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## Burden of non-communicable diseases from infectious causes in 2017: a modelling study

**Matthew M Coates,**

Program in Global Noncommunicable Diseases and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA; Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA

**Alexander Kintu,**

Program in Global Noncommunicable Diseases and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA; Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston, MA, USA

**Neil Gupta,**

Program in Global Noncommunicable Diseases and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA; Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA; Partners In Health, Boston, MA, USA

**Emily B Wroe,**

Program in Global Noncommunicable Diseases and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA; Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA; Partners In Health, Boston, MA, USA

**Alma J Adler,**

Program in Global Noncommunicable Diseases and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA

**Gene F Kwan,**

Program in Global Noncommunicable Diseases and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA; Partners In Health, Boston, MA, USA; Section of Cardiovascular Medicine, Boston University School of Medicine, Boston, MA, USA

**Paul H Park,**

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Correspondence to: Dr Gene Bukhman, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA 02115, USA [gene\\_bukhman@hms.harvard.edu](mailto:gene_bukhman@hms.harvard.edu).

Contributors

GB initiated the study. MMC and AK did literature searches. MMC did the analysis with guidance from GB, NG, EBW, AK, AJA, GFK, PHP, RR, and ALB. MMC wrote the initial draft of the manuscript. All authors contributed to results interpretation and critical evaluation and revision of the manuscript.

Declaration of interests

All other authors declare no competing interests.

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Program in Global Noncommunicable Diseases and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA; Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA; Partners In Health, Boston, MA, USA

**Ruma Rajbhandari,**

Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA; Harvard Medical School, Boston, MA, USA; Mount Auburn Hospital, Cambridge, MA, USA

**Anthony L Byrne,**

Socios En Salud Sucursal Perú, Lima, Peru; Centre for Research Excellence in Tuberculosis, Sydney, NSW, Australia; Heart Lung Clinic, St Vincent's Hospital Clinical School, University of New South Wales Sydney, Sydney, NSW, Australia

**Daniel C Casey,**

Public Health Seattle and King County, Seattle, WA, USA

**Gene Bukhman**

Program in Global Noncommunicable Diseases and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA; Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA; Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA; Partners In Health, Boston, MA, USA

## Summary

**Background**—Non-communicable diseases (NCDs) cause a large burden of disease globally. Some infectious diseases cause an increased risk of developing specific NCDs. Although the NCD burden from some infectious causes has been quantified, in this study, we aimed to more comprehensively quantify the global burden of NCDs from infectious causes.

**Methods**—In this modelling study, we identified NCDs with established infectious risk factors and infectious diseases with long-term non-communicable sequelae, and did narrative reviews between April 11, 2018, and June 10, 2020, to obtain relative risks (RRs) or population attributable fractions (PAFs) from studies quantifying the contribution of infectious causes to NCDs. To determine infection-attributable burden for the year 2017, we applied estimates of PAFs to estimates of disease burden from the Global Burden of Disease Study (GBD) 2017 for pairs of infectious causes and NCDs, or used estimates of attributable burden directly from GBD 2017. Morbidity and mortality burden from these conditions was summarised with age-standardised rates of disability-adjusted life-years (DALYs), for geographical regions as defined by the GBD. Estimates of NCD burden attributable to infectious causes were compared with attributable burden for the groups of risk factors with the highest PAFs from GBD 2017.

**Findings**—Globally, we quantified 130 million DALYs from NCDs attributable to infection, comprising 8.4% of all NCD DALYs. The infection–NCD pairs with the largest burden were gastric cancer due to *H pylori* (14.6 million DALYs), cirrhosis and other chronic liver diseases due to hepatitis B virus (12.2 million) and hepatitis C virus (10.4 million), liver cancer due to hepatitis B virus (9.4 million), rheumatic heart disease due to streptococcal infection (9.4 million), and cervical cancer due to HPV (8.0 million). Age-standardised rates of infection-attributable NCD burden were highest in Oceania (3564 DALYs per 100 000 of the population) and central sub-Saharan Africa (2988 DALYs per 100 000) followed by the other sub-Saharan African regions,

and lowest in Australia and New Zealand (803 DALYs per 100 000) followed by other high-income regions. In sub-Saharan Africa, the proportion of crude NCD burden attributable to infectious causes was 11.7%, which was higher than the proportion of burden attributable to each of several common risk factors of NCDs (tobacco, alcohol use, high systolic blood pressure, dietary risks, high fasting plasma glucose, air pollution, and high LDL cholesterol). In other broad regions, infectious causes ranked between fifth and eighth in terms of crude attributable proportions among the nine risks compared. The age-standardised attributable proportion for infectious risks remained highest in sub-Saharan Africa of the broad regions, but age-standardisation caused infectious risks to fall below dietary risks, high systolic blood pressure, and fasting plasma glucose in ranked attributable proportions within the region.

**Interpretation**—Infectious conditions cause substantial NCD burden with clear regional variation, and estimates of this burden are likely to increase as evidence that can be used for quantification expands. To comprehensively avert NCD burden, particularly in low-income and middle-income countries, the availability, coverage, and quality of cost-effective interventions for key infectious conditions need to be strengthened. Efforts to promote universal health coverage must address infectious risks leading to NCDs, particularly in populations with high rates of these infectious conditions, to reduce existing regional disparities in rates of NCD burden.

