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RESEARCH PAPER

Effect of measles prevalence and vaccination coverage on other disease burden: evidence of measles immune amnesia in 46 African countries

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ABSTRACT

Background: Measles is highly infectious that leads to a high disease burden among the vulnerable population, especially in developing countries, despite the availability of highly effective measles vaccine. Immune amnesia, the resetting of the immune systems of infected patients, has been observed in developed countries. This paper is the first to use various African countries to evaluate the extent of immune amnesia.

Methods: We used two panel datasets from 46 African countries between 1990 and 2018 among children, one is the disease prevalence from Global Burden of Disease, and another is on the measles vaccination coverage from WHO/UNICEF Joint Reporting Form. We used panel regression to estimate the effect of measles prevalence or measles vaccination coverage on other disease prevalence (diarrhea, lower respiratory infection, malaria, meningitis, and tuberculosis).

Results: We found the strong evidence that the increase in the measles prevalence led to an increase in other disease prevalence and mortality. We also found that the increase in the measles vaccination coverage decreased the prevalence of and the mortality due to other diseases.

Discussion and Conclusion: Measles vaccination can have a large impact on children's health because not only does it reduce the prevalence of measles cases and deaths but also could it potentially reduce the prevalence of and deaths due to other diseases.

Introduction

Measles is a highly infectious disease that kills many people across the globe every year. Despite the availability of measles vaccines, in 2019 alone, the annual number of estimated measles deaths was 207,500 worldwide, 147,900 (over 70%) of which were in African countries.[1] Approximately 134,200 children are estimated to die due to measles globally in 2015,[2] leaving measles a major public health problem.

Measles vaccines are safe, effective, and affordable, as MMR vaccines are 99% effective at preventing measles after the second dose.[3] Prior to measles vaccination, African continent had over 1 million cases of measles annually. Measles vaccination program was first introduced in African continents in the mid-1960s and the routine measles control program was established in Africa in the next ten to twenty years from the first introduction. Thanks to the wide distribution of the measles vaccines, the measles cases have been drastic.[4,5] Due to measles vaccines, the measles mortality was estimated to reduce by 62% between 2000 and 2019, and Africa observed 57% reduction in the same period of time.[1] The coverage of the first dose of measles-containing vaccine (MCV1) in Africa was 69% in 2019. Although this is a considerable improvement from 53% in 2000,[1] the coverage is not sufficient for the prevention of endemic transmission of the measles virus, which requires at least 93–95% of population immunity.[3]

Measles vaccines are not only effective in preventing measles itself but also can they be in preventing other infectious diseases.[6–8] Extant studies show that, the immune memory cells will be lost after a measles infection, resetting previously acquired immunity to other pathogens which results in the increased susceptibility to other infectious diseases. This is called "immune amnesia." Although the mechanism of immune amnesia is not fully understood, Researchers found that 2 to 3 years are necessary to restore protective immune memory.[6] Furthermore, it might take up to five years for children to develop immune systems again without measles virus immunesuppression.[6] This means that children who contracted with measles virus must be re-vaccinated or re-exposed to all previously infected pathogens to obtain immunity from other diseases again.[6,9] In this sense, the long-term impacts of measles infections devastate the continuous efforts of vaccinations of all infectious diseases.

The immune amnesia has been dominantly studied with simulation models and observed in industrial nations such as US, UK, Switzerland, and Denmark.[6,10,11] However, studies that examined the impacts of measles vaccines on other infectious diseases are scarce in developing countries, including Africa. A WHO-commissioned review of the effects of the measles vaccine in developing countries such as Guinea-Bissau, Bangladesh, Haiti, Malawi, and Senegal found that the vaccine was associated with a reduction in all-cause child

mortality.[12] However, the report concluded that their confidence in the effect of the measles vaccine on all-cause mortality is still limited. A study from Democratic Republic of the Congo (DRC)[13] looked at the association between past measles infection and the current fever prevalence to find that the fever prevalence was higher among children who were previously contracted with measles. Another study found that measles may have long-term negative impact on vaccine-induced immunity to tetanus in the same country (DRC).[14] A study conducted in Samoa also identified the negative effect of the measles induced amnesia on COVID-19 pandemic.[15]

This paper is the first to conduct a cross-country analysis of the evidence of immune amnesia in African countries. In particular, using the data from 46 African countries, this paper evaluates 1) the extent to which the measles infections lead to the increase of other disease infections and 2) the extent to which the measles vaccination helps reduce the infection of other diseases among children in Africa. We focused on the effect of measles infection and vaccination on five critical infectious diseases in Africa.

