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Bernard Janse van Rensburg, et al. Corresponding author.

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International Health Alerts May 2022 Abstracts

Child Health

1. BMJ Global Health 2022;7:e007798. Analysis

Alarming level of severe acute malnutrition in Indian districts

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Abstract

Over the last two decades, severe acute malnutrition (SAM) has been increasing in India despite favourable national-level economic growth. The latest round of the National Family Health Survey 5 (NFHS-5) results was released, allowing us to assess changes in the malnutrition trends. Analysis of the previous rounds of the NFHS (NFHS-4) has already shown disturbing levels of wasting, often co-occurring with other forms of anthropometric failures. These have been shown to occur in clusters of districts across India that already needed urgent policy and programmatic action. A rapid assessment of data from NFHS-5 for some of these districts for which data are now available shows an alarming increase in SAM in several malnutrition hotspot districts. Surprisingly, some districts outside hotspots and in states and regions that have previously not been known for high malnutrition too have shown increasing SAM prevalence in the latest round. The data from NFHS-5 was collected just before the COVID-19 pandemic and hence does not yet reflect the likely impact of the pandemic on food security, livelihoods and other social stressors among the most marginalised Indian households. Based on this emerging pattern of increasing SAM, we call for an urgent policy and programmatic action to strengthen the Anganwadi system, which caters to preschool children in India and community-based management of acute malnutrition based on recent evidence on their effectiveness.

2. BMJ Global Health 2022;7:e008110. Original research

Estimating stillbirth and neonatal mortality rate among Rohingya refugees in Bangladesh, September 2017 to December 2018: a prospective surveillance

Amsalu R, Costello J, Hasna Z, et al

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Abstract

Introduction There is limited literature on neonatal mortality in humanitarian emergencies. We estimated neonatal mortality and stillbirth rates; determined whether an association exists between proximity to a secondary health facility and neonatal mortality or stillbirth; and tested the correlation between the number of health facilities in a camp and neonatal mortality or stillbirth rates in Rohingya refugee camps in Bangladesh.

Methods We conducted a prospective community-based mortality surveillance in 29 out of 34 Rohingya refugee camps between September 2017 and December 2018, covering approximately 811 543 Rohingya refugees with 19 477 estimated live births. We linked mortality surveillance data with publicly available information on camp population, number of functional health facilities and camp and health facility geospatial coordinates. Using descriptive statistics and spatial analyses, we estimated the mortality rate and tested for correlations.

Results Overall, the estimated neonatal mortality rate was 27.0 (95% CI: 22.3 to 31.8) per 1000 live births, and the stillbirth rate was 15.2 (95% CI: 10.8 to 19.6) per 1000 total births. The majority of neonatal deaths (76.3%, n=405/531) and stillbirths (72.1%, n=202/280) occurred at home or in the community. A positive correlation existed between the camp population size and number of health facilities inside the camp (Spearman's rho=0.56, p value<0.01). No statistically significant correlation existed between the camp neonatal mortality rate or stillbirth rate and number of health facilities

inside the camp. Camps that were located closer to a secondary health facility as compared with a labour room/sexual and reproductive health unit had a lower neonatal mortality rate (p value<0.01). Conclusions The results provide insight into the neonatal mortality and stillbirth rates in Rohingya refugees camps in Bangladesh during 2017–2018. Prospective community-based mortality surveillance may be a feasible method to evaluate the effectiveness of humanitarian responses in improving neonatal survival and preventing stillbirths.

3. BMJ Global Health 2022;7:e007826. Original research

Optimising the management of childhood acute diarrhoeal disease using a rapid test-and-treat strategy and/or *Lactobacillus reuteri* DSM 17938: a multicentre, randomised, controlled, factorial trial in Botswana

Pernica JM, Arscott-Mills T, Steenhoff AP, et al

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Abstract

Introduction The study aim was to determine if rapid enteric diagnostics followed by the provision of targeted antibiotic therapy ('test-and-treat') and/or *Lactobacillus reuteri* DSM 17938 would improve outcomes in children hospitalised in Botswana with acute gastroenteritis.

