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Health-economics of vaccines in Ethiopia

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Chapter eight

GENERAL DISCUSSION

SUMMARY OF FINDINGS

An immunization program is one of the most effective preventive public health interventions against vaccine-preventable diseases (VPDs). It not only saves millions of lives every year, but it also drives a reduction in morbidity and disability, both of which can impair growth and cognitive development¹. Furthermore, as a result of advances in biomedical sciences and technology, several new vaccines have become available on the international market in addition to the classic vaccines used in the Expanded Program on Immunization (EPI), allowing more people of all ages to be protected from VPDs than ever before. Maintaining high levels of performance in an immunization program, on the other hand, appears to be complicated. As a result, the World Health Organization (WHO) estimated that about 20 million children under the age of one missed out essential life-saving vaccines in 2019, with 60% of these children residing in ten countries, one of them being Ethiopia². Hence, it must be meticulously planned and closely monitored to reap the full benefits of an immunization program and ensure its success.

This thesis is organized into two parts. In the first part, I investigate the factors influencing childhood vaccination coverage and the extent and determinants of socioeconomic inequalities in childhood vaccination in Ethiopia. The second part of the thesis focused on the health economic aspect of HPV vaccines. **Chapter 2** identified the drivers of the change in full vaccination coverage over time in Ethiopia (between 2000 and 2016) among children aged 12 to 23 months using Oaxaca-Blinder decomposition analyses. National representative data from the Demographic and Health Survey (DHS) was used in this study. The full vaccination coverage among the children rose from 14.3% in 2000 to 38.5% in 2016. The results revealed that the change in the effect of explanatory variables over time and other unmeasured characteristics (coefficient effect), which is attributable to various policy measures taken in Ethiopia over the period, was the most significant driver of the rise in full vaccination coverage (74% of the increment). At the same time, the change in the composition of the explanatory variables over time (endowment or compositional effect) explained the remaining 26% of the change in full vaccination coverage being maternal educational level and maternal health care utilization as the most important contributors.

Chapter 3 explored factors associated with the uptake of childhood vaccination in Ethiopia using rotavirus vaccine (RVV) and pneumococcal conjugate vaccine (PCV) as examples that were newly introduced in the national EPI schedule in Ethiopia. The study employed cross-sectional data from the Ethiopian DHS conducted in 2016.

Multivariate logistic regression analysis was performed to examine determinants of the uptake of complete schedules of RVV (two doses) and PCV (three doses). Among children aged 12 – 23 months, only 56% and 49% were vaccinated with the complete schedules of RVV and PCV, respectively. After controlling for other variables, children residing in the Afar region had 0.16 times lower chances of being fully vaccinated with RVV (AOR 0.16; 95%-CI 0.04–0.61) taking children in Addis Ababa as a reference. Similarly, children living in Afar and Gambela had 0.10 (95%-CI 0.03–0.38) and 0.25 (95%-CI 0.08–0.84) times lower chances of being fully vaccinated with the full dose of PCV compared to those in Addis Ababa, respectively. Mothers who had four or more ANC visits were 2.79 (95%-CI 1.73–4.51) and 3.27 (95%-CI 2.04–5.23) more likely to get their children fully vaccinated with RVV and PCV when compared to those who had no ANC visit at all. It is also worth noting that the likelihood of children vaccination with RVV and PCV tends to increase with increasing household socioeconomic position, measured by wealth index. Children from wealthier households were 1.69 (95%-CI 1.04–2.75) times more likely to receive the complete dose of RVV than their counterparts from the poorest households. Although it is not statistically significant, a similar pattern was observed also with PCV.

