Armed conflict and infectious disease: quantifying the association between mortality rate due to war and terrorism and measles incidence, 2000-2019

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Abstract

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Achieving the measles elimination goals included in the Measles and Rubella Strategic Framework 2021-2030 requires understanding the key factors driving the continued transmission of measles. Armed conflict is established as a factor in the continued delays in achieving polio eradication. Here, we investigate if armed conflict also plays a role in the spread of measles. We investigate evidence of changes to surveillance system quality during periods of conflict, generate conflict-free counterfactual estimates of vaccine coverage, and produce conflict-free counterfactual estimates of measles incidence in 106 countries from 2000 to 2019. To estimate incidence, we used war and terrorism mortality rate as a predictor in a mixed-effects linear model of measles incidence, controlling for our conflict-free counterfactual first- and second-dose measles vaccine coverage estimates and estimates of the war-associated decrease in vaccine coverage. We estimate that across all countries and years Syria has measles incidence most affected by war and terrorism, with 78.0% (23.3-96.8) of incidence in 2012 associated with war and terrorism. We cannot expect to eliminate measles without addressing armed conflict, however, we also find notable data gaps, highlighting the need for improved data collection and estimation methods in countries experiencing conflict.

Introduction

War and conflict disrupt systems essential to curbing the spread of measles, which prolongs the endemic transmission of measles and delays measles elimination (Figure 1). War harms health directly, through battlefield deaths, but most deaths resulting from conflict are attributable to the myriad indirect effects. In countries experiencing conflict, after removing battlefield deaths, increases in all-cause mortality rates remain, driven in large part by increases in infectious causes of death.[1]

Parties of armed conflict often disrupt agricultural and transit systems by destroying crops and blocking roads, which interrupts the production and flow of food to the population.[2] Combatants will also block the entry of humanitarian aid workers, which further exacerbates malnutrition in the population.[2] Malnutrition weakens the immune system, making individuals more susceptible to infectious diseases.[3]

War also harms health further upstream by damaging the health system and preventing administration of routine childhood vaccinations, increasing susceptibility to vaccine-preventable diseases. War often spurs health workers to migrate away, leaving an insufficient number of healthcare workers or facilities willing or able to vaccinate children.[4] In Northwest Cameroon, the number of facilities offering immunization declined by 53% because the facilities had to close after healthcare workers fled from their stations in the face of rising insecurity.[5] Health facilities able to remain open face challenges in getting vaccine product and with planning immunization activities.[5] Even when campaigns are able to recruit vaccinators, they are often unable to reach some children. There is a negative association between the accessibility of children to vaccinators and the insecurity level of a region: for example, the number of children inaccessible to vaccinators was 19.7% higher and vaccination rates were 5.3% lower in campaigns conducted in highly insecure areas compared to campaigns conducted in secure areas in northwest Pakistan.[6]

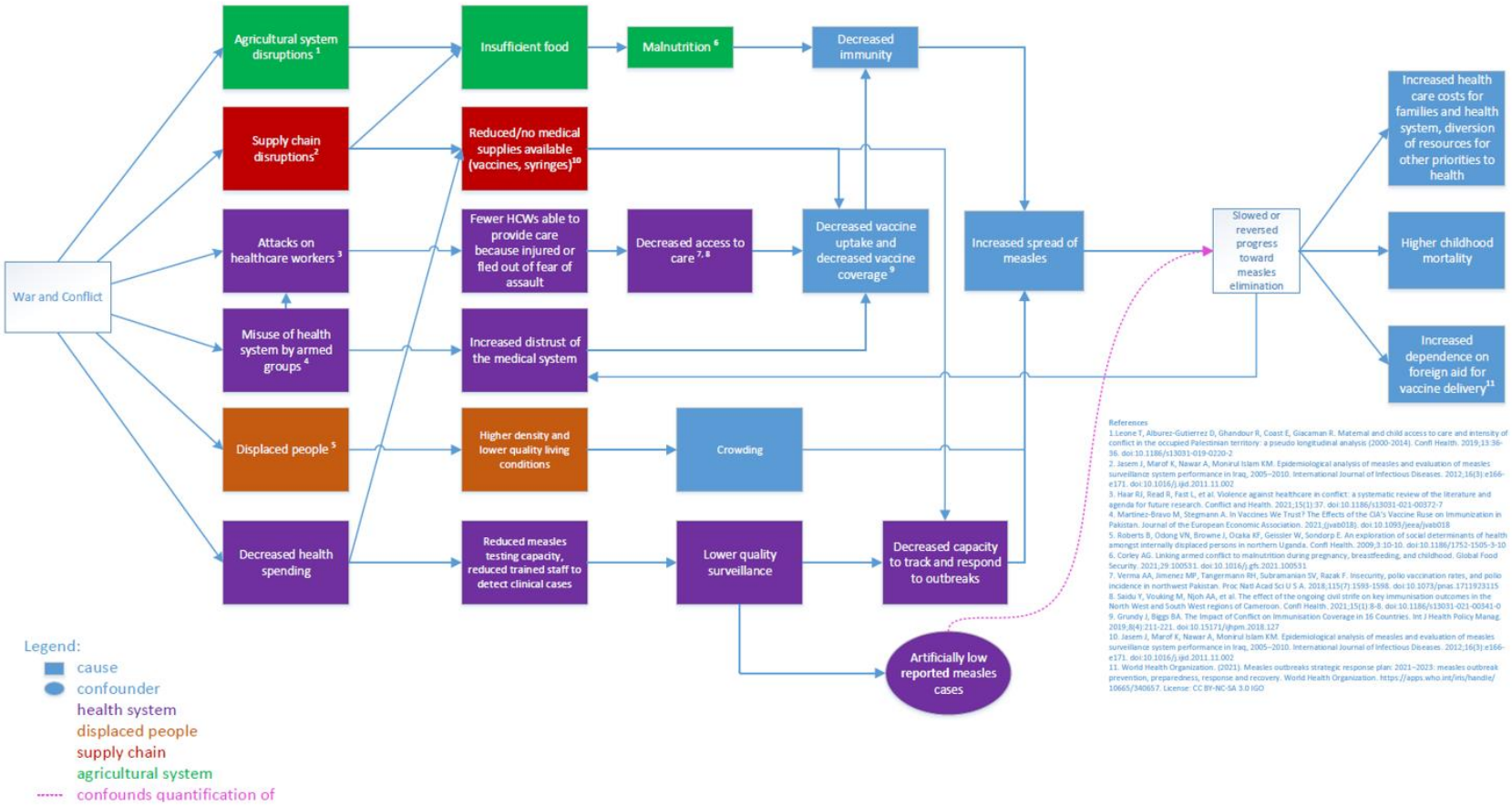


Figure 1. Problem diagram of the relationship between armed conflict and measles incidence.

Looting by armed groups decreases the number of available vaccine doses or supplies, so fewer children can get vaccinated.[4] Children under five, the target age range for most routine immunizations, suffer most directly since fewer gain immunity to the diseases for which vaccinations are available.[7] Reduced vaccination capacity during wartime negatively affects the entire population because progress toward herd immunity, from which the entire population would benefit, slows or reverses when any subpopulation is not vaccinated. Large (50%) and/or rapid (over the span of one year) drops in coverage of the final, third dose of the vaccine for diphtheria, tetanus, and pertussis (DTP3) can occur during periods of conflict, as have been observed in Syria, Yemen, and South Sudan.[7,8]

Beyond the low vaccine coverage associated with conflict, other disruptions caused by war contribute to the perfect storm for a disease outbreak. People displaced by war often live in high-density, low-quality housing, which increases opportunities for person-to-person transmission of disease.[8] Moreover, many vaccines must be kept cold to maintain their efficacy. War-induced disruptions to infrastructure can interrupt the cold chain such that the delivered vaccines are less effective.[9]

Together with reduced ability to vaccinate, the reduced number of health personnel, smaller number of functional health facilities, and war-associated reductions in health spending decrease the quality of the disease surveillance system.[10] Surveillance systems capture a smaller proportion of the cases during conflict events.

