論文題目　A comprehensive assessment of age-appropriate vaccination coverage in 41 low- and middle- income countries, 2000-2030（低・中所得国 41 カ国における 2000 年～2030 年の年齢別ワクチン接種率に関する包括的評価）

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Background: Childhood immunization is considered the most successful and cost-effective public health intervention in preventing childhood morbidity and mortality. The Immunization Agenda 2030 (IA2030) set a target to leave no child behind from the routine immunization in each country by 2030. To achieve this target, age-appropriate vaccination plays an essential role, as age-appropriate vaccination schedule is designed to reduce the risk of infection of vaccine preventable diseases (VPDs) among infants and children. Each vaccination schedule is designed based on when the immune system can safely respond to the vaccine and the age disease has the largest impact on morbidity and mortality. Hence, along with childhood immunization, progress of age-appropriate vaccination should be assessed to ensure that all children, regardless of their socioeconomic status or area of living, are protected from VPDs.

To date, no previous study has evaluated the coverage progress of age-appropriate vaccinations in low- and middle-income countries LMICs of Asia and Sub-Saharan Africa (SSA) at national level, as well as by place of residence and socioeconomic status. Therefore, the present study is the first attempt to estimate recent trends and projection in the coverage of age-appropriate vaccinations at the regional, and national level as well as by area of living and socioeconomic status. Additionally, this study assessed the expected magnitude of socioeconomic inequality in the coverage of age-appropriate vaccinations in 2030 and evaluated the impact of decreasing development assistance for health (DAH) and health workforce due to COVID-19 on age-appropriate vaccination coverage. Moreover, this study estimated the vaccination delays and its associated potential risk factors.

Methods: Data were extracted from 174 household surveys (such as Demographic and Health Surveys and Multiple Indicator Cluster Surveys) conducted between 2000 and 2020 in 41 LMICs from South Asia, South-East Asia, and SSA. Country level data on per capita government health expenditure, per capita development assistance for health (DAH), and sociodemographic index (SDI) was obtained from the 2018 Global Burden of Disease study, while data on health workforce (HW) was obtained from the Global Health Observatory Data Repository. The outcome variables of this study were single dose of Bacillus Calmette-Guerin (BCG), third dose of diphtheria, tetanus, and pertussis (DPT3), third dose of polio (polio3) and first dose of measles vaccine. The age-appropriate vaccination schedules have been introduced, according to the World Health Organization (WHO) recommendation, in accordance with respective national immunization schedules of each country.

A Kaplan-Meier method was used to calculate the age-appropriate and delay in vaccination based

on the national immunization schedule. A Bayesian hierarchical regression model was used to assess the trends and develop projections of age-appropriate vaccines up to 2030 at the regional level, national level, across wealth quintiles, and by area of residences. Moreover, to understand the potential impact of COVID-19 on coverage of age-appropriate vaccines, we projected three scenarios: (1) reference scenario with no DAH or HW reduction, (2) DAH reduction scenario, and (3) HW reduction scenario. The magnitude of absolute and relative socioeconomic inequality within countries for the coverage of age-appropriate vaccines were estimated using a regression-based slope index of inequality and relative index of inequality, respectively. In addition, a multilevel mixed effect logistic regression model was used to identify the key determinants of delayed vaccination.

Results: Overall, the coverage of age-appropriate BCG, DPT3, Polio3, and measles increased rapidly from 2000 to 2020, with an annual rate of change at 2.8%, 5.0%, 4.7%, and 3.0%, respectively. Around 3-7% increase in the coverage of vaccinations is required per year to reach 90% or more coverage between 2020 and 2030. None of the regions are predicted to achieve 90% or higher coverage of age-appropriate vaccines by 2030. In 2030, the coverage of age-appropriate BCG vaccine is predicted to be lowest in Central Africa (63.1%), whereas the coverage is predicted to be highest in South-East Asia (85.7%). In case of age-appropriate measles vaccine, the coverage in 2030 is predicted to be highest in South Asia (71.3%), followed by South-East Asia (62.9%), and East Africa (62.3%).

