Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2013;**42**:221–227
doi:10.1093/ije/dys135

Convergence of non-communicable and infectious diseases in low- and middle-income countries

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Accepted 23 July 2012

The convergence of non-communicable disease (NCD) and infectious disease (ID) in low- and middle-income countries (LMICs) presents new challenges and new opportunities to enact responsive changes in policy and research. Most LMICs have significant dual disease burdens of NCDs such as cardiovascular disease, diabetes and cancer, and IDs including tuberculosis, HIV/AIDS and parasitic diseases. A combined strategy is needed in surveillance and disease control; yet, experts, institutions and policies that support prevention and control of these two overarching disease categories have limited interaction and alignment. NCDs and IDs share common features, such as long-term care needs and overlapping high-risk populations, and there are also notable direct interactions, such as the association between certain IDs and cancers, as well as evidence of increased susceptibility to IDs in individuals with NCDs. Enhanced simultaneous surveillance of NCD and ID comorbidity in LMIC populations would generate the empirical data needed to better understand the dual burden, and to target coordinated care. Where IDs and NCDs are endemic, focusing on vulnerable populations by strengthening social protections and improving access to health services is crucial, as is the re-alignment of efforts to combine NCD and ID screening, treatment programmes, and the assessment of their impact. Integrating public health activities for ID and NCD should extend beyond health care services to prevention, which is widely seen as crucial to successful NCD and ID control campaigns alike. The convergence of NCD and ID in LMICs has the potential to overstretch already strained health systems. With some LMICs now focused on major health system reforms, a unique opportunity is available to address NCD and ID challenges with newfound urgency and novel approaches.

Keywords Chronic disease, infectious disease, development transition

Introduction

Low- and middle-income countries (LMICs) represent the nexus of non-communicable disease (NCD) and infectious disease (ID) challenges. Most LMICs have significant dual disease burdens of NCDs and IDs stemming from the classic risk overlap that drives their epidemiological transitions.[1] These include NCDs such as cardiovascular disease, diabetes mellitus and cancer, and IDs such as tuberculosis (TB), HIV/AIDS, malaria and other parasitic diseases. That the NCD and ID classifications represent a false dichotomy was noted >50 years ago by the epidemiologist Philip Sartwell, who asserted that the 'separation of acute from chronic, or infectious from noninfectious is arbitrary', and that epidemiological methods useful for ID and NCD 'differ superficially'.[2] Indeed, Sartwell himself pioneered models for estimating the incubation period of IDs, methods that were later adapted to estimate the time to (or age of) onset of NCDs.[3,4] Yet, a deep professional and institutional divide persists between NCD and ID in the public health professions, which has long frustrated leading epidemiologists like Reuel Stallones, who termed it an 'unfortunate schism',[5] and Elizabeth Barrett-Connor, who, observing a partitioning of epidemiology in 1979, argued that ID and NCD epidemiologists are not 'separate and unrelated species' and have much experience and methodology to offer each other.[6] In LMICs, experts, institutions and policies that support prevention and control of these two overarching disease categories reflect a similar partitioning, with ID and NCD programmes and initiatives having limited interaction and alignment. This is despite the fact that NCDs and IDs in LMICs share common features, such as long-term care needs and overlapping high-risk populations. There are also notable direct interactions, such as the association between certain IDs and cancers, as well as evidence of increased susceptibility to IDs in individuals with NCDs. With some LMICs now focused on major health system reforms, a unique opportunity is available to address NCD and ID challenges with newfound urgency and novel approaches that overcome the limits of historical divisions.

The magnitude of the dual public health burden in LMICs is clear. In India, for instance, diabetes prevalence is currently 5–15% among urban populations, 4–6% in semi-urban populations and 2–5% in rural populations, and prevalence is rising in all three settings.[7] In China, diabetes reached an estimated national prevalence of 9.7% among adults in 2008, totaling 92 million affected individuals.[8] At the same time, India and China are experiencing the world's first and second largest TB epidemics, with an estimated 2.0 and 1.3 million new cases every year, respectively.[9] The convergence of NCD and ID burdens in India and China, a situation common to many LMICs, suggests a combined strategy is needed in surveillance and disease control, and this is perhaps most clear in populations experiencing high disease burdens from both.