Periods of conflict are associated with subsequent high levels of vaccine preventable diseases (VPDs). Between 2007 and 2009, when US troops surged in Iraq, the incidence rate of infectious diseases increased significantly. Most diseases decreased again after the troops withdrew in 2011.[11] After three years of civil war in Yemen, a diphtheria outbreak began.[12] Prior to the civil war, there had been no serious outbreaks of diphtheria, but in late 2017 and early 2018, 1294 cases were reported. The odds of an outbreak were 11 times higher in districts actively experiencing conflict and three times higher in districts that had experienced conflict in the last year.[12] Conflict is widely accepted as a contributing factor in the reemergence of polio in some countries and to why polio has not yet achieved eradication.[6,8,13–15]

Here, we assess if conflict has played a similar role in delaying achievement of measles elimination in countries as it has for polio. WHO initially set measles elimination as a goal in the Global Vaccine Action Plan and it is now included as part of the Measles and Rubella Strategic Framework 2021-2030, under the umbrella of the Immunization Agenda 2030.[16] Because measles is so infectious, very high proportions of the population need to be immune (either from past infection or vaccination) to achieve herd immunity. High vaccine coverage is essential: global organizations often aim for 95% coverage with two doses of the measles vaccine.[17] Thus, it is plausible that war-induced decreases in vaccine coverage would spark increases in measles incidence like seen with polio, and quickly, because of measles' high degree of infectiousness.

In case studies, observed measles cases have increased during or after periods of conflict. Incidence increased in Syria to more than 7000 cases and spread to neighboring countries, including some with high vaccine coverage.[14] Somalia saw a surge in measles cases from 145 to 1542 cases per 1 million population during the 2010-2011 war, and continued to rise despite initiation of outbreak response vaccination campaigns.[18] While in some countries measles outbreaks have followed the start of conflict, to our knowledge there has been no systematic analysis that quantifies the association between measles incidence and conflict, like those for

polio. This paper aims to fill that gap in knowledge by evaluating the incidence of measles associated with mortality due to war and terrorism from 2000 to 2019 in 106 high policy priority low- and middle-income countries.

Methods

Overview

This analysis involved three main steps. First, we examined evidence of changes to measles surveillance system quality associated with war and conflict, as measured by the war and terrorism mortality rate. Second, we developed estimates of the change in vaccine coverage associated with war and conflict for each country-year. Then, we quantified the relationship between measles incidence and war and terrorism mortality, which we used to estimate the incidence of measles associated with war and terrorism.

Data Sources

All input data were secondary data, extracted from the Institute for Health Metrics and Evaluation (IHME) and the World Health Organization (WHO). These groups rely on reports from countries or other primary data sources when generating their estimates.

To evaluate measles surveillance system quality, the number of measles laboratory tests administered and the number of positive measles laboratory tests were obtained from WHO. WHO has collected these data since 2004. Location-years that only reported either the number of tests administered or the number of positive tests were excluded. These data were used to calculate the rate of non-measles febrile rash illness (NMFRI), the number of negative measles tests per 100,000 population, which serves as an indicator of measles surveillance system quality, akin to non-polio acute flaccid paralysis and polio surveillance.[19] In this analysis, IHME's healthcare access and quality index, which approximates access to care in countries using amenable mortality, served as a covariate.[20]

Annual case reports of measles are reported to WHO and UNICEF through the Joint Reporting Form (JRF).[21] This dataset includes the number of cases of measles each year, as reported by ministries of health and similar nationally representative bodies from each of the WHO's 194 member nations. IHME's age- and sex-specific population estimates were used to convert the reported case counts to incidence rates.[22]

To estimate the presence and intensity of conflict, we used IHME's war and terrorism mortality rates estimates.[23] These estimates are for all ages and both sexes combined and reflect deaths directly due to war and terrorism. They are produced by bringing together and standardizing primary estimates from several other groups. IHME's two primary source for these estimates are Uppsala Conflict Data Program (UCDP) and Armed Conflict Location and Event Database (ACLED). UCDP estimates deaths from three types of conflict: state-based armed conflict, non-state conflict, and one-sided violence while ACLED includes estimates of war related deaths for a broader set of types of conflict.[24]

Along with the war and terrorism mortality rate estimates, measles vaccine coverage estimates from IHME were used to estimate conflict-free vaccine coverage. IHME's first- and second-dose vaccine coverage estimates (MCV1 and MCV2) include doses delivered through routine immunization (RI) or supplemental immunization activity (SIA) by combining results from several models. These estimates reflect true coverage better than those generated using only RI data because they account for immunity derived from campaigns that may be carried out in

response to outbreaks or to fill gaps in coverage associated with war or other disruptions to vaccine delivery. Under the assumption that young children are most susceptible to measles, we used estimates of vaccine coverage in children under five from an age-specific cohort model. IHME's routine immunization vaccine coverage estimation methods have been described elsewhere.[25] Briefly, the routine-immunization estimates are modeled using spatio-temporal Gaussian process regression (ST-GPR), utilizing survey, country reported, and literature data on vaccine coverage over time and space, while accounting for biases in country reporting, vaccine stock-outs, and war induced disruptions to vaccine delivery.[25]

NMFRI Analysis

The rate of negative tests in a surveillance system is an indicator of surveillance system quality. Rarely does an entire population have a disease: if all tests are positive, the surveillance system is likely not testing enough people. NMFRI is a measure of the negative measles test rate (Equation 1). WHO has set the target for surveillance performance as NMFRI $\geq$ 2 per 100000 population.[26] With decreased funding and fewer healthcare workers in conflict years, the proportion of true disease cases that are not reported to surveillance systems may be systematically higher than in years without conflict. Any systematic difference in surveillance system quality during war would need to be adjusted for before analyzing the relationship between war and reported measles incidence.

Equation 1. Non-measles febrile rash illness rate, *l* and *y* represent country and year.

$$NMFRI\ incidence_{l,y} = \frac{discarded\ cases\ (measles\ IgM\ negative)\ with\ lab\ testing_{l,y}}{population_{l,y}}$$

To evaluate evidence of war-associated changes to the underlying quality of the surveillance system in a country, we tested mortality rate due to war and terrorism as a continuous predictor or a binary predictor of NMFRI. In continuous space, we fit a linear mixed effects regression model with log(NMFRI) as the independent variable and mortality rate due to war and terrorism and healthcare access and quality index as predictors (Equation 2).[20] We included a random intercept on country to control for baseline differences in surveillance system quality. We also tested war and terrorism mortality rate as a binary predictor. To evaluate if there is a war and terrorism mortality rate threshold above which countries are more likely to meet the WHO standard, we constructed an ROC curve with the binary outcome of whether the country meets WHO's goal NMFRI and different values of war and terrorism mortality as the varying threshold.