Therefore, **Chapter 4** further quantified the degree of socioeconomic inequality of RVV uptake among children aged 12–23 months in Ethiopia. The household's socioeconomic status was determined by a wealth index derived from housing characteristics and asset ownership data using principal component analyses. The Erreygers Normalized Concentration Index (ECI) of the RVV uptake was used to measure socioeconomic inequality in the present study. A decomposition analysis was then performed to identify the underlying driving factors for the measured socioeconomic inequality. I found significant socioeconomic inequalities in the uptake of RVV in Ethiopia, with an ECI of 0.27 ($P < 0.001$), favoring children from higher socioeconomic status households. The decomposition analyses revealed that antenatal care use (18%), institutional delivery (8%), media exposure (13%), and maternal educational level (10%) were major contributors to the observed socioeconomic inequalities. The findings in **Chapters 2, 3 and 4**, showed that suboptimal vaccination coverage in Ethiopia is accompanied by significant geographic/regional inequality and socioeconomic inequality in coverage.

I carried out an additional study to analyze how the socioeconomic inequality of vaccination uptake in Ethiopia has changed over time since 2005 (**Chapter 5**). It appeared that socioeconomic inequality persisted while overall national measles vaccine coverage increased in Ethiopia between 2005 and 2016. In line with the findings in **Chapter 4**, amongst others, maternal educational level, antenatal care

use, institutional delivery, and exposure to media were the major contributors to the observed socioeconomic inequalities.

Part II of my thesis delves into the health economics of HPV vaccination. **Chapter 6** is based on a commentary on an article published in *The Lancet Global Health* by Abbas *et al.*³. Their study recalculated the global impact of human papillomavirus (HPV) vaccination using the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model⁴. The model is primarily updated with new demographics, disability weight, and cervical cancer data. The revised estimate showed that HPV vaccination had a significantly greater health impact in terms of the number of cases averted, deaths averted, and disability-adjusted life-years averted. However, some issues could be identified that need to be addressed further to maximize the potential of HPV vaccination, including potential differences between vaccines, particularly between bivalent and quadrivalent vaccines, reduced vaccination schedules to one dose, and prevention of noncervical cancers (e.g., vaginal, penile, and anal cancer). Finally, in **Chapter 7**, a Markov model is used to evaluate the cost-effectiveness of a nonavalent HPV (9vHPV) vaccine compared to the quadrivalent HPV (4vHPV) vaccine in Ethiopia. This study also determined the maximum price per dose for the 9vHPV vaccine to remain cost-effective.

It was found that switch from the 4vHPV to the 9vHPV vaccine is very cost-effective, with an incremental cost-effectiveness ratio (ICER) of US\$ 470 per quality-adjusted life-year (QALY) gained as the ICER is less than one times GDP per capita for Ethiopia. The price thresholds for the 9vHPV vaccine were US\$ 8.4 and US\$ 15, to be very cost-effective and cost-effective, respectively. The univariate sensitivity analyses showed that changes in the discount rate of QALYs exerted the greatest influence on the ICER. In a probabilistic sensitivity analysis, the 9vHPV vaccine had a 91% and 100% probability of being cost-effective compared to the 4vHPV vaccine, considering a threshold of one and three times GDP per capita, respectively.

IMPLICATIONS AND FUTURE PERSPECTIVES

Various global initiatives have been put in place to increase vaccination coverage so that everyone receives recommended doses of vaccines at the appropriate time and benefit from the potential of immunization. For example, the WHO established EPI in 1974⁵. Gavi, the Vaccine Alliance, was founded in 2000 to provide more than seventy poorest countries with access to high-impact life-saving vaccines, which were once only accessible to high-income countries⁶. The other is the Global Vaccine

Action Plan (GVAP) for 2011–2020, which was a commitment to achieving the full potential of immunization and approved by the World Health Assembly in May 2012⁷. Notably, these initiatives have significantly directed efforts toward achieving the vision of universal access to immunization. However, there are still several unmet goals⁸. After GVAP expired in 2020, a new global strategy called Immunization Agenda 2030 (IA2030) was also recently launched for the decade 2021–2030. IA2030 envisions “a world where everyone, everywhere, at every age, fully benefits from vaccines for good health and well-being”¹. Aside from that, several local programs, plans, and strategies to improve vaccination coverage have been implemented in Ethiopia, including the health development army (HAD), reaching every district (RED), comprehensive multiyear immunization plans (cMYP), and the Health Sector Transformation Plan (HSTP)⁹.