If the current trends continue, out of 41 countries, 10 countries are predicted to reach 90% or higher coverage target for age-appropriate BCG vaccine by 2030, while only five countries are projected to meet the coverage target for age-appropriate DPT3 vaccine at the national level. The highest annual rate of change during 2000 to 2020 was observed in the Democratic Republic of Congo (11.8%) for BCG vaccine, and Zimbabwe (17.2%) for DPT3 vaccine. In case of age-appropriate polio vaccine, only three countries are predicted to achieve 90% or higher coverage, whereas none of the included countries are on track to meet the coverage target for age-appropriate measles vaccine by 2030. During 2000 to 2020, the largest rate of increase was observed in Zimbabwe (17.2%) for polio3 vaccine, and Pakistan (12.0%) for measles vaccine, respectively.

By 2030, if the recent trends continue, the coverage of age-appropriate vaccine between urban and rural areas are predicted to be larger in Ethiopia, Niger, Nigeria, and Central African Republic. On the other hand, coverage gap between urban and rural areas are projected be relatively narrower in Cambodia, Rwanda, Sierra Leone, and Sao Tome and Principe. If the present trends continue, by 2030, the coverage of age-appropriate BCG vaccine for both poorest and richest quintiles are predicted to be 90% or higher in seven countries (Burundi, Cambodia, Rwanda, Sao Tome and Principe, Sierra Leone, Uganda, and Zimbabwe), whereas only three countries (Rwanda, Sao Tome and Principe, and Togo) for DPT3 vaccine. The coverage gap between poorest and richest quintiles are predicted to be highest in Ethiopia (50.8%) for BCG vaccine, and Nigeria (50.4%) for DPT3 vaccine. In case of polio3 vaccine, by 2030, the coverage is predicted to be 90% or higher in three countries (Sao Tome and Principe, Rwanda, and Zimbabwe) among poorest quintile and nine

countries (Burundi, Cambodia, Democratic Republic of Congo, Ghana, Kenya, Rwanda, Sao Tome and Principe, Togo, and Zimbabwe) among richest quintiles. The coverage of age-appropriate measles vaccine among richest quintile is projected to be at least 90% in only five countries (Nepal, Cambodia, Burundi, Rwanda, and Burkina Faso), whereas none of the countries will achieve 90% or higher coverage in among poorest quintiles if the present trends continue.

In the DAH reduction scenario, none of the countries are expected to experience a huge reduction in the coverage of age-appropriate BCG, DPT3, polio3, and measles vaccine, compared to the coverage projected with the current trends' scenario. More than a 2% reduction is predicted to be observed in the Democratic Republic of Congo for the BCG and polio3 vaccine, Mozambique for the DPT3 vaccine, and Cambodia and Laos for the measles vaccine. However, in the HW reduction scenario, at least a 3% reduction is predicted to be observed, compared to the coverage projected with the current trends' scenario, in Mozambique and Kenya for DPT3 vaccine, and Rwanda for measles vaccine.

The overall median delays, based on 41 countries, was found to be 2.29 weeks for BCG, 10.85 weeks for DPT3, 10.29 weeks for polio3, and 8.57 weeks for measles, respectively. Factors associated with higher odds of having a vaccine delay include children with older age, residing in rural areas, being of lower socioeconomic status, and being an uneducated mother.

Discussion: This is the first study to provide a comprehensive assessment of age-appropriate vaccinations coverage among children under five in 41 LMICs of South Asia, South-East Asia and SSA. Findings suggest that the coverage of age-appropriate vaccinations among children increased substantially at the regional and national levels as well as by area of residence and socioeconomic status in most countries between 2000 and 2030. The largest increase in the coverage of vaccination was observed in East Africa, followed by South Asia and South-East Asia. Moreover, the coverage of age-appropriate vaccinations would be lower than 60% in Angola, Chad, Democratic Republic of Congo, Ethiopia, Mali, and Niger by 2030 unless a major change takes place in the distribution and supply of the vaccine. The possible barriers to access vaccination in appropriate time in the listed countries could be political instability, ongoing civil war, and ethnic conflicts. For instance, in Angola, the per capita government health expenditure decreased due to economic turmoil, which may affect the vaccination coverage.