Equation 2. Association between NMFRI reporting and war.

$$\log(NMFRI\ incidence_{l,y}) = \beta_o + \beta_1 war\ mort_{l,y} + \beta_2 HAQ + 1|country + \varepsilon_{l,y}$$

Counterfactual vaccine coverage estimation

We estimated the change in vaccine coverage associated with war and terrorism mortality using a counterfactual approach. First, we estimated MCV1 and MCV2 coverage in the absence of war and terrorism. Then, we subtracted existing conflict-inclusive estimates of coverage from IHME's Global Burden of Disease (GBD) study from the conflict-free estimates. Conflict-free MCV1 and MCV2 coverage were estimated by adjusting the RI and SIA portions of each dose's coverage estimate separately. ST-GPR models, as used for routine immunization estimates, include a "stage 1" linear model. The MCV1 routine immunization ST-GPR "stage 1" model includes mortality rate due to war and terrorism as a predictor (Equation 3). We apply an offset of 0.0001 to the war and terrorism mortality rate to allow for log transformation in countries with estimated war and terrorism mortality rate of zero. Since the model does not include a random slope term on war and terrorism mortality, this model assumes that the effect of war and terrorism mortality on MCV1 RI coverage does not vary across space and time. From the fitted model, we calculated conflict-free MCV1 RI coverage by predicting from the model with war and terrorism mortality rate set to 0 (Equation 4). MCV2 RI coverage is modeled in ST-GPR as the ratio of MCV2 coverage to MCV1 coverage and includes MCV1 RI coverage as a predictor in the stage 1 model (Equation 5). To estimate conflict-free MCV2 RI coverage, we predicted the MCV2/MCV1 ratio with conflict-free MCV1 RI coverage and multiplied the resultant ratio by conflict-free MCV1 RI coverage (Equation 6). That is, the counterfactual MCV2 estimates reflect the impact of war and terrorism mortality via its effects on MCV1. We assumed the efficiency of SIA at reaching children who were not already immunized through routine immunization was constant in the conflict-inclusive and conflict-free scenarios. The outputs of this process were a set of conflict-free counterfactual estimates of vaccine coverage and a set of estimates of the drop in coverage associated with war and terrorism mortality for each country-year.

In all equations, subscripts *y* and *l* indicate the year of interest and the country, respectively. The covariate *haq* is the healthcare access and quality index, *stockout* reflects the magnitude of country-reported or model-detected stockouts, and *introyears* is the number of years since introduction of the vaccine in the national immunization schedule for the country in year *y*. *War rate* is the war and terrorism mortality rate per 100,000, *super region*|*region*|*country* are random effects by geography, and ε is the random error. *MCV1* RI_{ci} is the GBD conflict-inclusive MCV1 RI estimate, *MCV1* RI_{cf} is the conflict-free MCV1 RI estimate, *MCV2* RI_{ci} is the GBD conflict-inclusive MCV2 RI estimate, *MCV2* RI_{cf} is the conflict-free MCV2 RI estimate.

Equation 3. GBD stage 1 ST-GPR model for MCV1 RI coverage.

$$logit\left(MCV1\ RI_{l,y}\right) = \beta_0 + \beta_1 haq_{l,y} + \beta_2 stockout_{l,y} + \beta_3 \log\left(war\ rate_{l,y} + 0.0001\right) + (1|super\ region|region|country) + \varepsilon$$

Equation 4. Conflict-free MCV1 RI coverage, estimated by country and year.

$$MCV1\ RI_{cf_{l,y}} = invlogit\left(logit\left(MCV1\ RI_{ci_{l,y}}\right) - \beta_3 \log\left(war\ rate_{l,y} + 0.0001\right) + \beta_3 \log(0.0001)\right)$$

Equation 5. GBD stage 1 ST-GPR model for the ratio of MCV2 RI to MCV1 RI coverage.

$$logit\left(\frac{MCV2\ RI}{MCV1\ RI_{l,y}}\right) = \beta_0 + \beta_1 haq_{l,y} + \beta_2 stockout_{l,y} + \beta_3 introyears_{l,y} + \beta_4 MCV1RI_{l,y} + \beta_5\left(introyears_{l,y} * MCV1\ RI_{l,y}\right) + (1|super\ region|region|country) + \varepsilon$$

Equation 6. Conflict-free MCV2 RI coverage, estimated by country and year.

$$MCV2\ RI_{cf_{l,y}} = invlogit\left(logit\left(\frac{MCV2\ RI_{ci}}{MCV1\ RI_{ci_{l,y}}}\right) + \beta_4\left(MCV1\ RI_{cf_{l,y}} - MCV1\ RI_{ci_{l,y}}\right) + \beta_5\left(MCV1\ RI_{cf_{l,y}} - MCV1\ RI_{ci_{l,y}}\right)\right) * MCV1\ RI_{cf_{l,y}}$$

Measles incidence rate in the absence of war and terrorism

We fit a linear mixed effects model to log-transformed measles incidence rate per 100,000 population. WHO measles case reports were converted to incidence rates for each location-year to control for differences in the population size. As in the current measles model for IHME's GBD the population of the birth cohort at the average age of notification (3 years old) is the denominator of incidence rate. Conflict-free MCV1 and MCV2 coverage, mortality rate due to war and terrorism per 100,000 (standardized using the mean and standard deviation), and the absolute change in MCV1 and MCV2 coverage associated with war and terrorism were included as covariates (Equation 7). Random effects on GBD super-region, region, and location were used to allow for differences in the baseline disease incidence between locations because differences in climate between regions have substantial effects on the seasonality, spread, and endemicity of measles.[27]

Equation 7. *MCV1* and *MCV2* are country- and year-specific conflict-free coverage estimates, Δ*MCV1* and Δ*MCV2* are the country- and year-specific estimates of change in coverage associated with war and terrorism mortality. *War* is the war and terrorism mortality rate. In years where *war* is 0, by definition Δ*MCV1* and Δ*MCV2* must also be 0. Subscripts *y*, *l*, *sr*, and *r* represent year, country, GBD super-region, and GBD region, respectively.

$$\log(inc\ rate) = \beta_0 + \beta_1 MCV1_{l,y} + \beta_2 MCV2_{l,y} + \beta_3 \Delta MCV1_{l,y} + \beta_4 \Delta MCV2_{l,y} + \beta_5 war + u_{sr,y} + u_{r,y} + u_{l,y} + \varepsilon$$

WHO verification of measles elimination in a country includes verifying the surveillance system meets certain quality metrics.[28] When predicting from the model, to adjust for

underreporting in countries that do not have verified measles elimination, we used a standard random effect of the average of the three highest net random effects (location+super-region+region RE for each country). After producing conflict-inclusive incidence estimates, conflict-free estimates were produced by setting ΔMCV1 and ΔMCV2 and war to 0. A variance-covariance approach was used to generate 95% confidence intervals. The output of this model was a set of conflict-free and a set of conflict-inclusive estimates of cases for all 106 countries from 2000 to 2019.

To evaluate if war and terrorism mortality exerts effects on measles incidence after the conflict ends, we tested a model that included additional covariates of the war rate lagged by one and two years. We compared RMSE values for the models with and without the lagged covariates to evaluate whether these additional covariates improved the model fit.

