Health effects of the Brazilian Conditional Cash Transfer programme over 20 years and projections to 2030: a retrospective analysis and modelling study

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Summary

Background In 2024, Brazil celebrated the 20th anniversary of the Bolsa Família Program (BFP), one of the world's oldest and largest conditional cash transfer (CCT) programmes, covering more than 50 million Brazilians. This study aimed to evaluate the effect of the BFP on overall mortality and hospitalisation rates over the past two decades, and to forecast the potential effects of expanding this programme until 2030.

Methods This study combined retrospective impact evaluations in Brazil from 2000–19 with microsimulation models up to 2030. First, the effect of the BFP on overall mortality and hospitalisation rates was estimated across different age groups, adjusting for all relevant demographic, socioeconomic, and health-care factors. Fixed-effect multivariable Poisson models were then applied to 3671 municipalities with adequate quality vital statistics data. The three exposure variables of BFP were target coverage, benefits adequacy (average transfer per family), and the interaction of coverage and adequacy. Several sensitivity and triangulation analyses were conducted, including difference-in-difference models with propensity-score matching. Previous longitudinal datasets were then integrated with validated dynamic microsimulation models to project trends up to 2030.

Findings High coverage of BFP was associated with a significant reduction in overall age-standardised mortality rates (rate ratio [RR] 0·824 [95% CI 0·807–0·842]). High adequacy of BFP was associated with a reduction in overall age-standardised mortality (0·849 [0·833–0·866]). Our models estimated that the BFP prevented 8 225 390 (95% CI 8 192 730–8 257 014) hospitalisations and 713 083 (702 949–723 310) deaths in 2000–19. Stronger effects were found in BFP high coverage and high adequacy scenario, resulting in large reductions in under-5 mortality (RR 0·67 [95% CI 0·65–0·69]) and hospitalisation of individuals older than 70 years (0·52 [0·50–0·53]). Expanding BFP coverage could avert an additional 8 046 079 (95% CI 8 023 306–8 068 416) hospitalisations and 683 721 (676 494–690 843) deaths by 2030, compared with scenarios of reduced coverage.

Interpretation CCT programmes have strongly contributed to the reduction of morbidity and mortality in Brazil, having prevented millions of hospitalisations and deaths in the past two decades. During the current period of polycrisis, the expansion of CCTs in terms of coverage and benefits could prevent a large number of hospitalisations and deaths worldwide, and should be considered a crucial strategy for achieving the UN health-related Sustainable Development Goal 3.

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For the Portuguese translation of the summary see **Online** for appendix 1

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Introduction

2024 marked the 20th anniversary of the Bolsa Família Program (BFP) in Brazil,[1] one of the world's pioneering and largest conditional cash transfer (CCT) programmes.[2,3] CCT programmes transfer cash to poor households on the condition that parents meet specific requirements (named conditionalities), focused on health and education, aimed at alleviating short-term poverty while breaking the intergenerational cycle of poverty.[4] In the case of BFP, eligibility is determined by per capita household income: families in poverty, if they have children (aged <7 years), pregnant women, or adolescents (aged <18 years) qualify for benefits. Conditionalities include school attendance, vaccinations, and prenatal care, reinforcing the role of BFP in improving human capital.[1]

Currently, the BFP covers more than 20 million families (55·1 million people), transferring an average of US$139 to each household monthly, with an overall budget of approximately US$34·5 billion in 2023. Since its inception in 2004, the BFP has had substantial effects on poverty reduction and educational indicators,[2,3,5,6] directly improving the quality of life of beneficiary families.

Research in context

Evidence before this study

To investigate the available evidence on the effects of conditional cash transfer (CCT) programmes on overall hospitalisation and mortality, we initially searched PubMed for studies published containing the following terms: "cash transfers" [MeSH Terms] OR "conditional cash transfer" [MeSH Terms] AND "mortality" OR "hospitalization". The search dates were from database inception until Nov 30, 2024. There were no restrictions on language of publication. We also checked the referenced studies of the selected articles.

Our search found several articles on CCTs, some of which were associated with health outcomes. Studies from various geographical regions and both high-income and low-income and middle-income countries (LMICs) were included. Previous studies indicated mixed results. Some studies suggested that cash transfers, particularly CCTs, are associated with improved health outcomes, including reduced hospitalisation rates and mortality, particularly in vulnerable populations, such as children and older adults. However, the evidence is heterogeneous, with some studies showing minimal or no significant impact. In terms of the Bolsa Família Program, previous studies investigated the effects of this CCT on specific diseases, such as tuberculosis, HIV/AIDS, and malnutrition. Other studies found effects on specific age groups, such as child or infant morbidity or mortality, especially through the mechanism of vaccination and nutritional monitoring, and poverty-related diseases, such as diarrhoea and malnutrition. All assessed studies evaluated CCT over relatively short periods (ie, up to 8 years), focusing on specific health outcomes and in specific age groups.

Added value of this study

To the best of our knowledge, this is the first study that used a robust analytical approach over a 20-year period to comprehensively evaluate the effects of one of the world's largest CCTs on hospitalisation and mortality rates, overall and stratified by age group. This study uses the datasets and parameters of the retrospective impact evaluations to develop forecasting analyses, comparing the effects of alternative policy implementation scenarios on overall hospitalisation and mortality up to 2030, the last year of SDGs. Moreover, it is the first study that uses different measures of CCT implementation, including coverage, adequacy, and the combination of both, to estimate the prevented burden of hospitalisation and mortality over the past two decades, as well as in the coming decade.

Implications of all the available evidence

Our analyses show that the implementation of a nationwide CCT programme in an LMIC can strongly contribute to the reduction of hospitalisation and mortality rates, potentially averting millions of deaths and hospitalisations, and making important contributions to the achievement of health-related SDGs.

Although the BFP, and many other CCT programmes worldwide, have been conceptualised and developed mainly to reduce poverty and socioeconomic inequalities, they have also had unexpectedly strong effects on many health outcomes, not only in children, but also in the adults living in the beneficiary families.[7,8] Therefore, CCT programmes can serve as crucial policies not only for the achievement of UN Sustainable Development Goal (SDG) 1, poverty eradication, but also for advancements in SDG 3, good health and wellbeing.

For more on the **Global Alliance Against Hunger and Poverty** see https://globalallianceagainsthungerandpoverty.org/

These co-benefits are particularly important considering that the consequences of the COVID-19 pandemic, climate change, and recent conflicts (the so-called three Cs) have caused substantial setbacks to global poverty and global health.[9] There have been repeated calls worldwide to expand poverty-reduction interventions as potential mitigation policies, increasing the number of benefits, and including the newly impoverished families among the beneficiaries. Conversely, the rise in public debt in most low-income and middle-income countries (LMICs), following the COVID-19 pandemic, could lead to the implementation of fiscal austerity policies, resulting in budget cuts for social protection and health-care systems.[9,10] Despite the importance of maintaining the financial balance of public accounts, continuing with social programmes, such as the BFP, should be considered paramount to reduce poverty and social inequalities and promote population health.

In this context, the Global Alliance Against Hunger and Poverty (GAAHP) was created by the Group of Twenty (G20) countries in 2024; its mission underscores the significance of social protection measures, such as the BFP, in tackling global poverty and inequality. By prioritising inclusive growth and poverty reduction, the GAAHP highlights income transfer programmes as essential tools to mitigate the economic impacts of crises, enhance resilience, and promote social stability. Moreover, the GAAHP advocates for innovative financing mechanisms and strengthened international cooperation to support these programmes, emphasising the urgent need to sustain and expand them—particularly in LMICs—to address economic instability and climate change challenges.

A substantial body of research has evaluated the effects of CCT programmes on the use of health services, nutritional status, and a wide range of health outcomes.[11–14] However, only a few studies have evaluated the effects of CCT programmes on country-wide mortality and hospitalisation rates,[7,15,16] and none have analysed the effects of different characteristics of their implementation and coverage over decades, estimating the prevented burden of disease and mortality, and forecasting their future impact.

This study aims to evaluate the effects of the first 20 years of the nationwide expansion of the Brazilian CCT programme, both in terms of coverage and benefits, on overall hospitalisation and mortality rates, and to forecast the health effects of alternative implementation scenarios up to 2030, the target year for the UN SDGs.

Methods

Study design

This study integrated a retrospective impact evaluation with forecasting analyses. The retrospective impact evaluation had a longitudinal ecological design, whereby municipalities (unit of analysis) were observed over time. This longitudinal dataset combined aggregated health, socioeconomic, and BFP data from several sources (all data used in this study are publicly available; appendix 2 p 6) from 2000–23. From the total of 5570 municipalities in Brazil, we selected a subset of 3671 municipalities with adequate quality of civil registration and vital statistics, as in previous studies with similar methodologies,[2,17,18] according to a validated multidimensional criterion that considered the age-standardised mortality rate of the municipality, the ratio between registered and estimated birth rates, the percentage of poorly defined deaths, and the mean deviation of all the previous parameters (appendix 2 pp 9–10).[17] Although the exclusion of municipalities with an inadequate level of vital information could reduce the external validity of the findings, it is considered an essential factor for strengthening the internal validity of the study and reducing any possible bias due to changes in the quality of the death notification system—mainly reduction of sub-notifications—during the study period.[17]

Models considering all Brazilian municipalities and models with a weighting based on the municipal population were also estimated (appendix 2 p 21). Age-standardised all-cause mortality and hospitalisation rates were calculated for the entire population and used as dependent variables. We also included analyses by major age groups as secondary dependent variables: younger than 5 years, 5–69 years, and 70 years and older. Complementary analyses by smaller age subgroups can be found in appendix 2 (pp 28–29).

The coverage of BFP was calculated, similarly to previous studies,[2,3,5] as the number of families enrolled in the BFP in a municipality divided by the number of eligible families (according to BFP criteria) in the same municipality (ie, the target coverage).[2] We also calculated the adequacy of BFP benefits as the total amount of money transferred to all families divided by the number of families enrolled in the BFP in a municipality. As in previous studies,[2,19,20] we categorised BFP coverage and adequacy to estimate the dose–response effect related to increasing degrees of implementation of the interventions. Using previously established reference thresholds,[2,18,20] we created four levels of BFP target coverage: low (0–29·9%), intermediate (30·0–69·9%), high (70·0–99·9%), and consolidated (100%). In the absence of reference values from the literature, adequacy was categorised using quartiles: low (0–24·9 percentile), intermediate (25·0–49·9 percentile), high (50·0–74·9), and consolidated (75·0–100·0 percentile).

All relevant time-variant demographic, socioeconomic, and health-care-adjusting variables, according to the literature,[2,19–21] were included in the models: poverty rate, illiteracy rate, Gini index, urbanisation rate, fertility rate, percentage of households with inadequate sanitation, percentage of households with piped water, number of physicians per 1000 individuals, number of hospital beds per 1000 individuals, and the coverage of other social programmes, such as social pensions (Benefício de Prestação Continuada) and primary health care (Estratégia de Saúde da Família). A wide range of other additional covariates was also tested in a sensitivity analysis (appendix 2 pp 15–16, 30). As in previous studies,[2,3,5] we dichotomised these covariates according to their median value over the period.[2,3,5,18,22] We included time dummy variables (for 2008–09, 2013–14, and 2015–16) to adjust for major economic shocks that occurred in Brazil in the past two decades.[21,22]

See Online for appendix 2

Data sources

The data on the number of deaths, hospitalisations, beds, and physicians were collected from the Brazilian Ministry of Health. The number of beneficiaries of the BFP and the total amount transferred per family were collected from the Brazilian Ministry of Social Development, and socioeconomic and demographic variables were obtained from surveys and censuses conducted by the Brazilian Institute of Geography and Statistics. The complete list of data sources and related detailed methods are available in appendix 2 (p 6).

Statistical analysis

The effect of BFP target coverage and BFP adequacy on overall mortality and hospitalisation in 2000–19 was measured using Poisson multivariable regression models with fixed-effects specifications. This consolidated methodological approach evaluates the effects of nationwide interventions on hospitalisation and mortality rates with aggregate-level panel data.[2,18,23] Fixed-effects models include a term to control for unobserved characteristics of the unit of analysis that are approximately constant during the study period (eg, some geographical, historical, or sociocultural aspects of each municipality), which were not included in the model as confounding variables and could be associated both with the outcome and with the implementation of the intervention.[24] The Poisson distribution with robust standard errors for heteroscedasticity and serial correlation is used to deal with the overdispersion of mortality data in the municipalities.[23] To

	Year			Change in rate (2004–19)	
	2004	2010	2019	Absolute	Relative
Mortality rate for age group (per 1000 individuals)					
Overall	7·57 (1·44)	6·29 (0·87)	5·65 (0·79)	–1·92	–25·36
<5 years (per 1000 livebirths)	24·32 (15·10)	15·62 (6·82)	13·85 (5·78)	–10·47	–43·05
5–69 years	3·84 (0·89)	3·56 (0·61)	3·36 (0·57)	–0·48	–12·50
≥70 years	68·03 (15·87)	56·47 (8·93)	52·34 (7·42)	–15·69	–23·06
Hospitalisation rate for age group (per 1000 individuals)					
Overall	2·00 (6·03)	1·47 (2·31)	1·38 (3·58)	–0·62	–31·00
<5 years (per 1000 livebirths)	799·30 (1484·37)	705·38 (1416·78)	644·14 (1320·49)	–155·16	–19·41
5–69 years	4·12 (12·48)	2·69 (6·66)	2·90 (7·63)	–1·23	–29·61
≥70 years	185·30 (276·42)	106·62 (149·83)	66·60 (95·12)	–118·70	–64·06
Bolsa Família Program					
Coverage of all population (%)	7·86 (7·70)	19·07 (14·63)	16·78 (14·14)	8·92	113·74
Coverage of target population (%)	50·67 (19·49)	98·75 (4·38)	99·25 (5·25)	48·58	95·88
Adequacy (BRL$)*	71·67 (6·57)	126·85 (12·29)	408·05 (52·21)	336·38	469·35
Other social programmes					
Benefício de Prestação Continuada coverage (%)	1·02 (0·64)	1·74 (0·95)	2·23 (1·11)	1·21	118·63
Estratégia de Saúde da Família coverage (%)	13·01 (21·76)	47·33 (31·20)	59·81 (27·71)	46·80	359·72
Other covariates					
Fertility rate (births per woman)	3·33 (0·67)	2·89 (0·49)	2·55 (0·38)	–0·78	–23·42
Poverty rate (%)	23·07 (17·85)	11·73 (11·79)	7·48 (9·23)	–15·59	–67·58
Proportion of individuals older than 15 years who are illiterate (%)	10·89 (8·93)	7·60 (6·72)	4·73 (5·02)	–6·16	–56·57
Gini index	56·70 (5·83)	53·17 (6·88)	52·43 (9·70)	–4·27	–7·53
Piped water coverage (%)	80·39 (20·45)	84·97 (16·86)	87·44 (15·90)	7·06	8·77
Adequate sanitation coverage (%)	11·97 (12·66)	22·50 (18·52)	27·28 (22·03)	15·31	127·90
Urbanisation rate (%)	86·71 (18·00)	88·96 (16·20)	90·66 (14·96)	3·95	4·56
Hospital bed rate (per 1000 individuals)	2·93 (2·04)	2·56 (1·63)	2·24 (1·43)	–0·69	–23·55
Physician rate (per 1000 individuals)	1·41 (0·93)	1·69 (1·13)	2·16 (1·46)	0·75	53·19

Data are mean (SD). Absolute change refers to the difference in values between two timepoints, whereas the relative change refers to the growth rate or percentage variation over time. The total number of municipalities included is 3671, which represents a subset of the total 5570 municipalities in Brazil. *The adequacy of the programme was calculated by dividing the total amount of money transferred to all families by the number of families enrolled in the BFP in a municipality.

Table 1: **Mean rates of municipal mortality, conditional cash transfer coverage, and other variables for selected municipalities of Brazil from 2004 to 2019**

evaluate the robustness of the estimates, several sensitivity analyses were carried out (appendix 2 pp 13–31). First, the models were fitted with continuous variables and changing variable thresholds to evaluate the influence of the categorisation. Second, the models were fitted with all 5570 municipalities in Brazil (ie, including municipalities with inadequate quality of civil registration and vital statistics) to assess the external validity of resultant estimates. Third, different sets of time variables were tested to investigate the influence and relevance of the time dummies. Fourth, negative binomial regression models were fitted and resultant estimates were compared with those of negative binomial models, in order to evaluate the stability of the results with alternative models. Fifth, the BFP effects on overall mortality rates due to external causes were estimated as an outcome for use as a negative control as they should not be affected by BFP.[2,5,21] Finally, to have a high degree of confidence in the causal inference and the overall impact evaluation, additional triangulation analyses[25] were performed, using difference-in-difference with propensity score matching,[26] evaluating the municipalities with low BFP coverage versus medium and high coverage in the years 2004 and 2019. Moreover, we evaluated all sensitivity, triangulation, and complementary results according to consolidated causal inference criteria (appendix 2 pp 13–31).[25] We used Monte Carlo simulations to estimate the number of hospitalisations and deaths averted by CCT programmes in 2000–19, comparing predicted outcomes to a counterfactual scenario without the programme (ie, no CCT coverage) and performing 10 000 iterations to ensure estimate stability. We used Stata (version 17.0) for database processing and analysis.

We used validated municipal-level microsimulation models to forecast the effects of potential BFP expansions or reductions on health outcomes until 2030. Microsimulation is considered to be one of the most accurate forecasting methods because it allows for modelling

	Age-standardised hospitalisation RR			Age-standardised mortality RR		
	Coverage	Adequacy	Adequacy × coverage	Coverage	Adequacy	Adequacy × coverage
Bolsa Família Program target population coverage						
Low (0–29·9%)	1 (ref)	..	..	1 (ref)	..	..
Intermediate (30–69·9%)	0·884 (0·874–0·893; p<0·01)	..	..	0·924 (0·912–0·937; p<0·01)	..	..
High (70–99·9%)	0·857 (0·847–0·867; p<0·01)	..	..	0·890 (0·880–0·899; p<0·01)	..	..
Consolidated (100%)	0·789 (0·779–0·799; p<0·01)	..	..	0·824 (0·807–0·842; p<0·01)	..	..
Bolsa Família Program adequacy						
Low (<BRL$61·44)	..	1 (ref)	..	..	1 (ref)	..
Intermediate (≥BRL$61·44 to <BRL$99·13)	..	0·852 (0·843–0·861; p<0·01)	..	..	0·900 (0·888–0·913; p<0·01)	..
High (≥BRL$99·13 to <BRL$151·23)	..	0·884 (0·877–0·892; p<0·01)	..	..	0·852 (0·834–0·871; p<0·01)	..
Consolidated (≥BRL$151·23)	..	0·844 (0·835–0·853; p<0·01)	..	..	0·849 (0·833–0·866; p<0·01)	..
Bolsa Família Program adequacy × target coverage						
Low adequacy × low coverage	..	..	1 (ref)	..	..	1 (ref)
Low adequacy × high coverage	..	..	0·949 (0·941–0·957; p<0·01)	..	..	0·920 (0·911–0·929; p<0·01)
High adequacy × low coverage	..	..	0·866 (0·853–0·879; p<0·01)	..	..	0·815 (0·804–0·825; p<0·01)
High adequacy × high coverage	..	..	0·775 (0·756–0·795; p<0·01)	..	..	0·723 (0·711–0·735; p<0·01)
Control variables*						
Others social programmes	0·997 (0·983–1·012; p>0·1)	1·024 (1·008–1·040; p<0·01)	0·966 (0·957–0·975; p<0·01)	0·972 (0·964–0·981; p<0·01)	0·986 (0·978–0·995; p<0·01)	0·985 (0·971–1·000; p<0·05)
Fertility rate	1·018 (1·003–1·034; p<0·05)	1·028 (1·012–1·045; p<0·01)	0·986 (0·976–0·996; p<0·01)	0·999 (0·989–1·008; p>0·1)	1·005 (0·993–1·018; p>0·1)	0·997 (0·981–1·013; p>0·1)
Poverty rate	0·956 (0·940–0·973; p<0·01)	1·01 (0·994–1·026; p>0·1)	0·967 (0·955–0·980; p<0·01)	0·966 (0·953–0·979; p<0·01)	1·012 (0·999–1·026; p<0·1)	0·953 (0·937–0·969; p<0·01)
Proportion of individuals older than 15 years who are illiterate	1·026 (1·005–1·047; p<0·05)	1·025 (1·004–1·046; p<0·05)	0·981 (0·967–0·994; p<0·01)	0·988 (0·975–1·002; p>0·1)	0·979 (0·965–0·994; p<0·01)	1·009 (0·989–1·030; p>0·1)
Gini Index	1·028 (1·014–1·042; p<0·01)	1·041 (1·027–1·055; p<0·01)	1·005 (0·994–1·016; p>0·1)	1·027 (1·017–1·038; p<0·01)	1·030 (1·019–1·042; p<0·01)	1·01 (0·996–1·023; p>0·1)
Piped water	0·988 (0·970–1·005; p>0·1)	0·972 (0·955–0·990; p<0·01)	1·032 (1·022–1·043; p<0·01)	1·027 (1·015–1·039; p<0·01)	1·023 (1·013–1·032; p<0·01)	1·003 (0·986–1·021; p>0·1)
Households with inadequate sanitation	0·898 (0·881–0·916; p<0·01)	0·886 (0·869–0·903; p<0·01)	1·035 (1·021–1·049; p<0·01)	1·019 (1·004–1·034; p<0·05)	1·017 (1·003–1·030; p<0·05)	0·908 (0·891–0·925; p<0·01)
Urbanisation rate	1·012 (0·989–1·036; p>0·1)	1·018 (0·993–1·042; p>0·1)	1·007 (0·994–1·021; p>0·1)	1·002 (0·989–1·015; p>0·1)	1·008 (0·996–1·020; p>0·1)	1·022 (0·999–1·047; p<0·1)
Hospital bed rate per 1000 population	1·150 (1·126–1·174; p<0·01)	1·155 (1·131–1·180; p<0·01)	0·993 (0·984–1·002; p>0·1)	1·002 (0·991–1·013; p>0·1)	1·003 (0·992–1·015; p>0·1)	1·132 (1·109–1·156; p<0·01)
Rate of physicians per 1000 population	1·022 (1·010–1·034; p<0·01)	1·027 (1·016–1·039; p<0·01)	1·006 (0·992–1·020; p>0·1)	1 (0·984–1·016; p>0·1)	1·002 (0·985–1·020; p>0·1)	1·028 (1·016–1·039; p<0·01)
Year	Yes	Yes	Yes	Yes	Yes	Yes
Number of observations	73 335	73 371	73 371	73 336	73 372	73 372
Number of municipalities	3669	3671	3671	3669	3671	3671
Avoidable events	8 225 390 (8 192 730–8 257 014)	..	..	713 083 (702 949–723 310)	..	..

Data are RR (95% CI; p value) unless otherwise specified. RR=ratio ratio. *All covariates are dichotomised based on their mean values, as described in the main manuscript.

Table 2: **RRs from the fixed-effect Poisson models for the association between age-standardised hospitalisation and mortality rates with the Bolsa Família Program coverage and adequacy**

municipality-specific characteristics and their associated outcome probabilities, in particular when developed as projections from the existing retrospective real-data cohorts, maintaining their original variable distribution, variable correlations, and municipal-specific trends.[26] Our modelling approach, based on previous studies,[18,22,27]

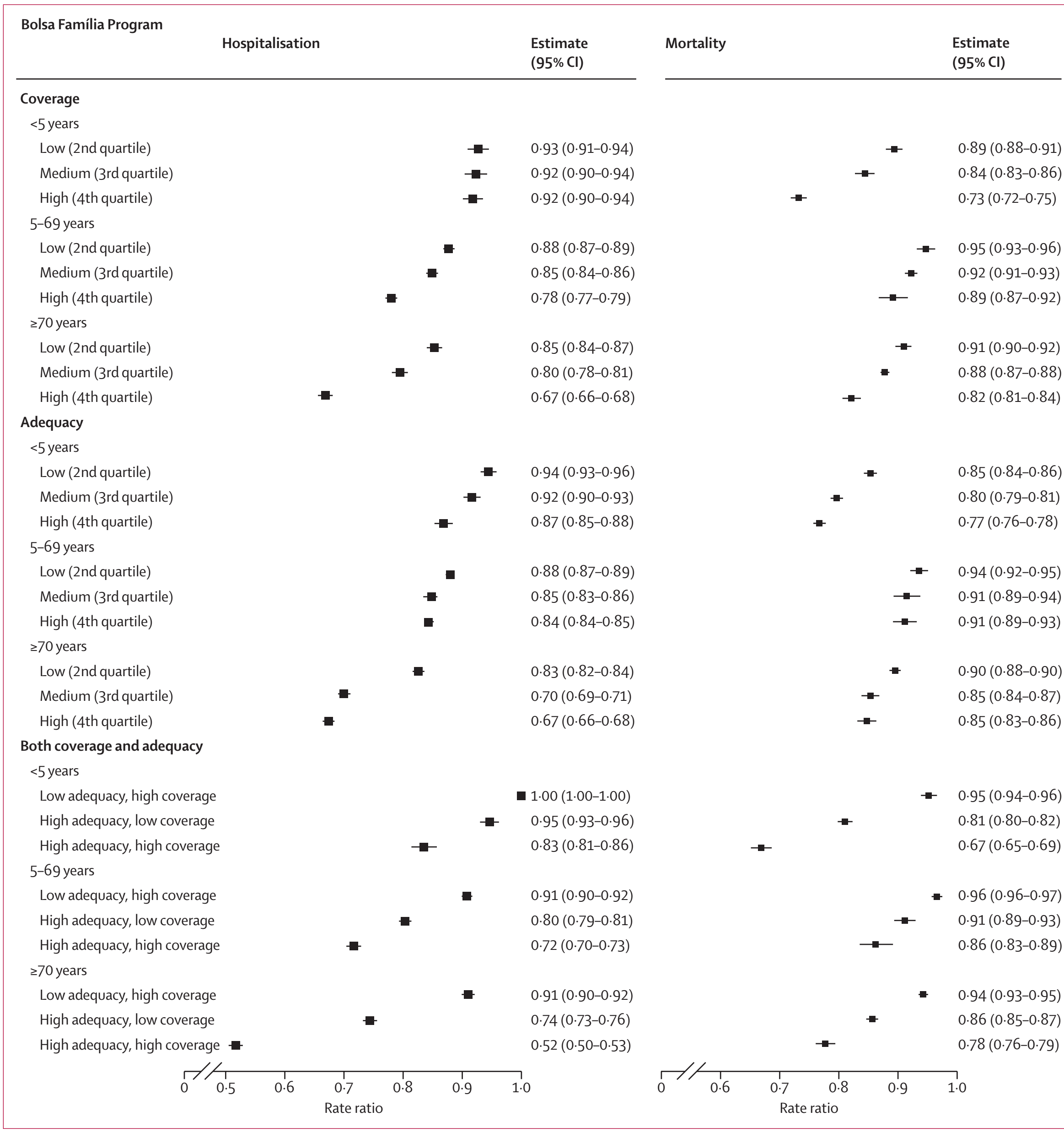

Figure 1: **Rate ratios for the association between hospitalisation and mortality rates with Bolsa Família Program coverage and adequacy**

was conducted in two stages. In stage 1, a synthetic cohort of all Brazilian municipalities for 2024–30 was created, which was extrapolated from and modelled on each municipal-level independent variable from the 2000–23 dataset. In stage 2, mortality and hospitalisation rates were predicted, using these independent variables as inputs in the same multivariate regression models used in the retrospective analysis, including estimates of their effects.