Methods

Data

This study uses two sets of data. One is the data on disease prevalence from Global Burden of Disease (GBD) data. The estimates of disease prevalence are based on the simulation model. We focus on the effect of measles on five other diseases: diarrhea, lower respiratory infection (LRI), malaria, meningitis, and tuberculosis (TB). These are main diseases that substantially attribute to the overall prevalence of deaths in African countries. To observe the effect of immune amnesia, we use the same criteria employed by the previous study.[6] There are three criteria: 1) the disease generally presents as an acute infection rather than a chronic infection; 2) the disease is present at a standard adequate frequency such that acquired immunity would be expectedly developed within the population; 3) the disease is not the result of an infection due to food poisoning or an animal biting. The previous study also used the fourth criteria: the disease is not a vaccine-preventable cause of death because it could distort results toward an association between mortality and measles if we include one. However, we omit these criteria because our purpose of the study is not to evaluate the accurate association between mortality and measles. The sample is children from 46 sub-Saharan African countries, with ages 1–4 years old and with 5–9 years old, separately. We used the annual data from 1990 to 2019.

Another dataset is the data on the measles vaccination rate from WHO/UNICEF Joint Reporting Form. The data is available annually for 46 sub-Saharan African countries from 1990 to 2018. We focus on the uptake of the first dose of measles vaccine.

Independent variables

To evaluate the effect of the measles prevalence on other diseases prevalence at year t in a country i, the main independent variable is the measles prevalence, which is defined as the average number of measles cases out of 100,000 children between year t and year $t-1$ in a country i.

To evaluate the effect of the measles vaccination rate on other diseases' prevalence at year t in a country i, the main independent variable is the measles vaccination rate, which is defined as the average vaccination rate of 1st dose of measles between year t and year $t-1$ in a country i.

Outcome variables

One set of the primary outcome variable is other disease prevalence. It is defined as the disease prevalence of the following diseases, separately: diarrhea, LRI, malaria, meningitis, and TB. The unit of the variables is the number of disease cases out of 100,000 children in a year.

Another outcome variable is the number of deaths due to other diseases. It is defined as the number of deaths due to other diseases (diarrhea, LRI, malaria, meningitis, and TB) out of 100,000 children in a year.

Estimation Strategy

To address how much the measles infections lead to the increase of other disease infection, we used the following estimation strategy:

$$y_{it} = \alpha + \beta(Measles\ prevalence_{it}) + country_i + year_t + \varepsilon_{it}$$

where y_{it} is prevalence or deaths due to other diseases (diarrhea, LRI, malaria, meningitis, and TB) in a country i in year t. $Measles prevalence_{it}$ is the measles prevalence as defined above. We included the country and year fixed effects in this panel regression to account for any unobserved cofounding factors which vary by country and over time.

To address how much the measles vaccination coverage helps reduce other disease infection, we used the following estimation strategy:

$$y_{it} = \alpha + \beta(Measles\ vaccination\ rate_{it}) + country_i + year_t + \varepsilon_{it}$$

where is the measles vaccination rate as defined above.

Results

Figure 1 presents the trend of measles prevalence and measles vaccination coverage over time, across 46 African countries, among children aged 1–4 years old. The measles prevalence decreased from 436.7 cases out of 100,000 children to 81.2 cases in 2019. The vaccination coverage increased from 0.58 in 1991 to 0.81 in 2018.

Table 1 presents the effect of measles prevalence on the prevalence of other diseases. When the measles prevalence increased by one case out of 100,000 children aged 1–4 years, then the prevalence of other diseases increased by the following per 100,000 children: 1.50 (diarrhea), 0.39 (LRI), 20.26 (malaria), 0.33 (meningitis), and 20.29 (TB). Similarly, if the measles prevalence increased by one case out of 100,000 children aged 5–9 years, then the prevalence of other diseases would increase by the following per 100,000 children: 1.24 (diarrhea), 1.35 (LRI), 159.71 (malaria), 3.31 (meningitis), and 159.59 (TB).
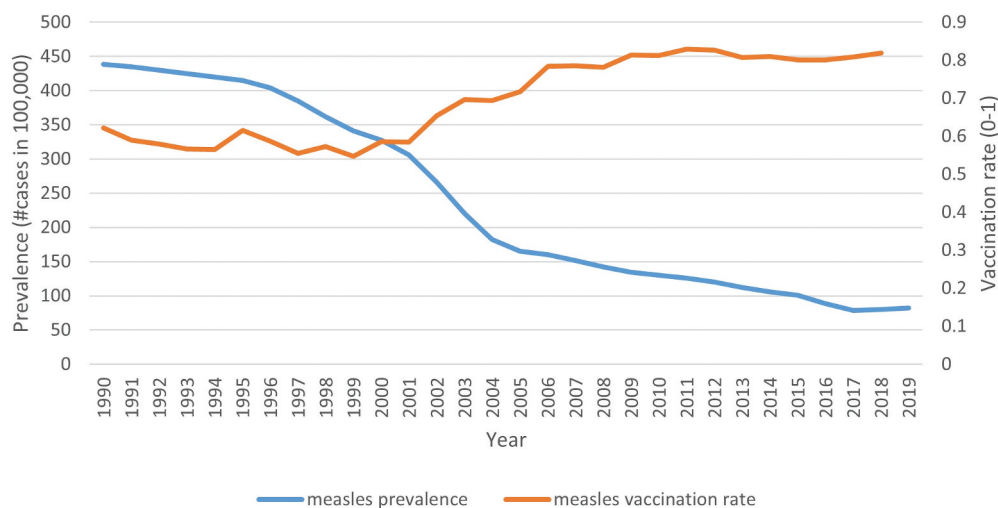
Figure 1. Measles prevalence and vaccination rate over time.