Results

NMFRI

We found war and terrorism mortality rate was a poor predictor of NMFRI incidence. As a continuous predictor, the sign coefficient on mortality due to war and terrorism was sensitive to log transformation of NMFRI incidence, indicating a poor model fit. From our ROC curve, war and terrorism mortality rate performed no better than chance at predicting if a country met the WHO standard (Figure 2). There was no optimal threshold value by which to dichotomize mortality rate due to war and terrorism that allows war and terrorism mortality rate to best determine whether countries are meeting the WHO standard. Of note, available NMFRI data are noisy and variably reported, which may affect the results of this analysis (Figure 3). Some countries with strong surveillance systems have not reported in all years. In some countries experiencing conflict reporting drops off during years with particularly high war and terrorism mortality rates.

Drops in vaccine coverage are positively associated with war and terrorism mortality rate

The mortality rate due to war and terrorism is negatively associated with MCV1 coverage, that is, conflict-free estimates of coverage are higher than conflict-inclusive estimates for all country-years with non-zero rates of mortality due to war and terrorism. For individual countries, the war and terrorism associated drops in coverage can be large. The largest absolute estimated war and terrorism associated decreases in MCV1 coverage were in Burundi and Syria. In 2000, during the Burundian civil war, we estimate a decline of 13.8 percentage points in Burundi's MCV1 coverage was associated with war and terrorism. Syria's estimated fall of 12.4 percentage points in 2012 aligns with a period of escalation in the Syrian civil war. Unlike Burundi in 2000, where MCV2 was not yet included as part of the routine immunization program, Syria was administering MCV2 through routine immunization in 2012 and coverage with the second dose of the vaccine also fell dramatically. In addition to the decrease in MCV1, in 2012 Syria also experienced the largest estimated absolute drop in MCV2 coverage of any country-year: coverage fell by 13.9 percentage points. This large decrease was not an isolated occurrence in the country as Syria also experienced the second largest absolute war and terrorism associated reduction in MCV2 coverage. In 2014, Syria's MCV2 coverage fell by an estimated 13.8 percentage points. Although Syria has large decreases in multiple years, other countries

have more sustained reductions, as defined by the highest average drop in coverage across all years. Afghanistan and Iraq were most persistently affected by conflict, for MCV1 and MCV2, respectively, with estimated war-associated decreases of 4.4 and 4.9 percentage points on average from 2000-2019. Across all country-years that have MCV2 administered through RI, the drops were, on average, larger for MCV2 than for MCV1 (Figure 4).

Trends and patterns in incidence

Supplementary table S1 includes the fitted beta values on each covariate in the incidence model. We find that, as hypothesized, war and terrorism mortality rate and drops in coverage of each dose are positively associated with measles incidence rate. The effect sizes for changes in coverage were larger than for the war and terrorism mortality rate. Although reductions in vaccination account for a large portion of the increase in measles incidence during wartime, some of the increases in incidence are not explained by vaccination.

In total, across all modeled countries, war and terrorism was associated with 4.66% of incident cases in 2000 and 2.75% of incident cases in 2000. However, summing across countries masks national-level variation. While the proportion of cases associated with war and terrorism had decreased over time at the aggregate level, for individual countries the same pattern does not hold. We find that at the country-level the range of proportions and the highest proportion, are larger in 2019 than in 2000 (Figure 5). This disparity between the overall and country-specific values occurs because countries with the most cases, like India, tend to have low rates of war and terrorism mortality and thus small proportions of incidence associated with conflict. At the aggregate level, this masks the higher proportional contributions from countries with smaller case counts.

In the subset of countries experiencing war and terrorism mortality the model suggests that, on average, in 2019, 5.5% of cases were associated with war and terrorism. Although values ranged from <0.01% to 52.2%, the maximum is in Afghanistan, where we estimate that the incidence rate would have been 52.2% (-0.4 – 79.1) lower had there been no conflict. In 2000, Burundi had the highest percentage of incidence associated with war and terrorism mortality at 51.9% (-76.2 – 93.3). Across all countries and years, Syria's 78.0% (23.3 – 96.8) of cases associated with war and terrorism in 2012 was the highest. While a single conflict event may contribute substantially to incidence in a single year, sustained lower levels on conflict might lead to persistently high levels of cases, which require different strategies to contain. Afghanistan is most persistently affected, with an average of 40.0% of cases associated with mortality due to war and terrorism over the 20 years included in modeling. Moreover, conflict-associated increases in incidence can reverse many years of progress towards elimination. In Syria in 2012 during conflict, we estimate incidence increased to levels not seen since before 2000 (Figure 6).

We did not find evidence of lingering effects of war and terrorism mortality rate across years: adding war and terrorism mortality rate lagged by one and two years as covariates in the model did not decrease the RMSE of the model (Table S2).

Discussion

Similarly to polio, we find that conflict is associated with the continued spread of measles, in part through changes in vaccine coverage. The positive association between conflict-associated drops in vaccine coverage and measles incidence underscore the need to minimize barriers to administering vaccines during periods of conflict to prevent associated increases in cases. Polio vaccine delivery during conflict has been more extensively studied than measles vaccine delivery and has yielded lessons about how to improve coverage during confict.[6,10,13,15] Differences in vaccination schedule, funding, and vaccine storage requirements between the two antigens will likely require development measles-specific strategies for delivering doses in conflict-afflicted areas.

However, even when controlling for vaccine coverage, war and terrorism mortality rate is positively associated with measles incidence, suggesting that pathways beyond decreases in vaccine coverage drive increases in measles cases during conflict. Therefore, focusing on vaccine coverage alone is not enough. Moreover, periods of conflict can diminish vaccine quality, likely because of disruptions to the cold chain, such that the administered doses are less effective.[9] That is, the proportion of those who acquire immunity after being vaccinated can be lower during periods of conflict than during peaceful times.

In order to achieve the ambitious goals of measles elimination set in the MSRF 2021-2030, addressing the effects of war and terrorism mortality on measles incidence, both through vaccination and other pathways, will be important. Countries with high proportions of incidence associated with war and terrorism will face particular challenges, however, even countries with lower proportions of incidence associated with conflict cannot ignore its contribution. In order to achieve measles elimination, even small factors contributing to increased transmission must be considered. The MSRF briefly mentions conflict-afflicted areas specifically, focusing on the importance of vaccination, outbreak response, and financing for health in the countries.[16] It will be important to ensure these areas are not neglected as the strategic framework is enacted.

Beyond achieving the WHO goal of measles elimination, addressing the impact of conflict on measles vaccination and incidence is a matter of health equity – disease and vaccination early in life are important determinants of public health outcomes.[29] In order to design programs that can mitigate the effects of war on the spread of disease, it is essential to understand the most important factors contributing to this spread. Despite an established understanding of some of these pathways, such as those outlined in Figure 1, challenges in collecting data in conflict settings result in sparse data. Further quantitative investigation of these pathways, perhaps through quasi-experimental studies of measles incidence during well-documented conflict events, is an important step to achieving health equity for those living in conflict-afflicted areas. Some of these pathways, such as the effect of conflict on trust of the medical system, are likely to be highly context-dependent while others may be more universal.[30,31]

In particular, the influence of conflict on surveillance system quality merits further investigation. Strong surveillance systems are integral to tracking, responding early to, and controlling outbreaks to minimize lives lost. We found no statistical evidence of association

between mortality due to war and terrorism and surveillance system quality, as measured by the NMFRI rate. However, our finding should not be taken as evidence that conflict does not harm the quality of the disease surveillance system. In our dataset, discontinuous reporting by some countries in years with high levels of conflict suggests that the missing years in the data may not be random which could prevent detection of any association. Indeed, single country case studies have reported significant breakdowns in surveillance, especially early in conflict periods, indicative of decreased surveillance quality during periods of conflict.[9,31]

Other measures of surveillance system quality that were not available for this study, such as the number of sites reporting testing results, may be better situated to measure the impact of conflict on surveillance quality. When conflict is concentrated in certain regions of a country, testing in conflict-afflicted regions may halt entirely or not be reported while sites in peaceful regions continue to report testing data. This could lead to an unchanged national negative test rate in the data examined for this study but would be reflected in data on the number of sites that report testing results. Surveillance data is the foundation of measles burden estimation and new data and approaches to quantify more accurately the effect of conflict on surveillance will be essential to improving estimates of the effect of conflict on measles epidemiology.