In stage 1, adjustments to the BFP eligibility criteria were simulated, with a focus on increasing the monetary threshold that determines family eligibility based on monetary poverty. Currently, the BFP eligibility criteria are nearly aligned with the World Bank's extreme poverty line of US$2·15 per day. Therefore, poverty thresholds based on half or a quarter of the Brazilian minimum wage (ie, BRL$1412 per month, equivalent to approximately US$291 in January, 2024, when the wage was established) were simulated (appendix 2 pp 33–34).

Regarding the policy response to this increase in the number of eligible families, three changes in BFP coverage were simulated: the expansion scenario (increasing coverage to include 100% of families with incomes below half of the minimum wage); the maintenance scenario (maintaining current coverage levels); and the severe fiscal austerity scenario (decreasing BFP coverage). The severe fiscal austerity scenario was derived from a validated model already used in previous studies,[22,27] which projected the effects of the current fiscal austerity measures on the coverage of the BFP (appendix 2 pp 33–34). The projection is proportional to the reduction of government expenditure on social protection observed from 2014–19.[28] For each outcome and each scenario, 10 000 Monte Carlo simulations were performed, allowing parameter values to vary in each simulation cycle according to their assumed underlying distribution. Further details of the modelling process, following the international model reporting guidelines (ISPOR-SMSM),[29] including calibration of models, internal and external validation, parameter distributions for Monte Carlo simulations, and model equations are provided in appendix 2 (pp 33–36). For the forecasting analyses, we used R (version 4.1.2).

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Results

In 2004–19, the mean age-standardised mortality rate of the 3671 municipalities studied decreased by 1·92% (table 1), with the strongest reduction in children younger than 5 years (–10·47%) and the least reduction in individuals aged 5–69 years (–0·48%). In the same period, the average age-standardised hospitalisation rates decreased by 0·62%. The target coverage of the BFP almost doubled between 2004 and 2019 (48·58%), whereas the coverage of the Estratégia de Saúde da Família increased by 46·80% and that of the Benefício de Prestação Continuada by 1·21%. Overall, socioeconomic, health-care, and living conditions improved during the study period.

Table 2 shows the adjusted associations of the overall mortality and hospitalisation rates with the coverage and adequacy levels of the BFP. Consolidated coverage of the BFP was associated with a statistically significant reduction in overall age-standardised mortality, with a rate ratio (RR) of 0·824 (95% CI 0·807–0·842). Consolidated adequacy of BFP was also associated with a statistically significant reduction of overall age-standardised mortality rates (RR 0·849 [0·833–0·866]). When combining these two measures of BFP, we found that municipalities with high coverage and high adequacy substantially reduced rates of overall age-standardised hospitalisation (RR 0·775 [0·756–0·795]) and mortality (RR 0·723 [0·711–0·735]). The low coverage and high adequacy group presented stronger effects in mortality rate reduction (0·815; 0·804–0·825) compared with the high coverage and low adequacy group (0·920; 0·911–0·929).

Based on these models, we estimated that the number of all-age all-cause deaths avoided during the past two decades (2000–19) due to the implementation of BFP was 713 083 (95% CI 702 949–723 310) and the number of hospitalisations avoided was 8 225 390 (8 192 730–8 257 014) (appendix 2 p 32).

Age-stratified models (figure 1) showed reductions in mortality and hospitalisation associated with increasing coverage and adequacy of the BFP in all age groups. The largest observed reductions at the BFP consolidated coverage level were for mortality in children younger than 5 years (hereafter referred to as under-5 mortality), with an RR of 0·73 (95% CI 0·72–0·75), and hospitalisation of people older than 70 years, with an RR of 0·67 (0·66–0·68). Municipalities with high coverage and high adequacy were able to reduce hospitalisation rates of individuals older than 70 years (RR 0·52 [95% CI 0·50–0·53) and under-5 mortality (RR 0·67 [0·65–0·69]). All sensitivity analyses confirmed the robustness of the findings, and all triangulation analyses showed a high degree of confidence in causal inferences (appendix 2 pp 13–31).[25,26]

Projections of expanded BFP eligibility criteria until 2030, as well as three scenarios of BFP coverage—expansion, baseline, and severe fiscal austerity—are explored in appendix 2 (p 34). The forecast for overall mortality rates for the respective austerity scenarios is also presented in appendix 2 (p 34). In the expansion scenario, mortality will decrease over the next decade; in the baseline austerity scenario, rates will slightly increase; and in the severe austerity scenario, mortality rates will significantly increase.

In table 3, RR is reported for the comparison between scenarios. In 2030, the RR between the expansion and baseline scenarios was 0·920 (95% CI 0·919–0·921) for overall mortality and 0·907 (0·907–0·908) for hospitalisations. These RRs corresponded to 683 721 (95% CI 676 494–690 843) averted deaths and 8 046 079 (8 023 306–8 068 416) averted hospitalisations from 2020 to 2030 if expansion strategies were implemented (table 3), instead of keeping their coverage at the baseline level. The RRs and the number of averted deaths that result from modelled combinations of policy responses are comparable in magnitude (appendix 2 pp 33–36).

	Hospitalisations	Deaths
Year		
2025	0·920 (0·919–0·920)	0·930 (0·929–0·932)
2030	0·907 (0·907–0·908)	0·920 (0·919–0·921)
Avoidable events		
2025–30	8 046 079 (8 023 306–8 068 416)	683 721 (676 494–690 843)

Data are rate ratio (95% CI) or n (95% CI).

Table 3: **Rate ratios and number of avoidable deaths and hospitalisations from the comparison of forecast scenario of expansion versus baseline scenario from 2025 to 2030**

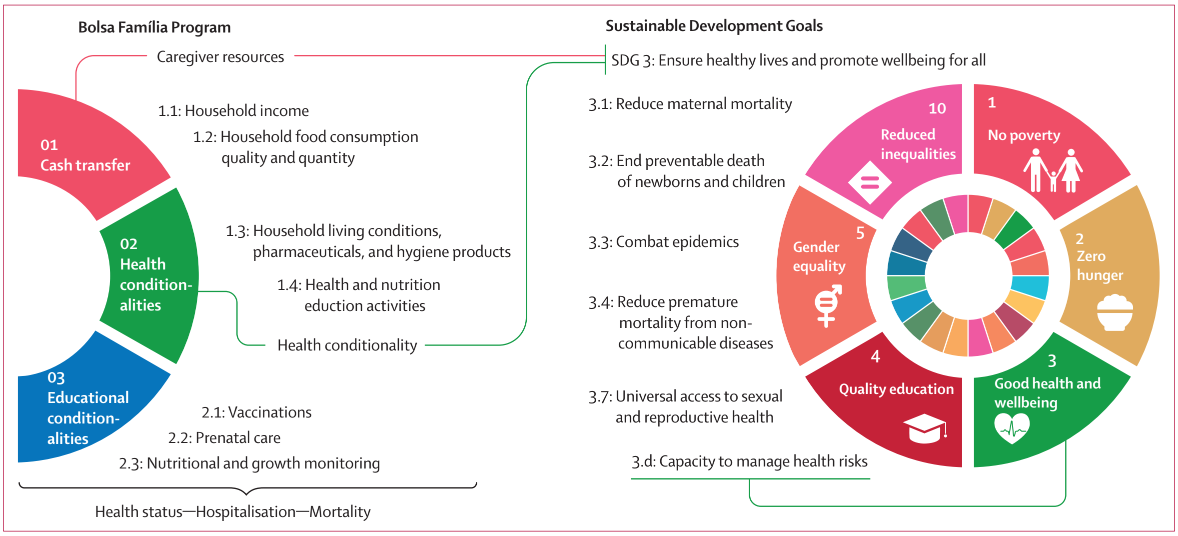

Figure 2: **Mechanisms linking the Bolsa Família Program to health outcomes and Sustainable Development Goals**

Discussion

To the best of our knowledge, this study is the first comprehensive impact evaluation of one of the world's largest CCT programmes on all-age all-cause mortality and hospitalisation, covering its 20-year implementation and integrating projections of the effects of alternative implementation scenarios up to 2030. Our results show that this CCT programme significantly reduced hospitalisations and deaths in Brazil over the past two decades, with the most notable effects observed in under-5 mortality and hospitalisation of individuals older than 70 years. We found that the expansion of BFP has averted 8 225 390 hospitalisations and 713 083 deaths over the last two decades in Brazil and could be able to prevent an additional 8 046 079 hospitalisations and 683 721 deaths up to 2030.

Many studies and reviews have evaluated or summarised the effects of CCT programmes on a wide range of health-related factors, including the use of health services, nutritional status, and health outcomes, often finding positive impacts, although with varying effects depending on the specific programme, country, and contextual characteristics of implementation.[12–14] Furthermore, a 2022 systematic review[11] found no solid evidence that CCTs are more effective than unconditional cash transfers, suggesting that their effects probably depend on the access to and quality of health-care services provided by the country. Only a few studies have been able to assess the effects of CCTs on mortality. A 2023 global evaluation using data from 37 LMICs associated CCT coverage with a 20% reduction in women's mortality and an 8% decrease in under-5 mortality.[30] Similarly, evaluations of Mexico's CCT programme, Oportunidades, showed an 11% reduction in maternal mortality (RR 0·890, 95% CI 0·820–0·950) and a 4% decrease in overall mortality.[31,32] Other studies have indicated reductions in infant mortality linked to CCT programmes in Ecuador and India.[15,16]

In Brazil, previous evaluations have also shown that BFP has been able to reduce child, maternal, and disease-specific mortalities, such as mortality from HIV/AIDS and tuberculosis, especially in populations that are the most vulnerable.[7,14,21,22] However, to our knowledge, no study has ever comprehensively evaluated the association between the BFP and overall and age-stratified mortality and hospitalisation over the past two decades of implementation. Previous attempts have evaluated the effects of the BFP on overall mortality in shorter periods of time and in specific sub-populations,[8] or within the framework of the Brazilian welfare state expansion.[2,7] The success of the BFP in reducing morbidity and mortality in Brazil can be attributed to the multisectoral design of CCT programmes, which integrate direct cash transfers with specific conditionalities. This approach aligns with the Health in All Policies framework,[33] leading to substantial improvements in population health outcomes and advancing progress towards UN SDG 3 (good health and wellbeing) and its related targets. The BFP can affect overall mortality and morbidity through the income effect and the conditionality effect, that is, by transferring direct income to the beneficiary families, improving families' nutrition and living conditions, and by conditioning the income transfer to the use of basic health services for child and maternal health.[10] CCTs are also able to improve a wide range of socioeconomic factors that affect health, such as improved education, reduced income inequalities, and social exclusion.[22] CCT programmes could contribute to psychological and affective pathways that influence health behaviours, for example, by reducing stress and cognitive load, thus enabling more accurate decision making,[34] particularly regarding food security and health promotion. In municipalities with high programme coverage, the large-scale transfer of resources due to BFP could have important spillover effects on the rest of the community, especially in the poorest regions, substantially improving health outcomes, even for non-beneficiaries of the BFP.[35]

Figure 2 provides a comprehensive description of the mechanisms that could explain the large impact of the BFP on health outcomes (appendix 2 pp 3–5).

The mechanisms that connect the BFP structure to health outcomes align this public policy closely with the UN SDGs, particularly SDG 3: ensure healthy lives and promote wellbeing for all at all ages.[36] Our results suggest that increased coverage and adequacy of the Brazilian CCT programme are linked to reductions in morbidity and mortality across all age groups, with particularly significant effects on under-5 mortality and hospitalisation of individuals older than 70 years. Regular health monitoring helps prevent diseases and improve the general health of beneficiary families, resulting in improved public health indicators. Monitoring also contributes to regular access for benefiting families to the Unified Health System, affecting overall mortality in the long term. Furthermore, by providing a minimum income to families, BFP also contributes to food security, ensuring that children and adults have access to nutritious food. In the panel, we highlight how this programme aligns with and can contribute to each specific goal.

The GAAHP of the G20 has increasingly recognised the crucial role of CCT programmes, such as the BFP, in addressing global poverty and inequality, particularly as nations grapple with economic instability, climate change, and post-pandemic recovery. As a forum representing the world's largest economies, the G20 has underscored the importance of innovative financing mechanisms and international cooperation to sustain and expand social protection systems. These efforts include leveraging income transfer programmes to foster inclusive growth, mitigate socioeconomic vulnerabilities, and build resilience in low-income populations. Such global emphasis reaffirms the importance of BFP as a model for integrating poverty alleviation with health and education outcomes, setting a benchmark for achieving the UN SDGs.[2]

This study has limitations. First, the exclusion of municipalities with an inadequate level of vital information could have reduced the external validity of the findings, but it was an essential factor in strengthening its internal validity and reducing biases due to changes in the quality of the death notification system—mainly reduction of sub-notifications—during the study period. However, the municipalities included in the study account for over 87% of Brazil's total population, as those with low-quality vital data are also the least populous. Additionally, these quality criteria are commonly used in similar studies in Brazil and Latin America,[9,11,14] and our sensitivity analyses showed that the main results were maintained when all municipalities were considered (appendix 2 p 21). Another limitation was the uncertainty of the forecasted scenarios, as the economic and political situation is sometimes volatile. For this reason, different responses to new BFP eligibility criteria were predicted, showing consistent comparison estimates between alternative policy responses.

Another key concern is the possibility of non-random variation in BFP coverage across municipalities, which might be influenced by local implementation capacity and other unmeasured factors related to governance and service provision. To mitigate this, we used municipal fixed-effects regressions to control for time-invariant

Panel: Alignment between the Bolsa Família Program (BFP) and the UN Sustainable Development Goal 3 targets

Target 3.1: Reduce maternal mortality

Prenatal care and vaccination monitoring for mothers are some of the health conditionalities of the BFP. Improved financial stability facilitates access to nutritious food and healthier living conditions, reducing risks during pregnancy and childbirth. Previous studies have shown that the risk of maternal death was 18% lower in women who received BFP.[37]

Target 3.2: End preventable deaths of newborns and children

Food security provided by BFP through the nutritional monitoring of children younger than 7 years is crucial for the health of newborns and children. Previous studies have shown that increased income allows families to purchase higher quality food and access preventive and curative medical services, decreasing infant mortality.[2,3,38]

Target 3.3: Combat epidemics

Several studies have already shown the positive impact of the BFP in reducing the incidence and lethality of AIDS,[39–41] tuberculosis,[42,43] malaria,[3,44] and other infectious diseases.[2,3,5] The programme can fund access to essential treatments and medications for communicable diseases. Improvements in living conditions and basic sanitation resulting from increased income reduces exposure to and spread of neglected tropical diseases and other communicable diseases.[45,46]

Target 3.4: Reduce premature mortality from non-communicable diseases

Financial support from BFP can be directed towards preventing and treating non-communicable diseases.[45,46] The programme facilitates access to healthy food and mental health services, promoting a healthier lifestyle and reducing premature mortality.

Target 3.7: Universal access to sexual and reproductive health

Prenatal care is one of the health conditionalities of the BFP, enabling improved pregnancy monitoring.[2,37,47] Increased family income allows women to have higher access to sexual and reproductive health services, including family planning and education. This increased access results in better reproductive health decisions and integration of these needs into national health programmes.

Target 3.d: Capacity to manage health risks

BFP improves the economic conditions of families and facilitates access to health services and information, which can directly strengthen the capacity of people to manage health risks through the adoption of healthier behaviours (eg, healthier food, physical activities, and preventive services) and better living conditions (eg, sanitation, security, and housing). This strengthening, in turn, enhances the national capacity to respond to health emergencies and manage national and global health risks.

unobservable characteristics, such as administrative capacity and institutional quality. Furthermore, regressions were controlled by key socioeconomic and policy-related variables to help capture differences in governance, economic conditions, and health-care access, reducing the potential bias associated with local implementation disparities. We also restricted the sample to municipalities with high-quality vital statistics, which minimised biases linked to poor data reporting practices, which are often correlated with weaker governance structures. Additionally, we conducted a robustness check incorporating the Decentralized Management Index for the available years (2015–19), confirming that local implementation differences do not significantly alter our findings. Despite these efforts, residual unobserved variation might persist. Nonetheless, the robustness of our results across multiple sensitivity analyses supports the reliability of our findings.

The main strength of our study was the large range of sensitivity analyses performed, which confirmed the robustness of the findings. The triangulation analyses using difference-in-difference models with propensity-score matching models showed a high degree of confidence in the effect evaluation results[25] and conferred robustness to the forecasted scenarios of validated models (appendix 2 pp 13–31).

Moreover, our aggregate-level approach, which has been applied in several other impact evaluations of the BFP,[2,3,5] allowed us to capture the direct effects of CCTs on beneficiaries, as well as the spillover effects on the broader community, which have been shown to be particularly important in the case of the BFP,[48] and can have substantial additional effects on the municipality's morbidity and mortality rates.[2,3]

In conclusion, our study shows that the expansion of one of the world's largest CCT programme has been able to strongly reduce morbidity and mortality over the past 20 years in Brazil, preventing millions of hospitalisations and deaths. CCT programmes have played a vital role in promoting the health and wellbeing of vulnerable populations in LMICs and have made, and will continue to make, important contributions towards achieving the UN SDG 3 targets by 2030.

Contributors
DMC and DR developed the study concept. DMC and JAO collected the data. ALM, CC, PH, and AFdS accessed and verified the data. DMC, DR, AFdS, and JAO designed the study investigation. DMC and JAO did the data analysis. AFdS accessed and verified the codes and routines. DMC and DR wrote the first draft of the manuscript. All authors contributed to data interpretation and reviewed and edited the manuscript. All authors consented to submit the manuscript, with DR and DMC taking responsibility for the final decision to submit for publication. DR supervised the study process.

Declaration of interests
DR and AFS declare funding from the National Institute of Allergy and Infectious Diseases, National Institutes of Health (1R01AI152938). All other authors declare no competing interests.

Data sharing
The data used are public and available from the Brazilian Ministry of Health (DATASUS), Brazilian Statistics Institute and Ministry of Social Development websites: http://www2.datasus.gov.br/DATASUS/index.php; https://aplicacoes.mds.gov.br/sagi/ vis/data3/data-explorer.php; https://sidra.ibge.gov.br/home/ipca/brasil.

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ANNUAL REVIEWS

Annual Review of Public Health

Extreme Weather and Climate Change: Population Health and Health System Implications

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Keywords

climate change, climate variability, extreme events, population health, health systems

Abstract

Extreme weather and climate events, such as heat waves, cyclones, and floods, are an expression of climate variability. These events and events influenced by climate change, such as wildfires, continue to cause significant human morbidity and mortality and adversely affect mental health and well-being. Although adverse health impacts from extreme events declined over the past few decades, climate change and more people moving into harm's way could alter this trend. Long-term changes to Earth's energy balance are increasing

the frequency and intensity of many extreme events and the probability of compound events, with trends projected to accelerate under certain greenhouse gas emissions scenarios. While most of these events cannot be completely avoided, many of the health risks could be prevented through building climate-resilient health systems with improved risk reduction, preparation, response, and recovery. Conducting vulnerability and adaptation assessments and developing health system adaptation plans can identify priority actions to effectively reduce risks, such as disaster risk management and more resilient infrastructure. The risks are urgent, so action is needed now.

1. INTRODUCTION

Worldwide, in 2019, there were 396 disasters[1] that killed 11,755 people, affected 95 million others, and cost nearly US$130 billion (28). Asia was the most affected continent with 40% of the events, 45% of the deaths, and 74% of all people affected. Floods and storms accounted for 68% of the number of affected people worldwide. Anthropogenic greenhouse gas (GHG) emissions, land use change, and other activities impacting the global energy balance are altering the frequency and intensity of many extreme weather and climate events, with some regions experiencing increases in heat waves, floods, and droughts (84). Events influenced by climate change, particularly wildfires, also are increasing.

Risks from extreme weather and climate events arise from the intersection of the physical hazard (e.g., wind and rain), the extent of exposure to the hazard, the vulnerability of individuals and communities, and the capacity to prepare for, manage, and recover from extreme events.

A disaster generally is defined as a sudden, calamitous event that disrupts the functioning of a community or society and that exceeds its ability to cope using its own resources (81). The occurrence of an extreme event is not required for a community or region to experience extreme impacts, such as a large increase in mortality; an extreme impact can arise from a moderately strong event when it occurs in a highly vulnerable population. The converse also is true, that an extreme event may not result in extreme impacts when communities are prepared.

Roughly 20% of disasters in 2019 occurred in North America, including the Caribbean and Central America, for total damages of US$55 billion, of which US$29 billion were insured (130). Loss events included Hurricane Dorian, which caused billions of dollars in damage, especially in the Bahamas, in late August to early September. Heavy losses that year also resulted from severe weather, floods, and a winter storm in the United States. A mixture of snowmelt triggered by unusually high temperatures in March and storms with torrential rain led to sustained and extensive flooding in Nebraska, South Dakota, Iowa, and Mississippi (49).

Overall, the numbers and costs of disasters have been increasing for several decades due to increases in exposure (more people moving into harm's way and increases in the values of property and infrastructure at risk), vulnerability of people and infrastructure, and climate change (170). Since 1980, the United States has experienced 265 weather and climate disasters in which the overall damages reached or exceeded US$1 billion; the total costs were greater than US$1,775 trillion (132), with an estimated 14,223 deaths (an average of 356 per year), although the numbers of deaths are likely an underestimate (178).

Beyond the damage to infrastructure, extreme weather events and disasters can affect the health and well-being of individuals and can have catastrophic impacts on communities and health

[1]Natural disasters are not solely the consequence of biophysical, meteorological, or climatological events; human activities, such as placement of infrastructure and movement of people into vulnerable regions, also are required.

systems. People can suffer from a wide range of physical effects (e.g., heat exhaustion, injuries in severe storms, and respiratory illnesses from molds due to floods) as well as longer-term impacts on mental health. Health systems and facilities can be affected by impacts on patients and health care staff, medical and nonmedical supplies, facility operations, and critical infrastructures. To prepare for climate change, health-sector and emergency-management officials—as well as urban planners, neighborhood services staff, and others—require information about how hazards are projected to change, possible future exposures of people and property, likely changes in population health and health care infrastructure vulnerabilities, and needed capacities to prepare for and manage the events and their aftermath.

We review (*a*) the current impacts and projected risks of climate change on the health of populations and health systems from extreme weather and climate events and from wildfires, (*b*) the value of disaster management to reduce health risks from these changes, and (*c*) adaptation and mitigation measures that can explicitly address climate change in policies and planning processes.

2. EXTREME EVENTS INFLUENCED BY CLIMATE CHANGE

Global land-surface air temperature has risen 1.53°C since the preindustrial period of 1850–1900, with considerable variation in regional warming; this increase is much larger than the observed warming combined over land and oceans (0.87°C) (84). Climate models project robust differences in regional climate characteristics, including extremes.

Detection and attribution analytic methods are increasingly being applied to determine the effects of climate change on the frequency and/or magnitude of extreme events. For example, in mid-September 2019, torrential rainfall from Tropical Storm Imelda caused large-scale flooding in Southeast Texas, affecting an estimated 6.6 million people and resulting in rescues of over 1,000 people and 5 deaths (171). The recorded precipitation at the station with the highest total amount of rainfall from this event would be expected only approximately once every 1,200 years.

The 2019 Intergovernmental Panel on Climate Change Special Report on Climate Change and Land (84) concluded that warming since the period 1850–1900 has resulted in an increased frequency, intensity, and duration of extreme events in most land regions, including the following observations:

- The intensity of heavy precipitation events increased across the globe.
- The frequency and intensity of droughts increased in some regions (including the Mediterranean, West Asia, many parts of South America, much of Africa, and Northeastern Asia).
- Desertification in some dryland areas (including in sub-Saharan Africa, parts of East and Central Asia, and Australia) was associated with increased land-surface air temperature and evapotranspiration and decreased precipitation amounts in interaction with climate variability and human activities.
- The frequency and intensity of dust storms increased over the last few decades due to land use and land cover changes and climate-related factors in many dryland areas, such as the Arabian Peninsula and the broader Middle East and Central Asia.

Further, climate change is projected to continue and exacerbate these trends, including the following:

- The frequency, intensity, and duration of extreme heat events are projected to continue to increase through the twenty-first century, with all regions expected to experience unprecedented temperatures.

- The frequency and intensity of extreme rainfall events are projected to increase in many regions.
- The frequency and intensity of droughts are projected to increase, particularly in the Mediterranean region and southern Africa.

There is a range of possible futures for each additional unit of global warming. For example, regional projections of annual maximum temperatures across climate models where the Earth warms 1.5°C under a scenario of high GHG emissions indicate there may be little change in the single hottest day in a year in many regions if realized warming falls into the lower quartile of projections (154). Alternatively, increases of 3°C to 5°C in maximum temperatures could occur over most regions in the upper quartile of projections. With Earth projected to warm 1.5°C between 2030 and 2052, the next few decades could be similar to today in many parts of the world; or regions could experience significant and very rapid warming. These projections have implications for the frequency and duration of extreme heat events; the extent of increases in precipitation, including from hurricanes; and the rate of sea-level rise that affects the health of future populations (particularly but not exclusively in coastal regions) and their health systems.

2.1. Tropical Cyclones or Hurricanes

Tropical cyclones (TCs) that make landfall are among the most dramatic and costly disasters. They have different names depending on the basin where they occur (hurricanes in the northern Atlantic and northeastern Pacific, typhoons in the northwestern Pacific, and cyclones in the southern Pacific or Indian Ocean) but are the same meteorological phenomena. They cause strong winds and flooding from intense rainfall and a surge of ocean water that causes dramatic damage to buildings and infrastructure along coastlines, often including widespread utility outages. TCs have cost the United States close to US$1 trillion since 1980 (157). Low- and middle-income countries (LMICs) have suffered smaller total economic losses, but the losses are often a larger proportion of their nations' economies and arguably have greater consequences for well-being (67).

Alongside physical damages, TCs are highly detrimental to human health (107). From 1963 to 2012, there were 2,544 deaths in the United States (~50 per year) directly caused by the forces of TCs (e.g., drowning in floods caused by storm surge or extreme rainfall, or physical trauma caused by windborne debris) (142). A comparable number of TC-related deaths are indirectly caused in individuals with preexisting conditions exacerbated by the stress or strain of a storm. Hurricane Katrina alone caused 520 direct deaths and 565 indirect deaths (143). Accounts of individual TCs clearly indicate upticks in a variety of other health problems that do not necessarily result in death, including injuries, diseases, skin infections, and mental health impacts (e.g., 43, 73, 87, 141). New data sets of TC exposure history are increasing possibilities for robust, long-term epidemiological studies of these diverse health impacts from TCs (e.g., preterm birth; see 4a, 161) that will enhance our ability to predict and prepare for future TC health impacts.

