sector to report on paralytic cases. As part of protocol, stool specimens are gathered and sent to one of eight WHO-accredited labs in the country to test for polio. Presently, this data is instrumental in identifying targeted populations to prevent future outbreaks (34). The NPSP has also expanded to monitoring for measles, Japanese Encephalitis and other immunization campaigns (35).

The challenges and successes encountered by India in this long process may serve as a guide for other countries still battling polio. By following India's example of consistent effort, supplemented with political will and international support, Nigeria, Afghanistan and Pakistan may soon eliminate polio, thus bringing the world closer to the goal of global eradication.

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#### **Appendix**

bOPV: bivalent oral poliovirus vaccine

CDC: Centers for Disease Control

DALYs: disability-adjusted life years

DPT: diphtheria, polio, and tetanus vaccine EPI: Expanded Programme on Immunization

GAVI: Global Alliance for Vaccines and

**Immunization** 

**GPEI: Global Polio Eradication Initiative** 

**IEAG: India Expert Advisory Group** 

IPV: inactivated poliovirus vaccine

NIDs: National Immunization Days

NPSP: National Polio Surveillance Project

OPV: oral poliovirus vaccine

PPI: Pulse Polio Immunization

RI: routine immunization

SIA: Supplementary Immunization Activities

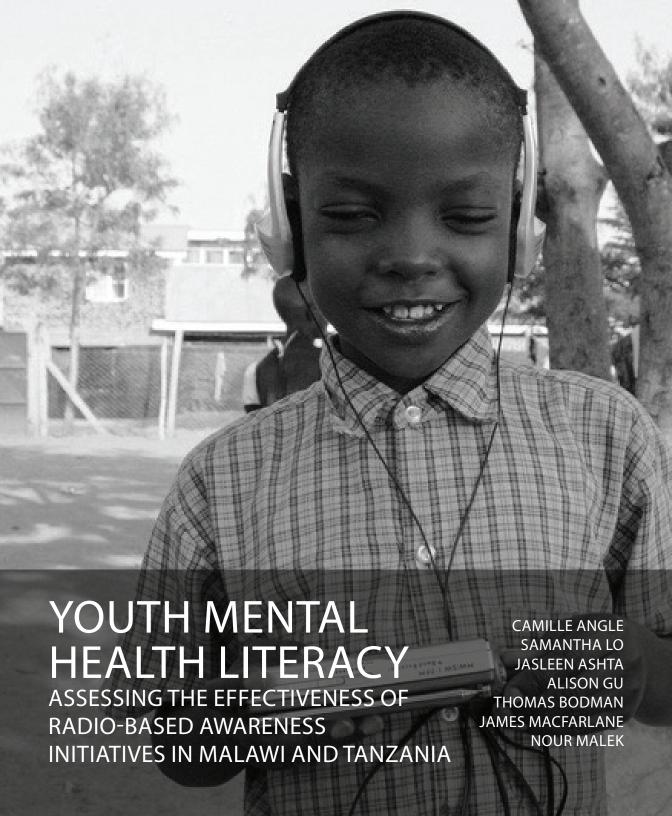
tOPV: trivalent oral poliovirus vaccine

**UP: Uttar Pradesh** 

VDPV: vaccine-derived poliovirus

WHO: World Health Organization

WPV: wild poliovirus



This paper evaluates the effectiveness of an intervention meant to expand treatment for adolescents with mental illness in Malawi and Tanzania. The researchers developed radio programs addressing mental health for youth and provided training on mental disorders for educators and healthcare workers in Malawi and Tanzania. At a cost of CA\$2.7 million, the program treated over 1,000 adolescents for depression and other mental illness.

#### Introduction

Despite often being left out of the greater discussion on global health, mental health disorders represent a significant burden worldwide. Roughly 5% of any human population is affected by neuropsychiatric illnesses such as psychoses, dementias, drug and alcohol dependence, and depression (1). Approximately 5.9% of total global DALYs lost are due to mental disorders, with the highest burden occurring between the ages of 20 to 30 years old (2). Mental disorders also contribute significantly to global mortality; for example, suicide is reported to be a leading cause of death for youth in China and India (3). Compared to physical and biomedical pathologies, mental illnesses tend to be more difficult to identify and understand, and are thus neglected as a global health concern (4). Depression is projected to soon be responsible for the highest burden of disease in young people worldwide (5).

A large proportion of the population in both high-income countries (HICs) and low and middle income countries (LMICs) are affected by mental illness. People living in LMICs face increased exposure to social and health risk factors for mental illness such as poverty, malnutrition, and violence. LMICs also have a high percentage of youth within their populations. Specifically, 60-70% of people living in Malawi and Tanzania are under age 25, with children between 0-14 years of age comprising 45% of their total populations (5). Over half of the population in Malawi lives in poverty (6, 7). Additionally, in Malawi, 2.1 million adolescents aged 10-19 live

with HIV (7). And while the exclusive prevalence of mental disorders among youth in both Malawi and Tanzania is unknown, the prevalence among youth in sub-Saharan Africa is between 13% and 20% (8, 9). Furthermore, these sub-Saharan LMICs also suffer from poor quality of health care. The lack of mental health literacy among the public and training among healthcare workers, coupled with high levels of stigma, result in large treatment gaps for mental illness—especially for youth. In addition, Malawi's youth struggle to receive an education due to the lack of infrastructure and resources. In 2014, 69.4% of Malawi youth aged 15-24 did not progress beyond a primary school-level of education (5, 6).

In Malawi, it could be argued that treatment of mental illness is neglected due to the country's focus on infectious disease treatment and prevention. In 2012, only 0.9% of the country's healthcare budget was allocated to mental health, amounting to US\$0.293 per capita (10). Furthermore, tertiary mental health services are only available through three sources in the country: two hospitals associated with the Ministry of Health and a non-governmental organization, Scotland-Malawi Mental Health Education Project (SMMHEP; mostly tailored to graduate students and medical doctors rather than the younger population). In 2012, there were only four registered psychiatrists and psychologists in the entire country. There are simply not enough mental health experts and clinics to meet the needs of Malawi's 16 million inhabitants. This

problem is compounded by the stigma surrounding mental health, causing affected individuals to become isolated from their communities and unable to receive the necessary care. This stigma has also discouraged people from entering into psychology-related fields of study and work, further perpetuating the problem.