Methods This was a multicentre, randomised, factorial, controlled, trial. Children aged 2–60 months admitted for acute non-bloody diarrhoea to four hospitals in southern Botswana were eligible.

Participants were assigned to treatment groups by web-based block randomisation. Test-and-treat results were not blinded, but participants and research staff were blinded to *L. reuteri*/placebo assignment; this was dosed as 1×10^8 cfu/mL by mouth daily and continued for 60 days. The primary outcome was 60-day age-standardised height (HAZ) adjusted for baseline HAZ. All analyses were by intention to treat. The trial was registered at [Clinicaltrials.gov](https://clinicaltrials.gov).

Results Recruitment began on 12 June 2016 and continued until 24 October 2018. There were 66 participants randomised to the test-and-treat plus *L. reuteri* group, 68 randomised to the test-and-treat plus placebo group, 69 to the standard care plus *L. reuteri* group and 69 to the standard care plus placebo group. There was no demonstrable impact of the test-and-treat intervention (mean increase of 0.01 SD, 95% CI –0.14 to 0.16 SD) or the *L. reuteri* intervention (mean decrease of 0.07 SD, 95% CI –0.22 to 0.08 SD) on adjusted HAZ at 60 days.

Conclusions In children hospitalised for acute gastroenteritis in Botswana, neither a test-and-treat algorithm targeting enteropathogens, nor a 60-day course of *L. reuteri* DSM 17938, were found to markedly impact linear growth or other important outcomes. We cannot exclude the possibility that test-and-treat will improve the care of children with significant enteropathogens (such as *Shigella*) in their stool.

Communicable diseases

4. BMJ Global Health 2022;7:e007490. Analysis

Recently developed drugs for the treatment of drug-resistant tuberculosis: a research and development case study

Perrin C, Athersuch K, Elder G, et al

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Abstract

Two drugs with novel mechanisms of action, the diarylquinoline bedaquiline and the nitroimidazole delamanid—as well as pretomanid from the same class of drugs as delamanid—have recently become available to treat drug-resistant tuberculosis (DR-TB) after many decades of little innovation in the field of DR-TB treatment. Despite evidence of improved efficacy and reduced toxicity of multidrug regimens including the two agents, access to bedaquiline and delamanid has been limited

in many settings with a high burden of DR-TB and consistently poor treatment outcomes. Aside from regulatory, logistic and cost barriers at country level, uptake of the novel agents was complicated by gaps in knowledge for optimal use in clinical practice after initial market approval. The main incentives of the current pharmaceutical research and development paradigm are structured around obtaining regulatory approval, which in turn requires efficacy and safety data generated by clinical trials. Recently completed and ongoing clinical trials did not answer critical questions of how to provide shorter, less toxic treatment DR-TB treatment regimens containing bedaquiline and delamanid and improve patient outcomes. Voluntary generation of evidence that is not part of this process—yet essential from a clinical or policy perspective—has been left to non-sponsor partners and researchers, often without collaborative efforts to improve post-regulatory approval access to life-saving drugs. Additionally, these efforts are currently not recognised in the value chain of the research and development process, and there are no incentives to make this critical research happen in a coordinated way.

5. Lancet 2022;399(10325):629-55

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

Antimicrobial Resistance Collaborators. Correspondence to: Dr Mohsen Naghavi <nagham@uw.edu>

Background: Antimicrobial resistance (AMR) poses a major threat to human health around the world. Previous publications have estimated the effect of AMR on incidence, deaths, hospital length of stay, and health-care costs for specific pathogen-drug combinations in select locations. To our knowledge, this study presents the most comprehensive estimates of AMR burden to date.