A confounding challenge in projecting future TC impacts is the relatively low confidence in projections of TC changes with climate change. Projections suggest the most intense TCs will likely increase in frequency and exhibit higher precipitation rates; however, there is uncertainty whether the overall number of TCs may increase or decrease, with different trends projected depending on the modeling approach (46, 103, 154). However, other trends are clearly heightening TC risks to individuals and communities. Exposure to TCs is increasing as people move to and settle along coastlines (57), and potential damages from storm surge are increasing with sea-level rise (113).

2.2. Compound Events

Complicating projections of extreme-event impacts is the fact that many disasters are the result of combinations of extremes (sometimes called compound, interacting, interconnected, or cascading events) (140, 154). Compound extreme events consist of two or more events interacting across time and/or space, such as back-to-back extreme heat events or an extreme heat event coincident with a drought (184). The range of compound extremes that might endanger human health is large. The study of compound extremes is a nascent and rapidly evolving research area. In many cases, understanding of present and projected risks of a particular compound extreme event is lacking, including key societal drivers of vulnerability (144). We highlight a few types of compound climatic extreme events.

Heat waves are exacerbated when combined with other extreme events. Heat waves can enhance the buildup of ozone and other pollutants, leading to combinations of heat and air pollution dangerous for human health (4, 111). A particularly striking example is the combination of high temperatures, wildfire, and smoke that results in high levels of air pollution across broad geographic areas. In recent summers, the western United States has been afflicted with multiple such episodes; these are projected to become increasingly common in the future because of climate change (114).

Positive feedback loops also occur between heat waves and droughts that heighten temperature and desiccation (76, 185). Certain types of atmospheric waves can cause multiple simultaneous heat waves distributed across the Earth; this may increase the risk of multiple breadbasket failures (105). Many of the most impactful heat waves in terms of mortality might be better understood as the combination of a number of heat extremes occurring in sequence, separated by short cooler breaks—a temporally compound heat wave event. The proportion of heat wave hazards coming from these temporally compound heat waves is robustly projected to increase with global warming (7).

Past events highlight the dangers of compound extreme events involving TCs or extreme precipitation and related flooding. For example, in 2005, Hurricane Katrina led to massive flooding in New Orleans (153). Only a few weeks later, Hurricane Rita rebreached weakened levees, leading to flooding once again. These events' impacts likely added nonlinearly by affecting the vulnerability of protective infrastructures. Significant research remains to understand the dynamics of such compound hydrological extremes and to quantify risks to populations and communities (144).

3. POPULATION HEALTH AND HEALTH SYSTEM RISKS FROM EXTREME EVENTS INFLUENCED BY CLIMATE CHANGE

There is high annual variability in the numbers of deaths from all disasters, with an average of 60,000 deaths annually over the last decade, or 0.1% of all global deaths (148), with an irregular and overall declining trend. Most of these deaths were in a few intensive disasters, indicating that while the events may not be preventable, much of the loss of life can be avoided through improved forecasts and early warnings, more resilient infrastructure, and improved disaster risk management. However, there is a concern with climate change that future events may be too large or intense for effective preparation.

The next sections summarize population health and health system risks from high ambient temperatures, droughts, floods, and wildfires, followed by a discussion of the mental health risks associated with extreme events influenced by climate change.

3.1. High Ambient Temperatures

The range of health effects of high ambient temperatures include discomfort, severe illnesses requiring hospital care, mortality, and interactions with and modifications of work patterns, recreation, and other activities.

3.1.1. Morbidity and mortality from heat waves. At the global scale, the number of hot days and nights has increased since the 1950s, while cold days and nights decreased (154). Rising temperatures are directly connected to human health through heat-related illnesses (e.g., heat exhaustion, heat syncope, and heat stroke) and death, with each individual's risk highly dependent on their exposure, location, and susceptibility. There is a wide range of heat tolerance within populations and across regions. The human body can physiologically adapt to heat to a certain extent depending on individual factors, local climate, and types of heat exposure. Physiological factors (e.g., age, sex, preexisting illness, and medication or drug use) (23, 98) and behavioral or contextual factors (e.g., employment, activity, clothing, income, and housing type) (6, 118) are known to affect thermoregulation across day-to-day or hour-to-hour heat exposures. For example, in Maricopa County, Arizona, 47% (93/197) of heat deaths in 2019 involved drug use as a cause of death or contributing factor (124). Extreme heat events can disrupt health systems and services, for example, through a surge in patient volumes, by closing operating theatres in high heat and humidity conditions, or through impacts on health care professionals and patients (156).

Reducing risks to health from current and projected high temperatures—outdoors and indoors—depends not only on physiological acclimatization but also on planned adaptation by public health officials in concert with partners in other sectors. Heat action plans and early warning systems that include a proactive response to assist vulnerable populations and build awareness among the public and key stakeholders can lead to the adoption of protective behaviors and reduction in morbidity and mortality (75, 156). Common components of heat action plans and warning systems include opening of public cooling shelters, targeted messaging, wellness checks, and water distribution (e.g., 9, 19). A study by Eisenman et al. (44) found that as temperatures increased, heat-related mortality was lower in census tracts with more publicly accessible cool spaces in Maricopa County, Arizona. These and other preventative measures that may reduce heat exposures and increase coping capacity as the climate warms are important for protecting health. Over longer time scales, communities can be modified or designed with new or altered technologies and infrastructures (e.g., cool facades, green roofs, shade structures, and reflective surfacing) to reduce heat exposures in urban areas (119, 172). Heat-health adaptation measures can be cost-effective and reduce utilization of health systems (61) but should be developed and updated based on information about projected climate conditions (74).

Heat-related mortality has been declining in many industrialized countries in recent decades (56). For example, deaths attributed to heat across 105 cities in the United States declined by almost 63% from 1987 to 2005 (12). However, the extent to which continued declines could be realized (or reversals avoided) largely depends on implementing effective adaptation strategies (60). Heat-related mortality trends and optimal adaptation pathways or measures differ by country based on culture, infrastructure, technology, and communication, among other factors. Few studies have assessed heat-related mortality in LMICs due to lack of data (56, 63, 134); over half of existing studies are from China (56%) or other Asian countries (14%). LMICs typically have low-resource environments [including a lower prevalence of air conditioning (AC)] and more often rely on altering behaviors and personal cooling to stay safe. These behaviors may include application of ice or ice towels, dousing skin, or saturating clothing with water with added ventilation (fans) (26). Yet the effectiveness of these actions depends on the climate context. For example, evaporative cooling with fans is more effective in humid locations, whereas self-dousing and/or wetting of clothing when using fans are preferable strategies in certain dry climates (128). Although AC use is growing exponentially as the most popular heat-exposure reduction strategy globally (11), it is costly and financially inaccessible for many of the most vulnerable, is energy intensive, emits waste heat into the environment (150), and can increase the risk of power outages.

Heat-reduction interventions may have economic and educational cobenefits. Park (137) found that high school student test performance was reduced by 14% on days with high (~32.2°C) outdoor temperatures compared to optimal (22.2°C) outdoor temperatures in New York State. Hot school days may also disproportionately impact minority students, accounting for ~5% of the racial achievement gap in the United States, in part because of inadequate access to AC (138).

Finally, there is growing evidence linking extreme heat and rising temperatures to increased hospitalizations for mood and behavioral disorders (22, 175) and evidence of increased risk of suicide related to heat waves and rising temperatures (17, 34, 99). These risks are projected to increase with further warming. Burke et al. (17) estimated that under a high GHG emission pathway, there could be 9,000 to 40,000 additional suicide deaths throughout Mexico and the United States by 2050. Mechanisms for how high temperatures impact mental health remain poorly understood, with various nonclimatic confounders to consider (e.g., macroeconomics and social factors); yet, biologically, there may be side effects from thermoregulation and neurological responses to heat that adversely affect mental health (17).

3.1.2. Occupational health. Individuals working under heat stress are more likely to experience physiological heat strain (51) and heat-related illness, and exertional heat stroke and death can occur in young, otherwise healthy workers performing heavy physical labor (64). A global meta-analysis by Flouris et al. (51) found that individuals working a single shift under heat stress conditions were four times more likely to experience occupational heat strain than in thermoneutral conditions (based on 11,582 workers across 9 studies), with ~0.7°C higher core temperatures (1,090 workers, 17 studies) and 14.5% higher urine specific gravity (a measure of solute concentration) (691 workers, 14 studies). In the United States between 2000 and 2010, 359 occupational heat-related deaths were reported (annual mean fatality rate 0.22 per 1 million workers), with agricultural and construction workers at particularly high risk (64). Indoor workers subject to inadequate ventilation and workers exposed to point heat sources are also at risk (152). Occupational heat stress is hypothesized to contribute to the global epidemic of chronic kidney disease of unknown etiology (177) and can lead to adverse birth outcomes among heat-exposed pregnant workers (106). Working populations with the most social and economic disadvantages are often more exposed to heat and may lack adequate health care access or other means to address exposures and health effects (122).

The risk of adverse occupational health effects is likely to increase as the frequency and severity of extreme heat waves increase (83). In a study of US agricultural workers, climate change at its current pace is projected to double crop worker heat risk by the mid-century and triple by the end-of-century, absent extensive restructuring of agricultural labor (164). Increasing temperatures from local land use changes can magnify the impacts of climate change, for example, in the setting of industrial clearing of tropical forests where communities depend on subsistence agriculture and other outdoor work (183) and in areas with growing urban heat island effects (152). In tropical and mid-latitude areas of the world, Dunne et al. (38) estimated that heat stress has already reduced labor capacity by 10% relative to the 1970s and projected a reduction of 40% by the year 2100 under a pathway of high GHG emissions. Further decreases in labor productivity and associated economic impacts are projected, assuming adherence to occupational heat stress guidelines (38, 51).

3.1.3. Recreation. High temperatures can also adversely affect people engaging in outdoor sports and recreation and represent a growing challenge for the sports industry (136). Heat is a leading cause of sudden death among athletes, and exertional heat illnesses cause thousands of debilitating health outcomes annually (18). For large events facing extreme heat (e.g., Tokyo Olympics), weather and climate data should be integrated into the decision-making process for event schedules and venue locations (79). Unpredictable disruptions from extreme weather may cost billions of dollars given the years of planning, hundreds of thousands of people involved, and global media attention, yet such safety precautions may help avoid serious risk to athletes (158). Coordination among local stakeholders in emergency medicine, public health, and events/operations is necessary to ensure that localized preparedness plans (e.g., identification of hot spots such as sun-exposed locations, expected crowds, and midday events) systematically provide adequate support for both athletic and social activities.

3.2. Droughts

The frequency and intensity of droughts are increasing with rising global temperatures and changing precipitation patterns (165). These trends and associated risks are expected to continue to intensify with climate change (77). Internationally, over the last two decades, droughts affected more than one billion people (27). Africa is a quintessential setting for examination of the roles that drought can play in human health and society, as droughts there have led to mass migration, conflict, and devastating famine (54, 58). In the United States since 1980, droughts classified as billion-dollar disasters were estimated to have caused 3,865 deaths, with most of the deaths due to heat waves accompanying drought (132).

Because of the difficulty in defining the beginning and end of a drought, the causal pathways connecting droughts to health outcomes can be complex and difficult to monitor (10, 117). The most commonly identified pathway is a reduction in water availability for societal uses, both in quantity and quality as concentrations of pollutants increase (129). Stagnant, warm waters from drought produce ideal conditions to promote growth of many freshwater pathogens (32). Simultaneously, sudden heavy rains during drought conditions can increase the likelihood of flooding.

Droughts are slowly evolving, and the disruptions to human systems can last for long periods with slow recoveries that can have delayed health impacts (159), such as through agricultural losses and environmental degradation (47). Increased particulate matter (PM) in the atmosphere resulting from drought and high winds can also lead to respiratory health issues and death (10, 29). These conditions can contribute to the spread of pathogens causing respiratory illnesses (such as coccidioidomycosis and meningitis; see 25, 53). Drought has also been linked to mental health issues and conflict (59, 173).

3.3. Floods

Based on the Emergency Events Database, from 1969 to 2018, 10,009 extreme weather events that resulted in disasters caused over two million deaths and just under four million cases of disease (83). Floods (47%) and storms (30%) were the most common extreme weather events worldwide over the period 1969–2018, with an increasing trend (97). Globally, most direct weather-related deaths were caused by storms (39%), droughts (34%), and floods (16%). Drowning is the most common cause of death after the onset of flooding (139). Morbidity continues for more than 10 days after a severe flooding event. A comprehensive review of the health impacts of worldwide flood and storm disasters between 1985 and 2014 concluded that the health impacts of these extreme events differ (151). The health impacts include increases and sometimes decreases in

- Injuries, especially wounds, and carbon monoxide and gasoline poisoning after storms;
- Cases of infectious and parasitic diseases, such as gastrointestinal illnesses, respiratory infections, and skin or soft tissue infections, after storms and floods;
- Exacerbations of noncommunicable diseases after storms and floods;
- Increased contact with health services after floods; and
- Cardiopulmonary (floods) and skin complaints (storms and floods).

The results indicate increased needs for emergency and routine health care services.

Differential vulnerabilities increase risks during and after floods and storms. During Hurricane Harvey (Texas, 2017), physical health problems primarily affected individuals who did not evacuate. Disparities exist in disaster-related flooding exposure. Older adults were more likely to live in a household exposed to flooding from Superstorm Sandy (New York, 2012) (109). Socioeconomic disparities also were present, with poorer residents having higher risk. Increases in posttraumatic stress disorder (PTSD), depression, and anxiety are associated with flooding (131, 174) and hurricanes (135). Floods also can decrease health-related quality of life (149).

Health care access and infrastructure can be severely affected by floods, including loss of records, impacts on water supplies and laboratory functions, reduced access to health care, and evacuation, with subsequent consequences for the communities served (21, 139). Health care access was particularly reduced for persons living in households where someone lost their job after Hurricane Harvey (50).

3.4. Wildfires

Many parts of the world have seen increases in the length of the wildfire season and increases in burned area (92). While there are many drivers of these increases (including historical wildfire suppression and increased intrusion of humans into wildland areas), climatic changes, including drought, have been implicated as a major contributor to changes in fire season length and acres burned (1, 179). These trends are projected to continue under a range of global climate models, with particular agreement among models in the mid-to-high latitudes (127). Globally, the mortality burden from wildfire smoke is estimated to range between 260,000 and 600,000 (90); however, this estimate could now be considered an underestimate given increases in population globally and increases in extreme wildfires in North America, Australia, Brazil, and other locations since that study's publication in 2012.

Wildfire smoke emits a variety of chemicals, including PM (suspended solid and liquid particles) and gases such as carbon dioxide, carbon monoxide, nitrogen oxides, and volatile organic compounds. Additionally, many of these chemicals react to form more PM and ground-level ozone (85). Most studies of the population-health impacts downwind from wildfires focus on PM_{10} and $PM_{2.5}$, as data on these are readily available and there is a robust literature on the health impacts of these particles. More research is needed to understand the health impacts of other components of wildfire smoke.

Wildfire smoke exposure is most consistently associated with adverse respiratory health outcomes (20, 145), with the clearest evidence for exacerbations of asthma whether measured in hospitalizations, emergency department visits, or physician visits (15, 55, 160). Many studies find that lung function among people with asthma does not decline with exposure to wildfire smoke (112, 145), but there is some evidence of lung function decline of nonasthmatics (86, 100). These contradictory findings could be due to higher medication usage among those with asthma, thus protecting them from exacerbations during exposure. Many (15, 45) but not all (91) studies that investigate the relationship between wildfire smoke exposure and refills of rescue medications often used for asthma report significant positive associations. Associations between wildfire smoke exposure and other respiratory endpoints are not as consistent, but there is increasing evidence of associations for exacerbations of chronic obstructive pulmonary disease and respiratory infections (145).

Wildfire smoke may impact specific cardiovascular endpoints such as out-of-hospital cardiac arrests (33, 93) and emergency department visits, particularly among the elderly (180). Studies with sufficient statistical power demonstrate a small but significant increase in mortality (37, 48, 89, 123). Additionally, there is increased interest in whether wildfire smoke affects birth outcomes. Babies whose gestation coincided with a wildfire had a significant but small decline in birth weight (78). An observed decline in birthweight was significantly associated with wildfire $PM_{2.5}$ across multiple fire seasons in Colorado, with increased risk of preterm birth, gestational diabetes, and gestational hypertension (2). Further, wildfires are associated with adverse mental health (16, 35).

Understanding the populations that are most affected by wildfire smoke exposure is important for targeting public health adaptations to increased wildfires under a changing climate, yet very few epidemiological studies have investigated differential risk (104). There are higher rates of emergency department visits for asthma among females compared to males (55, 160). Studies investigating differential impacts by age are not consistent except for studies of asthma exacerbations that showed the highest risks for the elderly, followed by working age adults, and the lowest risks among children (15). Very few studies have investigated differential impacts of wildfire smoke by race, ethnicity, or socioeconomic status (SES) (104, 145), but there is some evidence of stronger associations between wildfire smoke and visits to the emergency department and hospitalizations in lower-SES neighborhoods (146).

Two studies projected the health risks of air pollution from wildfires under climate change, with one focused on the western United States (115) and the other on the continental United States (52). The latter study projected that overall $PM_{2.5}$ concentrations would decrease owing to decreases in emissions from anthropogenic sources but that fire-related $PM_{2.5}$ emissions could offset some of these gains in some regions. The net result projected under high GHG emissions is that fire smoke could be the dominant source of annual average $PM_{2.5}$ exposure in all regions by the year 2100. Although $PM_{2.5}$ mortality is projected to decrease by 2100, the proportion of deaths due to wildfire-associated $PM_{2.5}$ could increase (52).

Wildfires can present many challenges to health systems and impact the operations of health facilities through increased stress on services, health risks to staff and patients, and damage to infrastructure and operations (e.g., smoke inundation of hospitals and clinics). In 2017, severe wildfires in the interior region of British Columbia, Canada, affected 19 health facilities or sites and led to the evacuation of 880 patients, caused the displacement of 700 health professionals, and cost the Interior Health Authority CAN$2.7 million (164a).

3.5. Mental Health

Extreme events and disasters can exacerbate or compound preexisting mental health needs or trigger new mental ill-health outcomes, acute or chronic and long-term (24). Substantive socioeconomic implications from destruction to homes, businesses, and communities can lead to financial stressors and community strain that can increase the likelihood for domestic or community-based violence (24). At the same time, many people exposed to extreme events demonstrate resiliency and experience very little to no mental distress (14). People exposed to extreme events also may experience a mixture of affirmative mental health outcomes like compassion, growth, and altruism as communities band together in the wake of a disaster and challenging mental health outcomes like stress, fear, anxiety, and compassion fatigue (71).

Climate change–related hazards (e.g., drought, sea-level rise, melting permafrost, and extreme weather events) affect well-being (24, 71). Impacts to mental well-being include a loss of a sense of place, referred to as solastalgia, and anxiety and grief related to a changing climate, often referred to as ecoanxiety, climate anxiety, climate trauma, ecogrief, or climate grief (3, 24, 30). These experiences are often framed as normative responses, so it is important to look broadly at the full range of mental health outcomes related to climate change and not to necessarily pathologize these outcomes (70). Those most at risk are those who already experience health inequities based on the social, environmental, and biological determinants of health (70).

Enhancing mental health literacy, access to mental health care and culturally relevant care, and a sense of community, as well as integrating mental health indicators into climate change and health assessments, support psychosocial adaptation to a changing climate (70). The cobenefits of climate change mitigation for mental well-being include active transportation that enhances mood and increased green space that can reduce stress levels and promote well-being through connections with the natural environment (80).

4. INCREASING THE RESILIENCE OF HEALTH SYSTEMS

A global adaptation gap exists in efforts by health-sector officials to prepare for climate hazards such as weather-related disasters (166). Multiple opportunities exist to increase the climate resiliency of health systems and health facilities (182). Ministries and departments of health generally have programs with responsibility for managing disaster risks. However, these programs were developed without explicitly incorporating climate change (e.g., considering the implications of projections of future risks), meaning they may be ill-equipped to manage the health impacts associated with increases in the frequency and intensity of extreme events. Furthermore, some climate-related hazards, like extreme heat, fall outside of the official or perceived domains of responsibility for professional disaster management agencies or are approached through a distributed governance model with no designated lead entity (68). The key policy levers for health-sector decision makers are climate change adaptation, GHG mitigation, and disaster risk management. To date, cross-sector adaptation efforts have been largely incremental, adjusting existing systems while maintaining their core structure and function. However, given the limitations of these systems to meet the increasing demands associated with experienced impacts or anticipated climate-related risks, transformational adaptations that seek to fundamentally change these systems are necessary (133).

Disaster risk management is often considered separately from adaptation, although there is growing integration between them to maximize protection of populations and health systems (8). Successful incorporation of climate change requires developing, implementing, evaluating, and modifying policies and programs to increase their effectiveness for what will be a very different future.

4.1. Adaptation and Mitigation

A major focus of adaptation is on promoting the development of climate-resilient health systems (182). Building blocks of such systems include (*a*) a knowledgeable health workforce with the tools needed to promote climate resilience; (*b*) health information systems that support effective management of the health risks of extreme events; (*c*) effective service delivery, including preparation for emergencies; and (*d*) adequate financing (40). Preparing health systems for climate extremes and disasters requires robust information about current impacts and projected risks to inform adaptation planning (182). A critical step is developing a health national adaptation plan (HNAP) or subnational plan, including conducting a vulnerability and adaptation assessment (181). An HNAP helps ensure that the health risks of climate change are prioritized at community to national levels of decision-making to reduce vulnerabilities and build needed capacity and resilience.

The process of developing an HNAP should be integrated with adaptation planning in other sectors (e.g., disaster risk management committees, hydro-meteorological services, agriculture, and water) and with development planning processes (181).

Vulnerability and adaptation assessments should include analyses of the ability of health systems and services to withstand extreme events and disasters; stress tests can provide information to officials to facilitate preparing for and managing more severe climate change–related shocks and stresses (39). The health impacts of extreme events can compound until a tipping point is reached, resulting in significant changes in the affected system and more severe population-health outcomes. This was illustrated in 2017 when Hurricane Maria resulted in an estimated 4,645 excess deaths in Puerto Rico, with a third of those deaths from delayed or interrupted health care (101).

Health-sector officials have a wide scope to help reduce the future magnitude and pattern of extreme weather and climate events through the reduction of GHGs given the large carbon footprint of health-related activities related to energy, food, anesthetic gases, and transportation (94). In addition, significant health cobenefits (e.g., better respiratory and cardiovascular health through improved air quality) that help build resiliency can accrue through well-designed GHG mitigation efforts (65).

4.2. Disaster Risk Management

Disaster risk management includes "strategies, policies, and measures to improve the understanding of disaster risk, foster disaster risk reduction and transfer, and promote continuous improvement in disaster preparedness, response, and recovery practices" (168). Health-emergency management policies and actions to reduce risks from climate-related hazards can contribute to adaptation and resiliency-building efforts if they are informed by climate change considerations and information. Opportunities to integrate disaster risk management and climate change adaptation include alignment of financing strategies and mechanisms; development of dual- or multipurpose government policies and strategies; integration of both disaster risk management and adaptation into national and international organizations, institutions, and programs; application of widely adopted disaster risk management participatory hazard assessment approaches; and promotion of locally led interventions or frameworks that comprehensively address disasters from all hazards and environmental problems (82). Examples of specific disaster risk management measures that may concurrently foster climate change adaptation include heat wave warning and response programs, infrastructure resilience, and overall disaster preparedness (167).

Disaster risk management strategies should consider local context and place emotional and cognitive experiences and identities that link people to places (13). Place attachment has both positive and negative relationships with natural environmental risk perception and risk coping, which have the potential to influence the effectiveness of disaster risk management strategies (13). For example, strong place attachment has been negatively associated with willingness to evacuate and relocate (13).

Community-based disaster risk management strategies are necessary to address community-specific risks, integrate priorities for vulnerable groups, and acknowledge community assets and coping strategies (155). Given the importance of implementing adaptation measures at the local level, local public health agencies are uniquely positioned to build resilience (95, 96). Public health actors are well positioned to address climate change due to their professional responsibilities, experience, and expertise (8). Prior to a disaster, community-focused public health strategies can reduce climate disaster risk by reducing human vulnerability (96). Furthermore, public health activities implemented in the context of disasters—including rapid needs assessments, surveillance, and epidemiological studies—will become more important as the frequency of climate-related hazards increases (5).

An opportunity for state and local health departments to engage in climate change adaptation activities is to build on existing all-hazards disaster preparedness and response capacity (36). A key action to close the health adaptation gap related to heat and weather extremes is to integrate disaster risk management into all health policies and to integrate health into disaster risk management plans and strategies (166). Additional collaborative opportunities, partnership, communication (within and across sectors), resources, authority, training, and capacity for state and local health department engagement in climate change adaptation activities are necessary (36).

4.3. Economic Considerations

Cross-disciplinary efforts combining population health, economics, and climate to value the adverse risks of exposures and benefits of adaptation strategies are a priority (83). While the reported estimates of economic losses associated with extreme weather events nationally (132) and globally (130) are huge, they provide limited information on the health impacts. The challenges in attributing health consequences to specific extreme events and/or variability in meteorological factors (e.g., temperature, precipitation, and humidity) limit economic valuation.

To assess the direct health costs associated with extreme events, studies used a combination of cost-of-illness measures (financial costs of utilizing medical care and pharmaceuticals) and willingness-to-pay-based estimates (e.g., value of statistical life) (147). Studies using reported medical diagnoses to estimate the changes in morbidity and/or mortality associated with a sample of climate-sensitive extreme events reported substantial health care costs (110). A statistical approach to determine the attributable fraction of morbidity and mortality associated with a specific environmental exposure, mostly extreme temperature (116), can be used in conjunction with climate and demographic projections to estimate future health care costs (108). Estimates of the economic burden in these studies are useful in informing local-level decision-making to prevent adverse outcomes (176).

Extreme temperatures impact health outcomes like labor productivity that have welfare implications for families, labor wages, and economies (102). Computable general equilibrium models can assess the economy-wide impacts of future climate scenarios based on a broader suite of human welfare indicators, such as nutrition (69). There is growing evidence of the economic impact of hurricanes on hospital evacuations and health care facilities (163).

In spite of the uncertainty and assumptions around capturing the health benefits and costs of climate impacts and solutions embedded across different sectors of the economy, these analyses provide critical inputs to policy decisions (66). The economic perspective is useful in choosing among alternatives given resource constraints. Coupled with spatially resolved information on the risk of climate hazards and vulnerable populations, this prioritization of health interventions could aid public health practitioners in implementing targeted interventions (120). Complementary to the health cobenefits of adaptation and mitigation strategies, health interventions related to water and sanitation could have larger societal benefits (121).

While the success of efforts to reduce GHGs and avoid increases in extreme weather events is uncertain, the projected economic benefits of avoided mortality are significant (169). From an equity perspective, it is important to note that the economic consequences for specific hurricane-affected communities could be substantial even though the macroeconomic consequences may appear small in these large-scale assessments of climate impacts (31).