This model is subject to several important limitations. First, the conflict-free counterfactual vaccine coverage estimates assume a location- and time-invariant effect of mortality due to war and terrorism. In reality, the effects may vary from country to country and depend on the geographic distribution of conflict in the country and the strength of the health system in the country, among other factors. Also, while we tested lagged effects in the incidence model, these coverage estimates do not allow for any carryover effects of conflict to years after the mortality occurred. Second, we assume the schedule and effectiveness of campaigns at reaching children not already vaccinated through routine immunization in a given country-year is the same in the conflict-inclusive and conflict-free scenarios. In reality, conflict may change whether a campaign occurs. But, the unpredictable schedule of campaigns even in non-conflict periods makes it hard to estimate what would have happened in the absence of conflict, so we assumed campaigns follow the same schedule in the conflict-inclusive and conflict-free scenarios. Moreover, conflict may change the effectiveness of a campaign itself at reaching unvaccinated children, especially if they are concentrated in areas of the country with active conflict but face similar challenges in estimating conflict-free effectiveness so assume constant effectiveness, which is subject to limitations. A third limitation of this study, that might explain the weak association we found between war mortality rate and measles incidence, is that of collinearity between drops in vaccine coverage and the mortality rate due to war and terrorism. To address this limitation, future work could explore using a two-stage modeling approach in which vaccine coverage and any other covariates of interest are included in the first stage model and mortality due to war and terrorism enters in the second stage. Fourth, the current modeling approach cannot account for any underreporting of measles cases associated with conflict events nor does the use of a standard random effect fully account for underreporting during peaceful times. Looking at drops in coverage and percent of incidence associated with war and terrorism ignores the baseline coverage and incidence values, which are also important to achieving elimination. Fifth, the model does not examine the effects of war and terrorism mortality rate on

measles incidence at geographic scales other than the national-level. Conflict is often concentrated in specific regions of a country and the effects on incidence may likewise be concentrated in that region: during a diphtheria outbreak in Yemen, the odds of an outbreak were 11 times higher in districts actively experiencing conflict.[12] Examining the association across countries at the national level, as we have done here, may result in under-estimation of the effects of conflict on measles incidence. Similarly, there may be multi-national effects of conflict on measles incidence that the current model cannot account because it operates at the country level. If refugees migrate to other countries, the relatively more peaceful country might experience the outbreak, as has occurred between Somalia and Kenya and Ethiopia.[32,33] The current modeling framework would not associate this outbreak with war and terrorism mortality in the refugees' home country. Lastly, we have fit a statistical model to measles incidence data but dynamic modeling approaches that account for different patterns of interaction between different populations likely have additional advantages.

Our main predictor variable, the war and terrorism mortality rate estimates, is subject to limitations as well. Challenges in collecting data in conflict settings may lead to over- or under-estimation of mortality rate. IHME triangulates from a number of sources to estimate war and terrorism mortality rate but there are likely under- or un-reported events, particularly among marginalized groups.

Our work finds war and terrorism mortality is a contributing factor in the continued spread of measles and must be addressed in order to achieve measles elimination. There is a need for context- and antigen-specific systems for vaccine delivery during conflict. However, that alone will not be enough, and we must work to understand the other pathways through which conflict increases measles incidence. Notably, data gaps affected this analysis. As countries work toward elimination, incidence and vaccine coverage monitoring systems that are robust to conflict events should be developed and implemented. These could help track and identify outbreaks to help to avoid significant setbacks in progress that we estimate occur during conflict periods. These data can serve a dual purpose; beyond disease and vaccine coverage monitoring, they are important to documentation and understanding of the toll war takes on health.

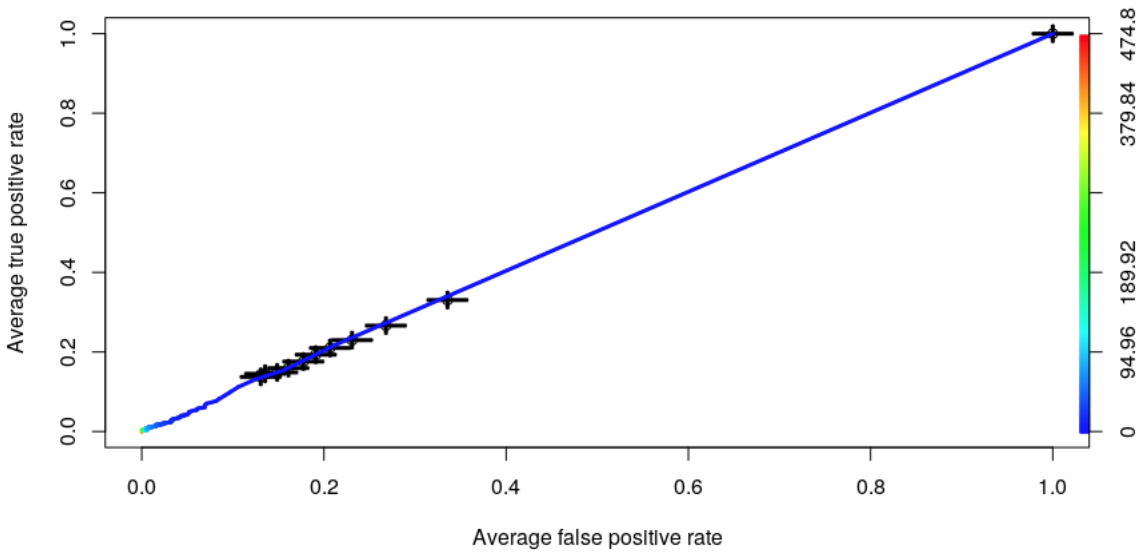


Figure 2 ROC curve of war and terrorism mortality rate as a predictor of whether a country meets the WHO NMFRI standard. The colors represent different threshold values of war and terrorism mortality rate and the shape of the curve indicates that war and terrorism mortality rate is as good as a random guess at predicting whether a country meets the WHO standard.