The United Republic of Tanzania suffers from a similar lack of mental health resources. Tanzania allocates a greater percentage of its budget to mental health than Malawi (2.4% of their budget or US\$0.647 per capita) (11), yet there remains a lack of mental health services. There are only four trained psychiatrists and one or two social workers for every one million Tanzanians. In addition, most clinics do not have protocols to guide the management and treatment of mental health disorders (11).

Studies conducted in Goa and Thirthahalli Taluk, India, as well as Uganda, have shown that groups who undergo interpersonal psychotherapy and/ or take antidepressant medications experience a greater decrease in symptoms than a non-treated control group (12, 13, 14). However, such treatments can only be provided and prescribed with appropriate training, thus emphasizing the need for better mental health literacy, training, and funding. As approximately 70% of mental disorders can be diagnosed before the age of 25, investments in these areas must target youth (15). Early diagnosis and treatment will increase life expectancy and participation in the labor force, contributing to an overall improvement in productivity (16).

This case study summarizes and evaluates the implementation of Canada's mental health literacy

program, The Guide, in Malawi and Tanzania, with the hopes of assessing the potential for scale-up to other countries in sub-Saharan Africa.

#### Intervention

Principal Investigator Dr. Stanley Kutcher of the Department of Psychiatry at Dalhousie University (Halifax, Nova Scotia, Canada) and his team put together an initiative to apply a unique, integrated Pathway Through Care program for young people with depression in Malawi (starting in 2012) and the Kilimanjaro region of Tanzania (starting in 2014). With a CA\$2.7 million contribution from Grand Challenges Canada (GCC), this initiative was carried out by Farm Radio International, a Canada-based not-for-profit organization dedicated to fighting poverty and food insecurity in Africa (Box 1). Farm Radio International contributed its expertise in radio-based and mobile phone-based communication, which are frequently used by farmers to promote greater collaboration, communication, and sharing of agricultural knowledge.

To pioneer their project, Dr. Kutcher's team worked to create relations with key policymakers in both Malawi and Tanzania. Additionally, the team conducted surveys to assess baseline knowledge of mental health and stigma among youth in Malawi and Tanzania. The survey gathered information about the respondents, their radio-listening habits, as well as their knowledge, attitudes and opinions about depression. The survey revealed that there is no word for "depression" in Chichewa, one of the main languages of Malawi, nor does it exist in other dialects native to sub-Saharan Africa. Victims of depression were stigmatized and labeled as either weak, lazy, or possessed by spirits, and were often punished as a result.

#### Box 1. Farm Radio

Farm Radio International is a Canadian not-forprofit organization which works with approximately 600 broadcasters in 38 countries across Africa to fight poverty and food insecurity using the medium of radio to provide information (31). Farm Radio International started out as Developing Countries Farm Radio Network (DCFRN) in the late 1970's. It was the brainchild of George Atkins, voice of CBC's noon farm radio program for 25 years. While visiting Africa, George Atkins saw the value in being able to reach farmers with information about affordable, sustainable farming techniques to improve self-reliance, increase food security, gender equality, and reduce poverty. Radio is a particularly efficacious method of reaching farmers in many places in Africa due to the prevalence of radio sets relative to other methods of communication. A 2011 study by Farm Radio International showed that only 2% of farmers had access to a landline, 3% to the internet, and 18% to mobile phones, yet 76% of farmers had access to a radio set (33). This, coupled with the low production cost of radio programs and relatively low cost of maintaining infrastructure, allows Farm Radio International to reach millions with Participatory Radio Campaigns at the cost of "pennies per farmer".

Reflecting these beliefs, health and government officials coined the term, matenda okhumudwa, which roughly translates to "disease of disappointment." Additionally, the survey also revealed that approximately 25% of students reported feeling hopeless on a daily basis. Dr. Kutcher et al. designed a set of unique interventions that: (i) raised mental health awareness through a radio program for youth, (ii) trained teachers with the use of a mental health literacy program adapted from a Canadian mental health curriculum, and (iii) instructed com-

munity health care providers on the identification, diagnosis, and treatment of adolescent depression. Together, these programs represent "An Integrated Approach to Addressing the Challenge of Depression Among the Youth in Malawi and Tanzania" (IACD).

The IACD was comprised of four integrated components (17, 18, 19, 20): (i) raise awareness, provide information, and broadcast first-person testimonies through the use of radio programs broadcasting music, a "soap opera" story of youth, and interactive discussion; (ii) decrease stigma through the development of youth listening clubs led by teachers or peer educators to guide discussions on the content; (iii) train teachers to increase mental health literacy through the implementation of a mental health school curriculum; (iv) train community health care providers in the identification, diagnosis, and treatment of youth depression, and encourage the development of a "hub and spoke" model, linking schools to these trained providers.

### Raising Awareness and Mental Health Literacy on Air and through Youth Groups

Three radio stations in Malawi and one in Tanzania broadcasted interactive radio programs tailored to youth, including a soap opera that addressed topics of mental health, sexual and reproductive health, and substance abuse (21). The radio program also recruited famous Malawian and Tanzanian personalities as ambassadors to break down stigma associated with mental health. The Diktator—a well-known Malawian rapper—was voted by youth to host the radio program Nkhawa Njee 'Yonse Bo' ("Depression Free, Life is Cool"). Since its debut four years ago, the program has reached over 500,000 youth in both Malawi and Tanzania. The aim of this intervention was to break down

negative stereotypes surrounding mental disorders. Using mobile phones, listeners were able to leave comments and feedback for radio hosts and mental health experts, ask questions, and participate in quizzes and polls.

To guarantee that youth both within and outside schools were tuning in to the radios shows, the IACD trained peer educators to lead radio listening clubs and promote discussions to improve mental health literacy. The in-school youth clubs were comprised of students and teacher mentors. The out-of-school clubs were comprised of school drop-outs as well as unemployed youth that had completed secondary school (aged 20-30 years). Additionally, listeners were given the phone number of an automated, interactive voice response system through which the location of their closest mental health provider could be obtained. These calls were provided free of charge. Over 3,000 youth approached teachers with concerns about mental health and more than 1,000 reached out to mental health providers to receive treatment.

Surveys, in the form of short questions, were used to assess youth awareness of mental health issues and available care options. Post-implementation surveys indicated that the mental health literacy of youth significantly improved in both Malawi (N≈500) and Tanzania (N≈200) (p<.001, paired t test) (22). In addition, attitudes towards mental health issues also improved (p<.001) (22). Students reported being more inclined to advise friends and classmates to seek mental health care, suggesting that the program promoted an impactful "pay it forward" effect (p<.001; Figure 1) (21, 22).