5. CONCLUSIONS

The coming decades will be characterized by increases in the frequency and intensity of many types of extreme weather and climate events, with the potential for significant impacts on populations and health care systems worldwide. Rigorous research conducted before, during, and after disasters can improve assessments of population health and health system vulnerabilities and capacities and help evaluate the effectiveness of integrated disaster risk management and adaptation strategies (126). Such strategies can be cost-effective; examples include city-level early warning systems (42), community intervention programs (88), individual-level occupational health interventions (162), and initiatives to build health facility resilience (72). The evidence base of additional health interventions that can cost-effectively reduce the health risks of extreme events needs to be expanded.

A major challenge is the mismatch between research needs and the funding priorities of major health institutions and organizations (142). Overall funding for health adaptation is negligible (<1% of international climate adaptation finance). This led the 2018 Adaptation Gap Report to conclude "there is a significant global adaptation gap in health, as efforts are well below the level required to minimize negative health outcomes" (166, p. XIV). Research funding to understand and manage the health risks of climate change is even smaller (41, 62). Underlying reasons include the original framing of climate change as an environmental problem instead of as a whole-of-society challenge. Although the situation is changing, there is a tendency for health funders and health systems to continue to consider climate change as one of many environmental issues, such as nitrogen deposition in our waterways, where any additional cases of morbidity and mortality could be managed in the normal course of business by health care and public health institutions. Because the health risks of a changing climate are not novel, funders do not see the need for additional research and intervention. Climate change is not yet consistently viewed as core to population health and is not widely considered a current, urgent issue. Another reason funding is so low is that health funders and institutions take a primarily reductionist, top-down perspective to health issues, focusing on proximate, individual-level risk factors (125). This medical-model view of population health has been highly successful in understanding and controlling many major causes of preventable morbidity and mortality but will be insufficient to protect health and well-being in the face of the significant social and environmental changes expected over the coming decades (41). Changing these mindsets through education and capacity building is vital. Investments in research, adaptation implementation, and evaluation guided by decision maker needs can increase resilience, helping to protect the most vulnerable individuals and health care infrastructure while addressing inequities in disaster risk, even as the climate changes.

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AUTHOR CONTRIBUTIONS

K.L.E. conceptualized the article; K.L.E., J.V., J.W.B., J.E.B., D.M.H., N.A.E., K.H., C.E.R., S.S., J.S., and P.B. contributed to the writing, editing, revising, and finalizing of the manuscript.

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Review Article

The greatest Dengue epidemic in Brazil: Surveillance, Prevention, and Control

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ABSTRACT

In this review, we discuss dengue surveillance, prevention, and control measures in Brazil. Data on dengue epidemics between 2000 and 2024 indicates an increase in the number of dengue cases and deaths. Global climate change is a key driver of this growth. Over the past 25 years, nearly 18 million Brazilians have been infected with the dengue virus, and the highest number of dengue cases in Brazil's history is projected to reach 2024. Dengue mortality in Brazil increased geographically over time. As of June, there were approximately 6 million probable cases and 4,000 confirmed deaths in Brazil, which represents the greatest dengue epidemic to date. Several technologies have been developed to control *Aedes aegypti*, including the deployment of *Wolbachia*-infected mosquitoes, indoor residual spraying, sterile insect techniques, and mosquito-disseminated insecticides. The Ministry of Health recommends integrating these technologies into health services. Brazil is the first country to incorporate the Takeda vaccine into its public health system, and the Butantan vaccine is currently undergoing Phase 3 clinical trials. Increasing the vaccination coverage and implementing novel *Ae. aegypti* control technologies could reduce the number of dengue cases in Brazil in the coming years. Community activities such as home cleaning and elimination of potential mosquito breeding sites, facilitated by social media and health education initiatives, must continue to achieve this reduction. Ultimately, a multisectoral approach encompassing sanitary improvements, mosquito control, vaccination, and community mobilization is crucial in the fight against dengue epidemics.

Keywords: Dengue. Epidemiology. Mosquito control. Prevention. Brazil.

INTRODUCTION

Dengue is an infectious disease caused by four related viruses that are transmitted by *Aedes* mosquitoes. Approximately half of the global population is at risk of dengue infection, with 100–400 million people developing deadly fever and 40,000 deaths from dengue each year[1]. *Aedes aegypti* is increasingly present in urban areas[2–4] and the number of dengue cases in the Americas has increased from 1.5 million in the 1980s to 16 million in the decade 2010-2019[5]. In Brazil, the first epidemic began in 1986[6] and a rapid expansion of dengue has been observed recently[7]. The four serotypes of the virus circulate simultaneously, and mosquitoes are present in every region of the country[8]. Between 2008-2019, approximately 6,429 Brazilians died of dengue[9]. Based on epidemiological data from June 2024, there were 10 million probable cases of dengue and approximately 5,000 confirmed deaths reported in the Americas[5] and Brazil is currently experiencing its greatest dengue epidemic to date. As of June 15th, there were approximately 6 million probable cases and 4,000 confirmed deaths[10].

Dengue epidemics have multiple causes, including rising temperatures and rainfall due to climatic changes, inadequate sanitation, insufficient numbers of health workers, poor efficacy of government interventions to control *Ae. aegypti*, discontinuity of activities throughout the year, population difficulty in eliminating domestic breeding sites, the resistance of mosquitoes to insecticides, and the presence of four serotypes circulating simultaneously in endemic countries that favor reinfection[7]. Furthermore, *Ae. aegypti* females can lay eggs in many different water-holding container habitats with different degrees of

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cleanliness, resist drought, adapt to warming climates and increasing altitudes[11]. However, new technologies have been developed for surveillance, control, and prevention of dengue[12–19]. Integrated vector control methods, including mosquito control technologies and vaccines, offer a critical boost to combating dengue epidemics. However, active public and government engagement must complement these efforts. This requires educating and mobilizing the population to maintain cleanliness in their homes and eliminate potential breeding sites. Continuous outreach through social media, community-based initiatives like "D-Day against Dengue," and creative public awareness campaigns are essential to this multisectoral approach[16,17].

We reviewed documents published on dengue in Brazil over the last 25 years, updated the epidemiological scenario, and provide a critical analysis of strategies for the surveillance, prevention, and control of the disease in Brazil. Our narrative review[20] provides a critical overview of these subjects and their perspectives regarding Brazil. We included epidemiological data from the Notifiable Diseases Information System (SINAN, accessible at: ftp://ftp.datasus.gov.br/dissemin/publicos/SINAN/), Ministry of Health of Brazil. The epidemiological scenario was based on data from the 21st century. We excluded data prior to 2000 because they were not available in the public database. Our search included the terms "dengue" and "Brazil" and all types of references related to the topics (original articles, reviews, commentaries or opinion pieces in PubMed, gray literature, reports, or digital media in English, Portuguese, and Spanish) were considered. This review also incorporated additional references identified through manual search. This review describes the increase in dengue cases and deaths in Brazil and the geographical expansion of dengue cases and deaths by age group. Considering that the classification of Dengue cases has changed over the years in Brazil, we used the following categorization: dengue A which includes the old definition of classic dengue and the current definition of dengue; Dengue B, which includes dengue with complications, dengue with alarm signs, and dengue hemorrhagic fever types I and II and Dengue C, which includes severe dengue and dengue shock syndrome, which are dengue hemorrhagic fever types III and IV. These definitions are available in the epidemiological and health surveillance guides as well as in the notification forms and data dictionary of the SINAN. Global climate change has been highlighted as one of the main causes of this growth, and new technologies for controlling *Ae. aegypti* are described. In addition, advances in dengue vaccines and prospects for surveillance, control, and prevention are outlined.

SURVEILLANCE

Dengue has been a notifiable disease in Brazil since 1961 (Decree nº 49.974-A, January 1961). However, electronic registration through the Notifiable Diseases Information System was only implemented in 1993. Currently, the system consolidates records across the country into a centralized database at the federal level. Dengue cases without complications are transferred weekly, whereas severe cases and deaths must be transferred within 24 h of detection by the health service. Brazil is currently experiencing an unprecedented dengue epidemic in 2024. The historical series of dengue epidemics in Brazil between January 2000 and June 2024 (**Figure 1**) showed that until 2012, the number of cases was close to or below 200,000. An epidemic with more than 400 cases/100,000 only occurred in 2024. The highest number of dengue deaths/1000,000 inhabitants in the

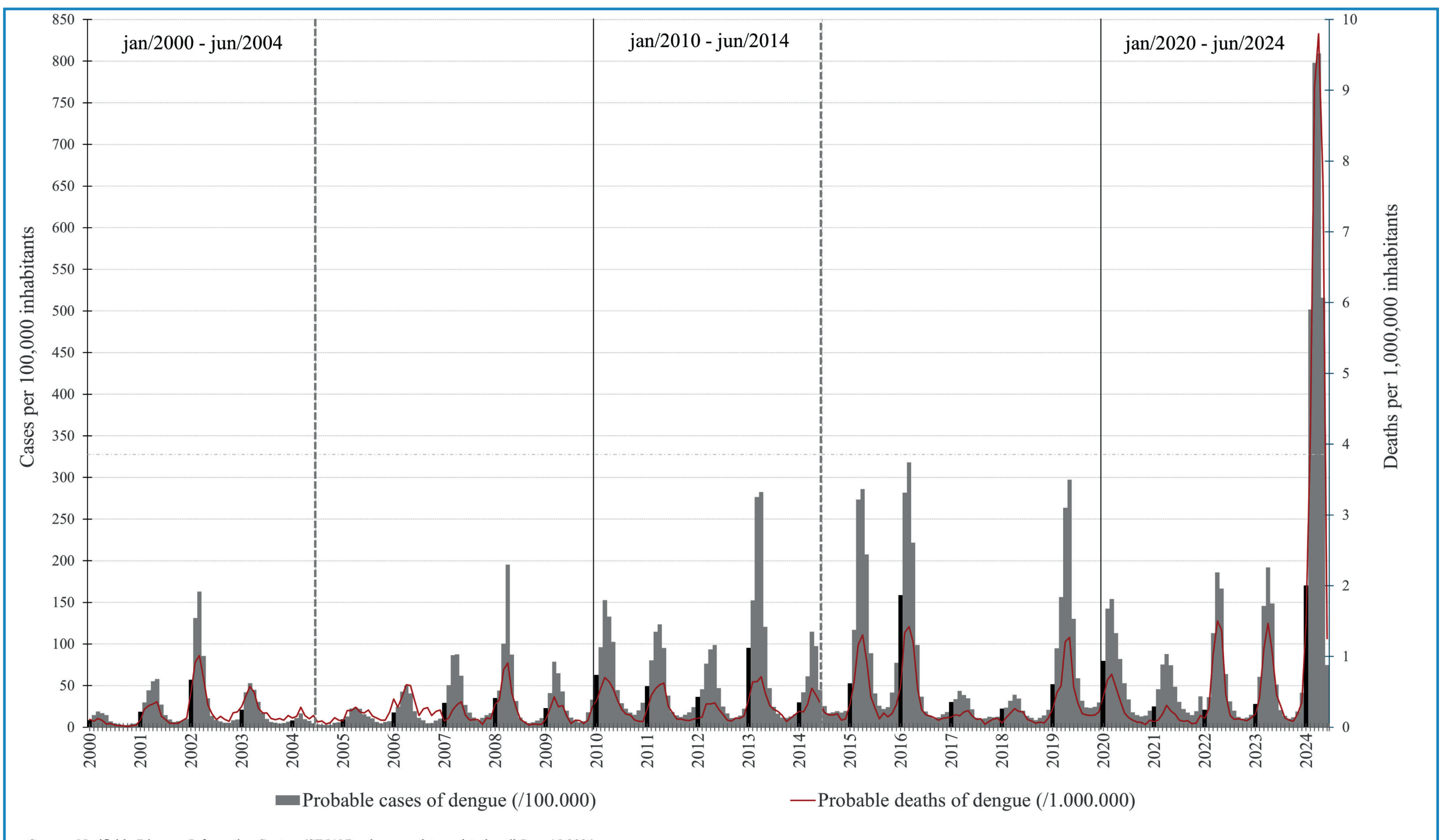


FIGURE 1: Dengue epidemics in Brazil between 2000 and 2024. The historical series shows probable cases of dengue/100,000 (gray) and probable deaths of dengue/1000,000 inhabitants (red) recorded by month in each year. The small black bars indicate the probable cases of dengue/100,000 in January for each year. The longer black bar indicates the decades. The vertical dotted lines mark the first 4.5 years of each decade.

history of the disease in Brazil is projected to reach 2024. We analyzed epidemiological data from the first 4.5 years of each decade to establish equivalence with the 2020-2024 period. Between January 2000 and June 2004, 2,073,194 probable dengue cases were reported in Brazil. In the same period of the following decade, between January 2010 and June 2014, there were 6,260,684 probable cases, representing a percentage increase of approximately 202% compared to the previous period. In the most recent decade, between January 2020 and June 2024, 11,236,426 probable cases of dengue were recorded, representing a percentage increase of about 442% compared to the period 2000 to 2004 and an increase of about 80% compared to the period 2010 to 2014. These data highlighted the progression of dengue during these periods (**Figure 1**, **Supplementary file 1**).

There is a marked peak in dengue cases with warning signs by 2024 (**Figure 2**). The number of dengue deaths under investigation and confirmed deaths from dengue per 1,000,000 inhabitants in Brazil will increase significantly by 2024 (**Figure 3**).

Preliminary data for 2024 up to June 15th shows ~ 6 million probable cases of dengue, five times the number in the same period in 2023. The average incidence of dengue in the first three months of 2023 and 2024 is 69 and 187 cases per 100,000 inhabitants, respectively. Additionally, in the first six months of 2024, there were approximately 80,000 cases with warning signs and other complications and 6,791 severe cases of dengue (**Supplementary file 1**), which is 5-6 times higher than the numbers observed in the same period in 2023. Additionally, the death rate was seven times higher in June 2024 than that in the same period in 2023. These data indicate a greater impact of the 2024 dengue epidemic. The historical record of dengue cases with warning signs and other complications, dengue deaths, or deaths under investigation shows that 2024 has reached much higher numbers than all other dengue epidemics in Brazil (**Figures 1-3**). We evaluated deaths under investigation from previous years to show that not all cases were closed because some municipalities do not have a committee to investigate deaths. Approximately 90% of the deaths under investigation are already dengue deaths and have not been reclassified, owing to operational limitations at the municipal level. During the latest epidemic (until June 2024), the number of dengue deaths was higher among the elderly (**Figure 4**). This differs from the pattern observed in other epidemics, where severe dengue cases were higher among children aged 6-10 years[21]. These data suggest that targeting both the elderly and young age groups could help reduce severe disease outcomes.

Dengue serotypes have spread throughout Brazil[7], and the predominance of DENV-2 is possibly responsible for increased dengue mortality[22,23]. DENV-2 has emerged and caused epidemics in severe cases and hospitalizations[24,25]. Severe dengue includes multiple organ failure and renal involvement, and may be associated with increased mortality[25]. Experimental data show an increase in kidney weight in mice infected with DENV-2[26], and epidemiological data show that severe dengue is associated with DENV-2[27]. Dengue epidemics occur in different regions of the country, and cases of DENV-1, DENV-2, and DENV-3 have been reported in all states. DENV-4 cases were identified in the northern region and Rio de Janeiro[6].

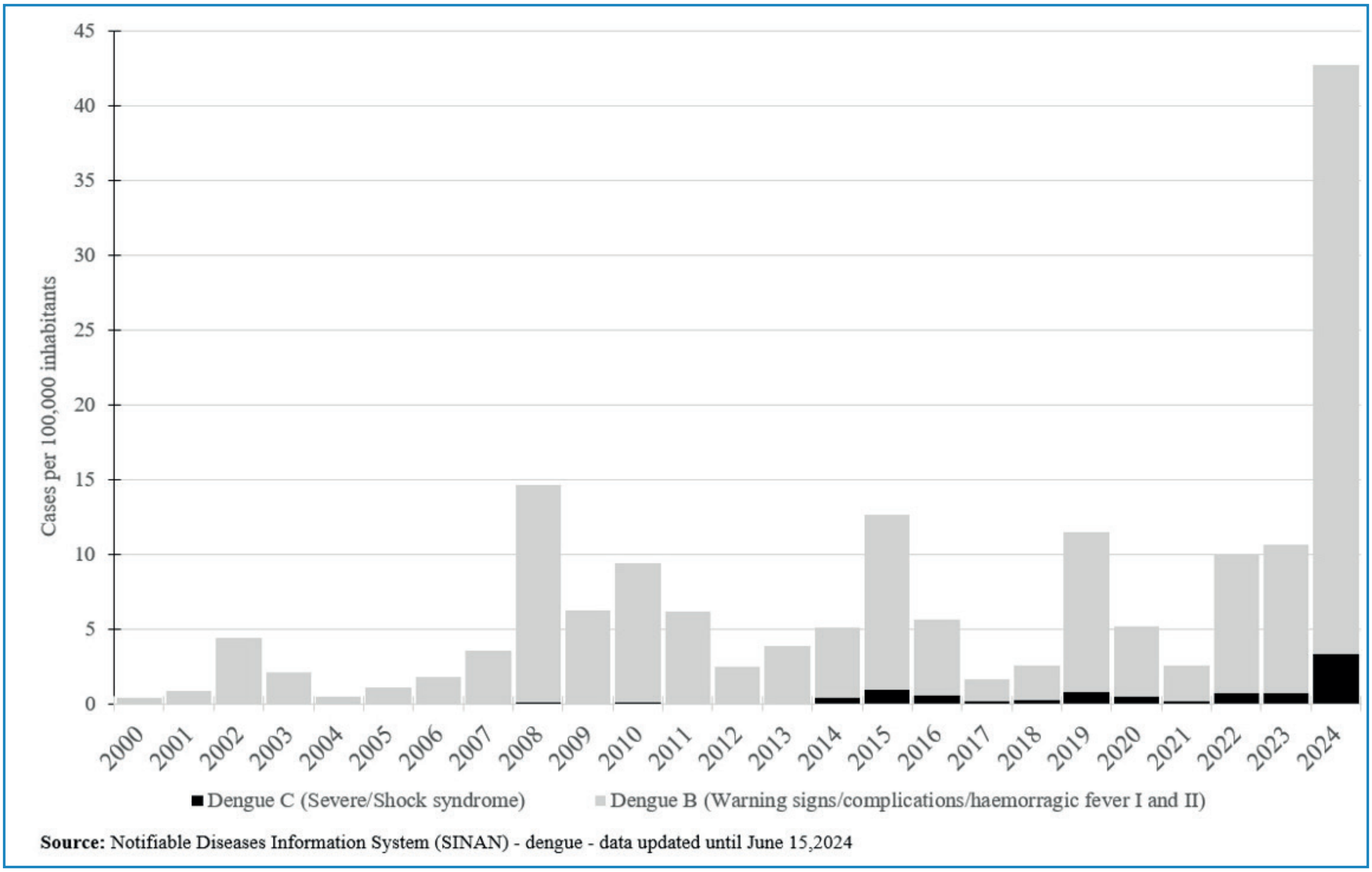
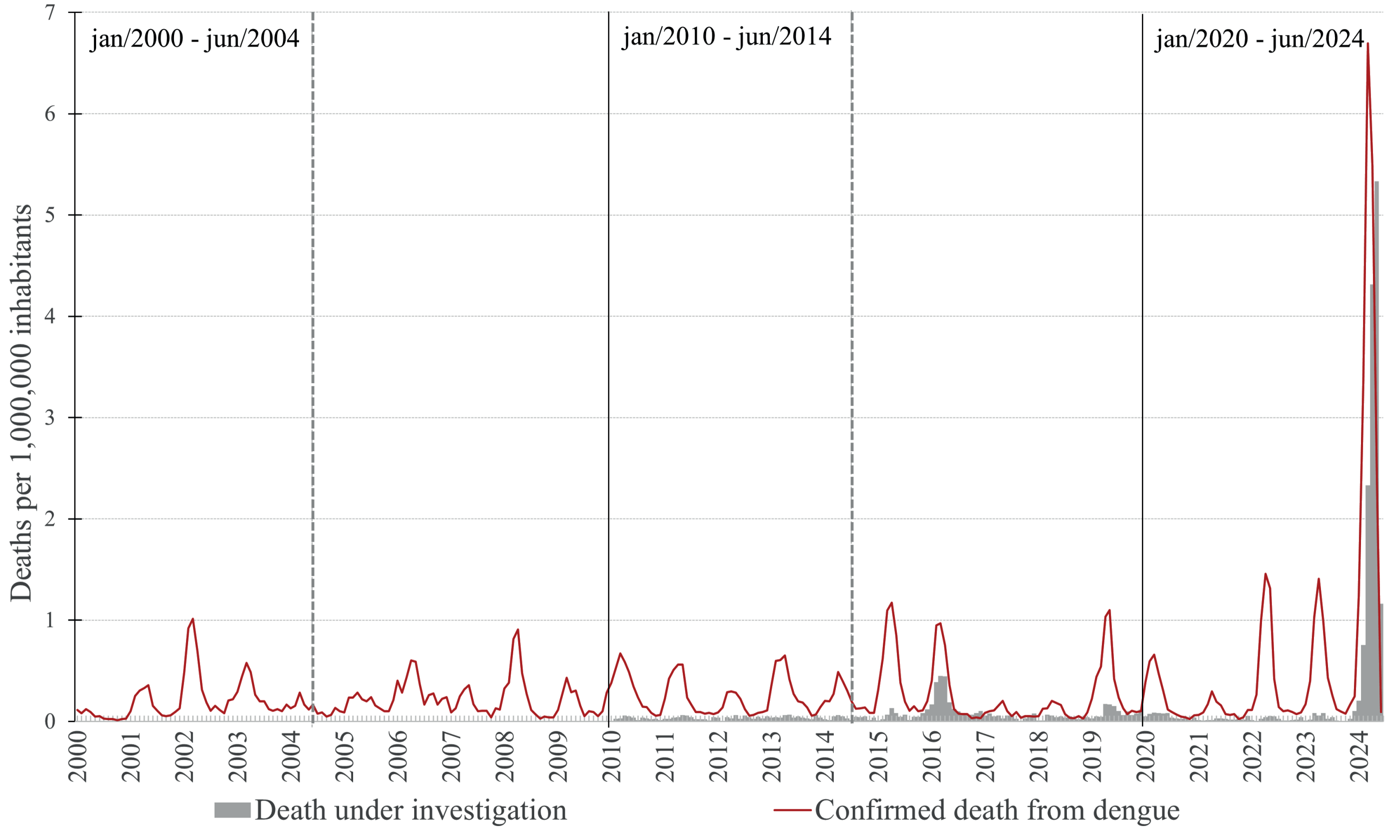


FIGURE 2: Number of severe/shock syndrome (black bars) and dengue with warning signs and other complications (gray bars) reported in Brazil between 2000 and 2024.



Source: Notifiable Diseases Information System (SINAN) - dengue - data updated until June 15,2024

FIGURE 3: Number of dengue deaths under investigation (gray) and confirmed death from dengue (red)/1,000,000 inhabitants in Brazil between 2000 and 2024. The longer black bar indicates the decades. The vertical dotted lines mark the first 4.5 years of each decade.

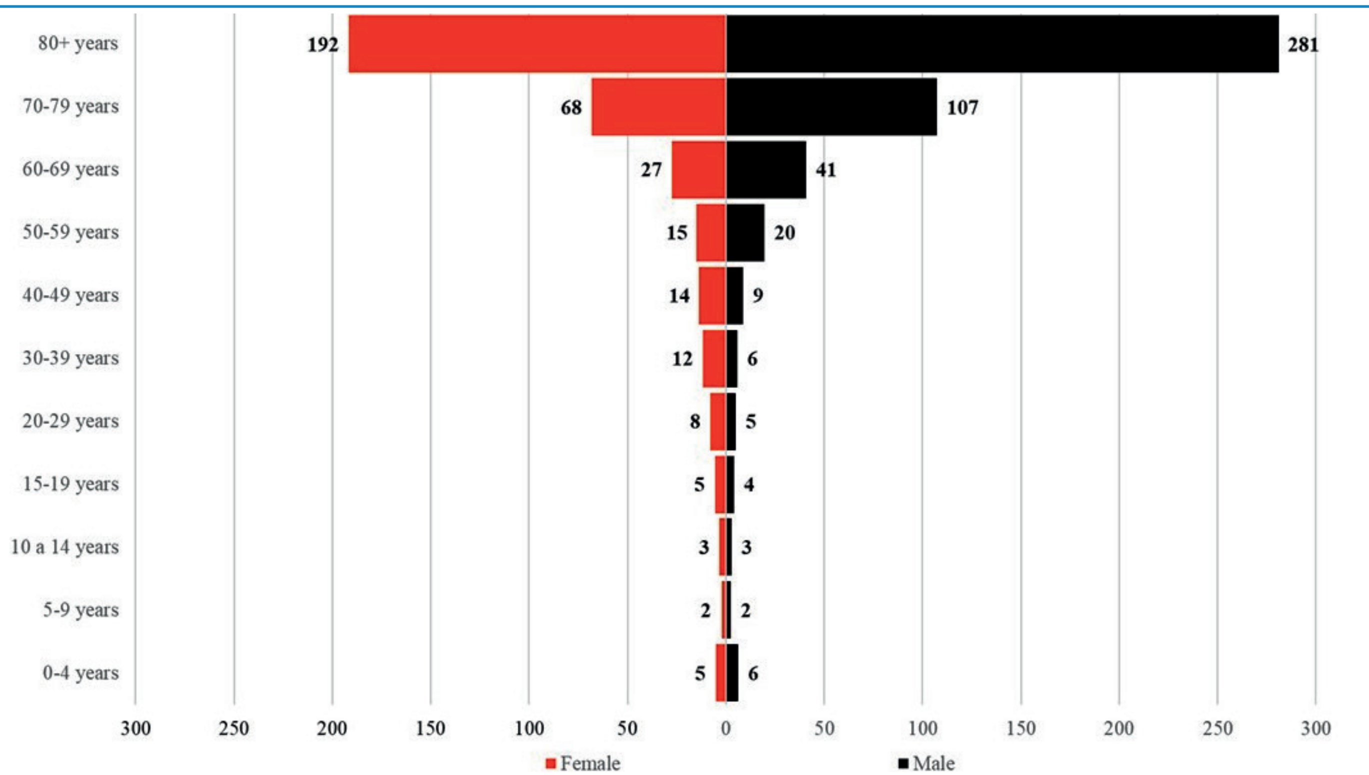


FIGURE 4: Dengue incidence rate reported in Brazil in 2024, until June. The bars represent the number of deaths by age/1,000,000 inhabitants and the color represents the sex (male: black, female: red). Source: Notifiable Diseases Information System (SINAN).

By 2024, emergency decrees were issued across 11 federal units, affecting 602 municipalities. **Figure 5** displays the mortality rates (per 1 million inhabitants) of each Brazilian municipality organized by health region for four years (2000, 2010, 2020, and 2024). The data reveal an increase in dengue mortality in Brazil over time. In 2000, the mortality rates were higher in more isolated healthy regions, excluding the south. From 2010 onwards, there was an expansion to the east and west of the country. Finally, in 2024, expansion to the south will become evident, as has already been observed[7]. Additionally, a higher mortality rate was observed in states such as Goiás, the Federal District, and Minas Gerais.