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## Introduction

In 2017, non-communicable diseases (NCDs) accounted for 73% of global deaths.<sup>1</sup> Adjusting for differences in population age patterns, death rates from NCDs are higher in low-income and middle-income countries (LMICs) than in high-income countries (HICs).<sup>1</sup> Behavioural risk factors such as diet, physical inactivity, alcohol consumption, and tobacco use, and related metabolic risks such as high blood pressure, obesity, high cholesterol, and high blood sugar are the primary focus of global action frameworks dedicated to the control of NCDs.<sup>2</sup> Air pollution had previously been identified as a neglected risk for NCDs of particular importance in LMICs, and in 2018, at the third high-level meeting of the United National General Assembly on the prevention and control of NCDs, it was explicitly added to the adopted resolutions.<sup>3</sup> Other factors, such as periconceptional developmental dynamics, transgenerational epigenetic effects, and early childhood undernutrition, are important risks related to NCDs, particularly among families living in poverty.<sup>4–6</sup> Given the high burden of infectious diseases in LMICs and expanding biological and epidemiological evidence indicating links between specific infectious pathogens and subsequent development of NCDs, infectious diseases have also been discussed as a risk factor particularly important in LMICs.<sup>7–10</sup>

Although many infectious diseases have been linked to NCDs, only two infectious pathogens, hepatitis B virus (HBV) and human papillomavirus (HPV), are addressed in the NCD Global Monitoring Framework from WHO. Previous studies have quantified the global burden of specific non-communicable illness resulting from infection, particularly among cancers.<sup>11–14</sup> These analyses have suggested that about 30% of new cancer cases can be attributed to infection in sub-Saharan Africa, although that proportion is as low as 4% in North America.<sup>11,15</sup> Some NCDs with high rates in LMICs, such as rheumatic heart disease

and cervical cancer, can be fully attributed to infection.<sup>16,17</sup> However, to our knowledge, no study has previously quantified the global burden of all NCDs attributable to infection, which could directly inform and enhance global and regional NCD prevention and treatment strategies. In this study, we estimate the global burden of NCDs attributable to infectious causes by country and region as part of a large ongoing effort to better quantify the causes of NCDs among the world's poorest people.<sup>18</sup>

## Methods

### Study design

We did a modelling study to determine infection-attributable NCD burden for the year 2017. We identified NCDs with known infectious risk factors and infections with long-term non-communicable sequelae, and did narrative reviews of previous articles to obtain estimates of relative risks (RRs) or population attributable fractions (PAFs). PAFs were calculated from RRs and estimates of exposure to infectious conditions, and we applied estimates of PAFs to estimates of disease burden from the Global Burden of Disease Study (GBD) 2017 for some pairs of infectious causes and NCDs, and for others, we used available estimates of attributable burden directly from GBD 2017.<sup>19</sup> We then aggregated and summarised our findings.

### Disease classification

The distinction between infectious diseases and NCDs is sometimes uncertain in global estimates of burden. For instance, GBD 2017 classified cellulitis, scabies, and fungal skin diseases in the skin diseases NCD subcategory.<sup>19</sup> Conversely, some long-term non-communicable consequences of infection (such as blindness from trachoma) are quantified as part of the burden of the infectious cause in GBD 2017, but can also be tabulated separately as so-called impairments that combine burden from multiple causes.<sup>19</sup> Some of these long-term impairments, such as epilepsy, can result from either infectious or non-infectious causes and are treated as NCDs in the health system.

When a microbe should be considered infectious is also not always straightforward. For example, the bacteria that contribute to dental caries are almost universally present, although variation in several factors, including the numbers of cariogenic bacteria, cause a varied burden of tooth decay across people.<sup>20</sup> Increasing studies are being done on the links between differences or changes in the microbiome and the development or expression of disease.<sup>21</sup>

For the purposes of our analysis, we considered viral, fungal, bacterial, and parasitic pathogens with described biological causal mechanisms leading to an NCD and quantitative epidemiological evidence for increased risk of a subsequent condition treated as an NCD. We report aggregate estimates for NCDs as classified by GBD 2017, plus the long-term non-infectious impairments (blindness, epilepsy, hearing loss, infertility, pelvic inflammatory disease, Guillain-Barré syndrome, intellectual disability, and heart failure) attributed to specific communicable diseases within the GBD that would be seen clinically as NCDs. We added these impairments to the overall NCD category in any aggregated estimates. For

comparability, we chose to include infectious causes classified as NCDs in GBD 2017, as this burden is included in the many studies citing the total burden of disease from NCDs from the GBD.

### Infectious causes identification and inclusion

We identified NCDs in the GBD hierarchy of diseases at least partially caused by infectious conditions and infectious diseases with long-term non-communicable sequelae. We did this via a combination of narrative reviews in PubMed and Google Scholar and a review of the GBD 2017 cause list for NCDs with possible infectious risks or direct infectious causes by clinician co-authors (AK, NG, EBW, GFK, PHP, RR, ALB, and GB) with clinical expertise in varied areas. An initial non-specific database search was done on April 11, 2018, and subsequent searches for evidence about particular conditions were done between April 11, 2018, and June 10, 2020, for articles published in English without publication date restrictions. Search terms were initially general (eg, “infection”, “non-communicable disease”, and “attributable”), but became specific for particular NCDs. We did narrative reviews for studies with RRs or PAFs that could be used to quantify attributable disease burden. Several key sources generated a large number of pairs of infectious causes and NCD outcomes.<sup>7,11,14,19</sup> In addition to searches in PubMed and Google Scholar with terms related to the diseases in question, we expanded our searches for quantitative effect estimates by examining references of the publications identified by our searches. Studies from which we drew quantitative effects were published between 2015 and 2020 although some were meta-analyses including earlier studies. Pairs of infectious conditions and NCDs with attributable burden that we quantified are shown in the appendix (pp 4–6).

The evidence across conditions was of variable quality. To represent this variability and convey the quality of our quantitative estimates, we assigned a quality index score for each risk–outcome pair. We based our approach on the Grading of Recommendations, Assessment, Development and Evaluations process and GBD 2016 quality scores for causes of death.<sup>22</sup> Briefly, to create the score, we assessed quality of information on several dimensions: quality of estimates of effect sizes between exposures and disease outcomes; geographical and demographic specificity of the estimates; and the quality and availability of the input data used to inform any modelling. We used the scores to assign qualitative quality rankings of high, medium, and low. The quality grades and full methods used to generate the scores are provided in the appendix (pp 3–6, 36–38).