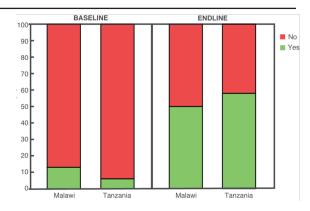


Figure 1.

The percentage of youth who advised a peer to get help from a healthcare professional in Malawi (MW;  $N\approx500$ ) and Tanzania (TZ;  $N\approx200$ ) before (baseline) and after (endline) being exposed to the radio program. Adapted from Kutcher, 2016.

# Improving Mental Health Literacy through School Curriculums

Oftentimes, teachers are the first contact to mental health literacy for adolescents through the school curriculum. Teachers provide an opportunity to enhance access to mental healthcare for youth that may have a mental disorder. Thus, it is necessary to train teachers to identify high risk students and refer them to trained health providers. To achieve this, Dr. Kutcher worked with local mental health experts in both countries to adapt a training program he had helped to develop in Canada, the Mental Health and High School Curriculum Guide (The Guide) (Box 2). As a result, the African Guide (AG) was assembled and three-day training workshops were provided to educators that included a module-by-module revision of the AG on mental health literacy and a how-to for integrating basic concepts of mental health and mental disorders into classroom teaching (23). Moreover, the training provided teachers with basic Cognitive BehavTherapy (CBT) based interventions to help them talk to students in distress and offered a program that helped them learn how to identify mental health problems in students and appropriately select a clinic for referral. In Malawi, the workshop involved 218 teachers and youth club leaders (121 males, 96 females, and 1 gender not provided) that were selected by Malawi's Ministry of Education from primary and secondary schools (22, 24, 25). In Tanzania, the program was conducted in fewer districts—namely, Arusha and Meru; 61 secondary school teachers (29 males, 29 females, and 3 of anonymous gender) participated (20).

To assess whether teachers' levels of mental health literacy and attitudes changed over the course of their training, they were given pre- and post-intervention questionnaires. These questionnaires assessed general mental health knowledge and consisted of questions with the options "true", "false", and "I don't know". Participants were encouraged to use "I don't know" to avoid guessing. They also answered eight questions about attitudes and stigma on a seven-point Likert Scale that ranged from "strongly agree" to "strongly disagree". Finally, participants responded "yes" or "no" to questions about their experience referring or advising others to seek professional help for a mental health problem, as well as questions about whether or not the teachers themselves personally recognized and/or sought professional help (21).

Prior to the training, educators in Malawi correctly answered an average of 58.3% (Mean (M) =  $17.5\pm4.07$ ) of the 30 questions about mental health, mental illness, and depression. This improved to 76.3% (M=  $22.94\pm2.89$ ) following completion of the workshop (22, 24, 25). A paired t-test indicated this to be a highly significant difference (p <

0.0001, paired t-test). Interestingly, this improvement did not differ by gender or region (p>0.05). In Tanzania, educators correctly answered 65.9% (M = 19.76 $\pm$ 3.57) of the 30 questions prior to training. This improved to 77.8% (M = 23.34 $\pm$ 2.63) after training (p < 0.001) (20, 22). Moreover, attitudes toward mental health (p < 0.001) and comfort levels for addressing mental health needs (p > 0.05) significantly improved after the workshop, signifying a decrease in stigma.

# Box 2. The Mental Health and High School Curriculum Guide (The Guide)

The Guide\* is a web-based mental health literacy curriculum comprising of a teacher self-assessment tool, a teacher self-study module, a student evaluation tool, and 6 classroom ready modules (23). The modules include learning objectives, lesson plans, classroom-based activities, and teaching resources (e.g., written materials, animated videos, and PowerPoint presentations). The 6 modules are as follows: the stigma of mental illness, understanding mental disorders and their treatments, experiences of mental illness, seeking help and finding support, and the importance of positive mental health. The Guide has been certified by Curriculum Services Canada, a pan-Canadian curriculum standards and evaluation agency, and endorsed by the Canadian Association for School Health. The Guide was field tested in numerous schools across Canada, and pilot studies have confirmed its effectiveness in the province of Nova Scotia (34) and in the city of Toronto, Canada's largest metropolitan area (35).

The efficacy of the workshops is further reflected in the percentage of educators that referred students to seek mental health care. 95% of teachers in Malawi and 84% in Tanzania reported that they identified students with mental health problems, and

a subset reported advising the students to reach out for help (Figure 2) (22). During this preliminary analysis of the intervention's impact, the trained educators had taught over 500 classes in 30 Malawian schools and over 300 in 20 Tanzanian schools. A later assessment conducted to measure the oneyear impact of improving mental health literacy in Tanzania demonstrated that the number of teachers trained in the guide increased to 159 and the number of students exposed reached about 4657 (M=145.53 per teacher) (26). Interestingly, not only did the same analysis show that teacher referrals increased by a factor of 3 over time, but roughly 400 students (M=13.76 per teacher) said they would approach teachers with a mental health concern. Similar significant improvements were found in Malawi (22).

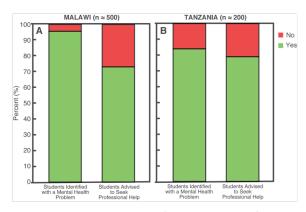


Figure 2. The percentage of students identified by teachers in Malawi (A) and in Tanzania (B) to have a mental health disorder (bar on the left) and referred to seek professional help (bar on the right). Adapted from Kutcher, 2016.

# Providing Mental Health Care, Not Just a Rare Service

Finally, utilizing AG training modules similar to those developed for teachers, the IACD program taught frontline healthcare practitioners how to screen for, diagnose, and treat depression, while also emphasizing mental health care provided by community healthcare providers rather than mental health services provided by mental health specialists. These healthcare providers worked in communities near the target schools and served as the resources to which the teachers were instructed to refer students.

A survey was conducted in two sections: the first assessed healthcare professionals' (HCPs) self-reported confidence regarding identification, diagnosis, and treatment of depression in young people; the second was a questionnaire featuring similar questions to those used to assess teachers' mental health literacy before and after training. The confidence self-reports used a 4-point Likert scale that asked HCPs to rate their confidence from "not confident" (1 point), "somewhat confident" (2 points), "very confident" (3 points), to "extremely confident" (4 points). Forty-six HCPs were on average "very confident" in their ability to identify, diagnose, and treat depression in adolescents, yet the average score of the knowledge assessment guestionnaire was only 55% correct answers (19). While the sample size was small, the results indicate that training of HCPs in Tanzania is inadequate, and that simply asking them about their competence is not an appropriate metric for assessing capability. In an attempt to compensate for this, Dr. Kutcher trained a group of 4-6 Master Trainers composed of a mix of psychiatrists, psychologists, counselors, and psychiatric nurses. The Master Trainers then trained 20 future trainers, who in turn trained community-based healthcare providers (27). In total, a year after the initial implementation of IACD, 94 HCPs had received training in Malawi, and 75 HCPs had received training in Tanzania (22).