Vulnerable populations and common risk factors

Rural-to-urban migrants, a growing group in rapidly urbanizing LMICs,[10] are one such population at high risk of both NCD and ID. A seminal study on chronic disease in a Chinese migrant population found that as rural residents migrate to urban environments, they exhibit an age-related rise in blood pressure on par with their new urban neighbours, and considerably higher than individuals who remained in rural villages.[11] As China's massive migrant population, totalling approximately 260 million, transitions from rural to urban lifestyles and diets, a range of cardiovascular disease risk factors are affected,[10,12] adding to other NCD disease risk factors such as tobacco use, which are known to be elevated in this group.[13] At the same time, rural-to-urban migrants can carry traditional IDs, such as parasites, at levels higher than their rural home communities,[14] and their working and living conditions can put migrants at higher risk of TB infection than permanent residents.[15] The dual burden paradigm is applicable beyond migrants in China. Similar patterns of convergence have been documented in India, where the emergence of NCDs in slums, namely, cardiovascular disease and diabetes, is occurring alongside risk factors associated with IDs, such as informal living conditions, overcrowding and poor access to safe water and sanitation.[16]

Although certain risk factors for NCDs (e.g. obesity) are commonly associated with increased affluence, studies in India have long shown that risk factors for NCDs are also present among those of lower socio-economic status (SES), in an apparent 'reversal of the social gradient'.[17] In Accra, Ghana, a rapidly urbanizing centre in West Africa, a gradient of ID and NCD convergence has been documented: although a chronic disease burden alone was common in areas of high SES, populations with lower SES tended to experience both high infectious and non-communicable disease burdens, the latter mainly resulting from hypertension and obesity.[18,19] This finding, and others like it,[16,20] highlight the importance of identifying groups that are most vulnerable to the dual burden in LMICs, but also raise questions as to whether the magnitude of the dual burden is 'dose-dependent', contingent on a group's demographic, geographic and SES profile. A life-course perspective further complicates the influence of low SES, as factors influencing growth and development during foetal and infant life can have ID and NCD consequences in adulthood. For instance, recent findings on maternal and childhood under-nutrition and certain environmental exposures have highlighted important links between early-life insults and

susceptibility to IDs and NCDs later in life.[21–24] If evidence continues to build that *in utero* and early-life conditions constitute common risk factors for ID and NCD in adulthood, the outcome of pregnancy in these settings will need to be assessed in the context of maternal health and the health of the infant and child, as well as by its experience with ID and NCD in adulthood.[21,25] This is especially relevant, particularly in LMICs at the stage of economic development where multiple adverse conditions commonly co-exist. Moreover, IDs themselves can constitute early-life insults, leading to pre-dispositions to NCD later in life, including cancers.[26]

Cancers with infectious aetiology

Cancer burden is on the rise in many LMICs—a trend mediated by longer life expectancies and changes in diet, level of physical activity and environmental exposures.[27–30] The distribution of cancer aetiology is not uniform, and cancers associated with IDs continue to disproportionately impact LMICs.[28,29] After lung cancer, gastric and hepatic cancers are the second and third leading causes of cancer mortality globally, respectively.[29–31] Both demonstrate substantial infectious involvement,[29,32] and LMICs are particularly affected. In 2008, for instance, LMICs accounted for an estimated 70% of incident cases of stomach cancers.[31] Of these, a large proportion is due to chronic or recurrent infection with the bacterium *Helicobacter pylori*,[30] which is causally associated with 60% of non-cardia gastric cancers and gastric lymphomas globally.[29,32] Based on a systematic review and meta-analysis of prospective cohort studies, chronic infection with *H. pylori*, which is defined as seropositivity for 10 years, increases the risk of gastric cancer nearly 6-fold (95% CI 3.4–10.3).[32] Likewise, infection with hepatitis B (HBV) and C, which are strongly associated with hepatocellular carcinoma, accounted for approximately three-quarters of global cases of primary liver cancer in 2007.[29,30] LMICs are among the nations experiencing the highest incidence of liver cancer,[28,30,31] with 80% of new cases occurring in developing countries, particularly in west and central Africa and east and southeast Asia.[30,31] Despite WHO recommendations, routine HBV immunization of infants remains a challenge in high burden LMICs owing to logistical difficulties and costs.[30] In the case of hepatitis C, which accounts for one-third of liver cancer cases worldwide,[30] effective vaccines are unavailable, and alternative methods of prevention must be deployed.