Additional pairs with evidence for which insufficient data were available to generate quantitative estimates are discussed in the appendix (pp 28–36). For instance, we were unable to estimate the burden of cardiomyopathy or chronic kidney disease from HIV. We also did not quantify the protective effects of some infectious pathogens, such as that of *Helicobacter pylori* on inflammatory bowel disease, as quantitative characterisations of these relationships are still being more accurately described.<sup>23</sup>

### Data processing

We used publicly available estimates from GBD 2017, available via the GBD Results Tool, as the primary source of disease burden data. The available estimates contain rates and

counts of deaths, years lived with disability, years of life lost, and disability-adjusted life-years (DALYs) for the years 1990–2017, from which we extracted 2017 estimates. Each of these components was available by sex, location, and age groups (early neonatal [0–6 days], late neonatal [7–27 days], post-neonatal [28 days to younger than 1 year], 1–4 years, and 5-year age groups to 95 years and older). In addition to disease burden estimates from the GBD, we used estimates of RRs and PAFs from studies identified in our review, primarily meta-analyses, on associations between specific infectious causes and NCDs. Study references by condition are provided in the appendix (pp 4–6).

Our general approach for quantification was to multiply disease burden from a particular NCD by the PAF of a particular infectious cause. We used PAFs directly from previous studies or calculated them on the basis of RRs and prevalence estimates from previous studies, and we applied these fractions to the disease burden estimates from GBD 2017. The PAFs represented the estimated fraction by which burden of the NCD outcome would be diminished if absent of exposure to the infectious cause. Full details on PAF calculations are given in the appendix (pp 2–3). For some conditions, the GBD data already included burden from NCDs caused by infection (for example, liver cancer from HBV). For those conditions, we used the GBD estimates of resulting burden rather than multiplying by an estimated PAF. When possible, we used country-age-sex-specific estimates of PAFs and burden, according to the GBD age groups, for the year 2017 for each of our calculations. When necessary, we made assumptions that applied PAF estimates for aggregate geographies, ages, and sexes and applied them to estimates of burden in 2017. For example, the analyses of cancer cases attributable to various infections by the International Agency for Research on Cancer sometimes present PAFs by region or even globally in broad age groups.<sup>14</sup> In those cases, we applied the aggregate-level PAF to the more specific estimates of burden. Our methods and assumptions for each condition included are detailed in the appendix (pp 7–28). In addition, we did a crude exploratory quantification of burden attributable to infection for conditions that lacked sufficient evidence (appendix pp 28–36).

To summarise burden from multiple NCDs caused by the same infectious pathogen, we added attributable DALYs for all of the included NCDs attributable to each infectious cause. To summarise burden from multiple infectious pathogens causing the same NCD, our aggregation strategy differed by NCD according to whether we used PAFs or estimates of attributable burden from GBD 2017. The estimates of attributed burden from the GBD were aggregated by addition as designed in the study, whereas the estimates from PAFs were aggregated as they are in the comparative risk assessment component of the GBD (appendix pp. 24–25).<sup>24</sup> From the country-age-sex-specific estimates of attributable burden, we created aggregated estimates for all ages, both sexes, and by GBD region by calculating the sum of attributable burden. Our main reported estimates are total DALYs and attributable proportions globally, and DALYs per 100 000 of the population and attributable proportions by region. Crude rates were calculated with the relevant populations, and age-standardised rates were calculated with the GBD 2017 population standard.<sup>1</sup> We present both crude and age-standardised proportions of NCD burden attributable to infectious causes and rates of this burden. The geographical regions as defined by the GBD were used to aggregate country-level estimates (appendix pp 38–41).<sup>19</sup> Attributable proportions for these aggregate groups were calculated by dividing summed attributable burden by summed total burden.



The disease burden and risk factor attribution estimates from the GBD all have uncertainty intervals. However, uncertainty is propagated by random draws from distributions, and only the upper and lower bounds of the uncertainty interval are publicly available. We did not propagate uncertainty in this analysis, although we discuss implications of the uncertainty. We also show quality scores associated with the estimates for each condition (appendix pp 4–6), and report global infection-attributable NCD burden with and without the low-quality estimates. To contextualise the NCD burden attributable to infectious causes, we compared our estimates with crude and age-standardised attributable proportions for the groups of risk factors with the highest PAFs from GBD 2017—dietary risks, high blood pressure, tobacco use, high fasting plasma glucose, high body-mass index, air pollution, high LDL cholesterol, and alcohol use<sup>24</sup>—globally and by broad region as defined by the GBD. We downloaded these publicly available estimates from the GBD Results Tool. Relative rankings of infectious risk among these risk factors are reported.

All data processing steps were done with R software (version 3.6.1).

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Globally, the NCD burden attributable to infectious causes constituted a substantial number of DALYs (130 million) and 8·4% of the global NCD DALYs including impairments (appendix pp 4–6). When excluding estimates rated as low quality on our quality index, these numbers were 115 million DALYs and 7·4%. The infection–NCD pairs with the largest burden were gastric cancer due to *H pylori* (14·6 million DALYs), cirrhosis and other chronic liver diseases due to HBV (12·2 million) and hepatitis C virus (HCV; 10·4 million), liver cancer due to HBV (9·4 million), rheumatic heart disease due to streptococcal infection (9·4 million), and cervical cancer due to HPV (8·0 million). The NCDs with the highest infection-attributable DALYs and the infectious causes associated with the highest NCD DALYs are shown in the table. Epilepsy was a long-term consequence of a number of different infectious pathogens, totalling 5·7 million DALYs. Gastritis and duodenitis from *H pylori* (4·8 million DALYs) and chronic obstructive pulmonary disease from *Mycobacterium tuberculosis* (5·9 million DALYs) contributed high burden, but the estimates for these conditions were rated as low quality on our index.