Additionally, fluoxetine—the generic equivalent of Prozac and a relatively cheap medication (~CA\$0.78/20 mg capsule)—was made available for the first time by the Ministry of Health in both Malawi and Tanzania as the first-line pharmacological intervention in the treatment of adolescents with depression.

#### Discussion

The popularity, efficacy, and longevity of the radio-based mental health programs are key indicators of the value of this medium in reaching young people in sub-Saharan Africa. While the cost-effectiveness of these mental health programs has not been specifically assessed, analyzing studies of analogous farm radios in Africa may provide insight into this factor. In 2007, the African Farm Radio Research Initiative (AFRRI) examined the effectiveness and efficiency of radio communications in improving agricultural productivity and food security for rural communities in five countries: Malawi, Tanzania, Uganda, Mali and Ghana (28). The costs associated with installing Farm Radio in these countries are highly variable and depend on the type of station as well as other environmental factors. For example, a 'micro-station' in Mali with a broadcast range of 2.5 km costs US\$650 to set up, while a public broadcaster with the signal strength to serve the entirety of Tanzania costs roughly US\$8 million. The average cost of setting up a station for AFRRI partners was approximately US\$100,000. Indeed, running costs varied widely, as an AFRRI partner survey revealed costs ranging from US\$20,330-\$541,000 per annum for public broadcasters, US\$2,500-\$930,000 per annum for commercial stations, and US\$2,500-\$286,000 for community stations (28).

With GCC's funding coming to an end, constant revenue is essential for the radio initiative to be viable in the long-term. Farm Radio stations typically have two avenues of revenue available to them: 10% internally-generated (advertisements, competitions, subscription fee) and 90% externally-generated (grants and loans from NGOs/IGOs including the Canadian International Development Agency (CIDA), the Bill and Melinda Gates Foundation, Alliance for a Green Revolution in Africa (AGRA)) (29, 30, 31). However, this has led to a "too many cooks in the kitchen" effect causing disagreements over how farm radio in Malawi and Tanzania should be regulated and discouraging continued funding. A recent documentary, "Mental Health on Air," summarizes the impact of the IACD program and shows interviews and clips of children participating in the youth clubs. This documentary may help sway other funders to join the efforts to continue to combat the stigma surrounding depression in sub-Saharan Africa.

Enhancing mental health literacy through a school rather than a non-school curriculum approach has several advantages. For example, it does not require additional program development as it utilizes methods already used by Western educators that have been adapted for sub-Saharan cultures. The IACD approach worked well in both Malawi and Tanzania, appealing to major governmental institutions. For example, Malawi's Ministry of Education is reviewing the AG to incorporate it into the national school curriculum, rather than just the four districts where this case study was implemented. Furthermore, the Ministry of Health is recognizing the IACD as an integral component of the reform of Malawi's mental health policy and plan.

Finally, the potential for the cascade model of training to scale up is considerable. However, due to the lengthy training times, the HCP trainees must have sufficient resources to enable them to train without a drop in frontline care (27).

Unfortunately, the IACD approach has some limitations. The study lacks a control group, which means that it is not feasible to attribute the improvement in referrals made by teachers solely to the influence of the intervention—although other explanations are unlikely since no referrals were made prior to the intervention. In addition, while the number of mental health care referrals significantly increased, there is no data that indicates whether or not the advisees actually sought care. Moreover, data on whether those students continued to seek help and if their conditions improved is difficult to obtain due to the limited duration of the program. Fortunately, an extension phase funded by GCC is examining some of these areas. It is also worth noting that all results in this case study were obtained from the work of Dr. Kutcher and his colleagues; an independent source—ideally within Malawi and Tanzania—would be favorable to validate the data and impact. Finally, considering the positive influence that radio has had on the youth of Malawi and Tanzania, the authors of this case study question whether television could serve as an even more potent medium due to its visual nature. However, televisions are inconsistently available within sub-Saharan communities, which explains the need for the greater coverage achieved by radio.

#### Conclusion

Radio-based mental health awareness/literacy programs for youth have immense potential to proliferate. In 2014-2015, Farm Radio International worked with more than 600 broadcasters in 38 African

countries to reach an estimated 20 million farmers (32). The radio programs may be an effective way to raise awareness, but the capacity of these programs to improve mental health outcomes is limited without the support of the youth radio clubs, school-based mental health literacy programs, and HCP training and treatment availability.

The IACD approach increases mental health awareness among youth and members of their support networks because of its integrative approach and capacity-building initiatives. Further, IACD allows for community-based HCPs to provide treatment through closer training and provision of medications and psychological interventions known to be effective in treating depression.

The results of the studies conducted by Dr. Kutcher and his colleagues suggest that mental health-care outcomes among youth in sub-Saharan Africa could be substantially improved if the IACD approach were scaled up to cover the entirety of Malawi, Tanzania, or even the full extent of the Farm Radio International coverage area. Unfortunately, cost remains a barrier to the scale-up process. To this end, Farm Radio International and the IACD must strengthen partnerships with major health and aid organizations to ensure sustainability by securing funding, and to maintain accountability for ongoing improvement in training.

#### **Acknowledgments**

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# **Malaria Elimination in Sri Lanka**

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#### **Abstract**

Sri Lanka was declared malaria-free on 5 September 2016 by the World Health Organization. This success was the result of over a century of efforts that combined disease surveillance, vector control and treatment. By 2008, there was zero mortality from indigenous cases, and the country witnessed its last indigenous case in 2012. This process involved long-term, sustained financial support, particularly from the Sri Lankan Government, the World Bank and the Global Fund. Given that malaria is still a global health burden, there is much to be learnt from Sri Lanka's achievement in the ongoing efforts to reach a malaria-free world.