Kaposi's sarcoma (KS) gained international recognition in the wake of the HIV/AIDS epidemic. The putative agent is the KS-associated human herpesvirus (or human herpesvirus-8); although it is endemic in parts of central and eastern Africa,[32] progression to KS is facilitated by infection with HIV. The risk of developing KS is 1000–5000 times greater in those who are immunocompromized relative to those who are not.[32] The risk of developing KS increases with the level of immunocompromization,[33] and the use of highly active anti-retroviral therapy has been shown to be significantly associated with decreased incidence of KS.[34] Thus, KS is a unique example of an NCD that is not only associated with the staging of an ID[35] but also of where the NCD risk responds to the management of the ID.

Finally, of great relevance to LMICs is the link between Epstein–Barr virus (EBV) and nasopharyngeal cancer and Burkitt's B-cell lymphoma (BL). Nasopharyngeal cancers are rare globally but have exceptionally high incidence rates in certain LMICs, particularly in southern China, Malaysia and parts of North Africa where incidence is estimated to be 10–30 per 100 000 men.[36,37] Research examining this unusual epidemiology has implicated EBV in the development of this rare cancer,[37,38] and studies in LMICs have associated EBV with endemic BL[36,38,39] and have brought to light associations between EBV, BL and malaria[40,41] that suggest alternative pathways by which ID and NCD can interact.

NCD and susceptibility to ID

Evidence is mounting that an individual's NCD risk status may put the person at higher risk for key IDs that remain common in LMICs. Diabetes, for example, can interact with and complicate a number of globally important communicable diseases, and HIV-infected patients with access to anti-retroviral treatments can now expect prolonged survival and ageing. This favourable outcome has been accompanied by the emergence of complications such as diabetes and lipid disorders, both of which may subsequently result in increased risk for cardiovascular disease.[42] For another, the risk of contracting malaria may be greater among those with diabetes; although the causal relationship is poorly understood, a study in Africa found persons with diabetes had a 46% increased risk for infection.[43] Finally, the interaction between TB infection and diabetes is especially important to LMICs. Reports suggest that among those with diabetes, the risk of new TB infection is higher, and the clinical course may be more complicated.[44,45] Indeed, a global systematic review and meta-analysis of cohort studies found that compared with those without diabetes, those with diabetes had a 3-fold higher risk of developing active TB infection (RR 3.1; 95% CI 2.3–4.3) regardless of the study design and population, with others finding similar magnitudes of increased risk.[46–48]

The population impact of the diabetes burden on the TB burden is not well understood owing to a lack of data in many LMICs on diabetes and TB incidence. However, where data are available, or where reasonable assumptions about diabetes and TB prevalence can be made, the estimate of the impact is substantial.

Of India's 2 million annual new TB cases, recent estimates have attributed 12.9% (~250 000 cases) to diabetes, whereas for China's 1.3 million annual new TB cases, the figure is 7.8% (~100 000 cases).[49] Diabetes prevalence is expected to increase in these countries, and thus by 2030, the proportion of TB cases attributable to diabetes is also projected to increase, to 16.0% and 11.2% in India and China, respectively.[49] There is mounting evidence that beyond these population-level estimates, diabetes and TB do in fact co-exist at the individual level.[50,51] Additional data are needed, and late in 2011 a large-scale epidemiological study was proposed to estimate the prevalence of concurrent TB and diabetes in two provinces in China, the first study of its kind.[52] Many issues related to ID and NCD comorbidity must be resolved with further study, such as the risk of diabetes among TB patients, and whether the clinical course of TB is worse in persons with diabetes than those without.