Table 1. Effect of measles prevalence on the prevalence of other diseases.

	Prevalence rate (# cases out of 100,000)				
Sample: Age 1–4	Diarrhea (1)	LRI (2)	Malaria (3)	Meningitis (4)	TB (5)
Measles prevalence rate (average of current (t) + lagged 1 (t-1)) (# cases out of 100,000)	1.501***	0.392***	20.264***	0.328***	20.289***
	(0.070)	(0.008)	(1.109)	(0.012)	(0.402)
N	1334	1334	1334	1334	1334
r2	0.262	0.641	0.206	0.383	0.664
Mean of dependent variable in 1990	3815.948	382.608	24567.71	330.497	21917.42
Mean of dependent variable in 2019	3106.299	185.317	17558.47	195.484	11427.44
Sample: Age 5–9	Diarrhea (1)	LRI (2)	Malaria (3)	Meningitis (4)	TB (5)
Measles prevalence rate (average of current (t) + lagged 1 (t-1)) (# cases out of 100,000)	1.237***	1.345***	159.709***	3.313***	159.589***
	(0.158)	(0.030)	(8.723)	(0.120)	(3.044)
N	1334	1334	1334	1334	1334
r2	0.045	0.617	0.207	0.372	0.681

Table 2. Effect of measles vaccination on the prevalence of other diseases.

	Prevalence rate (# cases out of 100,000)					
Sample: Age 1–4	Measles (1)	Diarrhea (2)	LRI (3)	Malaria (4)	Meningitis (5)	TB (6)
Measles vaccination rate (average of current (t) + lagged 1 (t-1)), 0–1	−611.410***	−924.337***	−277.200***	−15078.546***	−266.737***	−14311.671***
	(19.818)	(70.594)	(9.517)	(1083.687)	(11.522)	(496.858)
N	1218	1218	1218	1218	1218	1218
r2	0.448	0.128	0.420	0.142	0.314	0.415
Mean of dependent variable in 1990	438.583	3815.948	382.608	24567.71	330.497	21917.42
Mean of dependent variable in 2019	82.462	3106.299	185.317	17558.47	195.484	11427.44
Sample: Age 5–9	Measles (1)	Diarrhea (2)	LRI (3)	Malaria (4)	Meningitis (5)	TB (6)
Measles vaccination rate (average of current (t) + lagged 1 (t-1)), 0–1	−79.870***	−118.753***	−127.591***	−15493.766***	−353.707***	−14573.612***
	(2.589)	(19.471)	(4.443)	(1113.958)	(15.496)	(492.630)
N	1218	1218	1218	1218	1218	1218
r2	0.448	0.031	0.413	0.142	0.308	0.428

Table 2 presents the effect of measles vaccination coverage on the prevalence of diseases. When the measles coverage increased from 0 (0%) to 1 (100%) among children aged 1–4 years, then the prevalence of diseases decreased by the following per 100,000 children: 611.41 (measles), 924.34 (diarrhea), 277.20 (LRI), 15,078.55 (malaria), 266.74 (meningitis), and 14,311.67 (TB). Similarly, if the measles coverage increased from 0 (0%) to 1 (100%) among

Table 3. Effect of measles prevalence on deaths due to other diseases.