Keywords: Elimination, malaria, Sri Lanka

#### INTRODUCTION

Malaria is a mosquito-borne disease caused by the *Plasmodium* genus of parasites and transmitted by the bite of infected female *Anopheles* mosquitoes. [1] The disease disproportionately affects marginalised groups in tropical and subtropical areas. [1] The World Health Organization (WHO) estimates that in 2015 there were 214 million clinical cases of malaria worldwide, leading to 438,000 deaths, most of them occurring in Africa in children under the age of five. [2] However, there has been tremendous progress in reducing both malaria incidence and mortality over the last 15 years. [1] While the particular numbers mask regional and country-specific disparities, the overall successes underscore the potential of achieving the WHO's vision of a malaria-free world by 2030. [1]

On 5 September 2016, the WHO officially certified Sri Lanka to be malaria-free. Located south-east of the Indian subcontinent, Sri Lanka is a tropical island nation with a population of roughly 21 million. Malaria transmission is seasonal as cases peak at the end of the country's monsoons. The country receives two monsoon periods every year: Maha season and Yala season. The Maha season brings rainfall to the north and south-eastern dry zones of the Island during the winter, while the Yala season brings rainfall to the south-western wet zone during the summer. The rainfall in

the wet zone inundates malaria vector breeding sites, washing them away, and thus, malaria incidence is lowest in the wet zone and most abundant in the dry zone.<sup>[6]</sup>

Over the past century, malaria has consistently been one of the most devastating health burdens in Sri Lanka. [7] Epidemics have occurred periodically, the worst of which was between 1934 and 1935, killing over 1.5% of the population. [7] Additional major epidemics in the following decades further intensified the public health challenges. [7] Until recently, out of Sri Lanka's 25 districts, only six had low to no risk of malaria. [7]

From July 1983 to May 2009, civil war ravaged the country, with a ceasefire period from 2002 to 2006. [4] This ethnic conflict was between the government and national forces and the Liberation Tigers of Tamil Eelam (LTTE). [8] The conflict led to the displacement of a large portion of the population and created significant barriers for access to health services. [4] While conflict has historically created a breeding ground for epidemic transmission, the case of malaria throughout Sri Lanka's civil war is unique. [4] Between 2000 and 2015, the country

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saw a reduction from 200,000 to zero indigenous cases.[3] This was due to continued vector control efforts targeted to at-risk populations in conflict regions made possible through partnerships with the Sri Lankan government's Anti-Malaria Campaign (AMC), non-governmental organisations (NGOs), humanitarian organisations, military, LTTE as well as the reduction in foreign nationals entering the country, thereby containing the epidemic within the national borders.[4] Since Sri Lanka is an island, there is reduced possibility for the migration of mosquitoes from the Mainland.[7] It is also one of the few tropical countries where only one principal vector, Anopheles culicifacies, exists. [9] This particular vector does not transmit malaria as efficiently as other Anopheles species and is more susceptible to vector control measures. [9] Sri Lanka's successful elimination of malaria, especially in the face of persistent civil conflict, is a testament to its own resilience as well as its unrelenting efforts.

# PROGRAM ROLLOUT

#### History of malaria elimination

Throughout the early 20th century, malaria epidemics occurred in Sri Lanka every 3-5 years.[10] Following the devastating epidemic of 1934-1935 (refer to Figure 1, a timeline of incidence and significant events throughout Sri Lanka's malaria elimination process)[11] Sri Lanka instituted an indoor residual spraying (IRS) programme with the pesticide dichlorodiphenyltrichloroethane (DDT), which successfully brought the number of cases down to only 17 in 1963.[4] However, due to a perceived lack of need, the government withdrew funding and scaled back IRS, resulting in regular epidemics in subsequent decades.<sup>[4]</sup> Following a massive epidemic in 1986-1987 with over 600,000 cases, the AMC decentralised and began operating under the central AMC Directorate, where it reorganised its programmes at the district level and replaced single-vector programmes, such as IRS, with an integrated vector approach.[4,12]

#### Parasitological surveillance

Surveillance was an essential part of the elimination effort consisting of tracking each case in the country and allowing for IRS and treatment programmes.<sup>[13]</sup> Since 1959, Sri Lanka

has used passive case detection (PCD), whereby all fever cases brought to public health facilities are clinically investigated for malaria.[11,13] In the late 1990s, the AMC introduced activated PCD (APCD), whereby fever cases are tested for malaria with microscopy, resulting in a dramatic increase in diagnostic effectiveness and informing better quality IRS and treatment. [4,13] APCD has since been the most important method of case detection, identifying 89.8% of cases in 1995 and 94.0% of cases in 2005.[4] In 1997, the World Bank International Development Association supported the establishment of active case detection (ACD), whereby mobile malaria clinics travelled to remote populations, often in conflict zones, expanding the range of service access throughout the country. [4] The majority of ACD diagnoses were made by microscopy. [4,13] In 2009, the AMC hired a private organisation, Tropical and Environmental Diseases and Health Associates (TEDHA), contributing to surveillance efforts, focusing on ACD in conflict zones and high-risk populations, especially pregnant females.[13]

In 2001, the Global Fund introduced rapid diagnostic tests (RDTs) to Sri Lanka, through the AMC Directorate. [4,14] Sri Lanka uses the CareStart<sup>™</sup> Malaria histidine-rich protein 2/parasite lactate dehydrogenase (HRP2/PLDH) RDT.[14] It includes antibodies to HRP2, which is specific to Plasmodium falciparum, and PLDH, which is responsive to all the species of *Plasmodium*. [14,15] The CareStart<sup>™</sup> test kit detects *P. falciparum* with 88.52% sensitivity and 98.26% specificity; it detects Plasmodium vivax with 90.77% sensitivity and 100% specificity. [16] Unfortunately, RDTs do not reliably detect low-density parasitaemia, which can occur in mildly symptomatic or asymptomatic individuals who act as reservoirs for the parasite and contribute to the spread of disease.[13] To guard against false results, RDT tests are confirmed by microscopy at the regional and national level. [4,13] RDTs have been used in emergencies, such as after the 2004 tsunami and by ACD mobile clinics in conflict zones.[4,14] In 2003, RDTs constituted 4% of the 1.2 million malaria tests conducted.[4] Now, their use is almost exclusive to ports of entry to detect imported cases.<sup>[13]</sup>

#### **Entomological surveillance**

After the 1934–1935 epidemic, Sri Lanka instituted an entomological surveillance programme aimed at tracking