Implications for policy

Fundamental data on ID and NCD comorbidity in LMIC populations are needed; yet, surveillance systems rarely address these conditions simultaneously, limiting our understanding of their overlap. Enhanced simultaneous surveillance of NCD and ID morbidity (e.g. diabetes and TB) would generate the empirical data needed to better understand the dual burden and to target coordinated care where both diseases are common. The WHO could play a key role in advocating for integration of ID and NCD surveillance systems in global programmes, and in facilitating uptake of this strategy at the country level by encouraging combined surveillance approaches that are tailored to national and regional needs. Indeed, the synthesis of diverse surveillance data in LMICs, such as for acute and chronic IDs, has proven essential for revealing important health disparities, and for highlighting gaps in infrastructure investment and policy.[53]

Although studies elucidating the complex aetiologies of cancers related to infectious agents are in the early stages, and research on their incidence in LMICs is limited, the strong association between IDs and cancers observed elsewhere underscores the prospect of managing NCDs through interventions historically associated with ID management. Certainly, prevention of cervical cancer has followed this model. In 2011, the U.S. Centers for Disease Control and Prevention recommended human papillomavirus (HPV) vaccine for both pre-adolescent boys and girls as a means of maximizing protection against HPV-associated cancers through herd immunity, especially where female vaccination coverage may be low.[54] Vaccination for males will also have direct benefits by preventing HPV-associated anal, oral-pharyngeal and penile cancer.[54] Where vaccines are widely available and affordable, such as for HBV, immunization campaigns in LMICs should be targeted to reach at-risk populations to prevent initial infections and thus pre-empt infection-associated cancers. Where effective vaccines are unavailable, as in the case for *H. pylori*, alternative methods should be considered, such as treatment of infection to prevent progression to cancer. One multi-centre prospective cohort study in Taiwan found that the eradication of *H. pylori* infection, through antibiotic treatment using amoxicillin and clarithromycin with omeprazole for 2 weeks, achieved regression in >60% of patients with low-grade mucosa-associated lymphoid tissue (MALT) lymphoma, and in 60% of those in early stages of high-grade MALT.[36,55] Where treatment of infection can limit progression to cancer, aggressive antimicrobial treatment early on can serve as a mode of cancer prevention. In the case of KS and HIV, increasing access to therapy is especially urgent in regions affected by the AIDS epidemic, such as sub-Saharan Africa where the control of HIV-associated malignancies would greatly benefit from increased availability of highly active anti-retroviral therapy.[56]

LMICs have an opportunity to target public health services to reach key populations experiencing converging ID and NCD risks and address their overlapping care needs. Focusing on vulnerable populations by strengthening social protections and improving access to health services is crucial. Prevalence of *H. pylori*, for example, is closely associated with poverty, overcrowding and poor sanitation early in childhood,[57] and these same risk factors are also conducive to TB, viral hepatitis, diabetes and cardiovascular disease. Public health responses to IDs and NCDs should be concomitant rather than mutually exclusive. Where IDs and NCDs are endemic, aligning prevention efforts, health education and health promotion could provide important benefits, such as in regions where both TB and diabetes are endemic. Screening and diagnostics should be coordinated by a clinical workforce skilled in preventing and treating both NCD and ID.[58] For instance, in high TB burden areas, strategies could include a low threshold for screening persons with diabetes during routine follow-up and when symptoms of, or recent exposure to, TB has occurred. Likewise, among new cases of TB, the clinical threshold should be low for screening for diabetes. The presentation of comorbid NCDs will likely complicate treatment of IDs in ways not fully understood, suggesting that clinical vigilance and targeted surveillance will be crucial and highlighting the importance of monitoring combined screening and treatment programmes to measure and assess their impact.