	Death rate (# deaths out of 100,000)					
Sample: Age 1–4	Measles	Diarrhea	LRI	Malaria	Meningitis	TB
	(1)	(2)	(3)	(4)	(5)	(6)
Measles prevalence rate (average of current (t) + lagged 1 (t-1)) (# cases out of 100,000)	0.615***	0.567***	0.358***	0.384***	0.095***	0.084***
	(0.012)	(0.017)	(0.010)	(0.017)	(0.004)	(0.003)
r2	0.686	0.458	0.507	0.292	0.314	0.350
Mean of dependent variable in 1990	304.71	394.815	265.059	326.991	70.642	61.657
Mean of dependent variable in 2019	29.48	97.529	66.331	119.759	18.416	14.205
Sample: Age 5–9						
	Measles	Diarrhea	LRI	Malaria	Meningitis	TB
	(1)	(2)	(3)	(4)	(5)	(6)
Measles prevalence rate (average of current (t) + lagged 1 (t-1)) (# cases out of 100,000)	0.554***	0.145***	0.072***	0.104***	0.066***	0.057***
	(0.010)	(0.007)	(0.003)	(0.009)	(0.003)	(0.003)
N	1334	1334	1334	1334	1334	1334
r2	0.717	0.262	0.273	0.093	0.312	0.278

Table 4. Effect of measles vaccination on deaths due to other diseases.

	Death rate (# deaths out of 100,000)					
Sample: Age 1–4	Measles	Diarrhea	LRI	Malaria	Meningitis	TB
	(1)	(2)	(3)	(4)	(5)	(6)
Measles vaccination rate (average of current (t) + lagged 1 (t-1)), 0–1	−434.935***	−416.698***	−262.497***	−230.716***	−70.866***	−59.386***
	(14.853)	(18.017)	(10.367)	(17.125)	(3.933)	(3.100)
N	1218	1218	1218	1218	1218	1218
r2	0.423	0.314	0.354	0.134	0.217	0.239
Mean of dependent variable in 1990	304.71	394.815	265.059	326.991	70.642	61.657
Mean of dependent variable in 2019	29.48	97.529	66.331	119.759	18.416	14.205
Sample: Age 5–9						
	Measles	Diarrhea	LRI	Malaria	Meningitis	TB
	(1)	(2)	(3)	(4)	(5)	(6)
Measles vaccination rate (average of current (t) + lagged 1 (t-1)), 0–1	−50.786***	−14.090***	−7.322***	−8.188***	−6.629***	−5.436***
	(1.730)	(0.688)	(0.418)	(1.159)	(0.346)	(0.312)
N	1218	1218	1218	1218	1218	1218
r2	0.424	0.264	0.207	0.041	0.239	0.206

children aged 5–9 years, then the prevalence of diseases would decrease by the following per 100,000 children: 79.87 (measles), 118.75 (diarrhea), 127.59 (LRI), 15,493.77 (malaria), 353.71 (meningitis), and 14,573.61 (TB).

Table 3 presents the effect of measles prevalence on the deaths due to diseases. When the measles prevalence increased by 1 cases out of 100,000 children aged 1–4 years, then the deaths due to diseases increased by the following per 100,000 children: 0.62 (measles), 0.57 (diarrhea), 0.36 (LRI), 0.38 (malaria), 0.10 (meningitis), and 0.08 (TB). Similarly, if the measles prevalence increased by 1 cases out of 100,000 children aged 5–9 years, then the deaths due to diseases would increase by the following per 100,000 children: 0.55 (measles), 0.15 (diarrhea), 0.07 (LRI), 0.10 (malaria), 0.07 (meningitis), and 0.06 (TB).

Table 4 presents the effect of measles vaccination coverage on the deaths due to diseases. When the measles coverage increased from 0 (0%) to 1 (100%) among children aged 1–4 years, then the deaths due to diseases decreased by the following per 100,000 children: 434.94 (measles), 416.70 (diarrhea), 262.50 (LRI), 230.72 (malaria), 70.87 (meningitis), and 59.39 (TB). Similarly, if the measles coverage increased from 0 (0%) to 1 (100%) among children aged 5–9 years, then the deaths due to diseases would

decrease by the following per 100,000 children: 50.79 (measles), 14.09 (diarrhea), 7.32 (LRI), 8.19 (malaria), 6.63 (meningitis), and 5.44 (TB).

Discussion

This paper evaluates the effect of measles prevalence on other diseases, as well as the effect of measles vaccination coverage on the prevalence of other diseases, among children in 46 African countries between 1990 and 2019.