Vaccination coverage is an essential indicator of immunization program success and access to basic healthcare services. Improving vaccination coverage has a wide range of implications. Optimal vaccination use ensures better health by preventing infection-related disease, disability, and death^{10–12}. Infection prevention through vaccination can also help to reduce healthcare costs, contributing to financial protection at a household level¹³. At a country level, vaccines can increase productivity by preventing diseases that affect children’s educational attainment and avoiding travel and trade restrictions caused by disease outbreaks, as seen in the current global pandemic caused by COVID-19. Overall, vaccines have been identified as playing a critical role in the achievement of the Sustainable Development Goals (SDGs), particularly SDG3: “Ensure healthy lives and promote well-being for all at all ages”¹

Evidence from a nationwide study may supplement existing mechanisms for increasing vaccination coverage. The findings in **Chapter 2** suggest that programs and policy measures to improve and sustain high immunization coverage in Ethiopia be revitalized, as the majority of the change in vaccination coverage between 2000 and 2016 (74%) is attributed to a change in the effect of the explanatory variables, which is primarily attributed to policy measures that increase the propensity to vaccination (structural change). Moreover, there is plenty of room for compositional change to improve further vaccination coverage, such as improving maternal education, increasing maternal antenatal care use, and institutional delivery. However, because unmeasured variables accounted for a large proportion of the increase in vaccination coverage, more research is needed to identify the influence of potential variables which are not explicitly considered in the present study.

Chapter 3 identified administrative region, wealth status, and antenatal care utilization as important predictors for Ethiopia's vaccine uptake. This demonstrates the need for targeted intervention in the Afar and Gambela regions, considering regional differences such as socio-cultural, economic, and political factors to achieve the global and national target and ensure universal vaccination coverage in Ethiopia. In addition, the findings also highlight the importance of expanding access to antenatal care to increase vaccination coverage in Ethiopia, as the information provided during their visit may have provided them with the necessary immunization knowledge. The findings also emphasize the importance of encouraging children from low-income households to get vaccinated. For example, providing an incentive package for families to help them overcome financial barriers such as transportation costs and lost income on vaccination days. In the present study, a reasonable number of dependent variables were included in the model as predictors of vaccination coverage. However, various factors that were discovered to be important determinants of vaccination coverage in developing countries, notably supply-side variables (e.g., vaccine stockout, non-functional cold chain equipment), were not studied in the current study due to a lack of such data in the datasets used in the present study¹⁴⁻¹⁷. Hence, additional quantitative and qualitative research incorporating both demands- and supply-side factors is recommended, especially in low-vaccination-coverage regions, to identify potential intervenable factors and design contextually tailored strategies to help improve national vaccination coverage.

The success of an immunization program is frequently measured in terms of the national average, with equity status often being overlooked. However, improving equity is critical for increasing global immunization coverage in a sustainable manner. As the disadvantaged segment of the population is disproportionately affected by vaccine-preventable diseases, equitable vaccination coverage will benefit them the most^{13,18-20}. Measuring inequity and accurately identifying which groups are not receiving vaccination has the practical benefit of allowing policymakers to seek context-specific solutions to promote vaccination among the disadvantaged subgroups and to ensure equity. **Chapter 4** and **Chapter 5** demonstrated the current status and the progress in socioeconomic inequality of immunization in Ethiopia. This dissertation brings out that despite the improvement in the overall vaccination coverage, there is a significant and persistent socioeconomic inequality. Hence, the policymakers in Ethiopia need to place an equal emphasis on equity gains as the national average vaccination coverage while evaluating the performance of their immunization program. The decomposition analysis identified maternal educational level, antenatal care use, institutional delivery, and exposure to media as the major contributing factors to the inequalities (**Chapter 4** and **5**). Therefore, apart from

overall poverty reduction, policymakers should focus on improving educational attainment, maternal health care use, and public awareness, mainly among mothers with low socioeconomic status, to bring a meaningful equity-oriented achievement in vaccination coverage in Ethiopia. Given numerous potential interventions to ensure equity in vaccination coverage, further studies on the cost-effectiveness of these interventions are needed to make informed decisions.