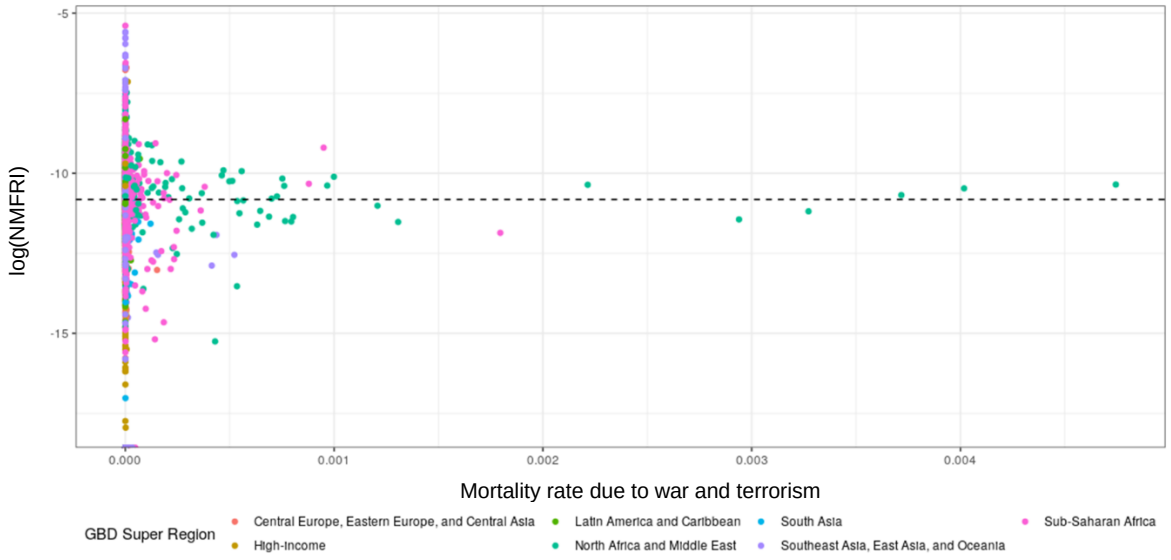


Figure 3 Measles testing data are noisy and variably reported. Some countries discontinue reporting when experiencing high levels of war and terrorism mortality.

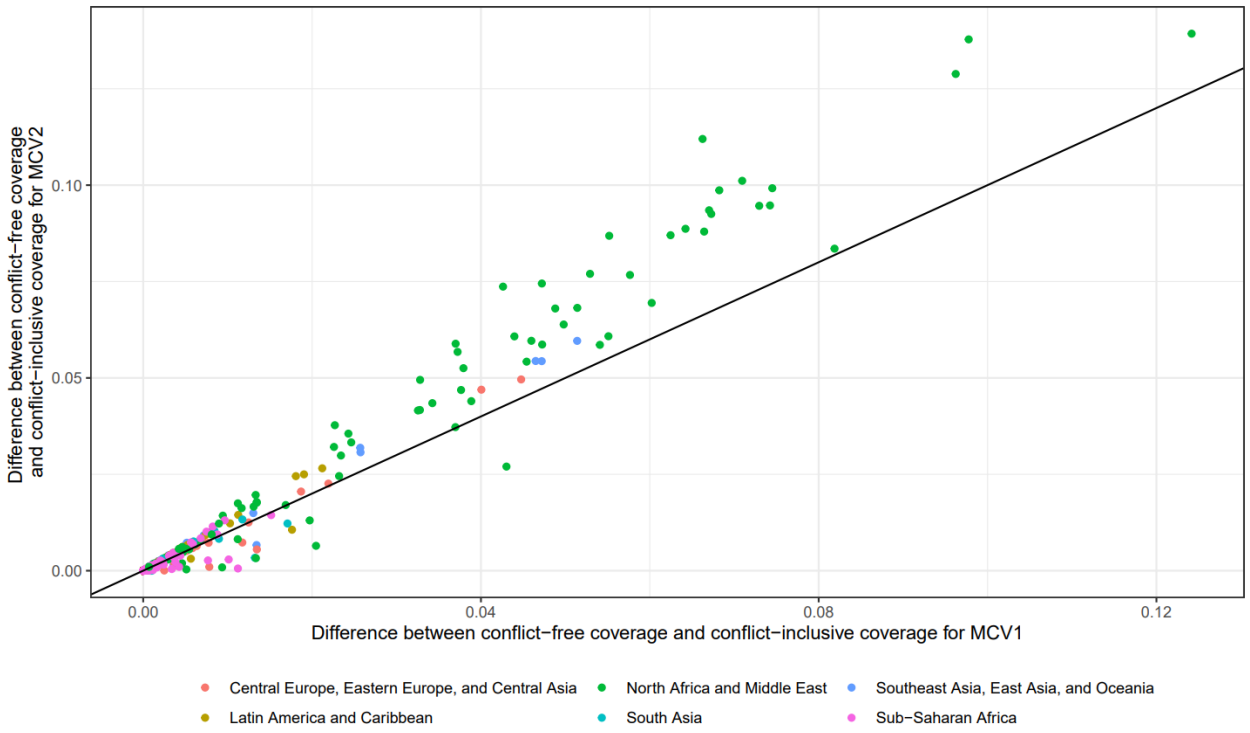
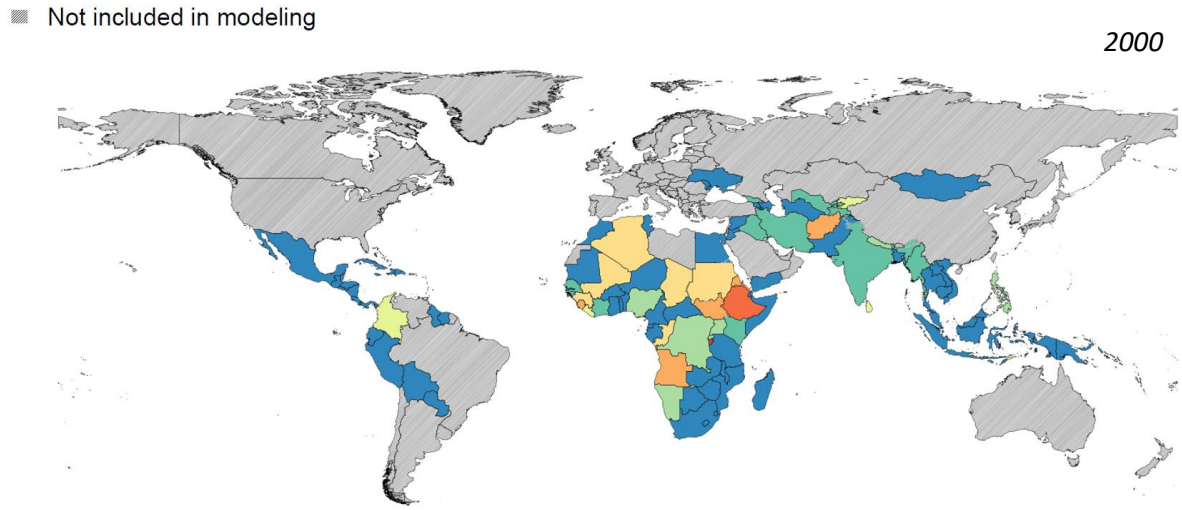
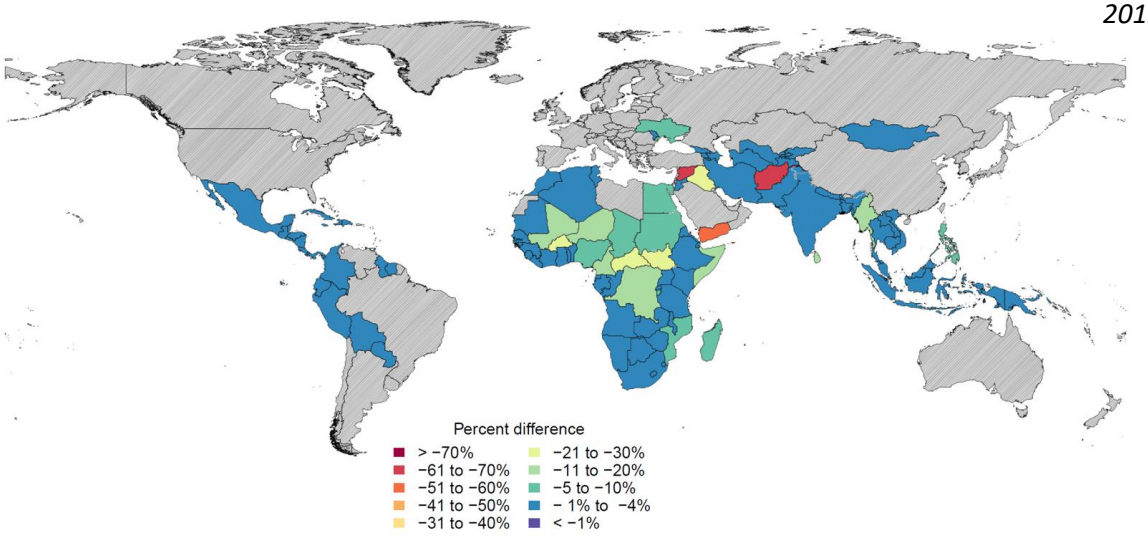