Methods: We estimated deaths and disability-adjusted life-years (DALYs) attributable to and associated with bacterial AMR for 23 pathogens and 88 pathogen-drug combinations in 204 countries and territories in 2019. We obtained data from systematic literature reviews, hospital systems, surveillance systems, and other sources, covering 471 million individual records or isolates and 7585 study-location-years. We used predictive statistical modelling to produce estimates of AMR burden for all locations, including for locations with no data. Our approach can be divided into five broad components: number of deaths where infection played a role, proportion of infectious deaths attributable to a given infectious syndrome, proportion of infectious syndrome deaths attributable to a given pathogen, the percentage of a given pathogen resistant to an antibiotic of interest, and the excess risk of death or duration of an infection associated with this resistance. Using these components, we estimated disease burden based on two counterfactuals: deaths attributable to AMR (based on an alternative scenario in which all drug-resistant infections were replaced by drug-susceptible infections), and deaths associated with AMR (based on an alternative scenario in which all drug-resistant infections were replaced by no infection). We generated 95% uncertainty intervals (UIs) for final estimates as the 25th and 975th ordered values across 1000 posterior draws, and models were cross-validated for out-of-sample predictive validity. We present final estimates aggregated to the global and regional level.

Findings: On the basis of our predictive statistical models, there were an estimated 4.95 million (3.62–6.57) deaths associated with bacterial AMR in 2019, including 1.27 million (95% UI 0.911–1.71) deaths attributable to bacterial AMR. At the regional level, we estimated the all-age death rate attributable to resistance to be highest in western sub-Saharan Africa, at 27.3 deaths per 100 000 (20.9–35.3), and lowest in Australasia, at 6.5 deaths (4.3–9.4) per 100 000. Lower respiratory infections accounted for more than 1.5 million deaths associated with resistance in 2019, making it the most burdensome infectious syndrome. The six leading pathogens for deaths associated with resistance (*Escherichia coli*, followed by *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*,

Acinetobacter baumannii, and *Pseudomonas aeruginosa*) were responsible for 929 000 (660 000-1 270 000) deaths attributable to AMR and 3.57 million (2.62-4.78) deaths associated with AMR in 2019. One pathogen-drug combination, methicillin-resistant *S aureus*, caused more than 100 000 deaths attributable to AMR in 2019, while six more each caused 50 000-100 000 deaths: multidrug-resistant excluding extensively drug-resistant tuberculosis, third-generation cephalosporin-resistant *E coli*, carbapenem-resistant *A baumannii*, fluoroquinolone-resistant *E coli*, carbapenem-resistant *K pneumoniae*, and third-generation cephalosporin-resistant *K pneumoniae*.

Interpretation: To our knowledge, this study provides the first comprehensive assessment of the global burden of AMR, as well as an evaluation of the availability of data. AMR is a leading cause of death around the world, with the highest burdens in low-resource settings. Understanding the burden of AMR and the leading pathogen-drug combinations contributing to it is crucial to making informed and location-specific policy decisions, particularly about infection prevention and control programmes, access to essential antibiotics, and research and development of new vaccines and antibiotics. There are serious data gaps in many low-income settings, emphasising the need to expand microbiology laboratory capacity and data collection systems to improve our understanding of this important human health threat.

6. Lancet 2022;399(10325):678-90

Review: Measles

Hübschen JM et al., Department of Infection and Immunity, Luxembourg Institute of Health, Esch-sur-Alzette, Luxembourg <judith.huebschen@lih.lu>