The rapidly growing burden of NCD in many LMICs, even with a diminishing ID burden, has the potential to overstretch already strained LMIC health systems.[59–61] Integrating NCD management into existing primary care systems in LMICs—into systems that tend to emphasize IDs—will be essential.[62] Many IDs and their sequelae are chronic and, like NCDs,

demand long-term follow-up, treatment and care. This is certainly true for HIV/AIDS, as it is for chronic HBV, TB and some parasitic diseases. Some have argued for synergistic care for HIV/AIDS and NCDs to promote efficiency in the use of scarce resources,[63] and major efforts by the Global Fund to identify and provide anti-retroviral treatment to the tens of thousands who are in need could benefit from the integration of NCD management.[64] At the global level, pooled supply systems, such as those in place for vaccine procurement, could be expanded to include essential drugs for NCDs.

Importance of prevention

The convergence of NCD and IDs is neither trivial nor transient; it represents a phase in the epidemiological transition that presents new challenges and new opportunities to enact responsive changes in policy and research. Integrating public health activities for ID and NCD should extend beyond health care services to prevention, which is widely seen as crucial to successful NCD control.[65] Recently, some have argued that more attention must be paid to prevention of certain IDs, where, for instance, environmental interventions can reduce the need for clinical care.[66] These arguments resonate strongly with similar calls for NCD prevention measures that take a structural approach, especially those outside the health sector.[10,65]

Strategies for intervention should consider underlying risk factors applicable for both ID and NCDs, such as demographic and environmental factors, and screening high-risk individuals for both IDs and NCDs could help to guide treatment and long-term follow-up. Prevention of NCDs already focuses on major risk factors that have relevance to IDs, such as tobacco use reduction, improved dietary intake and reducing the harmful use of alcohol. NCD prevention strategies can highlight the role of reducing these risk factors in NCD and ID prevention—especially for key diseases such as TB.[67,68] This type of strategy will require close collaboration between NCD and ID programme leadership, and LMICs preparing to tackle NCDs must plan strategically such that efforts in ID prevention and treatment are not abandoned but rather supplemented by efforts in NCD management. Opportunities to strategically align the prevention, diagnosis and treatment of NCDs and IDs could reap substantial benefits in LMICs, and should be a focal point for future health policy reforms.

Funding/Support

This work was supported in part by the National Institute for Allergy and Infectious Disease [grant no. K01AI091864; J.V.R.]; the NIH/NSF Ecology of Infectious Disease Program [grant no. 0622743; J.V.R.] and by the Emory Global Health Institute Faculty Distinction Fund [J.V.R.]. M.E. is a US federal government employee at the US Centers for Disease Control and Prevention and his support is solely from the Federal Government. The funders had no role in the decision to publish or prepare the manuscript. No payment was received on the part of any of the co-authors for the preparation of this manuscript. The corresponding author had final responsibility for the decision to submit for publication. The views expressed in this article are solely those of the authors, and may not reflect the policies or views of their agencies, or the funding agencies.

Acknowledgements

J.V.R conceived the idea for the article. All authors wrote the article. All authors had full access to all the data in the study, and read and approved the final version. The corresponding author had final responsibility for the decision to submit for publication and acts as guarantor for the article. The funders had no role in the preparation, review or approval of the manuscript.

Conflict of interest: None declared.

KEY MESSAGES

- The convergence of NCD and ID in LMICs presents new challenges and new opportunities to enact responsive changes in policy and research.
- In LMICs, experts, institutions and policies that support prevention and control of these two overarching disease categories have limited interaction and alignment.
- NCDs and IDs share common features, such as long-term care needs and overlapping high-risk populations.
- There are notable direct interactions between NCDs and IDs, such as the association between certain IDs and cancers, as well as evidence of increased susceptibility to IDs in individuals with NCDs.
- With some LMICs now focused on major health system reforms, a unique opportunity is available to jointly address NCD and ID challenges with newfound urgency and novel approaches.

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