Age-standardised proportions of NCD DALYs attributed to infectious causes ranged from 4·1% to 14·6% across countries (median 7·5% [IQR 6·0–9·9]), and age-standardised attributable DALY rates ranged from 635 DALYs per 100 000 population to 4120 DALYs per 100 000 (median 1562 DALYs per 100 000 [IQR 1079–2305]). The crude proportions ranged from 3·8% to 15·5% (median 7·5% [5·4–10·2]), and crude rates ranged from 567 DALYs per 100 000 to 3186 DALYs per 100 000 (median 1614 DALYs per 100 000 [1213–1846]). Age-standardised attributable DALY rates were highest in sub-Saharan Africa, Oceania, parts of Latin America, and central, south, and southeast Asia (figure 1).

Attributable proportions showed a similar pattern, although six HICs had higher age-standardised attributable proportions than the median, but ranked in the lower half in terms of age-standardised attributable rates (Brunei, Chile, Japan, Poland, Singapore, and South Korea). Some countries in south and central Asia and eastern Europe had higher age-standardised rates of attributable burden than the median, but lower age-standardised attributable proportions than the median (Afghanistan, Azerbaijan, Georgia, Kazakhstan, Russia, Ukraine, and Uzbekistan; figure 1, appendix p 42). HICs such as Belgium, Canada, Malta, and Switzerland had the lowest age-standardised DALY rates attributed to infection (less than 700 DALYs per 100 000 population), whereas the Central African Republic, Lesotho, Mongolia, and Papua New Guinea had the highest (more than 3700 DALYs per 100 000; figure 1). Infection-attributable NCD burden remained high in sub-Saharan Africa and southeast Asia based on crude rates. High crude rates of infection-attributable DALYs were also seen in China, eastern Europe, and Russia, because of older populations with high overall NCD burden, and countries in these regions ranked in the highest sextile of crude attributable burden rates (appendix p 43).

Overall geographical variation was driven by differences in rates of specific infectious conditions and the related NCD outcomes (figure 2, appendix p 44). By region, age-standardised NCD rates attributable to infection were highest in Oceania (3564 DALYs per 100 000), followed by central sub-Saharan Africa (2988 DALYs per 100 000) and the other sub-Saharan African regions (eastern sub-Saharan Africa, 2503 DALYs per 100 000; western sub-Saharan Africa, 2457 per 100 000; and southern sub-Saharan Africa, 2296 per 100 000). Rates were lowest in Australia and New Zealand (803 DALYs per 100 000), followed by other high-income regions. Viral hepatitis (B and C) caused the highest age-standardised DALY rates from cirrhosis and liver cancer in southeast, east, and central Asia, central and western sub-Saharan Africa, and Oceania (more than 635 DALYs per 100 000 in each region). Age-standardised DALY rates from rheumatic heart disease caused by streptococcal infection were substantially higher in Oceania (946 DALYs per 100 000) than in other regions, although rates were also high in south Asia (267 DALYs per 100 000) and central sub-Saharan Africa (198 DALYs per 100 000). Cervical cancer burden from HPV infection was highest in sub-Saharan African regions and Oceania (more than 250 DALYs per 100 000 in each region) and in the Caribbean and Latin American regions (more than 125 DALYs per 100 000 in each region). Rates of gastritis and duodenitis, peptic ulcer disease, and gastric cancer from *H pylori* infection were highest in central sub-Saharan Africa, eastern Europe, and east Asia (more than 388 DALYs per 100 000 in each region). Infectious conditions with high prevalence in sub-Saharan Africa, such as malaria and neglected tropical diseases, caused a large burden of several impairments, most notably epilepsy. High HIV rates led to substantially higher rates of cardiovascular burden in southern sub-Saharan Africa than in other regions, and Kaposi sarcoma burden was also high in HIV-prevalent areas (173 DALYs per 100 000 in eastern sub-Saharan Africa, 123 DALYs per 100 000 in southern sub-Saharan Africa, and 65 DALYs per 100 000 in central sub-Saharan Africa, and lower than 20 DALYs per 100 000 in all other regions). Burden from chronic obstructive pulmonary disease attributable to *M tuberculosis* was high in Oceania, south Asia, and sub-Saharan Africa. Full results by NCD, infectious cause, and region are provided in the appendix (pp 45–167).



Globally, the overall proportion of quantifiable NCD burden attributable to infectious causes (crude proportion 8.4%) was higher than proportions attributable to some common risk factors, such as high LDL cholesterol (6.1%), air pollution (6.7%), and alcohol use (4.5%), but lower than the burden attributable to other factors, such as dietary risks (16.5%), increased systolic blood pressure (14.1%), and tobacco use (12.5%; figure 3). The relative ranks of different risks in terms of attributable proportions varied by broad region (figure 3). In sub-Saharan Africa, the crude attributable proportion of the burden from infectious causes (11.7%) was higher than that for any other risk category (each 9.5% or lower). The age-standardised infection-attributable proportion in sub-Saharan Africa was lower than the proportion from dietary risks, high systolic blood pressure, and high fasting plasma glucose. In other regions, infectious conditions ranked between fifth and eighth in terms of crude and age-standardised attributable proportions among the nine risks compared, ranking eighth in both measures in the central Europe, eastern Europe, and central Asia region and the north Africa and Middle East region. Although crude attributable proportions from infectious causes were high in the southeast Asia, east Asia, and Oceania region (9.9%), other risks (dietary risks [21.2%], tobacco [16.8%], high systolic blood pressure [16.4%], and high fasting plasma glucose [10.7%]) also had high attributable burden, lowering the relative rank of infectious risks.