Measles is a highly contagious, potentially fatal, but vaccine-preventable disease caused by measles virus. Symptoms include fever, maculopapular rash, and at least one of cough, coryza, or conjunctivitis, although vaccinated individuals can have milder or even no symptoms. Laboratory diagnosis relies largely on the detection of specific IgM antibodies in serum, dried blood spots, or oral fluid, or the detection of viral RNA in throat or nasopharyngeal swabs, urine, or oral fluid. Complications can affect many organs and often include otitis media, laryngotracheobronchitis, pneumonia, stomatitis, and diarrhoea. Neurological complications are uncommon but serious, and can occur during or soon after the acute disease (eg, acute disseminated encephalomyelitis) or months or even years later (eg, measles inclusion body encephalitis and subacute sclerosing panencephalitis). Patient management mainly involves supportive therapy, such as vitamin A supplementation, monitoring for and treatment of secondary bacterial infections with antibiotics, and rehydration in the case of severe diarrhoea. There is no specific antiviral therapy for the treatment of measles, and disease control largely depends on prevention. However, despite the availability of a safe and effective vaccine, measles is still endemic in many countries and causes considerable morbidity and mortality, especially among children in resource-poor settings. The low case numbers reported in 2020, after a worldwide resurgence of measles between 2017 and 2019, have to be interpreted cautiously, owing to the effect of the COVID-19 pandemic on disease surveillance. Disrupted vaccination activities during the pandemic increase the potential for another resurgence of measles in the near future, and effective, timely catch-up vaccination campaigns, strong commitment and leadership, and sufficient resources will be required to mitigate this threat.

7. Lancet 2022;399(10331):1227-41

Effectiveness and cost-effectiveness against malaria of three types of dual-active-ingredient long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs in Tanzania: a four-arm, cluster-randomised trial

Mosha JF et al., Department of Parasitology, National Institute for Medical Research, Mwanza Medical Research Centre, Mwanza, Tanzania

Background: Long-lasting insecticidal nets (LLINs) have successfully reduced malaria in sub-Saharan Africa, but their effectiveness is now partly compromised by widespread resistance to insecticides among vectors. We evaluated new classes of LLINs with two active ingredients with differing modes of action against resistant malaria vectors.

Methods: We did a four-arm, cluster-randomised trial in Misungwi, Tanzania. Clusters were villages, or groups of hamlets, with at least 119 households containing children aged 6 months to 14 years living in the cluster's core area. Constrained randomisation was used to allocate clusters (1:1:1:1) to receive one of four types of LLIN treated with the following: α -cypermethrin only (pyrethroid-only [reference] group); pyriproxyfen and α -cypermethrin (pyriproxyfen group); chlorfenapyr and α -cypermethrin (chlorfenapyr group); or the synergist piperonyl butoxide and permethrin (piperonyl butoxide group). At least one LLIN was distributed for every two people. Community members and the field team were masked to group allocation. Malaria prevalence data were collected through cross-sectional surveys of randomly selected households from each cluster, in which children aged 6 months to 14 years were assessed for *Plasmodium falciparum* malaria infection by rapid diagnostic tests. The primary outcome was malaria infection prevalence at 24 months after LLIN distribution, comparing each of the dual-active-ingredient LLINs to the standard pyrethroid-only LLINs in the intention-to-treat population. The primary economic outcome was cost-effectiveness of dual-active-ingredient LLINs, based on incremental cost per disability-adjusted life-year (DALY) averted compared with pyrethroid-only LLINs, modelled over a 2-year period; we included costs of net procurement and malaria diagnosis and treatment, and estimated DALYs in all age groups. This study is registered with ClinicalTrials.gov (NCT03554616), and is ongoing but no longer recruiting.

Findings: 84 clusters comprising 39 307 households were included in the study between May 11 and July 2, 2018. 147 230 LLINs were distributed among households between Jan 26 and Jan 28, 2019. Use of study LLINs was reported in 3155 (72.1%) of 4378 participants surveyed at 3 months post-distribution and decreased to 8694 (40.9%) of 21 246 at 24 months, with varying rates of decline between groups. Malaria infection prevalence at 24 months was 549 (45.8%) of 1199 children in the pyrethroid-only reference group, 472 (37.5%) of 1258 in the pyriproxyfen group (adjusted odds ratio 0.79 [95% CI 0.54-1.17], $p=0.2354$), 512 (40.7%) of 1259 in the piperonyl butoxide group (0.99 [0.67-1.45], $p=0.9607$), and 326 [25.6%] of 1272 in the chlorfenapyr group (0.45 [0.30-0.67], $p=0.0001$). Skin irritation or paraesthesia was the most commonly reported side-effect in all groups. Chlorfenapyr LLINs were the most cost-effective LLINs, costing only US\$19 (95% uncertainty interval 1-105) more to public providers or \$28 (11-120) more to donors per DALY averted over a 2-year period compared with pyrethroid-only LLINs, and saving costs from societal and household perspectives.