Mapping the dengue incidence and mortality rates in the country is crucial for targeting clinical management policies and reducing dengue hospitalizations and deaths in the future[6,28–30]. Brazil is a large country, and dengue occurs differently in various regions, states, and municipalities[31,32]. Recurrent annual dengue epidemics are currently common in less populated areas of Brazil that are free of dengue transmission[6]. There has been an increase in dengue deaths in Brazil since 1986[7] and our study shows that this trend has continued in recent years, with the worst year being 2024. In recent years, the central-west region has exhibited the highest dengue incidence and mortality rates. Epidemiological data indicated that municipalities that experienced an outbreak in the past were twice as likely to experience subsequent outbreaks[33]. Historically, the western Amazon, southern region, and northern coast of Brazil have been considered geographical barriers to dengue transmission. However, the historical series show that practically no area is protected against dengue. Climate change, mosquito adaptation, and growing urbanization with precarious housing and sanitation conditions in cities may also explain the higher occurrence of *Aedes* and incidence of dengue over the years[11,33–37]. The data revealed the spread of dengue to smaller municipalities in central-south Brazil, far from more urban centers, while larger cities were classified as having sustained transmission, which varies across Brazilian states, suggesting that other factors contribute to the rising cases in smaller towns[38].

Dengue fever has historically brought about substantial costs and societal impacts in Brazil[39]. Another critical aspect of the current public health challenge is the concurrent CHIKV outbreak, which has complicated the epidemiological landscape. This misclassification underscores the complexity of managing arbovirus outbreaks and the importance of accurate diagnostic capabilities to distinguish similarly presenting diseases. Moreover, the Brazilian Ministry of Health should improve the protocol for death confirmation and timely surveillance to reduce delays in death investigations. This can be achieved by strengthening

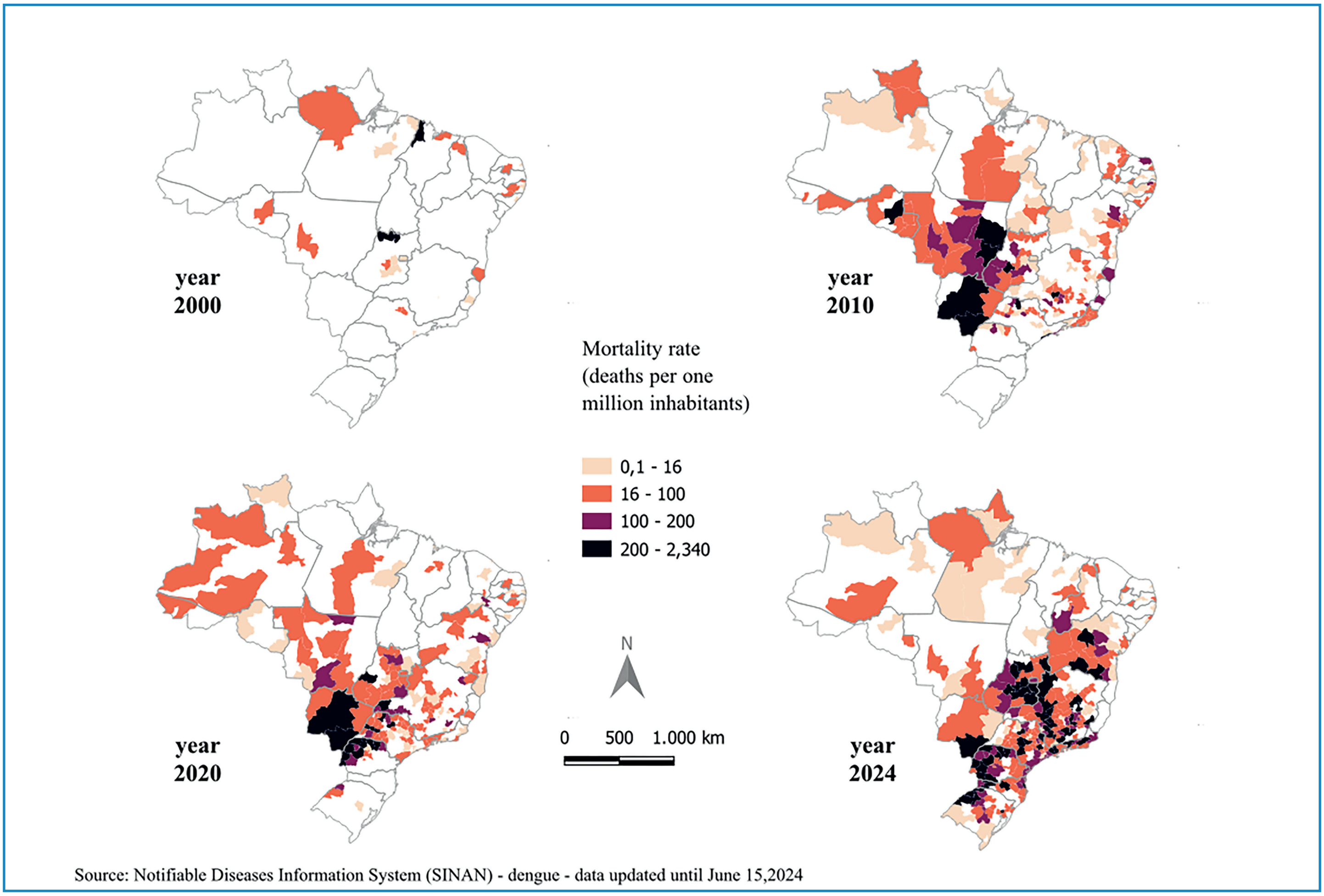


FIGURE 5: Mapping dengue mortality in Brazil. Maps show the mortality rates (/1 million inhabitants) of each Brazilian municipality (by health region) in four periods (2000, 2010, 2020 and 2024). The color gradient represents the variation in the mortality rate. These maps were created using QGIS (version 3.36.1) and SINAN mortality data until June 2024.

the surveillance team to complete the investigation in a timely manner. Such intricacies highlight the need for a more nuanced understanding of the severity of an outbreak and necessitate adaptive strategies for disease management and response.

The impact of climate change on the global spread of dengue fever, particularly in Brazil, is a critical issue requiring comprehensive understanding and action[40]. Climate change and its associated phenomena, such as rising temperatures, altered precipitation patterns, and extreme weather events, have profound implications for the life cycle and distribution of *Aedes* mosquitoes, the primary vectors of the dengue virus[41]. Warmer temperatures can accelerate mosquito breeding, increase biting rates, and shorten the viral incubation period within mosquitoes, potentially leading to higher transmission rates of dengue fever[42]. For instance, climate and weather alterations, including temperature, rainfall, humidity, and El Niño, have been identified as critical factors affecting the reproduction, survival, and geographic distribution of mosquitoes, ultimately influencing their capacity to transmit pathogens[33,43]. Dengue surveillance has been supported by nowcasting and forecasting data[2-4,16] based on climate data, and mosquito and dengue distribution forecasts.

In Brazil, studies have utilized data mining techniques to investigate the recent expansion and exacerbation of the dengue incidence, revealing that prolonged temperature anomalies, urbanization, and previous circulation of the virus were significant contributors to the increased incidence in the central region of the country. The occurrence of dengue outbreaks was positively associated with the number of months per year with favorable temperature conditions for *Aedes* mosquitoes[33]. Areas at higher altitudes, once natural barriers to dengue transmission, have now become hotspots for the disease, demonstrating the changing dynamics of disease distribution in response to climatic shifts[40]. This expansion towards new areas, including higher altitudes and latitudes, underscores the influence of climate change on altering the landscapes of vector-borne disease risks, necessitating adaptive strategies for public health planning and vector control efforts[33].

VECTOR CONTROL

The World Health Organization (WHO) is urging the integration of new technologies into health services, including the stratification method, *Wolbachia*-infected mosquito deployment method[44], mosquito-disseminated insecticide strategy[45], intradomiciliary residual spraying[46], and sterile insect techniques, which are recommended by scientific evidence[12] and the Brazilian Ministry of Health[47].

Stratifying areas based on epidemiological and environmental data is the key to organizing dengue surveillance and control efforts. This approach considers the seasonal patterns of the disease and helps to optimize the use of local resources. Research has highlighted the importance of continuous disease monitoring, timely data analysis, and prompt action as essential components to effectively combat dengue in Brazil. ArboAlvo[48] is an example of a stratification analysis based on socioenvironmental indicators recommended by the Brazilian Ministry of Health.

Releasing *Ae. aegypti* infected with *Wolbachia* is a promising strategy. Over time, the proportion of mosquitoes carrying *Wolbachia* tends to increase until the entire mosquito population was infected. *Wolbachia* reduces the lifespan of mosquitoes by 50% and inhibits the development of dengue virus within them[49]. This technology has been successful in reducing dengue incidence in Australia[50] and Indonesia[44]. Few randomized trials have evaluated the control methods for *Ae. aegypti*, without the use of the gold standard endpoint for virologically confirmed dengue. The results of a single trial conducted in Yogyakarta, Indonesia demonstrated the efficacy of *Wolbachia*-infected *Ae. aegypti* mosquitoes to control dengue transmission. The study demonstrated the significant potential of the *Wolbachia* method in public health, with a 77% reduction in virologically confirmed dengue cases and an 86% reduction in hospitalizations for dengue[36]. This intervention was equally effective against all four dengue serotypes, indicating its robustness and protective efficacy. In Rio de Janeiro, Brazil, the release of *Wolbachia*-infected *Ae. aegypti* resulted in 38%[51] and 69%[52] reduction in the incidence of dengue, respectively. Establishing stable *Wolbachia* strains in geographically diverse urban settings, such as Rio de Janeiro, appears to be more challenging than in other locations[51]. The release program requires specialized infrastructure in the municipalities, but it is likely to be a cost-effective strategy in the Brazilian context, considering that alternative scenarios have shown a favorable return on investment with a positive benefit-cost ratio[53].

The mosquito-disseminated insecticide strategy is a low-cost technology for controlling *Ae. aegypti* breeding sites. The technique is based on the deployment of dark plastic pots filled with water (dissemination station, DS hereafter), in which a larvicide (an insect juvenile hormone analog, such as pyriproxyfen) is impregnated in a cloth that covers the pot internally. When mosquitoes land on DS, the larvicidal particles stick to their bodies and are transferred by the mosquitoes themselves to other larval habitats[54,55]. DS has yielded promising results in trials at the scales of neighborhoods[45] and towns[56]. Garcia et al.[57] using a cluster-randomized controlled trial with 16 months of field data and a rigorous statistical modeling strategy and showed that DS can significantly reduce adult mosquito densities by 66%. Moreover, DS can block the transmission of mosquito-borne viruses[56]. Because of the low cost and elimination of hidden, difficult-to-access breeding sites, DS should be adopted by control services, as recommended by the Ministry of Health, as it is an easy method to be executed by health agents who deal with vector control. This method should be used along with other vector control initiatives, and future studies should evaluate the effectiveness of DS on the incidence of dengue[47].

Intradomiciliary residual spraying involves the application of residual insecticides to the interior walls of buildings and is commonly used to control vectors of malaria, Chagas disease, and leishmaniasis. When mosquitoes land on walls, they are exposed to insecticides and die. Previous studies demonstrated that this method is effective against *Ae. aegypti* despite difficulties in training, equipment calibration, insecticide costs, and mosquito resistance to insecticides[46,58,59]. The Brazilian Ministry of Health recommends its use before the start of the epidemic period, especially in buildings with many people (schools, health units, and community centers)[47]. Currently, the insecticide Fludora® Fusion is recommended for indoor residual spraying against the *Ae. aegypti* mosquito. According to a technical report, the Ministry advises that this residual application should be conducted every two months, and periodic evaluation and monitoring efforts should be implemented to assess the efficacy of this control activity[47].

The use of sterile insects is another strategy recommended by the Ministry of Health. This technique is based on the release of *Ae. aegypti* sterile males in an area, with the objective of promoting the copulation of these males with females in the area and making the offspring unviable. Despite advances in the development of this technique and examples of successful application[60], its expansion to larger areas depends on optimizing protocols for handling, transporting, and releasing male mosquitoes[61]. This tool is indicated in areas where mosquitoes are highly resistant to insecticides and periodic releases of males are available[47].

Finally, control of *Ae. aegypti* must be planned according to the local health structure and based on surveillance data that can indicate the best control strategy, or even the use of combined strategies, including the eco-social context. There were no silver bullets to control *Ae. aegypti*. Brazil has 5,700 municipalities with different socioeconomic, geographic, and climatic characteristics; even within a single municipality, there are variations. In addition to inter- and intra-urban heterogeneity, transmission dynamics are influenced by the patterns of population mobility and the large number of asymptomatic infected individuals circulating, which enhance mosquito infection and dengue transmission. Therefore, analysis of entomological and epidemiological data over a short period is crucial. Moreover, stratification analysis is important for selecting the appropriate strategy or best combination of strategies for each municipality[62]. In this integrated strategy, the Ministry of Health is the key to fostering the intersectoral actions needed to plan, finance, and implement priority activities outlined in municipal control, as proposed in the multisectoral approach to the prevention and control of infectious and vector-borne diseases[63,64].

PREVENTION

Development of a dengue vaccine has been a noteworthy endeavor in the field of infectious diseases. Sanofi's Dengvaxia was the first study to make significant progress in providing partial protection against four dengue virus serotypes[65]. Its development represented a significant milestone in dengue prevention. However, the effectiveness of the vaccine varies by serotype, and was later found to be associated with severe dengue in seronegative individuals, thereby limiting its widespread use[13]. The potential consequences of a fully effective vaccine for all four serotypes are substantial and promising for reducing the global burden of dengue, provided that it can overcome safety challenges and has broad serotype efficacy.

The Takeda vaccine candidate, TAK-003, demonstrated its potential through its tetravalent formulation. Early trial results were favorable, suggesting protection against multiple serotypes and a satisfactory safety profile[14]. The vaccine has received approval from Indonesian, European, and Brazilian regulatory agencies, and the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) group has recommended its use in areas with high disease prevalence in children aged 9–16 years, with vaccination initiated 1–2 years prior to peak incidence in this age group. In December 2023, Brazil became the first country to approve the incorporation of the vaccine into its public health system, with 8·5 million doses expected to be available by 2024. TAK-003 shows high efficacy against symptomatic cases and hospitalizations, particularly against dengue serotypes 1 and 2, although additional data on serotypes 3 and 4 in seronegative individuals are still pending[14]. A study was conducted in Dourados, Brazil, evaluating the influence of a planned mass vaccination program against dengue, aiming to immunize 100,000 individuals aged 4–60 years from January to August 2024. This study provides information on the impact of the mass vaccination campaign in a city with a population of 243,368. Furthermore, this study aimed to determine the effectiveness of the vaccine against dengue. If there are sufficient cases of autochthonous transmission of dengue serotypes 3 and 4 in Dourados over the next 5 years, the researchers plan to assess the vaccine's effectiveness against specific serotypes (JC, personal communication).

The Butantan Institute and National Institutes of Health (NIH) have collaborated to develop a live-attenuated vaccine candidate that could elicit a robust immune response against all four dengue serotypes. The findings of a phase 3 trial of the Butantan–Dengue Vaccine (Butantan-DV), a single-dose vaccine, have recently been published. The trial was conducted across various locations in Brazil and aimed to assess the vaccine's efficacy and safety in a diverse demographic spanning children to adults aged 2–59 years. The trial participants were stratified by age and randomized to receive either Butantan-DV or a placebo, with the primary objective of evaluating the vaccine's efficacy against symptomatic, virologically confirmed dengue of any serotype after 28 days of vaccination and to monitor safety up to 21 days post-vaccination. Over a 2-year follow-up period, Butantan-DV demonstrated a significant efficacy rate of 79.6%, with notable efficacy across different age groups and dengue serostatuses at baseline. The vaccine's efficacy was particularly strong against DENV-1 and DENV-2 serotypes, with rates of 89.5% and 69.6%, respectively[15]. Additionally, the vaccine was well tolerated, with adverse events more commonly reported in the vaccine group than in the placebo group within the first 21 days post-vaccination, but without serious safety concerns. These findings underscore the potential of Butantan-DV as a single-dose vaccine for significantly reducing the burden of dengue across a broad age range, marking a significant advancement in the global fight against dengue.

Although the development of a pan-serotype dengue vaccine has made significant progress, significant obstacles remain. Two of the most promising dengue vaccine candidates have limited efficacy and safety data for serotypes 3 and 4. Additionally, the risk of antibody-dependent enhancement (ADE), observed in Sanofi's Dengvaxia poses a challenge for the deployment of new vaccine candidates. It is crucial to recognize that only real-world data on the effectiveness and safety of both vaccines will fill this gap. Ensuring the absence of ADE in new vaccines is essential for the global acceptance of new dengue vaccines.

CONCLUSIONS AND OUTLOOK

Since 1986, Brazil has experienced frequent dengue epidemics, resulting in significant social and economic impact. A historical series of dengue epidemics between 2000 and 2024 indicated an increase in the number of dengue cases and deaths. Over the past 25 years, nearly 18 million Brazilians have been infected with the dengue virus, and the highest number of dengue cases in Brazil's history is projected to reach 2024. Data show that dengue mortality in Brazil has expanded geographically over time. Approximately 17,000 Brazilians have died of dengue in the last 25 years. As of June 2024, there have been approximately 6 million probable cases and 4,000 confirmed deaths in Brazil, representing the greatest dengue epidemic to date, with the co-circulation of different dengue serotypes. Global climate change is one of the main factors contributing to this growth. Viruses and mosquitoes have expanded their distribution throughout the country, causing epidemics in new areas where health systems are unprepared to handle a high number of cases. The Ministry of Health has promoted policies to manage dengue epidemics, including the introduction of the NS1 rapid test, establishment of a Center of Emergency Operations (CEO), financial transfers to support states and municipalities in arbovirus surveillance and prevention activities, and investments in innovation for dengue control[66–68]. The CEO was established by the Ministry of Health in February 2024 to improve planning and coordinate responses against arboviruses in an integrated and articulated manner with the states and municipalities throughout the country[68]. However, the CEO faces challenges in implementation in the municipalities due to the constant change of professionals and insufficient training of health teams to implement clinical management guidelines. Brazil needs to move towards more anticipated surveillance actions by applying nowcasting and forecasting models, considering that dengue is a seasonal disease, and healthcare should be prepared before the epidemic begins. An additional limitation regarding the impact of dengue fever in Brazil is the quality of diagnostic procedures, which encompasses inaccuracies in the identification of arboviral infections, as well as the recognition of the clinical signs and symptoms[8,67]. During significant dengue outbreaks, such as the 2024 epidemic, doctors may face substantial pressure to diagnose dengue cases. This could have led to an inflated number of reported cases, particularly in smaller municipalities, where many healthcare providers lack the necessary experience to accurately diagnose the disease. Consequently, training programs are recommended to improve the diagnosis and clinical management of dengue in the healthcare systems of the affected municipalities.

Our appraisal provides an updated synthesis of new technologies for the control *Ae. aegypti* in Brazil. Effective control is limited by the difficulty in identifying and controlling mosquito breeding sites, which is worsened by the resistance of mosquitoes to most insecticides. Most dengue mosquito breeding sites are situated within household premises, underscoring the need to collaborate with residents for effective control measures. Additionally, surveillance with active engagement of health workers throughout the year is critical for successful dengue management. These surveillance efforts should be supported by public policies aimed at enhancing professional development, communication, mobilization, and education of the population. Recently, new technologies have been developed to control *Ae. aegypti* and are now recommended by the Brazilian Ministry of Health. Integrating these technological solutions into the healthcare systems of Brazilian municipalities, tailored to their specific circumstances, represents the next critical challenge. While these technical interventions may assist in controlling future dengue outbreaks, their effectiveness depends on various external factors, including climate change, inadequate sanitation infrastructure, the introduction of new dengue virus serotypes in different regions, and the implementation of appropriate public health policies at the national, state, and municipal levels. Given the varying environmental, sociodemographic, and healthcare scenarios across municipalities in Brazil[38,69], it is crucial for managers to determine, with support from state and federal levels, which strategies to implement for dengue control (e.g., *Wolbachia* method, mosquito-disseminated insecticide strategy, and others recommended by the Ministry of Health). Otherwise, dengue control will continue to be based on traditional measures that have not been able to reduce the growth of mosquito populations and, consequently, dengue transmission. It is important to emphasize that the monitoring and control methods described here depend on the services provided by a group of health agents that must be expanded and valued. We believe that continuous education is needed to raise awareness of the importance of keeping residential environments free of *Ae. aegypti* breeding sites. It is important to note that most breeding sites were located in homes. To intensify the mobilization of the population, social media and collective actions, such as D-Day against Dengue, 10 minutes against dengue, and creative advertising campaigns, can be employed. Moreover, real-time mapping, social media platforms, such as DengueChat, and alerts to health professionals in at-risk areas are promising strategies for dengue surveillance and control[70,71].

Dengue vaccine development has made notable strides and has led to significant advancements in public health efforts to mitigate the global burden of dengue fever. This journey began with Sanofi's Dengvaxia, the first vaccine to offer partial protection against the four dengue virus serotypes. Despite its groundbreaking achievements, the varied efficacy of Dengvaxia among serotypes and its association with severe dengue in seronegative individuals limits its universal application. Takeda's TAK-003 emerged as a promising candidate, showcasing protection across multiple serotypes and a favorable safety profile, receiving endorsements from international and national regulatory bodies. The incorporation of TAK-003 into Brazil's public health system and planned mass vaccination programs represents a pivotal moment in dengue prevention efforts, especially against serotypes 1 and 2, with ongoing investigations of its efficacy against serotypes 3 and 4. Moreover, collaboration between the Butantan Institute and NIH has led to the development of the Butantan–Dengue Vaccine (Butantan-DV), a single-dose, live-attenuated vaccine candidate. Early phase 3 trial results in Brazil demonstrated its significant efficacy and safety across a wide age range, affirming its potential as a crucial tool in reducing dengue prevalence. Nevertheless, challenges remain, notably the need for comprehensive efficacy and safety data across all serotypes and avoidance of the antibody-dependent enhancement risks seen with previous vaccines. The path forward requires real-world data to confirm the effectiveness and safety of these vaccines, which is a crucial step toward achieving global acceptance and eliminating dengue as a public health concern. However, the vaccine supply and coverage also have critical limitations. Current dengue vaccine manufacturers are unlikely to produce sufficient doses over a subsequent two-year period to achieve satisfactory vaccination rates across the Brazilian population. Consequently, it is imperative to maintain conventional control strategies and amplify preparedness drills to evaluate state and local contingency plans, thereby mitigating the impact of future dengue outbreaks.

Increasing tetravalent vaccination coverage and the implementation of a novel *Ae. aegypti* infection control technologies could reduce the number of dengue cases in Brazil in the coming years. Community engagement through activities such as home cleaning and elimination of potential mosquito breeding sites, facilitated by social media and health education initiatives, must continue to achieve this reduction. Ultimately, a multisectoral approach encompassing sanitary improvements, mosquito control, vaccination, and community mobilization is crucial in the fight against dengue epidemics.

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Tuberculose, vulnerabilidades e HIV em pessoas em situação de rua: revisão sistemática

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RESUMO

OBJETIVO: Analisar, sistematizar e compilar os fatores de vulnerabilidade (social, individual e programática) associados à tuberculose e HIV em pessoas em situação de rua.

MÉTODOS: Revisão sistemática de literatura de publicações quantitativas sobre tuberculose em pessoas em situação de rua entre os anos de 2014 e 2020, seguindo o guia de recomendações PRISMA e, para análise de viés, a ferramenta *Joanna Briggs Institute Critical Appraisal.* Agrupou-se as publicações segundo as vulnerabilidades.

RESULTADOS: Entre 372 publicações encontradas, selecionaram-se 16 segundo os critérios de elegibilidade. Em 10 estudos, foi descrita ocorrência de tuberculose e HIV. Os fatores de vulnerabilidade individual, social e programática mais descritas foram uso de drogas, coinfecção com HIV e falha no tratamento da tuberculose, respectivamente. A média de tempo em situação de rua também se mostrou relacionada à maior frequência de tuberculose e da infecção latente da tuberculose segundo literatura.

CONCLUSÃO: O estigma e a desumanização associados às pessoas em situação de rua foram descritos em todos os estudos revisados, sendo importantes barreiras no acesso aos serviços de saúde. A vivência na rua potencializa os riscos para a ocorrência de doenças crônicas e infecciosas, bem como a priorização de questões mais pragmáticas à manutenção da vida, como segurança e alimentação, em detrimento à saúde. Os resultados encontrados podem ser utilizados para embasar hipóteses para futuras pesquisas e para reforçar e direcionar políticas públicas de saúde e sociais já existentes para o enfrentamento da tuberculose e HIV na pessoa em situação de rua.

DESCRITORES: Pessoas em Situação de Rua. Tuberculose. Infecções por HIV. Coinfecção, epidemiologia. Vulnerabilidade em Saúde. Vulnerabilidade Social.

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INTRODUÇÃO

A tuberculose é uma doença respiratória causada pelo agente *Mycobacterium tuberculosis* que está entre as dez doenças que mais matam no mundo atualmente e é a primeira colocada em causas de óbito entre as doenças infecciosas[1]. Sua transmissão ocorre por inalação de aerossóis e conduz a uma infecção granulomatosa em trato respiratório inferior[2] e sua ocorrência está associada a fatores socioeconômicos, visto que, segundo a ONU, 95% dos casos ocorrem em países de média e baixa renda[3] e, no topo do ranking de casos estimados e de mortes para a doença, estão o continente africano e as Américas[1].

A estimativa global de infecção pela tuberculose em 2020 foi de 10 milhões de casos, com uma incidência estimada de 132/100.000 habitantes, e de 1,2 milhão de mortes no ano, além de 208 mil óbitos entre pessoas HIV+[1]. A estratégia *END TB*, proposta pela Organização Mundial da Saúde, tem como metas diminuir a incidência da tuberculose para menos de 10/100.000 habitantes e reduzir o número de óbitos em pelo menos 95%, dessa forma a tuberculose poderia deixar de ser considerada um problema de saúde pública mundial[4].

No Brasil, a tuberculose é um importante problema de saúde, com uma taxa de óbitos de 2,2/100.000 habitantes e uma incidência de 31,6/100.000 habitantes[5] e conta com programas específicos do Sistema Único de Saúde (SUS) para seu combate, como o Programa Nacional de Controle da Tuberculose e o estabelecimento do tratamento diretamente observado pela rede básica de saúde[6]. Porém, a adesão dos pacientes é baixa[7] e o abandono do tratamento e a administração errada ou intermitente dos medicamentos fazem com que o número de óbitos permaneça elevado e que se crie resistência aos fármacos utilizados[7].

As pessoas em situação de rua (PSR) estão constantemente expostas a diferentes tipos de vulnerabilização e condições de vida degradantes, o que aumenta o desafio para o cuidado em saúde, necessitando de intervenções específicas para essas pessoas[4,8]. Em consequência dessa exposição e precarização de suas vidas, a tuberculose entre PSR é muito frequente e apresentam 56 vezes mais chances de serem acometidas por esse agravo no Brasil.