Figure 4 Conflict-associated drops in MCV2 coverage tend to be larger than drops in MCV1. Each point represents a county-year in which MCV2 is included in the routine immunization schedule.



a.

2019



b.

Figure 5 The proportion of incidence rate that is associated with war and terrorism mortality in each modeled country in (a) 2000 and (b) 2019. There are more countries in the greater than -70% category in 2019 than in 2000, indicating that conflict continues to be associated with measles incidence.

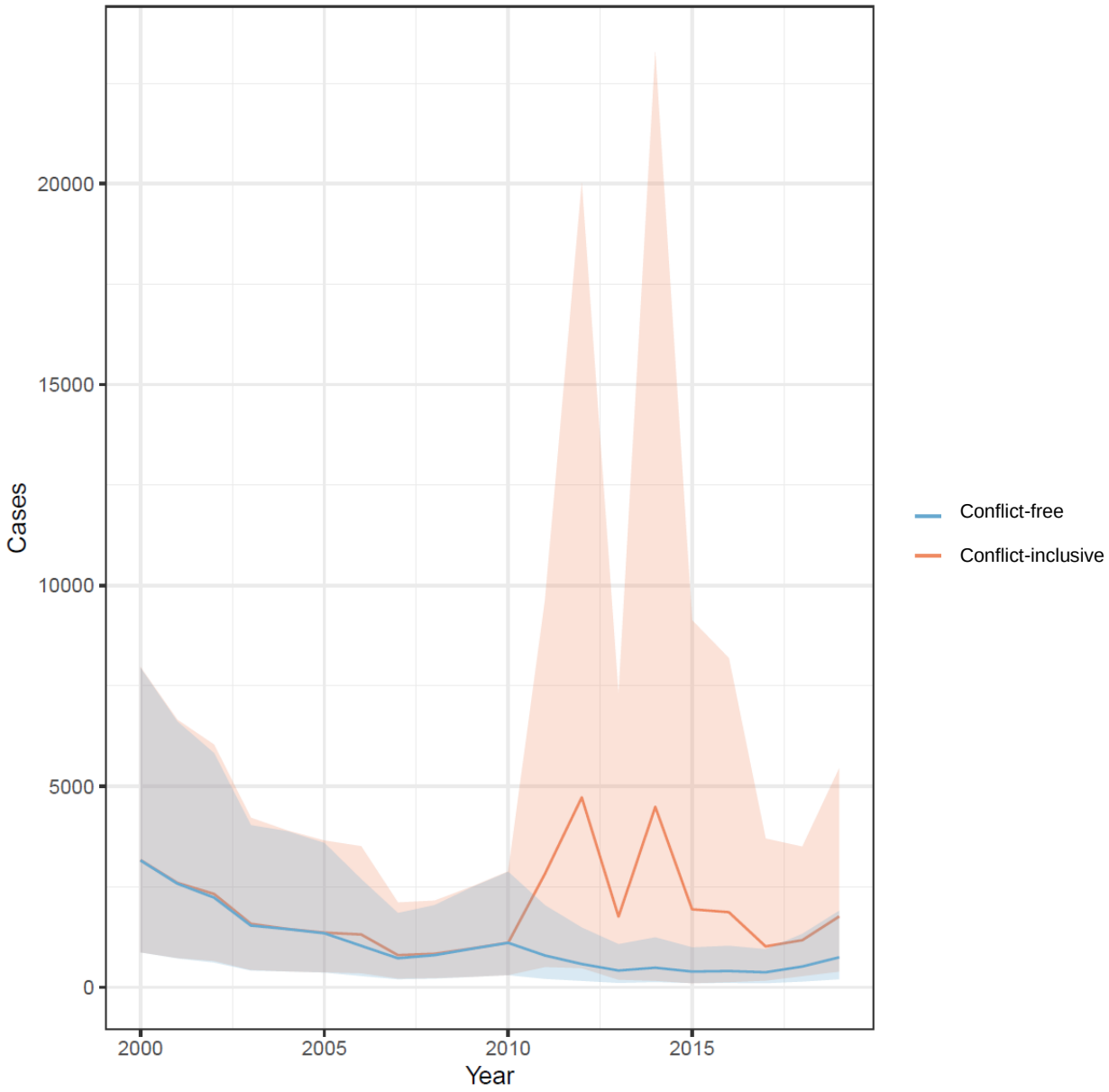


Figure 6 Conflict-free and conflict-inclusive measles incidnece estimates in Syria. Conflict is associated with a large increase in incidence in 2012 to levels not seen since before 2000, a notable loss of progress toward measles elimination.

Table S1 Measles incidence model fitted beta coefficients

	Beta	SE
Intercept	7.22	0.81
MCV1	-3.05	0.86
MCV2	-3.16	0.37
MCV1 drop	7.79	6.88
MCV2 drop	5.85	7.17
war	0.004	0.08

Table S2 RMSE in measles incidence models with and without lagged war and terrorism mortality rate covariates

	Model 1	Model 2
RMSE	1.959	1.971

Where model 1 is:

$$\log(inc\ rate) = \beta_0 + \beta_1 MCV1_{l,y} + \beta_2 MCV2_{l,y} + \beta_3 \Delta MCV1_{l,y} + \beta_4 \Delta MCV2_{l,y} + \beta_5 war + u_{sr,y} + u_{r,y} + u_{l,y} + \varepsilon$$

And model 2 is:

$$\log(inc\ rate) = \beta_0 + \beta_1 MCV1_{l,y} + \beta_2 MCV2_{l,y} + \beta_3 \Delta MCV1_{l,y} + \beta_4 \Delta MCV2_{l,y} + \beta_5 war + \beta_6 war_{l,y-1} + \beta_7 war_{l,y-2} + u_{sr,y} + u_{r,y} + u_{l,y} + \varepsilon$$

References

1. Jawad M, Hone T, Vamos EP, Roderick P, Sullivan R, Millett C. Estimating indirect mortality impacts of armed conflict in civilian populations: panel regression analyses of 193 countries, 1990–2017. *BMC Med*. 2020;18(1):266. doi:10.1186/s12916-020-01708-5

2. Corley AG. Linking armed conflict to malnutrition during pregnancy, breastfeeding, and childhood. *Glob Food Secur*. 2021;29:100531. doi:10.1016/j.gfs.2021.100531

3. Schaible UE, Kaufmann SHE. Malnutrition and infection: complex mechanisms and global impacts. *PLoS Med*. 2007;4(5):e115-e115. doi:10.1371/journal.pmed.0040115