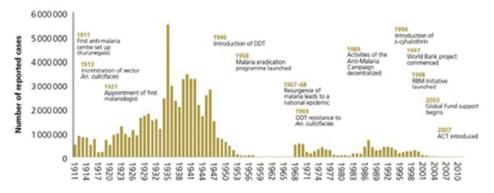


Figure 1: Timeline of incidence and significant events throughout Sri Lanka's malaria elimination process

mosquito breeding patterns to identify the potential location and timing of epidemics. [4,17] Adult mosquitoes were captured by trained mosquito catchers using cattle-baited traps and window exit traps. [4] Larvae were collected from bodies of water using nets.<sup>[17]</sup> Genetic tests were employed at regional and national laboratories to assess insecticide resistance.[4] These activities were essential in guiding Sri Lanka's vector control efforts, which consisted mainly of IRS and bed net distribution.[18]

#### **Vector control**

IRS involves spraying insecticide on the inside of dwellings in malarious regions to kill mosquitoes and prevent disease transmission.<sup>[4]</sup> Sri Lanka has a long history of IRS use, beginning with DDT in 1946.[4] The AMC transitioned to using the pesticide malathion in 1975 following reports of DDT resistance and growing health concerns.<sup>[4,11]</sup> The WHO recommendations in 1993 led to a more targeted IRS approach, with priority given to areas of historical transmission. chloroquine-resistant cases (chloroquine being one of the main treatments), a higher proportion P. falciparum and proximity to mosquito breeding sites.<sup>[4]</sup> Lambda-cyhalothrin, a synthetic pyrethroid pesticide, was introduced in 1994 and malathion was abandoned in 2002 due to increasing resistance in A. culicifacies. [4,11] The LTTE collaborated with the AMC to deploy IRS in conflict zones; in 2000, 24% of the at-risk population was covered by IRS. [4] As the prevalence of malaria declined and the AMC focused on more targeted spraying, IRS coverage decreased steadily from 64.8% in 1995 to 22.5% in 2005 and to 5.9% in 2010.[4] Larvivorous fish and chemical larviciding were also used as supplementary vector control measures.[11]

Insecticide-treated nets (ITNs) and long-lasting insecticidetreated nets (LLINs) were also crucial to vector control. [4,11] While ITNs last for about 6 months before requiring re-impregnation with insecticide, LLINs last for approximately 3 years. [4,11] The Global Fund supported the introduction of ITNs in 1999 and LLINs in 2004.[4] Approximately 300,000 LLINs were distributed from 2005 to 2007, which benefitted from high uptake; a survey conducted in 2008 of 2467 Sinhalese, Tamil and Muslim households found that 90.2% of respondents used their net every night while sleeping.[19] Mosquito nets were most useful in remote regions and conflict zones where regular IRS was impractical.[4,11]

#### **Treatment**

Sri Lanka's national health-care system provides free consultation and treatment at public hospitals.[4] From the mid-1990s to 2006, malaria cases were treated with chloroquine and primaquine (0.25 mg/day for adults), with a 5-day regimen in low-transmission areas and a 14-day regimen in high-transmission areas.<sup>[4,11]</sup> Primaquine treatment became more prominent after 2006, and sulphadoxine-pyrimethamine was used as a second-line treatment for chloroquine-resistant cases.[4,11] Due to rising drug resistance and sustained levels of imported malaria cases, artemisinin-based combination therapy was introduced in 2008.<sup>[4]</sup> Since not all people could reach public hospitals, the use of mobile clinics to offer these treatment services was also crucial.[4]

#### **Maintaining elimination**

While the last indigenous malaria-related mortality was in 2008 and the last indigenous case was in 2012, imported cases remain an issue. [9] Screening at ports of entry, predominantly with RDTs, is crucial in detecting incoming cases. Maintained parasitological and entomological surveillance informs targeted IRS in areas of high vector density and those that surround imported cases.<sup>[4,9]</sup> Treatment remains free at public health facilities and residents travelling to malaria-endemic countries are provided with complementary prophylaxis.<sup>[9]</sup>

#### **IMPACT**

Sri Lanka's efforts led to successful malaria elimination status in 2016.[4] The annual parasite incidence fell from 11.9 cases/1000 people at risk in 1995 to 1/1000 in 2005 and to 0.1 in 2010.[4] This reflected a drop in the number of cases from 264,549 in 1999 to 736 in 2010 and to 175 in 2011, only 124 of which were indigenous.<sup>[4,20]</sup> Imported cases continue to raise concern, with 70 imported cases in 2010 and 95 in 2013, affirming the need to maintain surveillance and screening programmes.[9]

Deaths due to malaria declined steadily from 76 in 1995 to 40 in 2005. [4] As the last indigenous case fatality was in 2008, the remaining 25 deaths in 2010 were from imported cases.<sup>[4]</sup> The malaria-specific mortality rate for all ages experienced an increase from 0.31/1000 people at risk in 1990 to a peak of 0.55/1000 in 1997, subsequently declining steadily to 0.13/1000 in 2010.[21]

#### Cost

Given that the elimination campaign has been ongoing since the early 1900s, a precise estimate for the total cost of efforts is unavailable at this point. However, major contributors to Sri Lanka's malaria elimination success were the Sri Lankan Government, the USAID, the UNICEF, the Global Fund and the WHO – first through the global malaria eradication effort and then through the Roll Back Malaria partnership. [4,20] Of these bodies, the most significant sources of funding were the Sri Lankan government and the Global Fund. [20] All dollar amounts mentioned in this section are in USD.

In 1996, the World Bank contributed \$18.8 million to the Sri Lankan health services project, which focused on a range of health issues including malaria.<sup>[22]</sup> In 1999, the Sri Lankan government partnered with the WHO Roll Back Malaria programme.[4] The Sri Lankan president agreed to provide support for several activities involving the prevention, early diagnosis and treatment of malaria as well as research initiatives pertaining to drug resistance, drug therapy and

surveillance.<sup>[11]</sup> These activities, financed by the World Bank, were rolled out in five pilot districts: Jaffna, Kilinochchi, Mullaitivu, Anuradhapura and Monaragala, where malaria was most deadly.<sup>[11]</sup> The World Bank also supported the creation of ACD to complement the APCD that was already established.<sup>[11]</sup>

Financial support from the Global Fund contributed significantly to malaria elimination efforts. [4] Beginning in 2003, Sri Lanka applied for and received funding for its malaria program in Rounds 1 (2002), 4 (2004) and 8 (2008) of funding from the Global Fund. [4,23] To date, the Global Fund has signed \$42,058,140, committed \$38,157,830 and disbursed \$35,662,201 towards malaria elimination in Sri Lanka. [23] This funding has been used for scaling up IRS, active surveillance through mobile clinics, diagnosis and treatment and LLIN distribution. [24]