Essa vulnerabilização tem três dimensões[9]: 1) Individual – determinada pelo que o indivíduo dispõe de informações, de sua capacidade de pô-las em prática, e de aspectos materiais, culturais, cognitivos e morais, entre tantos outros que participam da construção do “ser” humano; 2) Social – pautada pelos contextos sociais e cenários culturais; 3) Programática - que diz respeito às instituições, principalmente de saúde, educação, cultura e assistência social, permitindo contextos desfavoráveis, incrementando essas condições sociais.

O tratamento da tuberculose em PSR é mais caro e complexo quando comparado ao restante da população, com menor adesão ao tratamento, segundo a Rede para Políticas Informadas por Evidências do Ministério da Saúde do Brasil[4], questões como segurança, alimentação e descanso competem em importância com o cuidado da saúde na PSR. Além da tuberculose, o HIV/aids, doenças dermatológicas (incluindo hanseníase) e hipertensão arterial são as principais doenças incidentes nessa população, bem como acompanhamento psicossocial devido ao abuso de drogas e álcool[10]. As pessoas em situação de rua vivem marginalizadas e distantes das políticas públicas e sem o efetivo cumprimento de seus direitos básicos, inclusive quando se trata de atendimento médico na atenção básica no SUS[11].

Em todo o mundo, a tuberculose é a principal causa de morte em HIV positivos, representando um terço das mortes em decorrência da aids[12]. As pessoas HIV positivas têm 28 vezes mais chances de se infectar com a tuberculose[13] e essa coinfecção representa quase 29% das mortes no Brasil[14]. No ano de 2018 no Brasil, a incidência de tuberculose em pacientes HIV-positivos foi de 5,2/100.000 habitantes. No mesmo ano, dos novos casos de tuberculose, 75,5% foram testados para HIV e, dentre os positivos, apenas 47,4% fizeram o tratamento antirretroviral concomitantemente ao tratamento para a tuberculose[15].

Diante dos avanços tecnológicos nos tratamentos de tuberculose e HIV/aids e dos compromissos assumidos pelos países membros da Organização Mundial da Saúde, esse cenário é problemático e desafiador, visto que essas doenças apresentam uma importância histórica[16]. Fomentar a produção de conhecimento e o debate no contexto da epidemia da tuberculose referente à vulnerabilidade social, individual e programática na população em situação de rua é fundamental para o enfrentamento desses agravos no país, principalmente no contexto atual da epidemia de covid-19, onde a atenção em saúde compete para os atendimentos das diferentes demandas. O objetivo do artigo foi analisar, sistematizar e compilar os fatores de vulnerabilidade (individual, social e programática) associados à tuberculose e tuberculose+HIV, coletados junto aos estudos sobre esses agravos na população das pessoas em situação de rua entre os anos de 2014 e 2020.

MÉTODOS

Foi realizada uma revisão sistemática de literatura para os agravos de tuberculose e tuberculose+HIV no período de 2014 a 2020 na população em situação de rua. A revisão sistemática é um método de pesquisa que, na área da saúde, consiste em buscar e selecionar, avaliar, compilar e apresentar as evidências publicadas sobre um tema importante e de impacto na saúde das populações. Neste artigo, utilizamos o protocolo *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA)[17].

Estratégia de Busca

A busca de referências foi realizada a partir dos descritores *Tuberculosis, Homeless persons, HIV, Social Vulnerability, e Health Vulnerability* e suas combinações entre si nas plataformas de pesquisa PubMed e Literatura Latino-americana e do Caribe em Ciências da Saúde (Lilacs), como pode ser observado na tabela 1. As análises dos artigos foram realizadas por duas pesquisadoras em dois momentos distintos e os resultados foram compilados.

Tabela 1. Estratégias de busca.

Plataforma	Descritores	Resultados
Pubmed http://www.ncbi.nlm.nih.gov/pub med	*("homeless persons"[MeSH Major Topic] AND "tuberculosis"[MeSH Major Topic]) AND "hiv"[MeSH]*	4
Pubmed http://www.ncbi.nlm.nih.gov/pub med	*("tuberculosis"[MeSH Major Topic]) AND "homeless persons"[MeSH Major Topic]*	229
Pubmed http://www.ncbi.nlm.nih.gov/pub med	*(("Tuberculosis/analysis"[Mesh] OR "Tuberculosis/epidemiology"[Mesh] OR "Tuberculosis/mortality"[Mesh] OR "Tuberculosis/statistics and numerical data"[Mesh] OR "Tuberculosis/transmission"[Mesh])) AND ("Homeless Persons/epidemiology"[Mesh] OR "Homeless Persons/mortality"[Mesh] OR "Homeless Persons/statistics and numerical data"[Mesh])*	104
Lilacs http://lilacs.bvsalud.org/en/	*tuberculose [Descritor de assunto] AND pessoas em situação de rua [Descritor de assunto]*	13
Lilacs http://lilacs.bvsalud.org/en/	*pessoas em situação de rua [Descritor de assunto] AND vulnerabilidade social [Descritor de assunto],*	
Lilacs http://lilacs.bvsalud.org/en/	*pessoas em situação de rua [Descritor de assunto] AND vulnerabilidade social [Descritor de assunto] AND tuberculose [Descritor de assunto]*	1
Lilacs http://lilacs.bvsalud.org/en/	*vulnerabilidade social [Descritor de assunto] AND tuberculose [Descritor de assunto]*	5
Lilacs http://lilacs.bvsalud.org/en/	*vulnerabilidade em saúde [Descritor de assunto] AND tuberculose [Descritor de assunto]*	5

Critérios de Elegibilidade

Nas análises foram incluídas as publicações de delineamento quantitativo que abordavam a tuberculose e tuberculose+HIV e os fatores de vulnerabilidade associados aos agravos nos idiomas inglês, espanhol e português, publicados entre 2014 e 2020.

Análise de Viés

A análise de viés das publicações analisadas foi realizada por par e com o uso da ferramenta *Joanna Briggs Institute Critical Appraisal (JBI – Systematic Rewiews tools).* O JBI é composto por perguntas que avaliam a qualidade metodológica do estudo segundo seu delineamento. Os estudos transversais foram avaliados com o *JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies* com as perguntas: (i) critérios de inclusão e exclusão claramente definidos; (ii) temática e método descritos em detalhes; (iii) exposição mensurada de forma apropriada; (iv) critérios de definição objetivos e padronizados para determinar a condição estudada; (v) identificação de fatores de confundimento; (vi) estratégias para lidar com fatores de confundimento; (vii) desfecho mensurado de forma apropriada; (viii) análise estatística apropriada[18]. Para as análises dos estudos de coorte, utilizou-se o *JBI Critical Appraisal Checklist for Analytical Cohort Studies*, com 11 perguntas: (i) os dois grupos recrutados da mesma população; (ii) as exposições medidas de forma similar para atribuir os dois grupos, expostos e não expostos; (iii) exposição mensurada de forma apropriada; (iv) identificação de fatores de confundimento; (v) estratégias para lidar com fatores de confundimento; (vi) os participantes estavam livres do desfecho no início do estudo; (vii) desfecho mensurado de forma apropriada; (viii) o tempo de estudo suficiente a ocorrência do desfecho; (ix) acompanhamento completo/se não, suas razões descritas e exploradas; (x) estratégias para lidar com acompanhamento incompleto; (xi) análise estatística apropriada[19]. Os estudos ecológicos foram avaliados pelo *JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies* modificado segundo critérios propostos por Dufault e Klar[20], que descrevem a avaliação metodológica para esse tipo de desenho de estudo, com as seguintes perguntas: (i) explicação sobre delineamento e tamanho amostral escolhido; (ii) critérios de inclusão e exclusão claramente definidos; (iii) temática e método descritos em detalhes; (iv) critérios de definição objetivos e padronizados para determinar a condição estudada; (v) exposição mensurada de forma apropriada; (vi) identificação de fatores de confundimento; (vii) estratégias para lidar com fatores de confundimento; (viii) desfecho mensurado de forma apropriada; (ix) esforços para reduzir possibilidade de viés; (x) análise estatística apropriada; (xi) estratégias para lidar com acompanhamento incompleto; (xii) limitações do estudo apontadas[18,20].

RESULTADOS

Foram encontradas 374 produções nas plataformas pesquisadas, sendo selecionadas 103 de publicações dentro do período do estudo, das quais duas foram excluídas por serem documentos governamentais oficiais para políticas públicas, 23 foram descartadas por se apresentarem em duplicidade e nove por não estarem indexadas para leitura integral. Ao final, restaram 71 publicações para análise por meio da leitura dos resumos e leitura dinâmica, dos quais foram selecionados 16 segundo os critérios de elegibilidade. A maioria dos estudos se deu entre países do continente europeu (6/16), seguido pela Ásia (3/16), América do Norte (4/16), América do Sul (2/16), com uma publicação brasileira, e África (1/16) (Figura). Em relação ao delineamento, sete dos estudos quantitativos eram transversais, oito de coorte e um ecológico. Complementamos os resultados com a média de 2,7 publicações anuais, que se manteve entre os anos analisados, com o mínimo de um e o máximo de quatro trabalhos publicados em cada ano.

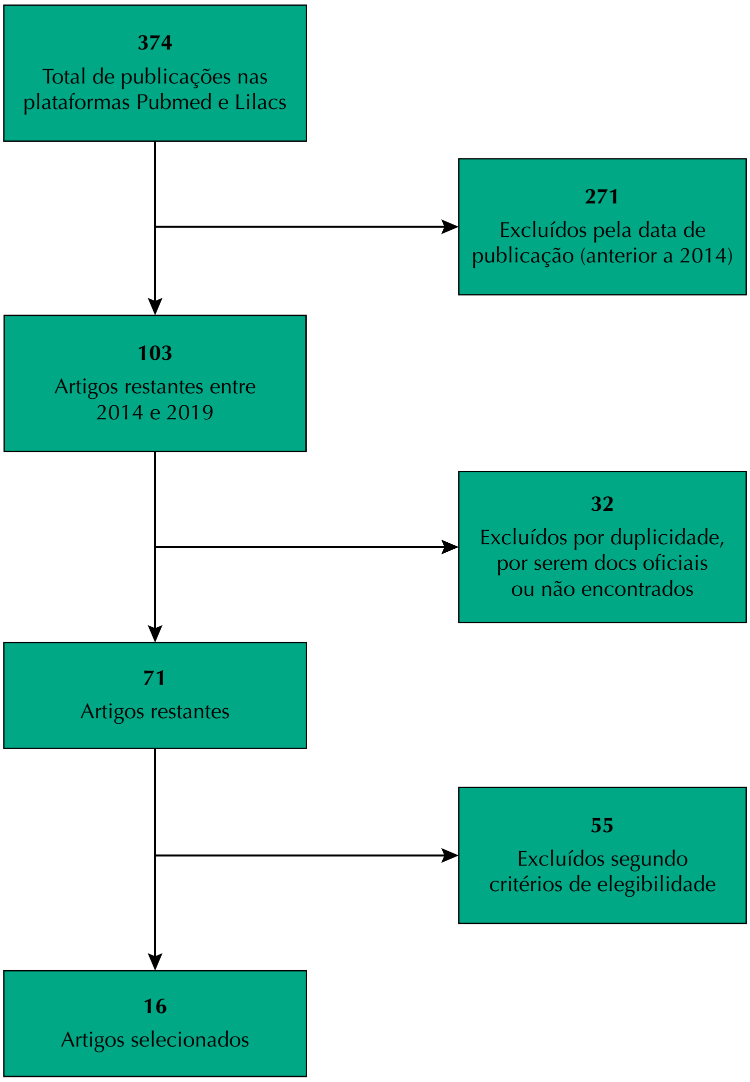

Figura. Fluxograma de resultados.

A coleta das publicações foi realizada entre junho de 2019 e abril de 2021 e todos os dados foram digitados em planilha *Microsoft Excel* contendo os segmentos: autores, população do estudo, ano de publicação, país de publicação e desenho de estudo.

Entre os artigos selecionados, identificamos os seguintes fatores de vulnerabilidade para os desfechos: uso de álcool[21–28], tabagismo[21,22,25,28,29], uso de drogas ilícitas[21,24,26–31], entre elas, injetáveis[21,27–29], podendo haver compartilhamento de agulhas[29,30], e metanfetamina[29], histórico de encarceramento[21,29], imigração[26,32,33], distúrbio psicológico[24,28,30], prostituição[29], inclusive entre homens que fizeram sexo com homens, analfabetismo[22,29], desnutrição[22], e coinfecção por HIV[21,22,24–29,34] e outras doenças crônicas como diabetes[27,28], insuficiência renal crônica[27,28] e hepatites B e C[21,28,29].

Em todos os estudos analisados, a maioria dos pacientes acometidos pela tuberculose era da raça/cor preta ou parda[24,28,30,32], do gênero masculino e com de idade média de 49,8 anos (DP ± 5,2) e a média de tempo em situação de rua está relacionada à maior ocorrência de tuberculose e infecção latente de tuberculose segundo literatura[21,22,29].

Os desfechos relacionados à ocorrência da tuberculose e infecção latente de tuberculose são apresentados na tabela 3. A não completude do tratamento[22,24,25,27,28,30,31,34,35] ou seu fracasso[22,24,26], o óbito[22,24,25,27,30,31,34], desenvolvimento de resistência aos fármacos de tratamento[22,25–29] e ocorrência de tuberculose extrapulmonar[22,26,27]. Os principais meios

Tabela 2. Descritores e artigos selecionados entre as publicações.

Autores	População de estudo	Ano	País	Descritores	Desenho de estudo
Aldridge et al.[21]	491 pessoas em situação de rua	2018	Inglaterra	Tuberculose + Pessoas em Situação de rua	Estudo transversal
Semunigus et al.[22]	351 pessoas em situação de rua	2016	Etiópia	Tuberculose + Pessoas em Situação de rua + HIV	Estudo transversal
Vieira et al.[23]	População de 18 distritos portugueses	2018	Portugal	Tuberculose + Pessoas em Situação de rua	Estudo ecológico
Ranzani et al.[24]	1.726 pessoas em situação de rua	2016	Brasil	Tuberculose + Pessoas em Situação de rua	Estudo de coorte
Hwang et al.[25]	3.292 pessoas em situação de rua	2017	Coreia do Sul	Tuberculose + Pessoas em Situação de rua	Estudo de coorte
Dias et al.[26]	92.053 pessoas em situação de rua	2017	Portugal	Tuberculose + Pessoas em Situação de rua	Estudo de coorte
Agarwal et al.[27]	543 pessoas em situação de rua	2019	EUA	Tuberculose + Pessoas em Situação de rua	Estudo transversal
Nwana et al.[28]	393 pessoas em situação de rua	2019	Estados Unidos	Tuberculose + Pessoas em Situação de rua	Estudo de coorte
Amiri et al.[29]	593 pessoas em situação de rua	2014	Irã	Tuberculose + Pessoas em Situação de rua	Estudo transversal
Powell et al.[30]	110 ocorrências de tuberculose multirresistente	2017	EUA	Tuberculose + Pessoas em Situação de rua	Estudo transversal
Gomez et al.[31]	544 pessoas em situação de rua positivas para tuberculose	2019	Colômbia	Tuberculose + Pessoas em Situação de rua	Estudo de coorte
Munn et al.[32]	64 pessoas em situação de rua	2015	EUA	Tuberculose + Pessoas em Situação de rua	Estudo de coorte
Streit et al.[33]	142 pessoas em situação de rua	2019	Alemanha	Tuberculose + Pessoas em Situação de rua	Estudo transversal
Dolla et al.[34]	301 pessoas em situação de rua	2017	Índia	Tuberculose + Pessoas em Situação de rua	Estudo transversal
Korzeniewska-Koseła et al.[35]	2.349 pessoas em situação de rua	2015	Polônia	Tuberculose + Pessoas em Situação de rua	Estudo de coorte
Pendzich et al.[36]	117 pessoas em situação de rua	2015	Polônia	Tuberculose + Pessoas em Situação de rua	Estudo de coorte

diagnósticos foram citologia de escarro[22,24,26,27,29,31], R-X torácico[24,27,33], cultura[27,29–31], exame molecular[27] e diagnóstico clínico[27].

Entre as 16 publicações analisadas, em 10 foi descrita a associação entre as comorbidades tuberculose e HIV. Na produção de Semunigus et al.[22], a proporção de coinfecção chegou a 55,5%. Segundo Dias et al.[26], ser HIV positivo se mostrou 2,1 vezes mais provável ter um desfecho desfavorável e a comorbidade estava presente em 32,6% dos pacientes analisados. Para Ranzani et al.[24] 17,3% das pessoas em situação de rua eram HIV positivas. Segundo Agarwal et al.[27] 16% dos participantes com tuberculose eram HIV positivos e a razão de chance para mortalidade nesses indivíduos foi 3.57 maior do que para os com exame de HIV negativo. Na publicação de Hwang et al.[25] 5,7% tinha coinfecção tuberculose+HIV. No estudo de Amiri et al.[29] 1,2% das PSR eram HIV positivos e tinham infecção latente de tuberculose, proporção similar (1,8%) ao achado por Nwana et al.[28] Gomez et al.[31], em seu estudo, achou a proporção de 20,6% de PSR com as comorbidades. Vieira et al.[23] relatam que o aumento de 100 casos da coinfecção por HIV+tuberculose na população em geral leva ao aumento da incidência da tuberculose entre pessoas em situação de rua a 14 casos por 100 mil habitantes. No de Dolla et al.[34], o único paciente HIV+ em sua amostra, veio a óbito.

Tabela 3. Sumarização dos fatores de vulnerabilidade.

Fator de vulnerabilidade	Dimensão de vulnerabilidade	Autor
Distúrbio psicológico	Individual	Ranzani et al.[24] (2016); Nwana et al.[28] (2019); Powell et al.[30] (2017)
Uso de álcool	Individual e social	Aldridge et al.[21] (2018); Semunigus et al.[22] (2016); Vieira et al.[23] (2018); Ranzani et al.[24] (2016); Hwuang et al.[25] (2017); Dias et al.[26] (2017); Agarwal et al.[27] (2019); Nwana et al.[28] (2019)
Tabagismo	Individual e social	Aldridge et al.[21] (2018); Semunigus et al.[22] (2016); Hwuang et al.[25] (2017); Nwana et al.[28] (2019) Amiri et al.[29](2014)
Uso de drogas	Individual e social	Aldridge et al.[21] (2018); Ranzani et al.[24] (2016); Dias et al.[26] (2017); Agarwal et al.[27] (2019); Nwana et al.[28] (2019); Powell et al.[30] (2017)
Baixa escolaridade	Individual e social	Semunigus et al.[22] (2016); Ranzani et al.[24] (2016); Amiri et al.[29] (2014)
Imigração	Social	Dias et al.[26] (2017); Munn et al.[32] (2015); Streit et al.[33] (2019)
Encarceramento	Social	Aldridge et al.[21] (2018); Amiri et al.[29] (2014); Powell et al.[30] (2017)
Atuação em trabalhos ilegais (roubo, furto, tráfico de drogas e prostituição)	Social	Amiri et al.[29] (2014)
Desnutrição	Social	Semunigus et al.[22] (2016)
Coinfecção por HIV e outras doenças como hipertensão arterial, hepatites e sífilis, além de recorrência da tuberculose	Social	Aldridge et al.[21] (2018); Semunigus et al.[22] (2016); Ranzani et al.[24] (2016); Hwuang et al.[25] (2017); Dias et al.[26] (2017); Agarwal et al.[27] (2019); Nwana et al.[28] (2019); Amiri et al.[29] (2014)
Pardos e negros	Social	Powell et al.[30] (2017); Munn et al.[32] (2015); Dolla et al.[34] (2017)
Falha no tratamento	Programática	Semunigus et al.[22] (2016); Ranzani et al.[24] (2016); Hwuang et al.[25] (2017); Dias et al.[26] (2017); Agarwal et al.[27] (2019); Nwana et al.[28] (2019); Gomez et al.[31] (2019); Streit et al.[33] (2019); Dolla et al.[34] (2017); Korzeniewska-Kosela et al.[35] (2015)

Tabela 4. Incidências e prevalências achadas nos estudos revisados.

Autores (ano)	Incidência para tuberculose	Prevalência para tuberculose	Prevalência infecção latente de tuberculose	Prevalência tuberculose+HIV	Prevalência infecção latente de tuberculose+HIV
Aldridge et al.[21] (2018)			16,50%		
Semunigus et al.[22] (2016)	505/100 mil hab	2,60%		55,50%	
Ranzani et al.[24] (2016)		2,80%		17,30%	
Hwuang et al.[25] (2017)				5,70%	
Dias et al.[26] (2017)	122/100 mil hab			32,60%	
Agarwal et al.[27] (2019)		4,10%		16%	
Nwana et al.[28] (2019)					1,80%
Amiri et al.[29] (2014)			46,70%		1,20%
Gomez et al.[31] (2019)				20,60%	
Streit et al.[33] (2019			16%		
Dolla et al.[34] (2017)	270/100 mil hab			20%	

Em relação aos vieses encontrados, grande parte dos estudos não apresentou similaridade dos grupos recrutados[24,25,36], identificação dos fatores de confundimento[26,27,29,30,33–36], estratégia para lidar com esses fatores[26,27,29,30,32–36] ou com o acompanhamento incompleto dos participantes[25,26,36]. Poucos estudos trouxeram suas limitações descritas[24,26,28,29,31,34] e aqueles que apresentaram tinham falhas na exposição da metodologia e dos resultados[29,30,32,36].

DISCUSSÃO

Podemos observar uma recorrência entre os resultados relacionada ao consumo de álcool, tabaco e drogas ilícitas – fatores da vulnerabilidade social a partir do estigma associado ao vício e que também é uma susceptibilidade individual –, seja para a fuga da realidade de sofrimento ou ainda para buscar uma melhoria do bem-estar geral[37,38]. Assim, essa sobreposição de vulnerabilidades pode aumentar a exposição à tuberculose e HIV na população do estudo. O sexo e idade, assim como a coinfecção por outras doenças transmissíveis e histórico de encarceramento, também são fatores que despertam discriminação na nossa sociedade, embora em níveis diferentes.

A falta de completude do tratamento e desenvolvimento de resistência aos medicamentos de tratamento estão incluídos na esfera da vulnerabilidade programática, pois demonstram a falha do sistema de saúde em fornecer tratamento, informação e estrutura de forma adequada para o tratamento desses pacientes.

Encontramos uma variabilidade na quantidade de publicações anuais com os temas tuberculose e HIV para a população de PSR. A média anual foi de menos de três (2,67), considerado pouco na comparação com outras populações também classificadas como vulneráveis. Tratando-se de um agravo muito importante de saúde pública mundial, a ponto de estar listada entre os Objetivos do Desenvolvimento Sustentável, chama a atenção algumas falhas metodológicas como: pequeno tamanho da amostra, o que fragiliza os resultados e conclusões apresentados; falta de acesso direto aos pacientes positivos para tuberculose[29]; subestimação do número real de pessoas em situação de rua[24,26]; e da incidência e prevalência da tuberculose nessa população[26,34]; amostra composta somente de pessoas com tuberculose[24], excluindo-se as formas extrapulmonares.

Vulnerabilidade Individual

Entre as publicações revisadas, o uso de drogas ilícitas, álcool ou tabaco que fazem parte dos fatores de vulnerabilidade individual e social apontaram para importância dessas susceptibilidades na vida da PSR, apontando para a necessidade de uma atenção singular desses aspectos no enfrentamento da tuberculose entre a PSR.

O uso constante de drogas pode levar ao desenvolvimento de transtornos mentais, como afirma o último relatório mundial sobre drogas, em 2020, do Escritório de Drogas e Crimes da Organização das Nações Unidas (UNODC). Em duas publicações[24,30] foi descrita a variável "transtorno mental", evidenciando sua constante ocorrência entre as amostras usadas para os estudos. O rompimento com familiares, seja por não adequação ao seu modelo estrutural, seja por histórico de violência e assédio, ou mesmo por não aceitarem formas de sustento escusas e o próprio vício, expõe essas pessoas a uma condição de vulnerabilidade social e individual, pois não podem contar com suas famílias num momento de dificuldade[39,40].

Vulnerabilidade Social

A redução da situação de vulnerabilidade social é enfrentada pelo Estado com a implantação de programas de transferência de renda pelo governo, que são artifícios para diminuir o número de pessoas abaixo da linha da pobreza e dar a elas melhores condições de alimentação[41]. Essa importante medida é considerada programática, com consequências sobre a vulnerabilidade social e deve ser ampliada, pois pode reduzir a vulnerabilidade das pessoas na linha abaixo da miséria. A sobreposição ou intersecção das dimensões de vulnerabilidade ajudam a ampliar o olhar da epidemiologia para a forma de adoecer e alertar os gestores para as questões de saúde oportunizando um enfrentamento mais qualificado desses problemas entre PSR.

A produção de vidas vulnerabilizadas e não integráveis faz com que as pessoas em situação de rua convivam continuamente com a dificuldade no acesso à educação, trabalho, cuidado e serviços de saúde, entre outros, além da sua invisibilidade, o que pode levar algumas dessas pessoas ao envolvimento em atividades como prostituição, associação ao tráfico, roubo e furto e trabalho análogo à escravidão.

A vulnerabilidade social também envolve características marcadas pela classe social baixa, local de moradia, raça negra, entre outras. A proporção de pretos e pardos entre os resultados encontrados nas publicações foi de 63,6%. A idade média dos participantes dos estudos é de 49,8 anos (DP ± 5,2), provavelmente devido à maior mobilidade espacial se comparado às mulheres ou pessoas de diferentes faixas etárias, como idosos, que transitam menos pelas ruas, se expondo menos em seus trajetos[42].

O histórico de encarceramento foi frequente entre os estudos usados nessa revisão. O sistema prisional, incumbido de reabilitar e reinserir o apenado à sociedade, falha nessa tentativa de reinserção devido ao estigma que o condenado carrega após o cumprimento de sua pena, seja pela sociedade em geral, pela falta de apoio familiar ou pela falta de oportunidade de emprego, o que faz com que muitos acabem sem recursos monetários para continuarem sua vida e tenham que recorrer à vida nas ruas, algumas vezes atuando em trabalhos ilegais, o que não rompe o ciclo de reincidência[43].

Segundo *ranking* realizado pelo *World Prison Brief* (2021)[44], o Brasil tem a terceira maior população carcerária do mundo, fato intrinsecamente ligado ao racismo estrutural e, consequentemente, à marginalização sistemática de pessoas pretas e pardas, compreendendo 61,7% dos encarcerados[45]. Com isso, podemos observar que esses fatores de vulnerabilidade relacionados ao recorte social, racial e econômico se perpetuam nas populações mais precárizadas.

Vulnerabilidade Programática

Essa dimensão da vulnerabilidade, relacionada ao acesso aos equipamentos públicos e institucionais do Estado, revelou-se uma importante dimensão da análise das susceptibilidades de populações vulnerabilizadas em relação à tuberculose e ao HIV, nos estudos epidemiológicos[46], pois fornece evidências da precariedade e fragilidade desses recursos. A falta de completude do tratamento e desenvolvimento de resistência aos medicamentos de tratamento estão incluídos nessa dimensão, pois demonstram a falha do sistema de saúde em fornecer tratamento, informação e estrutura adequados para o tratamento desses pacientes[47]. Entre as consequências está a coinfecção com outras doenças, visto que a habitação nas ruas e sua exposição ambiental potencializam os riscos para algumas doenças crônicas e infecciosas[38], pois questões prioritárias à manutenção da vida, como segurança e alimentação, são mais urgentes que o cuidado com a saúde, e diante das dificuldades de acesso, o cuidado com a saúde fica em segundo plano ou quando surgir uma oportunidade[38,48].