Interpretation: After 2 years, chlorfenapyr LLINs provided significantly better protection than pyrethroid-only LLINs against malaria in an area with pyrethroid-resistant mosquitoes, and the additional cost of these nets would be considerably below plausible cost-effectiveness thresholds (\$292-393 per DALY averted). Before scale-up of chlorfenapyr LLINs, resistance management strategies are needed to preserve their effectiveness. Poor textile and active ingredient durability in

the piperonyl butoxide and pyriproxyfen LLINs might have contributed to their relative lack of effectiveness compared with standard LLINs.

8. Lancet 2022;399(10333):1429–40

Seminar: Cholera

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Cholera was first described in the areas around the Bay of Bengal and spread globally, resulting in seven pandemics during the past two centuries. It is caused by toxigenic *Vibrio cholerae* O1 or O139 bacteria. Cholera is characterised by mild to potentially fatal acute watery diarrhoeal disease. Prompt rehydration therapy is the cornerstone of management. We present an overview of cholera and its pathogenesis, natural history, bacteriology, and epidemiology, while highlighting advances over the past 10 years in molecular epidemiology, immunology, and vaccine development and deployment. Since 2014, the Global Task Force on Cholera Control, a WHO coordinated network of partners, has been working with several countries to develop national cholera control strategies. The global roadmap for cholera control focuses on stopping transmission in cholera hotspots through vaccination and improved water, sanitation, and hygiene, with the aim to reduce cholera deaths by 90% and eliminate local transmission in at least 20 countries by 2030.

9. Lancet 2022;399(10335):1573

Editorial - Malaria in 2022: a year of opportunity

The theme of this year's World Malaria Day, April 25, is "Harness innovation to reduce the malaria disease burden and save lives." WHO is calling for investment and innovation in vector control, diagnostics, and treatments to help countries eliminate malaria after several years of stalled progress.

In 2015, the World Health Assembly adopted a strategy to guide efforts towards elimination. But the first milestone—to achieve a 40% global reduction in malaria mortality rate and case incidence by 2020—was missed. Funding for malaria control has levelled off. Malaria mortality and incidence rates have not changed appreciably since 2015. There were an estimated 627 000 malaria deaths and 241 million malaria cases in 2020 (a 12% and 7% increase, respectively, compared with 2015). Given the stagnation of recent years, what cause is there to hope for a real change now?

Scientific advances are providing new tools for malaria control. RTS,S—the world's first effective malaria vaccine—was approved last year. Last month, The Lancet published results of a clinical trial showing the effectiveness of a new chlorfenapyr long-lasting insecticidal net that could help to mitigate the impact of insecticide resistance among mosquitoes. The roll-out of new interventions such as these is crucial to curtail malaria mortality, but it is not possible without funding.

In December, 2021, the Gavi board approved an initial investment for the procurement and delivery of RTS,S to sub-Saharan Africa. Later this year, the Global Fund will host its seventh replenishment meeting. It is asking for US\$18 billion to support its 2024–26 programmes for malaria, HIV, and tuberculosis, to strengthen health systems, and to reinforce pandemic preparedness. Modelling by the Global Fund predicts that, if it is fully funded, the malaria mortality rate would drop by 66% by 2026, and case incidence by 69%. By contrast, a counterfactual scenario of continued COVID-19

disruption would see a rapid and severe resurgence of malaria deaths and cases, resulting in an additional 2 million deaths and 654 million cases that could have been avoided. The replenishment scenario makes ambitious assumptions about the scale-up of malaria treatment and bednet distribution, as well as roll-out of the RTS,S vaccine. But the model presents countries and donors with a stark choice.