First, we found that the decline in the measles prevalence was significantly associated with the reduction in other disease prevalence, as well as in the deaths due to these diseases. When the baseline prevalence for a particular disease was high, then the effect size of the measles prevalence on other disease prevalence was also large. For example, when the measles prevalence increased by 1 case out of 100,000 among children aged 1–4, the number of malaria cases increased by 20.26. The effect size is large as compared to other diseases such as LRI (0.39). This is because the malaria prevalence at the baseline in 1990 was also high, 24,567 cases per 100,000, while the prevalence of LRI in 1990 was much lower, 382.61. If we convert the effect size in terms of the percentage to the baseline prevalence, the biggest effect size was 0.10% for LRI and Meningitis, followed

by 0.09% for TB, and 0.08% for malaria. These results mean that if the measles prevalence increased by 1 case out of 100,000 among children, the disease cases would increase by 0.10% for LRI and Meningitis, 0.09% for TB, and 0.08% for malaria. The smallest effect size was 0.04% for diarrhea. Overall, these effect sizes in terms of the percentage to the baseline were similar, regardless of the type of disease. Similarly, if we also convert the effect size on the death rate to the percentage to the baseline, here is the percentage increase of the death due to other diseases when the measles prevalence increases by one case out of 100,000: 0.20% (measles), 0.14% (diarrhea, LRI, TB), 0.13% (meningitis), and 0.12% (malaria). The effect should depend on how measles prevalence increases other diseases' prevalence, as well as on the fatality rate of each disease.

Second, the higher measles vaccination coverage was significantly associated with the reduction in the other diseases prevalence and deaths. The effect size on the disease prevalence when the measles vaccination coverage increased from 0% to 100% in terms of percentage to the baseline was as follows: 80.71% (meningitis), 71.33% (LRI), 65.30% (TB), 61.38% (malaria), and 24.22% (diarrhea). These results mean that when the measles vaccination coverage increased from 0% to 100%, the disease prevalence would increase by the aforementioned percentage of each disease. Similarly, the effect size on the disease mortality when the measles vaccination coverage increased from 0% to 100% in terms of percentage to the baseline was as follows: 142.74% (measles), 105.54% (diarrhea), 100.32% (meningitis), 99.03% (LRI), 96.32% (TB), and 70.56% (malaria).

These results indicate that the increase in the measles vaccination coverage is effective in preventing the prevalence of measles and mortality due to measles the most as compared to other diseases. In addition to that, we also found that, as we hypothesized, the measles vaccination coverage also helped reduce the prevalence and the mortality of other diseases. This result is consistent with findings from the literature that found the evidence of the immune amnesia due to the contraction to measles in developed countries[6,7,11] as well as with studies conducted in developing countries[12–15] which found the correlation between the measles prevalence and the fewer cases of other diseases and overall mortality. Studies which examined the impacts of measles vaccination on the prevalence of other infectious diseases are, however, extremely scarce especially in developing countries.

This paper has an important policy implication. Because we found that measles vaccination not only prevented measles, but also could it potentially prevent other diseases, the effect of the measles vaccination could be underestimated if we do not take into account of its effect on other diseases. Measles vaccine is proven to be highly cost-effective in the existing literature.[16,17] For example, supplementary immunization activities (SIAs) have played a vital role in measles control efforts.[18] However, existing studies that conducted cost-effectiveness or benefit analyses of SIAs did not include averted disease cases and deaths due to immune amnesia.[19,20] Thus, future studies should investigate the cost-effectiveness of the measles vaccination, accounting for the full effect of measles vaccination on other diseases' prevalence.

Limitation

This paper has several limitations. First, this paper does not address the causal relationship. Because the measles prevalence or measles vaccination coverage is unlikely to be exogenous, the interpretation of results needs caution. Second, we did not differentiate between immunity obtained by vaccination and natural infection through a biological study. Future studies should address this issue. Third, this research analyzed younger children whose ages range from 1–4 and 5–9 years old due to the availability of data. However, it is vital to understand how young infants and older age groups contribute to the measles virus transmission.[4] Fourth, we focus on the first dose of measles vaccine in our analysis due to the data availability. When data are available, it is important to evaluate the effect of the full vaccination. Fifth, although we have included the country- and year-fixed effects in the regression specification to control for any unobserved confounding factors, we did not control for other unobserved factors that vary within a country over time. Thus, we should be cautious in interpreting the magnitude of effect size. We expect that the magnitude of impact would be different once we control for such factors.

Conclusion

Measles vaccination can have a large impact on children's health because not only does it reduce the prevalence of measles cases and deaths but also could it potentially reduce the prevalence of and deaths due to other diseases.

Disclosure statement

Funding

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Authors contributions

RS and MH conceived the idea. RS analyzed the data. RS and MH drafted the manuscript. Authors contributed equally to work.

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