## Discussion

We quantified a substantial global NCD burden from infectious causes (8.4% of overall NCD DALYs in 2017). The crude proportion of NCD burden from infectious causes was greater than 10% in 57 countries, including 44 in sub-Saharan Africa, ten in Asia and Oceania, and three in Latin America. In sub-Saharan Africa, infectious conditions accounted for a larger crude proportion of NCD burden than many common risk factors including dietary risks, high systolic blood pressure, tobacco use, and alcohol use. However, the young age of this population contributed to the high relative ranking of infectious conditions among other risk factors in the crude proportions, compared with the age-standardised proportions. In other regions, the proportion of NCD burden from infectious causes was higher than that from some traditional risk factors such as high cholesterol and alcohol use. We were able to quantify burden attributable to infectious causes from at least one infectious condition in many NCD subcategories, including cancer, cardiovascular disease, chronic respiratory disease, digestive disease, neurological disorders, mental disorders, kidney disease, skin disease, sense organ disease, congenital disorders, urogenital diseases, and dental conditions. Certain infectious risks were of increased importance in specific geographical regions. Cervical cancer burden from HPV was high in sub-Saharan Africa and Oceania; liver cancer from HBV and HCV was high in Asia, and cirrhosis and other chronic liver diseases from these infections was high in many regions of Africa and Asia; high rheumatic heart disease burden was observed in Oceania; and cardiovascular burden from HIV was high in southern sub-Saharan Africa.

Prevention of HBV and HPV is included in the WHO global action plan for the prevention and control of NCDs,<sup>2</sup> and members of the WHO African Region have recognised infections as a common risk factor for NCDs.<sup>9</sup> However, cancers were the only subcategory of NCDs for which relatively comprehensive estimates of infection-attributable burden were available.

11,14 In a modelling study that used estimates for the year 2018 from cancer registry data, Parkin and colleagues showed the importance of infectious risks to cancers in Africa in particular.<sup>15</sup> They estimated that infection accounted for a larger proportion of cancer cases (29%) than traditional risks such as smoking, alcohol, and unhealthy diet (collectively around 13%).<sup>15</sup> In addition to cancers, many types of NCDs have been linked to infectious risks.<sup>7</sup> In our narrative review, we found meta-analyses quantifying RRs, odds ratios, or hazard ratios for many infection–NCD pairs.

Despite the studies we identified, the quality of the quantitative evidence on risks and overall burden was varied and in some cases highly uncertain. Particularly in LMICs, data were often sparse. We assessed the reliability of our estimates using a quality index. Excluding the estimates that were low on our quality index lowered the global proportion of NCDs attributable to infectious causes by approximately 1 percentage point (8.4% to 7.4%). Estimates should be treated with a considerable degree of uncertainty, particularly those of lower quality on our index. In the appendix (pp 28–36), we discuss additional pairs of NCDs and infectious causes for which we were unable to generate quantitative estimates. Given these additional conditions and future infection–NCD links yet to be determined, we believe our estimates are likely to represent a minimum to which additional attributable burden might be added as quantitative evidence expands.

Relationships between infectious causes and NCDs can be complex. The hygiene hypothesis, which posits that asthma and atopy might occur at increased rates in individuals unexposed to pathogens in childhood, has transpired to be nuanced in nature; exposure to some microbes seems to confer a protective effect against asthma, while exposure to others might exacerbate or lead to an increased risk of asthma.<sup>25</sup> Additionally, the pathophysiological mechanisms for some possible infection–NCD pairs have not been fully characterised, for instance, the link between periodontal pathogens and Alzheimer’s disease.<sup>26</sup> Variations in the microbiome are associated with diverse NCDs, such as depression, autism, cancers, and inflammatory bowel disease, and some NCDs might be viewed as communicable via the microbiota.<sup>21,27</sup> Although the resultant differences in NCD burden might be attributable to differences in bacterial colonisation, whether they should be attributed to infection is unclear. Some communicable diseases, such as HIV, create immune changes that allow for other pathogens to increase risk of NCDs, as is the case with human herpesvirus 8 and Kaposi sarcoma.<sup>28</sup> Infections can also cause increased severity of chronic NCDs, even if they did not contribute to initial development of the noncommunicable condition.<sup>29</sup> Non-biological mechanisms such as social stigma and the loss of loved ones are other pathways by which infection could lead to negative mental health outcomes.<sup>30,31</sup> Historical pressure from infectious diseases has led to the development of NCDs over many generations. Sickle cell disorders are a direct result of the evolutionary pressure of malaria and account for a substantial amount of NCD burden (about 2.9% of NCD DALYs in western and central sub-Saharan Africa).<sup>19,32</sup> Causality between infectious diseases and NCDs can run in the other direction; for example, diabetes and sickle cell anaemia can cause an increased risk and severity of infection.<sup>33,34</sup>

Evidence-based and cost-effective interventions have been proposed to address much of the disease burden we quantified. The essential Universal Health Coverage (UHC) package for

LMICs defined in *Disease Control Priorities*, 3rd edition (DCP3), includes at least 73 interventions that target the infectious conditions leading to NCDs identified in this study (appendix pp 168–70).<sup>35</sup> Among these interventions are immunisation for HBV, HPV, tetanus, haemophilus influenzae type b, and meningococcal infection; treatment of acute pharyngitis in children and secondary prophylaxis with penicillin for rheumatic fever or rheumatic heart disease; multiple preventive and treatment measures for malaria, HIV, and *M tuberculosis*; mass drug administration for several neglected tropical diseases including schistosomiasis and trachoma; treatment of childhood respiratory and diarrhoeal diseases; and prevention and treatment strategies for several sexually transmitted infections. Although not specifically targeted by the DCP3 essential UHC interventions, skin diseases would be addressed in part by the availability of antimicrobials and other basic care included.<sup>35</sup> Additional evidence-based interventions outside the DCP3 set, such as treatment of HBV and test-and-treat strategies for *H pylori* in high-risk groups, have been found to be effective and might also be recommended.<sup>36,37</sup> About 125 million (96%) of 130 million NCD DALYs attributable to infection that we quantified are caused by diseases targeted by these evidence-based, effective interventions. Much of the remaining burden would be affected by the same interventions, even if not a specific target of the interventions. For example, endocarditis risk can be lowered with good oral health and availability of antimicrobials.<sup>38</sup>