Malaria activities in Sri Lanka are financed primarily through domestic sources, representing 58% of total funding (\$8.8 million) in 2014.<sup>[24]</sup> Domestic spending includes funding from the Sri Lankan government for the AMC, solely directed towards malaria-specific initiatives. [24] Only 0.94% of total government spending on health (an estimated \$934.1 million) was devoted to malaria in 2014, marking an increase from 0.80% that was spent the year before. [24] With a donation of \$3.7 million, the Global Fund accounted for the remaining 42% of the total funding for malaria in 2014.[23,24] Sources of funding vary widely across districts as the AMC, the Ministry of Health and the Global Fund determine which districts to include in grant proposals.<sup>[4]</sup> At the district level, the median cost for malaria control was \$195,316 in 2014 with a cost per capita ranging from \$0.21 to \$0.54 and an overall estimated national cost per capita of \$0.50.[24] In the light of the difficulty in obtaining data from the AMC, a 2012 study focused on the districts of Anuradhapura and Kurunegala in 2004 and 2009. [4] As the AMC is part of a decentralised health system, detailed programmatic and cost data are kept at district levels, managed by regional malaria officers and overseen by the Regional Director of Health Services. [25] Therefore, evaluating the cost of the anti-malaria programme in these two previously high-burden districts offers a more in-depth look at the cost and allocations of malaria expenditure at the district level. Please refer to Table 1 for the costs of different vector control interventions implemented in Sri Lanka.<sup>[25]</sup>

With the last indigenous malaria case in 2012, Sri Lanka now focuses on preventing reintroduction. To ensure sustained elimination, existing surveillance and screening programmes must be maintained. The Sri Lankan National Malaria Strategic Plan (NMSP) estimated that an annual budget of \$10 million (from 2015 to 2018) is required to prevent reintroduction. However, assuming a steady economic growth rate of 6.4% including existing human resource and capital costs that the NMSP budget did not consider and basing the projection off of the current strategies rather than proposed activities, the University of California, San Francisco Global Health Group, estimated an annual budget of \$14 million (from 2015 to 2020) to prevent reintroduction.

#### REASONS FOR SUCCESS

The AMC distinguished itself as the main driver of malaria elimination thanks to a comprehensive approach of vector control, surveillance and case management. The AMC was a centralised body until 1989 when it began project implementation through eight provincial programs headed by the national AMC Directorate. After joining the WHO Roll Back Malaria partnership in the 1990s, the government solidified multiple partnerships with funders such as the World Bank and the Global Fund as well as local and international NGOs, which allowed for the scaling up of its anti-malaria programmes.

In addition to excellent programming and partnerships, Sri Lanka's strong institutions were critical to its success (Nadira Karunaweera, personal communication, 23 November 2016). The country has an impressive adult literacy rate (91.2% between 2008 and 2012), which contributed to high levels of public compliance to available health-care measures (Nadira Karunaweera, personal communication, 23 November 2016). [26] It also has a national health-care policy that facilitates a strong primary health-care system by offering free health care to all citizens through a network of government hospitals and health-care centres (Nadira Karunaweera, personal communication, 23 November 2016). [4]

Throughout Sri Lanka's civil war, the conflict-marred regions experienced increased parasite incidence as their primary

Table 1: Operating and capital costs of various vector control interventions									
Intervention	Operating cost* per day	Number protected households per day	Operating costs per household per intervention day	Number of interventions per year needed for protection	Annual operating cost per household	Annual capital cost per household	Total annual cost per individual protected		
Spraying fenitrothion	\$172.04	25	\$0.67	3	\$20.66	\$0.65	\$4.25		
Lambda-cyhalothrin	\$198.79	25	\$0.78	2	\$15.84	\$0.43	\$3.27		
Malathion	\$124.10	25	\$0.48	3	\$14.93	\$0.65	\$3.12		
Bednet impregnation (permethrin)	\$141.07	50	\$0.27	2	\$5.65	\$0.86	\$1.29		
Larviciding (temephos)	\$44.44	56	\$0.08	4	\$3.23	\$0.43	\$0.73		

<sup>\*</sup>All costs have been converted to 2016 USD levels. Source: Konradsen et al

health-care services were disrupted.<sup>[7]</sup> The AMC recognised the deficit of treatment and prevention measures in these areas, and along with regional malaria teams, NGOs and the military scaled up treatment protocols.<sup>[7]</sup> The LTTE were themselves impacted by high infection rates and eventually agreed to support control efforts, which was critical in ensuring treatment and prevention for as many people as possible despite ongoing conflict.<sup>[7]</sup> The AMC as well as the UNICEF, the WHO and the Sri Lankan NGO Sarvodaya worked to distribute ITNs across the country, with the Global Fund supporting the introduction of LLINs later in the conflict.<sup>[4,7]</sup> The Sri Lankan Red Cross, the International Committee of the Red Cross, Médecins Sans Frontières, TEDHA and local health workers provided access to diagnostic and treatment services, largely through mobile clinics. [4,7] By 2005, the annual parasite incidence rates in both conflict and non-conflict areas had stabilised and were well below previous levels.[4,7] Sustained ACD, treatment and vector control in these areas was a crucial factor in the eventual elimination of malaria. [4,7]

The use of DDT in the IRS programme had excellent results, but its subsequent scaling back led to a dramatic resurgence of cases. [7] The shift from malathion to pyrethroid insecticides in 1994, in response to drug resistance in mosquitoes, not only marked the uptake of a more effective insecticide but also increased community acceptance of IRS, as pyrethroids were less pungent and left less residue where they were sprayed. [4] An effective entomological surveillance program was critical in informing targeted IRS for high-risk areas, which became more important as malaria prevalence declined. [4] In addition, the use of ITNs and LLINs was particularly effective in areas inaccessible to IRS teams. [7,11]

The development and refinement of both parasitological and entomological surveillance systems allowed for high case detection.<sup>[4]</sup> More microscopists were able to employ APCD in publicly run health facilities, and ACD could be remotely dispatched to difficult-to-reach areas.[4] In 2009, the AMC developed standard operating procedures for each confirmed or suspected infection, including post-treatment follow-up, household malaria screening and IRS within a 1-km radius of the case.[4] This protocol offered treatment as well as data collection opportunities for ongoing monitoring. [4] In addition, regional malaria control officials, some of whom had doctorate degrees, received research training and used their advanced education to enhance these efforts (Nadira Karunaweera, personal communication, 23 November 2016). Sri Lanka was also one of the first countries to adopt the WHO Global Malaria Eradication Programme's surveillance reporting system and submitting quarterly progress reports.[11] This type of surveillance was critical in tracking the disease to its end and will continue to be essential in ensuring that imported cases do not spur new epidemics.[11]