In **Chapter 6**, the need to refine the updated PRIME model was highlighted. Remarkably, given the growing body of literature demonstrating that single-dose HPV vaccination provides adequate protection against HPV-related diseases^{21,22}, the results of a health-economic modeling exercise comparing single-dose HPV vaccination to the current two-dose and/or no-vaccine scenario can be used as an important input to inform policymakers. Aside from alleviating the current global shortage of HPV vaccines, a single-dose HPV vaccination strategy would be more logistically feasible as well as less expensive, allowing more people to be vaccinated. Updating the PRIME model to include the vaccines' protective effects against other types of cancers caused by HPV infection beyond cervical cancer will also help to demonstrate the true value of HPV vaccines, which is especially important to inform the decision in low cervical cancer incidence settings which have already resisted the implementation of the vaccine considering only its effect on cervical cancer. As evidence from some clinical trials demonstrated cross-protection for both bivalent and quadrivalent HPV vaccines (with the former having a higher capacity for cross-protection), it is worth recommending that cross-protection be taken into account in the modeling exercise. However, a recent systematic review found that the cross-protection provided by the HPV vaccines was inconsistent across non-vaccine HPV types, and its long-term durability has yet to be determined²³. Furthermore, it is relevant how the innovative nonavalent human papillomavirus (9vHPV) vaccine relates to all these aspects. My study in **Chapter 7** found that a switch from the 4vHPV vaccine to the 9vHPV vaccine leads to substantial reductions in morbidity and mortality associated with cervical cancer caused by HPV infection. These findings could help guide policymakers in Ethiopia and beyond who embarked on a global strategy to eliminate cervical cancer as a public health problem with an ambitious elimination target of four cases per 100,000 women-years in all countries²⁴. HPV vaccination has been identified as one of the primary drivers for this global cervical cancer elimination strategy²⁵. When compared to the 4vHPV vaccine, vaccination with the 9vHPV vaccine is cost-effective up to a vaccine price of US\$ 15 per dose and even very cost-effective when the 9vHPV vaccine price is less than US\$ 8.4 per dose. This data needs to be taken into account while determining the optimum price for the HPV vaccine and budget impact analysis. In **Chapter 7**, a static model that is unable

to capture a benefit from the indirect effect of vaccination was used, so the impact of vaccination is underestimated. Thus, future research employing a dynamic model is suggested to estimate the cost-effectiveness of HPV vaccines in Ethiopia accurately, as it takes the benefit from herd immunity into account.

To summarize, my studies found that, while overall childhood vaccination uptake in Ethiopia is suboptimal and accompanied by persistent socioeconomic inequalities, there has been a remarkable increase in the uptake over time, primarily due to structural changes in the country's healthcare system. In order to improve vaccination uptake even further, public health policymakers should place a greater emphasis on equity gains for the most disadvantaged administrative regions and the poorest segments of the population. My findings suggest that reducing poverty, improving maternal educational attainment, improving maternal healthcare use, and raising public awareness among mothers with low socioeconomic status could be used as policy instruments to improve vaccination uptake equitably and sustainably in Ethiopia. My studies also found that switching from the current 4vHPV vaccination program to the 9vHPV vaccination program in Ethiopia provides an additional health benefit and that the decision to switch is cost-effective, given that the 9vHPV vaccine price per dose does not exceed US\$ 15.

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