CONCLUSÃO

O Brasil, segundo o Instituto de Pesquisa Econômica Aplicada, contava com mais de 100 mil pessoas vivendo nas ruas em 2016[49]. Atualmente, diante das perspectivas socioeconômicas brasileiras, inclusive no contexto da pandemia da covid-19 aliado ao cenário econômico e político, já se observa um aumento da pobreza e na quantidade da PSR[50]. Entre as consequências é possível que se observe a curto prazo um aumento da tuberculose na PSR, como também em outras populações vulnerabilizadas, a exemplo das populações de baixa renda, moradores de favelas ou ainda nos moradores de habitação precária[51], visto que já existe um panorama sobre o aumento da pobreza e miséria no Brasil, assim como em outros países da América Latina[50,52].

Nosso olhar pela perspectiva do conceito de vulnerabilidade permitiu verificar que os resultados encontrados nas publicações analisadas evidenciaram a questão social e programática dos fatores associados à tuberculose e HIV entre PSR, destacando as diferentes dimensões da precarização das vidas e atenção a sua saúde. Assim, esse conceito foi um suporte fundamental para classificar e entender os diferentes tipos de susceptibilidades que permeiam a vida das PSR e dificultam o tratamento da tuberculose e HIV, bem como falha no tratamento por descontinuidade e, consequentemente, aparecimento de cepas resistentes.

Mesmo com protocolos e diretrizes estabelecidas, portarias e normas técnicas para a prevenção e tratamento dos agravos aqui abordados para a PSR, percebeu-se que a execução dos planos de ações traçados pelas estratégias governamentais apresenta importantes falhas, evidenciando as fragilidades do Sistema de Saúde e políticas públicas voltadas para PSR, bem como as questões de estigma e preconceitos sociais que se reproduzem nos serviços de saúde. Dessa forma, algumas vidas específicas estão mais expostas a situações de vulnerabilidade e, consequentemente, com menos acesso a prevenção e proteção, logo, mais susceptíveis à violência do Estado e da sociedade do que outras. Isso é produzido por variados atravessamentos que marcam essas vidas como mais vulneráveis e muitas vezes não reconhecidas, sendo invisibilizados.

Recomendações

A partir dos resultados dessa revisão, recomenda-se uma maior atenção e investimento em melhoria das ações de prevenção e intervenções para a tuberculose e tuberculose+HIV na PSR, desde a atenção básica, mantendo uma rotina de avaliação das vulnerabilidades das pessoas em situação de rua. Aos gestores e técnicos, avaliar a necessidade de alteração e ajustes dos protocolos da atenção básica para as PSR, além da distribuição integral de recursos para as demandas já conhecidas e aqui apresentadas. Também é necessário esforço e comprometimento político com a distribuição dos recursos destinados à saúde, políticas sociais e de assistência as PSR.

A sistematização dos fatores de vulnerabilidade pode ser utilizada para embasar hipóteses para futuras pesquisas, subsidiar políticas públicas de saúde e sociais para o enfrentamento da tuberculose e HIV na PSR. Os achados, quando comparados a outras revisões sistemáticas, parecem avançar ao discutir pela ótica do conceito de vulnerabilidade, o que é inédito nas publicações nacionais, para a população das pessoas em situação de rua no contexto da tuberculose e tuberculose+HIV.

Limitações

Esse estudo apresenta limitações, visto que mesmo que realizada uma ampla busca de trabalhos publicados por duas pesquisadoras, uma quantidade de textos pode ainda não estar disponível de forma digital nas plataformas e, devido à velocidade da dinâmica das publicações, alguns trabalhos podem ter escapado à busca e coleta de dados.

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Infectious disease in an era of global change

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Abstract | The twenty-first century has witnessed a wave of severe infectious disease outbreaks, not least the COVID-19 pandemic, which has had a devastating impact on lives and livelihoods around the globe. The 2003 severe acute respiratory syndrome coronavirus outbreak, the 2009 swine flu pandemic, the 2012 Middle East respiratory syndrome coronavirus outbreak, the 2013–2016 Ebola virus disease epidemic in West Africa and the 2015 Zika virus disease epidemic all resulted in substantial morbidity and mortality while spreading across borders to infect people in multiple countries. At the same time, the past few decades have ushered in an unprecedented era of technological, demographic and climatic change: airline flights have doubled since 2000, since 2007 more people live in urban areas than rural areas, population numbers continue to climb and climate change presents an escalating threat to society. In this Review, we consider the extent to which these recent global changes have increased the risk of infectious disease outbreaks, even as improved sanitation and access to health care have resulted in considerable progress worldwide.

In premodern times, colonization, slavery and war led to the global spread of infectious diseases, with devastating consequences (FIG. 1a). Human diseases such as tuberculosis, polio, smallpox and diphtheria circulated widely, and before the advent of vaccines, these diseases caused substantial morbidity and mortality. At the same time, animal diseases such as rinderpest spread along trade routes and with travelling armies, with devastating impacts on livestock and dependent human populations[1]. However, in the past two decades, medical advances, access to health care and improved sanitation have reduced the overall mortality and morbidity linked to infectious diseases, particularly for lower respiratory tract infections and diarrhoeal disease (FIG. 1d). The swift development of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine speaks to the efficacy of modern science in rapidly countering threats from emerging pathogens. Nevertheless, infectious disease burden remains substantial in countries with low and lower-middle incomes, while mortality and morbidity associated with neglected tropical diseases, HIV infection, tuberculosis and malaria remain high. Moreover, deaths from emerging and re-emerging infections, in comparison with seasonal and endemic infections, have persisted throughout the twenty-first century (FIG. 1c). This points to a possible new era of infectious disease, defined by outbreaks of emerging, re-emerging and endemic pathogens that spread quickly, aided by global connectivity and shifted ranges owing to climate change (FIG. 1d).

Here, we review how recent anthropogenic climatic, demographic and technological changes have altered the landscape of infectious disease risk in the past two decades. In terms of climate change, we consider both the influence of recent warming and projected future changes. For demographic change, we include trends such as urbanization (FIG. 1b), population growth, land-use change, migration, ageing and changing birth rates. For technological changes, we primarily consider advances that enable cheaper, faster global travel and trade (FIG. 1b), as well as improved health care. We do not explicitly address economic change; however, economic changes, including economic development, are crucial drivers of these three factors: climate, demography and technology. We also do not explicitly discuss natural drivers of pathogen evolution or biological processes unless they interact with human-driven global change.

New infections chart a pathway beginning with emergence, followed by local-scale transmission, movement beyond borders and possible global-scale spread. Global changes may differentially affect the risk of emergence, the dynamics of disease within a local population and the global spread of diseases between populations. We provide an overview of each step, first considering features of recent global change that have altered the risks of spillover of viral, fungal, bacterial and apicomplexan

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(malaria) infections into human populations, then detailing how spread within human populations, driven by the seasonal dynamics of transmission, may be impacted by global change, of relevance to both emergent and established pathogens. Finally, we consider changes to the drivers of global spread, focusing in particular on travel, migration and animal and plant trade.

Pathogen emergence into human populations

Recent decades have seen repeated pathogen emergence from wild or domestic animal reservoirs into human populations, from HIV-1 and HIV-2, to the 1918 influenza virus, to Middle East respiratory syndrome coronavirus, to SARS-CoV-2 (REFS[2–4]). For a novel pathogen to become a threat to human populations, first, contact between humans and the animal reservoir must occur; the pathogen must either have or evolve (BOX 1) the capacity for human-to-human transmission[5]; and finally, this human-to-human transmission must enable expansion of the pathogen's geographical range beyond the zone of spillover. Recent global changes have affected each of these steps.

Patterns of contact between human and wildlife reservoirs have increased as human populations move into previously unoccupied regions. Population growth and agricultural expansion, coupled with increasing wealth and larger property sizes, are driving factors for these interactions and the resulting habitat destruction. This may occur alongside behaviours that increase the potential for spillover, such as consumption of wild meat[6], or intensifying contact between wild and domestic animal hosts. For example, Nipah virus has been identified in several bat populations, particularly flying foxes, but in 1999 caused a severe disease outbreak in Malaysia, primarily among pig farmers[7]. It is hypothesized that the spillover of Nipah virus from bats to pigs was driven by three factors related to global change: pig farms expanding into the bat habitat; intensification of pig farming, leading to a high density of hosts; and international trade, leading to the spread of the infection among other pig populations in Malaysia and Singapore[8]. Expanding agriculture and its intensification may create conditions that favour pathogen circulation within domestic animal (or plant) reservoirs via high-density farming practices[9]. Beyond creating opportunities for emergence of problematic livestock pathogens, this could also increase opportunities for evolution of novel variants of risk to humans in domestic animal reservoirs. This may occur alongside increasing risk to workers interacting with animal populations[10] as a result of work practices. Global increase in the demand for and resulting intensification of meat production will importantly drive these processes, and associated use of antibiotics in domestic animals has the potential to select for resistant strains of bacteria with potential to affect human health[11].

The nature of human populations that are exposed to potential spillover is also changing. For example, the elimination of smallpox led to the cessation of smallpox vaccination, which may have enabled the expansion of monkeypox[12]. More generally, globally ageing populations may provide an immune landscape that is more at risk of spillover, as ageing immune landscapes are less capable of containing infectious agents[13]. The intersection between declining function of immunity at later ages[14] and globally ageing populations may increase the probability of pathogen emergence, but this remains conjectural and an important area for research. The changing global context may allow existing human pathogens to both evolve novel characteristics and expand in scope. Selection for drug resistance now occurs worldwide, and antibiotic resistance has and will evolve repeatedly[15]. As with antibiotic resistance, rapid global spread is commonplace for antimalarial resistance following evolution[16].

Climate change may play a role in the risk from pathogen spillover. Changing environmental conditions can alter species range and density, leading to novel interactions between species, and increase the risk of zoonotic emergence[17]. A series of compounded environmental

Fig. 1 | **Human connectivity and infectious disease outbreaks in premodern and modern times. a** | Examples of epidemic periods associated with different eras of human transportation (land, maritime and air travel) are shown. Overland trade networks and war campaigns are thought to have contributed to multiple epidemics in the Mediterranean in late classical antiquity (green), beginning with the Antonine plague, which reportedly claimed the life of the Roman emperor Lucius Verus[125–128]. Maritime transportation (red and grey) leading to European contact with the Americas and the subsequent Atlantic slave trade resulted in the importation of *Plasmodium falciparum* malaria and novel viral pathogens[129]. In modern times, air travel (purple) resulted in the importation of severe acute respiratory syndrome (SARS) coronavirus to 27 countries before transmission was halted[130]. **b** | In recent years, increases in air travel, trade and urbanization at global (left) and regional (right) scales have accelerated, indicating ever more frequent transport of people and goods between growing urban areas (source World Bank). **c** | Log deaths from major epidemics in the twenty-first century (source World Health Organization). **d** | Disability-adjusted life years lost from infectious diseases (source Our World in Data). MERS, Middle East respiratory syndrome; NTD, neglected tropical disease.

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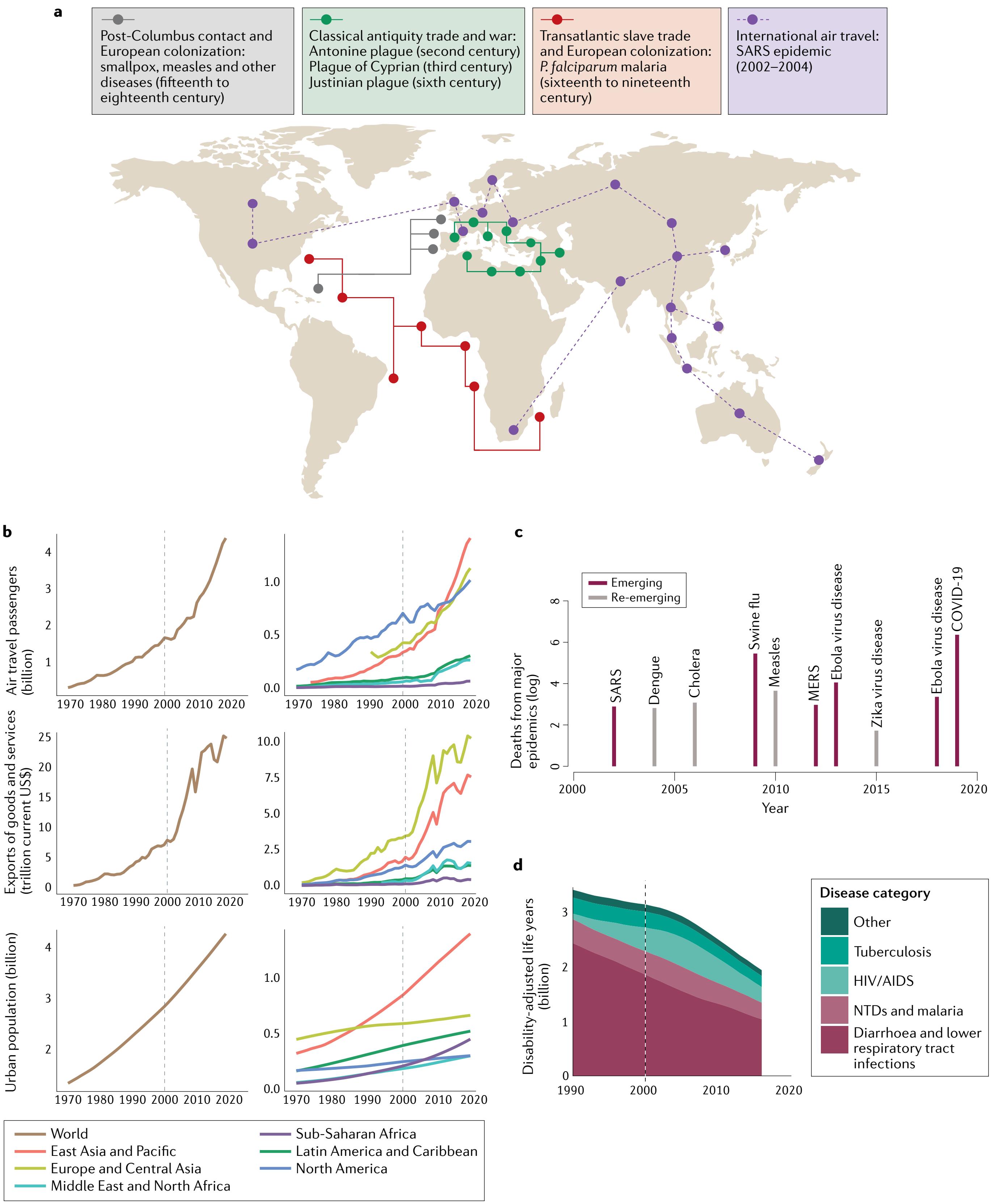


factors, including a long period of drought followed by extreme precipitation, is hypothesized to have driven an upsurge in rodent populations causing the emergence of pulmonary hantavirus in 1993 (REF. [18]). Similarly, evidence suggests that populations of the black flying fox in Australia, a key reservoir of Hendra virus, have moved 100 km southward in the past 100 years owing to climatic changes. This shifting range likely caused Hendra virus to spill over into southern horse populations, and these horses subsequently infected humans[19,20]. Patterns of change are likely occurring in other bat populations globally but remain understudied — a clear cause for concern given the crucial role bat populations play as a reservoir host for several high-fatality pathogens[21].

Rapid rates of urbanization in low-income and middle-income countries, and the increase in populations residing in crowded, low-quality dwellings, have created new opportunities for the emergence of infectious diseases (FIG. 2). Urbanization has promoted the emergence and spread of arboviral diseases such as dengue, Zika virus disease and chikungunya, which are transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes that are well adapted to urban areas[22–24]. Population density appears correlated with the preference of *Ae. aegypti* for human odour, and hence the evolution of human-biting — the transmission pathway for arboviral disease[24]. However the role of urbanization in vector-borne disease spread is complex: the preference of the *Anopheles* spp. vector for rural environments may have led to a decline in the prevalence of malaria in urbanizing regions[25]. Nevertheless, dense and highly connected urban areas are potential hot spots for the rapid spread of diseases such as COVID-19 and SARS, and cities can serve as a catalyst for rapid local and global transmission.

Box 1 | **Global change and evolution of hosts and pathogens**

Mutations constantly arise in the genomes of all species, from viruses to elephants. Some genetic changes may have no observable effects on fitness (and thus will be selectively neutral), but can be used to track pathogen spread; for example, to trace the impacts of global connectivity on an outbreak[70]. Some genetic changes will affect disease phenotypes, potentially increasing the transmissibility, virulence or immune escape of a pathogen lineage[133]. The degree to which such mutations increase in frequency or spread geographically will depend on the degree to which they increase fitness, as well as pathogen population dynamics, which may be modulated by the global change context. Increases in the density and geographical distribution of susceptible hosts (whether they be people, crops or livestock) may provide greater opportunity for novel variants to emerge[9] simply by amplifying pathogen populations and thus circulating mutations. While understanding the nuance of cross-scale selection (that is, how the selective context of the individual host translates into the selective context at the scale of populations) remains a challenging frontier[134], it is likely that ageing populations or the presence of immunosuppressive pathogens might further modulate selection pressures. Indeed, it has been suggested that the emergence of more transmissible or less immune-vulnerable variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was enabled in part by selection processes occurring during chronic infections in immunosuppressed individuals[135]. Greater global connectivity leads to more frequent exchange of this genetic material between populations of the same or different species, potentially leading to the erosion of evolved or engineered host resistance and increased rates of pathogen evolution[136]. Associated spillover followed by spillback can create scenarios that facilitate amplification and potentially selection of problematic pathogen variants[137], an issue highlighted by recent documentation of human to mink to human transmission of SARS-CoV-2 (REF.[138]). Likewise, increased rates of pathogen importation provide increased opportunities for pathogen populations to evolve the ability to utilize novel vectors (as has been observed in the Americas for malaria[129]). Increased population connectivity can also enable pathogens and their vectors to shift to novel host species, from infected mosquitoes travelling on boats or in planes to agricultural pathogens being inadvertently relocated. Hosts that have not previously been exposed to such pathogens, and thus have no co-evolved defences, yet are phylogenetically and/or genetically similar to the original host are often most at risk[139,140], a fact that makes homogenization of crops[141] or livestock a concern. Novel pathogen introductions can have large-scale population and ecosystem impacts, of which one famous example is the extirpation of the American chestnut tree by chestnut blight[142]. Changes in selection pressure resulting from changes in health-care strategies (for example, introduction of vaccination) may have the potential to select for different pathogen characteristics, and could potentially drive the evolution of virulence in pathogens[143,144].

Local-scale disease dynamics

Emerging, re-emerging and endemic pathogens in human populations may exhibit distinct dynamic patterns of spread at the local scale. These patterns will be governed by demographic factors, including the effects of human behaviour on transmission (for example, school terms drive transmission of many childhood infections[26] and sex-specific travel patterns may result in higher burdens of chikungunya in women in Bangladesh[27]) and immunity (which, for immunizing infections such as measles and rotavirus infection, is, in turn, shaped by replenishment of susceptible individuals via births[28,29] and depletion by vaccination where vaccines are available[30]). Transmission may also be affected by climatic variables acting spatially or over the course of the year in line with seasonal fluctuations[31,32]. Recent global changes have affected each of these drivers of local-scale dynamics (FIG. 3).

As school attendance not only modulates transmission of childhood infections[26] but also shapes human mobility[33], dramatic increases in rates of school attendance globally thus have the potential to substantially alter the dynamics of many infections. That this has yet to be documented is perhaps in part because this change has happened alongside expansion of access to vaccines that protect children against many of the relevant infections, as well as global declines in birth rates, which also facilitate control efforts by diminishing the size of the susceptible pool[34]. If the burden of disease is age specific, the intersection between immunity and shifting demography may be particularly marked: declining birth rates translate into a smaller pool of susceptible individuals and thus infected individuals, reducing the overall rate at which susceptible individuals become infected, and thus increasing the average age of infection or disease, as reported for dengue in Thailand[35] and rubella in Costa Rica[36] as these countries went through the demographic transition. Conversely, ageing populations may increase transmission; for example, longer shedding has been suggested with increasing age for SARS-CoV-2 (REF.[37]).

Demographic changes to population size and density via urbanization may also affect dynamics. Influenza, for example, tends to exhibit more persistent outbreaks in more populous, denser urban regions[38] (FIG. 2). A similar pattern was reported in the early COVID-19 pandemic[39]. If demographic change has importantly altered the context of infectious diseases in recent years, arguably an even larger effect is caused by changes in the occurrence of immunomodulatory infections, which, in turn, may affect other infections. For example, the emergence of HIV has amplified the burden of tuberculosis[40]. Mass drug administration efforts have reduced helminth prevalence, which will have knock-on effects on the burden of other infections, such as malaria, which may be increased in individuals experiencing a heavy worm burden[41]; both will also intersect with the efficacy of vaccination programmes[42].

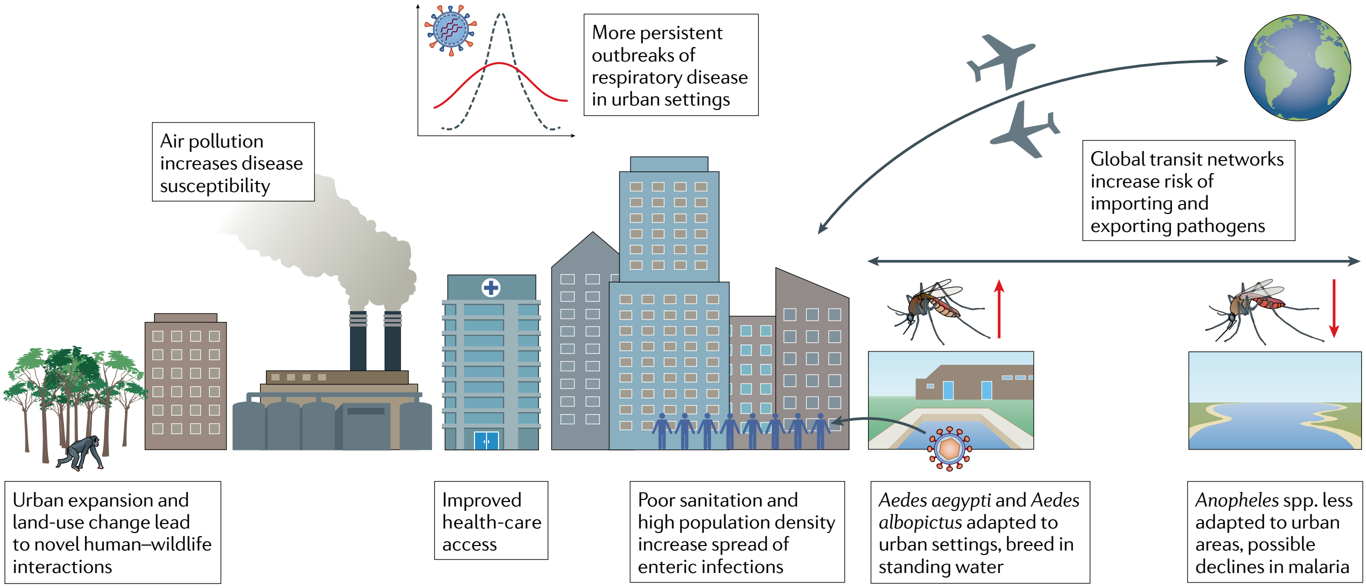


Fig. 2 | **Impacts of urbanization on infectious disease.** Interactions between urbanization and infectious disease are complex, with increased urbanization driving both positive and negative changes to global disease burden.

The climate plays a key role in driving the local-scale seasonal dynamics of many infectious diseases, which may thus be altered by global change in climatic conditions[43,44]. Considering these impacts requires recognizing that interactions with climate differ by pathogen type. For directly transmitted infections, the role of climate is revealed by marked latitudinal gradients in epidemic timing[32,45]. Several respiratory pathogens, including influenza virus, are more highly seasonal in temperate climates and exhibit greater year-round persistence in tropical locations[32,46]. Climate change is expected to lead to an expansion of these tropical patterns, with possible implications for pathogen evolution[43,47]. At the individual level, susceptibility to respiratory viral infections may be impacted by exposure to local air pollution, which is a concern for rapidly urbanizing locations, where urban air pollution may disproportionately affect low-income communities and communities of colour[48,49]. For example, non-Hispanic Black and Hispanic populations in the USA were found to have higher exposure to certain $PM_{2.5}$ components than non-Hispanic white populations[49]. At the same time, globally, a move to an urban location may bring benefits in terms of increased access to health care (FIG. 2).

For some bacterial and fungal diseases, climatic changes may affect the pathogen's environmental reservoir. Incidence of coccidioidomycosis (valley fever), caused by inhalation of fungal spores of *Coccidioides* spp., is expected to increase with climate change as the region with optimal conditions for fungal spore production expands[50]. Climate change may also have played a role in the emergence of the drug-resistant fungal pathogen *Candida auris*. *C. auris* emerged in several continents at the same time and has been shown to have increased thermotolerance compared with other closely related fungal species, which perhaps evolved in response to global warming[51,52]. This increased thermotolerance may have enabled the pathogen to jump from its environmental habitat into an intermediary avian host, given the higher body temperatures of avian fauna, before infecting humans[52].

Demographic change and technological changes may alter a host's interaction with the environmental reservoir. Cholera, caused by the bacterial pathogen *Vibrio cholerae*, persists in the environment, particularly in aquatic settings. Changes to environmental conditions, including elevated sea temperatures, lead to increased reproduction of the pathogen and local epidemics[53], with clear links to longer-term climate phenomena such as El Niño[54]. However, improved sanitation lowers the risk of exposure to *V. cholerae* and has led to a decline of the disease in many locations[53].

For vector-transmitted diseases, biological traits of both the vector and the pathogen may be sensitive to climate. Many transmission-related life cycle traits of the mosquito (biting rate, adult lifespan, population size and distribution) and the pathogen (extrinsic incubation rate) are temperature sensitive, and oviposition patterns depend on water availability[55]. Consequently, the geographical range for dengue, malaria and other vector-borne diseases[56–58] is affected by the local climate, and there is substantial effort to understand how these ranges may change with climate change[59–61]. For certain vector-borne diseases such as Zika virus disease, climate change may lead to an expanded range[62]. However, for other diseases, such as malaria, climate change may shift the spatial range of the infection to higher latitudes[63]. As ever, the footprint of human interventions may loom larger than these changes in local conditions[25].

At the local scale, one of the strongest footprints detectable on the dynamics of many endemic infections in recent years is declines in incidence associated with access to vaccinations[64]. However, the introduction of a vaccine does not imply immediate elimination.