A wider coverage gap between urban-rural and poorest-richest was observed in Ethiopia, Niger, Nigeria, and Central African Republic. This study also forecasted that higher level of wealth-based inequality, in both absolute and relative terms, will exist in 2030. In many LMICs, unvaccinated children are often from the same community, small areas, or hard-to-reach areas. The existing immunization programs in many countries often ignore inequities and thus fail to reach the underserved children. Therefore, effective strategies must be implemented to expand the coverage of age-appropriate vaccines, particularly among those living in rural and hard-to-reach areas.

The present study found that, only a few countries including Burundi, Cambodia, Rwanda, Sao Tome and Principe, and Zimbabwe have achieved 90% or high coverage of age-appropriate vaccine at the national level. The urban-rural gap in the coverage of age-appropriate vaccines in these

countries are relatively smaller. Several countries including Bangladesh, Cambodia, Nepal, Rwanda, Gambia, and Zimbabwe that have had success in immunization within a short period of time. These countries implemented different kinds of strategies such as multi-year national immunization plan, advocacy for better domestic funding for immunization, and evaluation of EPI activities including joint field missions, tracking vaccination defaulters, and data quality improvement. For example, Cambodia introduced a catch-up campaign aimed at children who had missed or not received doses of vaccines for any reason. During the COVID-19 pandemic, health workers were going "village to village" and "door to door" to maintain routine immunization service and protect Cambodians from COVID-19.

The median delay in vaccination varied across countries. The shortest delay was observed for BCG vaccine (2.3 weeks) whereas the longest delay was seen for the third dose of DPT (10.9 weeks). Vaccine hesitancy or refusal, distance to health facility, lack of access to vaccination services could be the possible reason for the longer delay in child vaccinations. This study found the factors—older age of children, having larger number of children, lower education in mothers, having no access to mass-media for mother, residing in rural areas, and being of lower socioeconomic status—to be significantly associated with higher odds in delay in vaccination. Therefore, policy makers in countries with longer delay of vaccination should also prioritize addressing these social determinants, as those factors along with the health system factors directly influence on-time vaccination. Focusing on education and mass-media campaigns could be an effective strategy to minimize the burden of vaccination delays. Several other factors such as cultural or religious factors, lack of knowledge, vaccine hesitancy, as well as supply side factors including availability and capacity of cold chain system and other logistic system can also influence the coverage age-appropriate vaccination. Especially, parental education and community engagement have been identified as key areas to improve upon to increase vaccination coverage.

Conclusion: Substantial improvement has been made in age-appropriate vaccinations coverage during past decades in LMICs of Asia and SSA, but in many countries, progress stalled from 2000-2020. Expect for measles vaccine, only 4 countries (Cambodia, Sao Tome and Principe, Rwanda, and Zimbabwe) are predicted to meet 90% or more vaccination coverage targets by 2030. Wider urban-rural disparities and socioeconomic inequalities in access to age-appropriate vaccination are observed in many countries particularly in Ethiopia, Mali, Niger, and Nigeria. There is still considerable delay in most of the vaccinations among the included countries. Older children, uneducated mothers, having no access to mass media, rural residence, and lower socioeconomic status were identified as potential factors associated with higher odds of having delayed vaccine. Therefore, LMICs countries of Asia and SSA must prioritize to increase age-appropriate vaccinations coverage, while decreasing inequality, through introducing appropriate policies and health system strengthening. In addition, these countries should introduce pro-poor national immunization policy to ensure the equity in vaccination coverage and target interventions should be focused to improve mothers' educational status and household socioeconomic status.