Global efforts have been made to address the leading infectious causes of NCDs. WHO has called for global action to eliminate cervical cancer and both hepatitis B and C.<sup>39,40</sup> Since their development, vaccines for HPV and HBV have become widespread, but large gaps in coverage remain.<sup>41,42</sup> In the past decade, efforts were expanded around the widespread prevention and curative treatment of HCV in both high-income and low-income settings.<sup>43,44</sup> Several key actions to eliminating rheumatic heart disease have been identified, requiring substantial investment at several levels of the health system.<sup>45</sup> Concerns have been raised about contraindications to treatment and antimicrobial resistance, but increasing evidence supports recommendations for strategies to treat *H pylori* for the prevention of gastric cancer.<sup>37,46</sup> Benefits associated with economic development, including clean water, improved sanitation systems, and living conditions less conducive to spread of infection, offer the opportunity for some progress against infectious diseases outside of the health sector.<sup>47,48</sup> In addition to expanding the prevention and treatment of infectious risks that cause NCDs in LMICs, services specifically for the NCDs that result, such as cancers, epilepsy, and heart failure,<sup>49–51</sup> should be continually expanded.

A number of limitations exist in the interpretation of exposures and burden in the present study, given the methods used. The longitudinal nature of exposure to infectious diseases creates challenges with the comparative risk factors assessment approach. For example, if history of previous infection conveys some additional NCD risk, measuring this past exposure rather than current prevalence of infection would be important for estimating attributable NCD burden. We used current prevalence to calculate PAFs for long-term chronic infectious diseases. For these infections, associations might exist between cumulative exposure time and NCD risk, or disease management might alter risk, as is likely to be true with HIV and cardiovascular disease.<sup>52</sup> We were unable to incorporate this level of detail into calculations of PAFs. Although we calculated the infection-attributable proportion for some diseases, the burden of other non-communicable conditions was estimated directly

in GBD 2017 as part of the infectious disease modelling process (for example, liver cancer due to hepatitis B). We were not able to incorporate uncertainty from the GBD study in our analysis because only summary measures of the underlying distributions of estimates were available, and these distributions are not symmetric. Our estimates should be interpreted with uncertainty from multiple sources, including from the disease burden estimates, estimates of the degree of risk resulting from infectious diseases, and the prevalence of infectious exposures. For some conditions, such as chronic obstructive pulmonary disease from *M tuberculosis*, the uncertainty from multiple inputs was quite high, as shown in a sensitivity analysis in the appendix (p 21). For others, such as cervical cancer, uncertainty came mainly from the estimates of disease burden. We did not do comprehensive sensitivity analyses for each condition.

Quantification of risk with different levels of exposure, improved estimates of exposures, more geographically specific and diverse sets of evidence, and methods development might improve estimates in the future. Such developments might add burden attributable to conditions assessed in this study, such as viral hepatitis, for which our estimates might not fully capture non-fatal burden from early chronic liver disease or deaths from outcomes of viral hepatitis that are not as directly liver-related.<sup>53</sup> There were many infection–NCD interactions for which quantifiable estimates of burden were difficult to obtain, either because of insufficient data or preliminary evidence about causality (crude exploratory quantification of some conditions not included in the main analysis is given in the appendix [pp 30–36]). Many of the conditions with additional unquantified burden— such as pericarditis, musculoskeletal conditions, and restrictive lung disease from *M tuberculosis*; Burkitt’s lymphoma from Epstein-Barr virus and other infections; cardiomyopathy from HIV; pulmonary hypertension from schistosomiasis; chronic kidney disease from HIV and infections other than HBV and HCV; additional congenital anomalies from maternal and congenital infection; and periodontal disease and tooth loss— disproportionately affect people living in LMICs (appendix pp 30–36),<sup>10,14,19,20</sup> suggesting that the degree of underestimation might be higher in these countries.

We identified a substantial NCD burden due to infectious diseases, particularly in world regions with many LMICs. These findings support calls for the inclusion of infectious conditions as an important target in NCD prevention efforts.<sup>8,9</sup> The infectious diseases in our analysis are largely preventable or treatable. Strengthening the availability, coverage, and quality of cost-effective interventions for key infectious conditions could have substantial effects on the global NCD burden. In particular, efforts working towards universal health care in LMICs must target infectious risks leading to NCDs, particularly in populations with high rates of these infectious conditions, to ensure equitable progress in reducing NCD burden globally.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Research in context