The case for commitment to investment and global collaboration for malaria is clear.

The UN Sustainable Development Goal of ending malaria as a public health threat by 2030 is at stake, and, with it, the lives of hundreds of thousands of people each year.

Community Health

10. Health Policy and Planning, Vol 37 (4), April 2022: 483 - 491

Five-year retention of volunteer community health workers in rural Uganda: a population-based retrospective cohort

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Community health workers (CHWs) effectively improve maternal, newborn and child health (MNCH) outcomes in low-to-middle-income countries. However, CHW retention remains a challenge. This retrospective registry analysis evaluated medium-term retention of volunteer CHWs in two rural Ugandan districts, trained during a district-wide MNCH initiative. From 2012 to 2014, the Healthy Child Uganda partnership facilitated district-led CHW programme scale-up. CHW retention was tracked prospectively from the start of the intervention up to 2 years. Additional follow-up occurred at 5 years to confirm retention status. Database analysis assessed CHW demographic characteristics, retention rates and exit reasons 5 years post-intervention. A multivariable logistic regression model examined 5-year retention-associated characteristics. Of the original cohort of 2317 CHWs, 70% were female. The mean age was 38.8 years (standard deviation, SD: 10.0). Sixty months (5 years) after the start of the intervention, 84% of CHWs remained active. Of those exiting ($n = 377$), 63% reported a 'logistical' reason, such as relocation ($n = 96$), new job ($n = 51$) or death ($n = 30$). Sex [male, female; odds ratio (OR) = 1.53; 95% confidence interval (CI): 1.20–1.96] and age group (<25 years, 30–59; OR = 0.40; 95% CI: 0.25–0.62) were significantly associated with 5-year retention in multivariable modelling. Education completion (secondary school, primary) was not significantly associated with retention in adjusted analyses. CHWs in this relatively large cohort, trained and supervised within a national CHW programme and district-wide MNCH initiative, were retained over the medium term. Importantly, high 5-year retention in this intervention counters findings from other studies suggesting low retention in government-led and volunteer CHW programmes. Encouragingly, findings from our study suggest that retention was high, not significantly associated with timing of external partner support and largely not attributed to the CHW role i.e. workload and programme factors. Our study showcases the potential for sustainable volunteer CHW programming at scale and can inform planners and policymakers considering programme design, including selection and replacement planning for CHW networks.

COVID-19

11. BMJ 2022;376:e070650 Analysis

It is not too late to achieve global covid-19 vaccine equity

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Gavin Yamey and colleagues say that a new, urgent push for global vaccine equity could help avert suffering and deaths, protect economies, and prevent new virus variants

During the covid-19 pandemic, we have seen the best of international collective action and its limits. Global scientific cooperation drove the development of safe, highly effective covid-19 vaccines in under one year. Yet we have also witnessed global vaccine inequity, in which low and middle income countries have “limited supply and limited vaccine brand options.”

With the omicron wave dissipating, several well vaccinated high income nations with stockpiles of covid-19 vaccines are rushing to declare the pandemic over, reminding us of how things unfolded with tuberculosis, malaria, and HIV/AIDS in the past. But the pandemic is not over and 2.8 billion people remain completely unvaccinated. Now is the time to recommit to, and further invest in, equitable and effective country led vaccination campaigns.

In this paper, we briefly examine how global vaccine inequity arose, lay out a renewed case for urgently ramping up our commitment to vaccine equity, and propose principles to ensure no one is left behind in the quest to vaccinate the world.

This article by Gavin Yamey and colleagues (BMJ 2022;376:e070650; doi:10.1136/bmj-2022-070650) did not mention the World Health Organization’s role in the South Africa mRNA vaccine hub. The online version has been corrected.