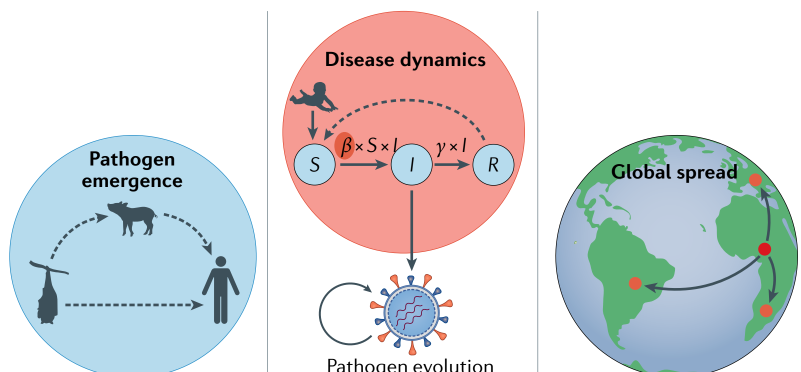
El Niño
A correlated series of climate events associated with the warm phase of the El Niño Southern Oscillation cycle.

As vaccination coverage increases, measles outbreaks, for instance, follow a pathway towards elimination defined by declines in mean incidence but high variability in outbreak size[34]. Imperfect vaccine coverage may allow population susceptibility to increase such that substantial outbreaks can occur if the disease is reintroduced; for example, the 2018 measles outbreak in Madagascar, which led to more than 100,000 cases[65]. Improved surveillance of the landscape of population immunity, via serological surveys, could help determine gaps in vaccination coverage[66].

Global spread

As local conditions alter demographically, or as a result of climate change potentially expanding the range of locations suitable to a particular pathogen or vector, increased global connectivity will enable pathogens to reach these new environments more rapidly (FIGS 3,4). Here, we review the impact of global change on three forms of global connectivity — international travel, human migration and local-scale mobility, and the international trade of animals, animal products and plants — while considering the impact on infectious disease risk. Technological change over the past two decades has dramatically lowered the cost of international travel, while demographic change has led to heightened demand for inexpensive flights (FIG. 1b). Demographic and climatic drivers have altered patterns of local mobility and regional migration, while rising demand and technological change have increased the trade of plants and animals. At the same time, an increasingly urban population is better connected than ever before to global travel networks (FIG. 4). These changes to global connectivity will present unique risk factors for infectious disease spread, enabling pathogens to travel further and faster than ever before.

International travel. The late twentieth century and the early twenty-first century have been marked by technological developments enabling ever swifter movement of people and pathogens over large distances — from trains to planes, and an expanding international airline network (FIG. 4). The total number of airline passengers doubled from just below two billion in 2000 to more than four billion in 2019 (FIG. 1b). This rampant increase in global connectivity brings with it new risks from emerging pathogens (BOX 2). However, many endemic pathogens also circulate via transit routes: seasonal influenza circulation in the USA can be predicted by flight patterns[67,68], with evidence that flight bans following the events of 9/11 caused a delayed outbreak, and a prolonged influenza season within the USA as measured by a 60% increase in the time to transnational spread[68]. Similarly, rapid global air travel is expected to have played a key role in the global spread of SARS-CoV-2. Genetic analyses demonstrate multiple introductions of SARS-CoV-2, driven by air travel, in the Middle East[69], northern California[70] and Brazil[71].



Climatic change	Drives range shifts for reservoir species	Affects transmission and susceptibility	Affects the geographical range of vectors
Technological change			
Transportation	Improved global surveillance		Air transit and high-speed rail affect pace and range of spread
Health care		Vaccination affects dynamics	Improved care reduces burden
Demographic change			
Population growth and land use	Increased contact with reservoir species	Population numbers affect evolution, birth rates affect dynamics	Larger population travelling
Urbanization	Depends on species	Density affects contact rate	Urban population more connected
Ageing	Imunosenescence affects spillover risk	Ageing population increases transmission	Possible larger burden

Fig. 3 | **Effects of climatic, technological and demographic change on disease emergence, dynamics and spread.** The table summarizes select recent global changes (rows) and their impacts on disease emergence, local-scale dynamics and global spread (columns). An example susceptible (*S*), infected (*I*), recovered (*R*) model is shown, where β represents the transmission rate and γ is the recovery rate.

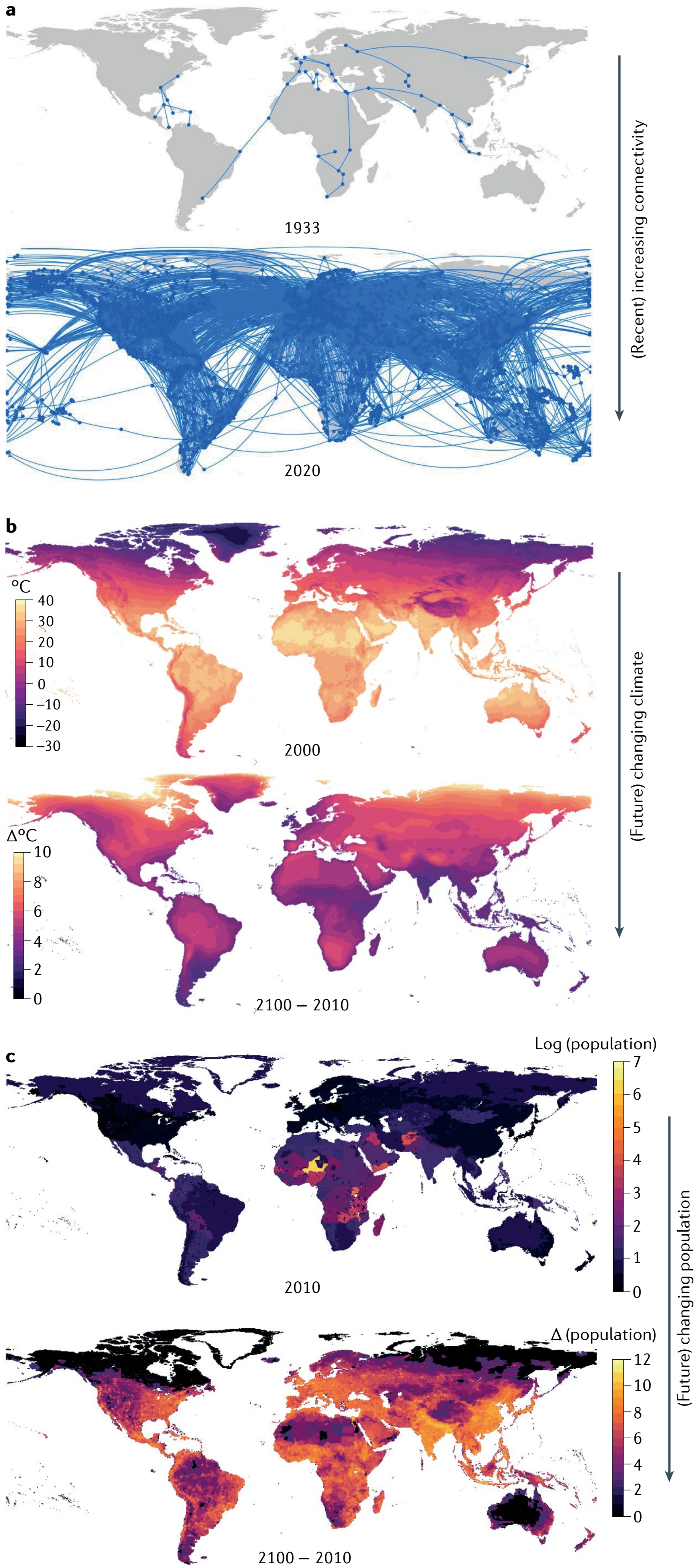
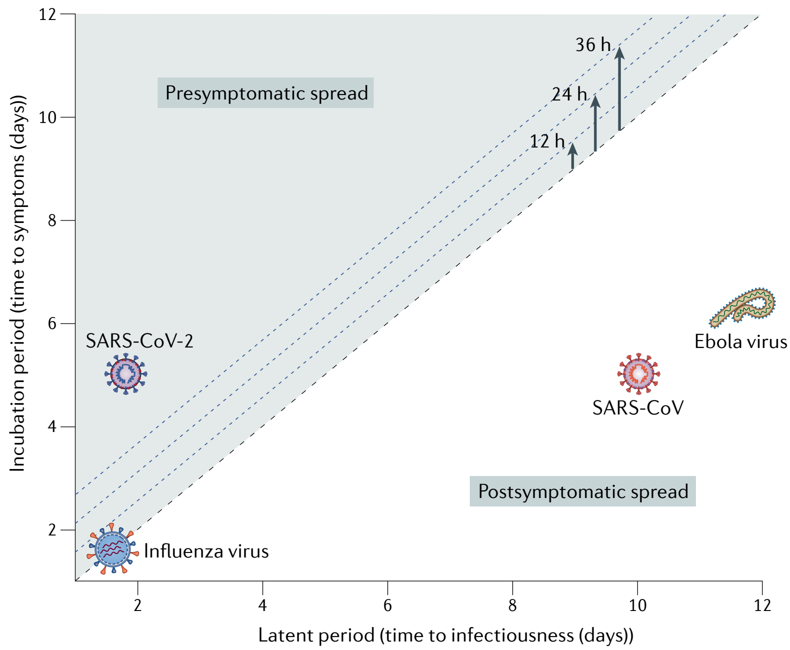


Fig. 4 | **Mapping changes to travel and climate.** **a** | The global international air travel network expanded substantially from 1933 to 2020 (data from WorldPop and REF.[131]). **b** | Average monthly maximum temperature in 1970–2000) and difference between 2070–2100 and 1970–2000 averages (data from WorldClim, Shared Socioeconomic Pathway 3 (SSP3)). **c** | Population projections under SSP3 in 2010 and relative population change projected until 2100 (source NASA Socioeconomic Data and Applications Center (REF.[132])). Part **a** adapted with permission from REF.[131], OUP.

International travel can lead to the global spread of vector-borne diseases via the introduction of new vectors into regions with suitable environmental conditions or the introduction of new pathogens into native and invasive vector populations. Historically, vectors have been introduced via trade routes: ships are thought to have been key to the global dispersal of *Ae. aegypti* and *Ae. albopictus*, which then became established in locations with appropriate environmental conditions[72,73]. *Anopheles gambiae*, the primary vector of malaria in Africa, was introduced into Brazil in the 1930s and became established in a region with a climate similar to that of its native Kenya[74]. Although malaria was already endemic in Brazil at the time, *An. gambiae* proved a much more effective vector, leading to a severe outbreak and a costly (but successful) eradication campaign[73]. There has been relatively little documented evidence of the introduction of new vectors via air travel. This is likely due to the low probability of vectors surviving the flight, and disembarking in a suitable region, in sufficient numbers to establish and drive an epidemic[75]. However, cases of 'airport malaria', that is, malaria transmitted within international airports, even outside endemic regions, are rare but becoming more common[76].

A more feasible scenario is that air travel can bring an infected human host into contact with a native or invasive vector population that then establishes local transmission. Climate change has driven a shift in the range of several key vectors, which may make this introduction more likely. The range of the biting midge *Culicoides imicola*, a vector of bluetongue virus, which causes disease in ruminants, has expanded over the past few decades from sub-Saharan Africa and the Middle East into Europe, bringing a wave of bluetongue epidemics[77]. Following this expansion, bluetongue virus then spread outside the range of *C. imicola* into native populations of *Culicoides* spp. in more northerly regions of Europe. In terms of air travel, the 2015 Zika virus disease epidemic in the Americas may provide a recent example of a pathogen spreading into a susceptible vector population, likely facilitated by high connectivity[78]. Zika virus is thought to have been introduced to Brazil from French Polynesia and vectored by *Aedes* spp., although the volume of air travel during this period makes it almost impossible to conclusively determine the origin[78]. Similarly, it is hard to pinpoint the pathway via which West Nile virus was introduced into the USA in the 1990s; however, transport by either shipping (transporting vectors) or aircraft (transporting a human host) is likely[79]. After introduction, West Nile virus spread in the native *Culex* spp. mosquito population. More broadly, climate change

Box 2 | **Will there be another pandemic like COVID-19?**



COVID-19 has had an unprecedented impact on both human lives and our society, and we will likely be dealing with the consequences for decades to come. As we reckon with these consequences, one concern is that a suite of global changes has increased the risk from emerging pathogens, such that pandemics similar to COVID-19 could be a more frequent occurrence. However, there are biological features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that have made the pathogen distinctly difficult to control, primarily the virus's ability to spread asymptomatically and presymptomatically. Many pathogens do not exhibit these features, which may be a cause for cautious optimism going forward.

The expansion of regional and global air travel, along with the increasing development of high-speed railway networks, has resulted in a substantial degree of connectivity between human populations[73]. At the same time, land-use change and climate change may have increased the risk of pathogen emergence. In combination, these drivers imply an era where pathogens are more likely to emerge, and more likely to spread globally on emergence. However, while the last century bore witness to several pandemics (FIG. 1), SARS-CoV-2 is unrivalled in its rapid, global reach. A key question is why SARS-CoV-2 was so successful at spreading globally and whether this was due to recent increases in global connectivity as opposed to epidemiological and biological characteristics of the virus itself[145].

A clear distinction between SARS-CoV-2 and other recently emerged pathogens (for example, SARS-CoV and Ebola virus) is that an individual infected with SARS-CoV-2 may become infectious before developing symptoms[146]. This presents a unique challenge from a disease control perspective. A standard approach for limiting the onward spread of a new outbreak is to isolate infected individuals when they show symptoms. Case isolation proved successful in mitigating earlier SARS[147] and Ebola virus disease[148] outbreaks. However, symptoms for SARS-CoV-2 infection likely occur after an individual is already infectious[146]. This possible presymptomatic spread limits the efficacy of case isolation interventions as by the time the infected individual is isolated, the person may have already spread the pathogen to others[149]. In the figure, we plot the time to infectiousness (latent period) against the time to symptom onset (incubation period) for four pathogens that have caused severe outbreaks in recent decades. When the latent period equals the incubation period (dashed line in the figure), symptoms occur at a similar time to infectiousness (for example, influenza). The shaded region to the right of this line in the figure indicates possible presymptomatic spread, which may be uniquely difficult to control.

The 2–3-day delay between infectiousness and symptom onset provides ample time for long-distance spread of the disease, given current transport networks (see the figure). Control policies, such as testing before travel, provide a more effective option in this context, yet developing and distributing a test takes time, during which time the disease may spread rapidly. The good news is that this presymptomatic spread appears somewhat unique to SARS-CoV-2, at least compared with other acute infections such as influenza, SARS and Ebola virus disease (FIG. 4). In comparison, asymptomatic spread explains some of the difficulty in controlling acquired immunodeficiency syndrome before antiretroviral measures were available.

complicates the picture in terms of possible future introductions. As the range of locations with environmental suitability for certain vector species changes, successful introductions of pathogens into these vector populations may become more likely[80]. At the same time, changes to population structure (for example, via urbanization) may alter the suitability of an environment for vector reproduction (FIG. 2).

Migration and local mobility. Human migration is an intrinsic component of population dynamics driven by socio-economic, political and environmental factors, and one that has undergone considerable upheaval in the modern era. It is estimated that globally the number of international migrants, those who intentionally relocate to a country other than their birth country, is almost 272 million, representing 3.5% of the world's population. By contrast, temporary migration, often considered 'seasonal migration', is driven largely by economic patterns, including agricultural seasons that require short periods of intense labour. The rate of migration continues to increase owing to both social, economic, political and environmental drivers in origin countries and economic opportunities, physical safety and security in destination countries. Projections for migration are unclear, with the UN projecting stable rates after 2050 (REF.[81]). However, climate change will likely provide an escalating push factor, with sea level rise and extreme weather events leading to forced migration from exposed regions[82].

Given the movement of people between countries, there remain risks of introduction of infectious diseases, including those common and uncommon in the country of migration[83]. It is possible for a infectious disease common in the source country, such as latent tuberculosis, malaria, viral hepatitis and infection with intestinal parasites, to be imported via this mechanism[84–86]. For example, in many destination countries, a large proportion of cases of tuberculosis are observed in the foreign-born population. However, the ultimate impact of these introduction events will depend largely on the population-level susceptibility and environmental suitability for sustained transmission in the destination country. More importantly, migrant groups often have more limited access to health care, treatment and resources, particularly those displaced, who are often provided with limited options to safely seek care and treatment[87]. Minimizing the impact of these possible disease threats depends on providing appropriate health care to these high-risk groups that takes into account the multifaceted social, political and economic components[88].

Within-country population mobility can also play a key role in disease spread; however, it is typically difficult to track these movements. Aggregated mobile phone data are a valuable tool for tracing patterns of local mobility and predicting future outbreaks[89]. In recent work, mobility data have been shown to be predictive of inequities in COVID-19 burden in the USA[90]. Similarly, population mobility was found to predict the spread of the 2011 dengue epidemic in Pakistan[91], while local travel following the Eid holidays was found to predict the spread of the chikungunya outbreak in 2017 in Bangladesh[92]. As the trend of urbanization continues, mobility to and from dense urban centres (that is, megacities) will likely play a future role in local spread of infections[92]. Better tracking of within-country population mobility, using novel data streams, may present an opportunity for forecasting future outbreaks[93].

Intensification of animal and plant trade

International trade has expanded rapidly in the modern era and has been matched by a global proliferation of infectious diseases affecting not only humans but also animals and plants[94,95]. Trade drives this pattern by facilitating the translocation of hosts and pathogens across the geographical and ecological boundaries that constrain their spread. The economic and environmental threats posed by trade-driven infectious diseases of plants and animals are increasingly being recognized, and calls for more stringent containment measures have intensified in recent years[96,97].

Plant trade. Deliberate transport of plant products has existed since the emergence of trade. Increases in the speed of transport during modern times have allowed more live plant tissue, and as a result more viable pathogen propagules, to be transported over long distances. Combined with the intensification of trade at the global scale, this pattern has driven a rise in long-distance transmission and disease emergence[98,99]. Trade drives the emergence of novel plant diseases by creating novel interactions between hosts and pathogens[100]. One pathway through which this can occur is the introduction of novel pathogens to native plants. For example, *Xylella fastidiosa*, a generalist bacterium vectored by xylem-feeding insects, was introduced into Europe in 2013 from the USA, likely as a result of trade. In Italy, *X. fastidiosa* is causing an ongoing epidemic of 'olive quick decline syndrome', resulting in severe losses of an economically and culturally important crop[101,102]. Trade can also drive the emergence of plant disease by introducing novel hosts to native pathogens. Eucalyptus rust, a disease caused by the fungal pathogen *Austropuccinia psidii*, emerged when the pathogen transferred from its native South American hosts in the myrtle family (Myrtaceae) to non-native *Eucalyptus* trees (which also belong to the myrtle family) being grown on plantations[103]. The disease now threatens to 'spill back' into naive endemic *Eucalyptus* populations in Australia.

Propagules
Pathogen units responsible for infection, such as a fungal spore or viral particle.

Animal and animal-product trade. Animal trade has contributed to multiple outbreaks and emergence events globally, which have had major consequences for the agricultural sector as a whole and pose substantial risk for animal and public health. Large numbers of livestock are traded annually between countries and may facilitate the spread of pathogens. Rift Valley fever, for example, is a zoonotic vector-borne viral disease causing abortion and high neonatal mortality in domestic ruminants. The disease is widespread on the African continent and has recently been detected in Saudi Arabia and Yemen. Live cattle movement between East Africa and the Arabian peninsula or from the Union of Comoros to Madagascar is thought to have contributed to the introduction of Rift Valley fever virus and caused outbreaks in these locations in 2000 (Arabian Peninsula) and 2008 (Madagascar)[104,105].

Additionally, the trade of animal-derived products such as meat may enable the movement of pathogens over large distances and between continents. For instance, African swine fever is a highly contagious viral disease affecting several members of the family Suidae, including domestic pigs and wild boars. Infection by African swine fever virus may result in up to 100% morbidity and mortality in affected pig herds and substantial economic losses for producers. In 2007, the accidental introduction of African swine fever virus to Georgia led to the first outbreak of African swine fever in Europe since the early 1990s[106]. The virus, which used to occur primarily in sub-Saharan Africa, was allegedly introduced to the Caucasian peninsula through meat products contaminated with viruses closely related to the ones found in Madagascar, Mozambique or Zambia[107]. Despite efforts to contain the virus, the disease has spread to more than 20 countries in Europe and Asia[108,109].

Similarly, in recent decades there has been an expansion in infections of *Vibrio parahaemolyticus* — a bacterial pathogen found in shellfish and the leading

Box 3 | Big data for disease

Recent technological advances in collecting, sharing and processing large datasets, from satellite images to genomes, represent a new opportunity to answer critical questions in global health. However, challenges remain, including the uneven geographical distribution of available data as well as biases in representative sampling. We highlight three areas of future growth.

Serological surveys

Serological surveys detect the presence of antibodies in blood — recent advances in testing now enable the detection of exposure to multiple pathogens with use of a small sample of blood[150]. Serological surveys have attracted attention during the COVID-19 pandemic as a means to track population exposure given under-reporting, although test performance characteristics differ widely between epidemiological contexts as well as the choice of assay used[151]. Historically, serological surveys have been financially and logistically expensive to run, but declining costs are leading to increased availability of serological data.

Genomic surveillance systems

Genomic surveillance systems are able to characterize and track the emergence of novel variants (for example, during the COVID-19 pandemic). Undoubtedly these data have enabled the rapid development of diagnostics and vaccines and, when combined with epidemiological information, are able to provide a more detailed picture of ongoing transmission dynamics. Efforts to develop national and international genomic surveillance networks are varied but with clear success stories[152,153] even in low-resources settings[154]. However, resource limitations, including sequencing platforms, bioinformatic pipelines and the regular collection of samples for processing, continue to limit the global expansion of sequencing.

Artificial intelligence and machine learning

These techniques are frequently proposed as tools for answering key public health questions, yet specific use cases remain elusive[155]. Using these tools to predict viral emergence, for example, may prove difficult due to microbiological complexities and the cost of data collection[156], yet could prove valuable for targeting sampling efforts[157]. In terms of uncovering population-level drivers of disease transmission, statistical approaches, including machine learning, can be used to leverage novel, and high-volume, data streams. However, more classical, mechanistic models may provide a more robust framework for projecting future outcomes for the disease system under demographic, technological and climatic change. Future work should aim to improve the integration of machine learning approaches within the traditional mechanistic modelling frameworks to rapidly and accurately assess prospective challenges.

cause of seafood-related illness globally. The pathogen is endemic to regions of the US Pacific Northwest but has recently spread to other parts of the USA, Europe and South America[110,111]. The concerning increase in *V. parahaemolyticus* infection is expected to have several drivers connected to global change. Declines in sea ice have increased ship traffic through the Bering Strait, with cargo ships possibly transporting *V. parahaemolyticus* in ballast water. At the same time, increasing sea temperatures may have increased the global environmental suitability for *V. parahaemolyticus* in the marine environment[110]. Finally, dispersal of the pathogen may have occurred via increasing global trade in shellfish, with evidence suggesting possible dispersal via Manila clams introduced into Spain from Canada[111]. This combination of possible drivers speaks to the complexity of understanding infectious disease risk in an era of global change, and the necessity of exploring concurrent changes.

Transboundary spread of diseases through legal and illegal trade of live animals may also have important consequences for biodiversity on a global scale. For example, the amphibian trade contributed to the expansion of novel strains of the fungal pathogen genus *Batrachochytrium* into naive hosts, devastating wild amphibian populations globally[112]. Conversely, infectious diseases also hamper trade, resulting in indirect economic losses in affected populations. Foot and mouth disease virus is a major reason for trade restrictions on livestock. While endemic in certain countries in Asia and Africa, foot and mouth disease virus causes outbreaks in naive populations, resulting in large economic losses[113]. While trade is a major driver of pathogen spread, food animal production has transformed in recent history into large-scale intensified systems with high-density, genetically homogenous populations, ideal for pathogen emergence and maintenance[114]. Critically, animal production systems often serve as the interface between wild and human populations, and multiple viral spillover events have occurred at this nexus. Nipah virus spilled over from fruit bats to the domestic pig population multiple times before subsequently infecting humans[115]. Pandemic variants of human influenza A virus are often the result of reassortment between human and avian viruses, with both domestic poultry and wild birds posited to play a role[116–118]. A non-viral example is the spillover of antimicrobial-resistant pathogens from livestock into humans: intensive antibiotic use in industrialized and smallholder livestock production systems to promote growth and prevent infections has been linked to the emergence of antibiotic resistance in humans[119]. Tackling emergence and disease spread in animal systems will require rethinking both food animal production and global trade of animals.

Reassortment
The mixing of genetic material of different pathogens within an infected cell.

A new era of infectious disease

In recent decades, declines in mortality and morbidity, particularly childhood mortality, have been one of the great triumphs of public health. Greater access to care, such as therapeutics (including antibiotics), improved sanitation and the development of vaccines[120] have been core drivers of this progress. Even as medical advances in the twenty-first century have spurred advances in population health, inequalities in access to these advances remain widespread between and within countries[121]. Reducing inequities in access to health care and improving surveillance and monitoring for infectious diseases in low-income and middle-income countries, and in underserved populations within countries, should be a priority in tackling pathogen emergence and spread.

While life expectancy continues to increase, and life years lost to infectious diseases decline, the new threat of infectious disease will likely come from emerging and re-emerging infections. Climate change, rapid urbanization and changing land-use patterns will increase the risk of disease emergence in the coming decades. Climate change, in particular, may alter the range of global pathogens, allowing infections, particularly vector-borne infections, to expand into new locations. A continued uptick in global travel, trade and mobility will transport pathogens rapidly, following emergence. However, there are counterpoints to this trend: the rapid growth of connectivity observed in the early twenty-first century may stabilize, and structural changes wrought during the COVID-19 pandemic may persist[122]. Increased investment in outbreak response, such as the recent formation of the WHO Hub for Pandemic and Epidemic

Multiplex serology
The measurement of antibody responses to multiple pathogens simultaneously.

Intelligence, could help mitigate the threat from future emerging infections. In addition, efforts to develop universal vaccines (that is, vaccines that engender immunity against all strains of influenza viruses or coronaviruses, for example) could provide a monumental leap forward in tackling present and future infections[123].

A changing world requires changing science to evaluate future risks from infectious disease. Future work needs to explicitly address concurrent changes: how shifting patterns of demographic, climatic and technological factors may collectively affect the risk of pathogen emergence, alterations to dynamics and global spread. More forward-looking research, to contend with possible future outcomes, is required in addition to the retroactive analyses that typically dominate the literature. Increasing attention needs to be paid to pathogens currently circulating in both wild and domestic animal populations, especially in cases where agriculture is expanding into native species' habitats and, conversely, invasive species are moving into populous regions due to climate change. As the battle against certain long-term endemic infections is won, institutional structures built to address these old enemies can be co-opted and adapted for emerging threats. At the same time, new technologies, including advances in data collection and surveillance, need to be harnessed (BOX 3). There is much recent innovation around surveillance, from reinterpreting information available from classic tools such as PCR[124] to leveraging multiplex serology approaches to identify anomalies that might suggest pathogen emergence, and there is increasing interest in integrating multiple surveillance platforms (from genomic to case data) to better understand pathogen spread. Finally, future research needs to align with a global view of disease risk. In an increasingly connected world, the risk from infectious disease is globally shared. The COVID-19 pandemic, including the rapid global circulation of evolved strains, highlights the need for a collaborative, worldwide framework for infectious disease research and control.

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