### Evidence before this study

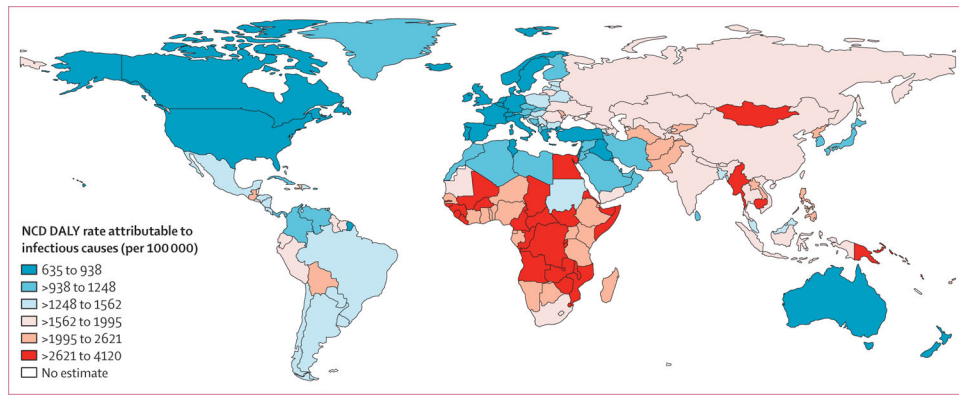
Vaccination coverage for two infectious diseases, hepatitis B and human papillomavirus infection, are included as indicators in the WHO Non-Communicable Disease (NCD) Global Monitoring Framework. There are established links between many other infectious pathogens and particular NCD outcomes. We did narrative reviews in PubMed and Google Scholar to identify articles in English quantifying the burden of disease for NCDs linked to infections, without date restrictions. An initial non-specific database search was done on April 11, 2018, and subsequent searches for evidence about particular conditions were done between April 11, 2018, and June 10, 2020. Search terms were initially general (eg, “infection”, “non-communicable disease”, and “attributable”), but became specific for particular NCDs. The search was expanded by reviewing the reference lists of studies identified by our searches, particularly from several key publications, and by clinician review of the cause list of the Global Burden of Disease Study (GBD) 2017 for candidate NCDs. Efforts have been made by the International Agency for Research on Cancer to quantify the global incidence of various cancers due to infectious cases. GBD 2017 quantified burden from particular pairs of infectious conditions and NCDs, although it did not specifically aggregate causes or comprehensively estimate burden. Other studies have discussed infectious risks qualitatively in non-systematic reviews, highlighting their importance in low-income and middle-income countries (LMICs), or done meta-analyses quantifying the risk of specific NCDs with exposure to particular infectious diseases.

### Added value of this study

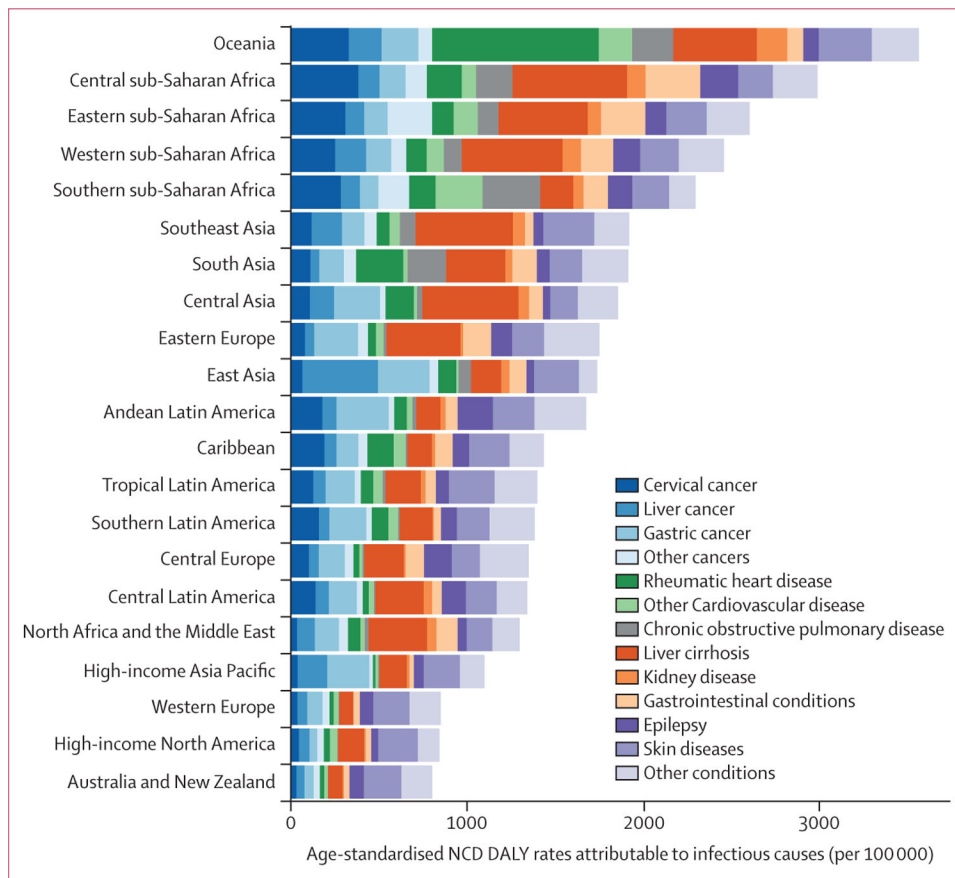
To our knowledge, this study is the first modelling attempt to quantitatively estimate the infection-attributed burden for all corresponding NCDs. Our estimates quantify the scale of NCD burden attributable to infection overall, and highlight the large proportions of NCD burden that could be addressed by the prevention and treatment of infectious diseases. We found that at least 8% of NCD burden could be attributed to infectious risks globally, with higher proportions in particular regions, including Oceania and sub-Saharan Africa. Within sub-Saharan Africa, NCD burden attributable to infectious conditions was higher than NCD burden from many common NCD risk factors, such as tobacco, high systolic blood pressure, and the dietary risks included in the GBD study. The findings can inform policies and health system strategies aimed at preventing NCDs, particularly in LMICs.

### Implications of all the available evidence

Infectious conditions lead to a substantial portion of the global burden of NCDs. This NCD burden attributable to infectious causes is highest in LMICs; in some countries, it is larger than the NCD burden attributable to individual behavioural and metabolic NCD risks such as tobacco, alcohol, increased blood pressure, and obesity. Increasing the coverage of interventions to treat and prevent key infectious diseases will have an important role in reducing the global NCD burden.