## IMPLICATIONS FOR GLOBAL HEALTH

If there is one takeaway from the case of Sri Lanka, it is that there is no silver bullet to malaria elimination. Sri Lanka's journey has spanned more than a century and does not owe its success to a singular approach but rather a sustained multidimensional programme that was responsive to changing biomedical and social factors. [3] Given that malaria is still a global concern, there is much that can be learnt from Sri Lanka's success. [3] Namely, countries seeking to mirror Sri Lanka's malaria-free status must recognise the critical interplay of the multiple interventions used and partnerships formed throughout this process. [3]

The coupling of both APCD and ACD allows for broad detection capacity within a country, and the use of RDTs at ports of entry screens for imported cases, which is especially important following elimination. [11,13] Vector control methods were used appropriately, with targeted IRS in areas of high vector density and in areas surrounding malaria cases. [4,9] Due to the inconvenience of regular IRS, ITNs and LLINs were relied on more heavily in remote regions and conflict zones. [4] Complementary measures such as larvivorous fish and chemical larviciding played minor roles but highlight the multidimensional and situation-specific uses of various vector control measures. [4,11] Of course, the success of vector control efforts relied on effective and reliable parasitological and entomological surveillance. [4]

It is critical to build and maintain partnerships with NGOs and other parties to ensure that almost all citizens have access to prevention and treatment measures, regardless of the country's sociopolitical environment. [4,11] This requires reflexive leadership that is committed to providing unrelenting support for these efforts. [4,11] Secure sources of funding are required to operate these programs not only throughout the elimination process but also afterwards to avoid relapsing into endemicity. [3] Thus, national governments must be willing to dedicate significant funds alongside their partners. [3]

While Sri Lanka's elimination is impressive, the country must remain vigilant to ensure that the disease is not reintroduced.<sup>[3]</sup> Community-centred approaches have strengthened biomedical ones, and this synergy was the ultimate driver of success.<sup>[4,14]</sup> This resonates with the tenets of public health and has the potential for global impact.

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#### **Conflicts of interest**

There are no conflicts of interest.

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# PPHS 511 Case Study Template

#### Title

Ensure the title is informative and implies the research question

#### Abstract

200-word summary of the case study and a visual abstract

### Tips:

• Write this part last

### Brief background and motivation for intervention

What is the context of the intervention? Who are the key players? What motivated the intervention?

Are there any previous or similar efforts that informed this intervention?

### Tips:

- Start this section broadly and then become more specific
- Establish the problem the intervention is addressing
- The term intervention is used loosely here, you can do a case study on a program, a product, a law, a new organization, etc.
- Should provide the information necessary for the reader to understand the case study question (next section)

# **McGill**

## Case study in PICOT format

Clearly identify the population, intervention, comparator, outcome(s) of interest and time period (optional) of your case study.

# Tips:

- Focus not only on feasibility of an intervention, but its impact and/or cost-effectiveness.
- The comparator could be a similar population that did not receive the intervention or a historical control (i.e. compare the situation after the intervention to the situation before the intervention)

### Goal of intervention

What, specifically, was the intervention trying to achieve? How was it anticipated to impact the outcome of interest?

# Strategy (methods)

What is the intervention? How/where/when was it implemented? What was the scale?

### Tips:

• Give a clear description of the mechanics of the intervention but don't get bogged down in the details

# **McGill**

# **Impact**

Did the intervention impact the outcomes of interest in your research question? Were there any unexpected or unintended consequences?

# Tips:

- Seek concrete (preferably numerical) evidence for the success or failure of the intervention (for some interventions, there may be published impact evaluations already available)
- If you are only able to show association and not cause, that's okay but be clear about this in the paper
- Incorporate 2-3 figures or tables that summarize your evidence

# W McGill

# Why it worked or why it didn't

What factors lead to the success/failure of this intervention? E.g.,

- Was it culturally appropriate?
- Made use of local knowledge?
- Was sufficiently funded?
- Had government support?
- Engaged key stakeholders (e.g. patient advocates)?
- Integrated into existing programs?
- Engaged new donors?

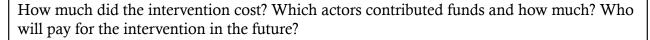
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# Tips:

• This is where you really tell a story. What should other people learn from this case study?

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### Financing



# Tips:

- Some intervention may have cost-effectiveness evaluations published which should be discussed
- You may need to contact involved actors or granting agencies to establish the amount of funding

# Future implications

What is the future fate of the program? If it was effective, does it appear sustainable? What are the key takeaway lessons for members of the global health community? Are there next steps you would recommend?



# General guidelines

- Before working on your own case study, please read the previous published case studies from this course to get a sense of how case studies are put together.
- Final case studies should be between 6-8 pages long (excluding references).
- Ensure that figure and tables are neat, readable and well labelled.
- Sources should be predominately from peer reviewed literature.
- Use citation software like EndNote (free for McGill students) to automatically cite papers and compile your bibliography.
- If you are seeking publication for your final case study, keep an eye on the copyright of figures you use from published literature. To publish you must have copyright permission for all figures that are not your own. Figures published in open access journals will be available under a Creative Commons license (<a href="https://creativecommons.org/licenses/by/2.0/">https://creativecommons.org/licenses/by/2.0/</a>) eliminating the need to seek and purchase copyright permission from the publisher.
- If certain details are not available in the published literature, you can contact the organizations overseeing the intervention, granting agencies etc.
- Do not copy and paste text verbatim from other sources if you do, you MUST attribute the quotations and cite the sources.

# Acknowledgements



Vaidehi Nafade Book design, case study template

Vaidehi completed her BSc. in Pharmacology at McGill University, where she worked in preclinical drug testing. Raised in India and Montréal, her coursework and clinical experiences in Canada and abroad led her to develop an interest in global health, and she then joined the Pai Global TB Group as an MSc. student.



**Sophie Huddart** *Case study template* 

Sophie received a BSc in Immunology and Infectious Disease from Penn State University and a MSc in Biostatistics from the University of Glasgow as a Fulbright Scholar. She has conducted research in immuno-parisitology and statistical clustering methodology but has always been an epidemiologist at heart and is now a PhD student with the Pai Global TB Group. In addition to being the team's number cruncher, Sophie works on diagnostics and patient mortality in the Indian TB epidemic.