4. Haar RJ, Read R, Fast L, et al. Violence against healthcare in conflict: a systematic review of the literature and agenda for future research. *Confl Health*. 2021;15(1):37. doi:10.1186/s13031-021-00372-7

5. Saidu Y, Vouking M, Njoh AA, et al. The effect of the ongoing civil strife on key immunisation outcomes in the North West and South West regions of Cameroon. *Confl Health*. 2021;15(1):8-8. doi:10.1186/s13031-021-00341-0

6. Verma AA, Jimenez MP, Tangermann RH, Subramanian SV, Razak F. Insecurity, polio vaccination rates, and polio incidence in northwest Pakistan. *Proc Natl Acad Sci U S A*. 2018;115(7):1593-1598. doi:10.1073/pnas.1711923115

7. Nnadi C, Etsano A, Uba B, et al. Approaches to Vaccination Among Populations in Areas of Conflict. *J Infect Dis*. 2017;216(suppl_1):S368-S372. doi:10.1093/infdis/jix175

8. Ngo NV, Pemunta NV, Muluh NE, Adedze M, Basil N, Agwale S. Armed conflict, a neglected determinant of childhood vaccination: some children are left behind. *Hum Vaccines Immunother*. 2020;16(6):1454-1463. doi:10.1080/21645515.2019.1688043

9. Jasem J, Marof K, Nawar A, Monirul Islam KM. Epidemiological analysis of measles and evaluation of measles surveillance system performance in Iraq, 2005–2010. *Int J Infect Dis*. 2012;16(3):e166-e171. doi:10.1016/j.ijid.2011.11.002

10. Ismail SA, Abbara A, Collin SM, et al. Communicable disease surveillance and control in the context of conflict and mass displacement in Syria. *Int J Infect Dis*. 2016;47:15-22. doi:10.1016/j.ijid.2016.05.011

11. Zhao Y, Lafta R, Hagopian A, Flaxman AD. The epidemiology of 32 selected communicable diseases in Iraq, 2004–2016. *Int J Infect Dis*. 2019;89:102-109. doi:10.1016/j.ijid.2019.09.018

12. Dureab F, Al-Sakkaf M, Ismail O, et al. Diphtheria outbreak in Yemen: the impact of conflict on a fragile health system. *Confl Health*. 2019;13:19-19. doi:10.1186/s13031-019-0204-2

13. Akil L, Ahmad HA. The recent outbreaks and reemergence of poliovirus in war and conflict-affected areas. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis*. 2016;49:40-46. doi:10.1016/j.ijid.2016.05.025

14. Sharara S, Kanj S. War and Infectious Diseases: Challenges of the Syrian Civil War. *PLoS Pathog*. 2014;10:e1004438. doi:10.1371/journal.ppat.1004438

15. Norris A, Hachey K, Curtis A, Bourdeaux M. Crippling Violence: Conflict and Incident Polio in Afghanistan. *PloS One*. 2016;11(3):e0149074-e0149074. doi:10.1371/journal.pone.0149074

16. World Health Organization. Measles and Rubella Strategic Framework 2021-2030. Published online 2020. https://s3.amazonaws.com/wp-agility2/measles/wp-content/uploads/2021/02/Measles-Rubella-Strategic-Framework-Updated.pdf

17. Wariri O, Nkereuwem E, Erondu NA, et al. A scorecard of progress towards measles elimination in 15 west African countries, 2001–19: a retrospective, multicountry analysis of national immunisation coverage and surveillance data. *Lancet Glob Health*. 2021;9(3):e280-e290. doi:10.1016/S2214-109X(20)30481-2

18. Kebede A, Ahmed HJ, Masresha BG, et al. Measles–Horn of Africa, 2010-2011. *MMWR Morb Mortal Wkly Rep*. 2012;61 34:678-684.

19. de Quadros CA, Hersh BS, Olivé JM, Andrus JK, da Silveira CM, Carrasco PA. Eradication of Wild Poliovirus from the Americas: Acute Flaccid Paralysis Surveillance, 1988–1995. *J Infect Dis*. 1997;175(Supplement_1):S37-S42. doi:10.1093/infdis/175.Supplement_1.S37

20. Fullman N, Yearwood J, Abay SM, et al. Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: a systematic analysis from the Global Burden of Disease Study 2016. *The Lancet*. 2018;391(10136):2236-2271. doi:10.1016/S0140-6736(18)30994-2

21. WHO Immunization Analysis and Insights Team. *Surveillance for Vaccine Preventable Diseases*. https://www.who.int/teams/immunization-vaccines-and-biologicals/immunization-analysis-and-insights/surveillance/surveillance-for-vpds

22. Wang H, Abbas KM, Abbasifard M, et al. Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950–2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. *The Lancet*. 2020;396(10258):1160-1203. doi:10.1016/S0140-6736(20)30977-6

23. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Covariates 1980-2019. Published online 2020. https://doi.org/10.6069/CFCY-WA51

24. Greg Bertolacci, Institute for Health Metrics and Evaluation, personal communication, November 2021.

25. Galles NC, Liu PY, Updike RL, et al. Measuring routine childhood vaccination coverage in 204 countries and territories, 1980–2019: a systematic analysis for the Global Burden of Disease Study 2020, Release 1. *The Lancet*. 2021;398(10299):503-521. doi:10.1016/S0140-6736(21)00984-3

26. Masresha B, Katsande R, Luce R, et al. Performance of National Measles Case-Based Surveillance Systems in The WHO African Region. 2012 - 2016. *J Immunol Sci*. 2018;Suppl:130-134.

27. Yang Q, Fu C, Dong Z, Hu W, Wang M. The effects of weather conditions on measles incidence in Guangzhou, Southern China. *Hum Vaccines Immunother*. 2014;10(4):1104-1110. doi:10.4161/hv.27826

28. WHO Regional Office for Africa. *WHO African Regional Measles and Rubella Surveillance Guidelines*. World Health Organization, Regional Office for Africa; 2015. https://www.afro.who.int/publications/who-african-regional-measles-and-rubella-surveillance-guidelines-0

29. Wilder-Smith A, Longini I, Zuber PL, et al. The public health value of vaccines beyond efficacy: methods, measures and outcomes. *BMC Med*. 2017;15(1):138-138. doi:10.1186/s12916-017-0911-8

30. Østby G, Shemyakina O, Tollefsen AF, Urdal H, Verpoorten M. Public Health and Armed Conflict: Immunization in Times of Systemic Disruptions. *Popul Dev Rev*. 2021;47(4):1143-1177. doi:10.1111/padr.12450

31. Mehtar S, AlMhawish N, Shobak K, Reingold A, Guha-Sapir D, Haar RJ. Measles in conflict-affected northern Syria: results from an ongoing outbreak surveillance program. *Confl Health*. 2021;15(1):95. doi:10.1186/s13031-021-00430-0

32. Polonsky JA, Ronsse A, Ciglenecki I, Rull M, Porten K. High levels of mortality, malnutrition, and measles, among recently-displaced Somali refugees in Dagahaley camp,

Dadaab refugee camp complex, Kenya, 2011. *Confl Health*. 2013;7(1):1-1. doi:10.1186/1752-1505-7-1

33. Navarro-Colorado C, Mahamud A, Burton A, et al. Measles Outbreak Response Among Adolescent and Adult Somali Refugees Displaced by Famine in Kenya and Ethiopia, 2011. *J Infect Dis*. 2014;210(12):1863-1870. doi:10.1093/infdis/jiu395