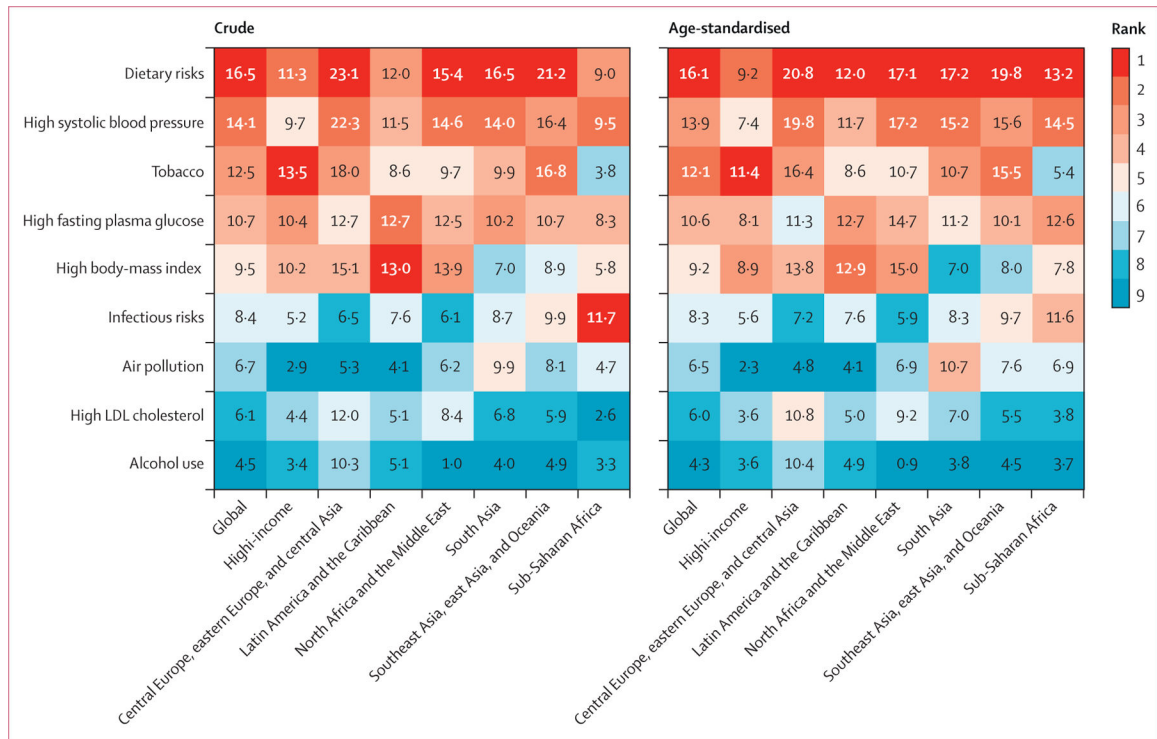


**Figure 1: Age-standardised rates of DALYs from NCDs attributable to infectious causes**  
 The appendix (pp 4–6) identifies pairs of infectious pathogens and NCD outcomes quantified in the figure. Rates were age-standardised with the Global Burden of Disease Study 2017 standard population. Maps of age-standardised percentages and crude percentages and rates including this figure for comparison are given in the appendix (pp 42–43). Results are stratified in sextiles. DALY=disability-adjusted life-year. NCD=non-communicable disease.



**Figure 2: Region-specific age-standardised rates of DALYs from NCDs attributable to infectious causes by NCD type**

Other cancers comprised bladder cancer, Hodgkin lymphoma, nasopharynx cancer, non-Hodgkin lymphoma, lip and oral cavity cancer, other pharynx cancer, larynx cancer, Kaposi sarcoma, and cancers of the anus, penis, vulva, and vagina. Other cardiovascular disease comprised ischaemic heart disease, ischaemic stroke, haemorrhagic stroke, and endocarditis. Gastrointestinal conditions comprised peptic ulcer disease, gastritis, and duodenitis. Other conditions comprised congenital heart disease, blindness and vision impairment, hearing loss, developmental intellectual disability, infertility, urinary tract infections, dental caries, other musculoskeletal conditions, and Guillain-Barré syndrome. Countries in each region are listed in the appendix (pp 38–41). Rates were age-standardised with the Global Burden of Disease Study 2017 standard population. Region-specific age-standardised rates of DALYs from NCDs attributable to infectious causes by infectious cause are given in the appendix (p 44).



**Figure 3: Crude and age-standardised proportion of burden from NCDs attributable to specific major risk factors**

Attributable proportions are expressed as percentages. Burden from risks other than infectious risks was estimated in the GBD 2017<sup>27</sup> and adjusted here for comparison by including the same NCD burden in the denominator (appendix pp 2–3). Dietary risks in the GBD comprised a diet low in fruits, vegetables, legumes, whole grains, nuts and seeds, milk, fibre, calcium, seafood omega-3 fatty acids, and polyunsaturated fat, and high in red meat, processed meat, sugar-sweetened beverages, trans fatty acids, and sodium. Air pollution as a risk factor comprised ambient particulate matter pollution, household air pollution from solid fuels, and ambient ozone pollution. Tobacco as a risk factor comprised smoking, chewing tobacco, and second-hand smoke. Percentages were age standardised with the GBD 2017 standard population.<sup>1</sup> GBD=Global Burden of Disease Study.

**Table:**

Infections and NCDs accounting for the largest quantifiable burden from infection-attributable NCDs

	DALYs, millions
<b>Infectious pathogen</b> *	
Hepatitis B virus	23.9
<i>Helicobacter pylori</i>	22.5
Hepatitis C virus	16.1
Human papillomavirus	9.4
Streptococcus	9.4
<b>NCD</b>	
Cirrhosis and other chronic liver diseases	22.6
Stomach cancer	14.6
Liver cancer	14.4
Rheumatic heart disease	9.4
Cervical cancer	8.0

Values represent NCD DALYs for each pathogen and infection-attributable DALYs for each NCD. NCD=non-communicable disease. DALY=disability-adjusted life year.

\* Results by infection do not include the NCD burden we were unable to separate by specific infectious pathogen (all infectious risks listed in the appendix [pp 4–6]). The NCDs from multiple unseparated infectious causes accounted for 26.5 million DALYs.