12. BMJ Global Health 2022;7:e007295. Original research

An in-depth statistical analysis of the COVID-19 pandemic’s initial spread in the WHO African region

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Abstract

During the first wave of the COVID-19 pandemic, sub-Saharan African countries experienced comparatively lower rates of SARS-CoV-2 infections and related deaths than in other parts of the world, the reasons for which remain unclear. Yet, there was also considerable variation between countries. Here, we explored potential drivers of this variation among 46 of the 47 WHO African region Member States in a cross-sectional study. We described five indicators of early COVID-19 spread and severity for each country as of 29 November 2020: delay in detection of the first case, length of the early epidemic growth period, cumulative and peak attack rates and crude case fatality ratio (CFR). We tested the influence of 13 pre-pandemic and pandemic response predictor variables on the country-level variation in the spread and severity indicators using multivariate statistics and regression analysis. We found that wealthier African countries, with larger tourism industries and older populations, had higher peak ($p<0.001$) and cumulative ($p<0.001$) attack rates, and lower CFRs ($p=0.021$). More urbanised countries also had higher attack rates ($p<0.001$ for both indicators). Countries applying more stringent early control policies experienced greater delay in detection of the first case ($p<0.001$), but the initial propagation of the virus was slower in relatively wealthy, touristic African countries ($p=0.023$). Careful and early implementation of strict government policies were likely pivotal to delaying the initial phase of the pandemic, but did not have much impact on other indicators of spread and severity. An over-reliance on disruptive containment measures in more resource-limited contexts is neither effective nor sustainable. We thus urge decision-makers to prioritise the reduction of resource-based health disparities, and surveillance and response capacities

in particular, to ensure global resilience against future threats to public health and economic stability.

13. Lancet, Glob health 2022;10(1):E2-E3 :

Comment: Fluvoxamine for outpatients with COVID-19: where do we stand?

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Advances in vaccine development have had a major effect on reducing the number of new symptomatic cases, hospitalisations, and deaths due to COVID-19, the viral disease caused by SARS-CoV-2, globally. Nevertheless, because of the unequal distribution and access to vaccines, a relevant proportion of individuals remain at risk for COVID-19, especially in low-income and middle-income countries. Therefore, the identification of beneficial interventions to prevent clinically relevant outcomes among patients with COVID-19 still represents a major medical need. This is particularly true for outpatients, who comprise the largest population of individuals infected with the SARS-CoV-2, and for whom few effective therapies exist.

Fluvoxamine is a selective serotonin reuptake inhibitor commonly indicated for the management of depression, obsessive-compulsive disorders, and other mental-health conditions. Owing to potential anti-inflammatory effects observed in initial experimental non-clinical studies, fluvoxamine has been proposed as a potential therapy for COVID-19. Accordingly, observational evidence has suggested favourable results of fluvoxamine with respect to symptom resolution and hospitalisations at 14 days.

In trial results published in 2020, 152 outpatients with mild COVID-19 were randomly assigned to receive 100 mg fluvoxamine three times daily or matching placebo for 15 days.⁵ The primary outcome was clinical deterioration, defined as shortness of breath or hospitalisation for shortness of breath or pneumonia, and oxygen saturation less than 92% on room air or need for supplemental oxygen to achieve oxygen saturation of 92% or greater. Within 15 days, none of the participants who received fluvoxamine and 8.3% of those who received placebo reached the primary endpoint (absolute risk difference 8.7%; 95% CI 1.8%–16.5%; $p=0.009$). Despite the promising results, limitations such as low statistical power and missing data for the primary outcome precluded definitive conclusions about the efficacy of fluvoxamine for the treatment of COVID-19.

In The Lancet Global Health, Gilmar Reis and colleagues report the results of TOGETHER, a randomised, adaptive, platform, placebo-controlled trial.⁶ A total of 1497 participants were randomly allocated to fluvoxamine, 100 mg twice daily, or matching placebo. All included participants had a positive test for SARS-CoV-2 and known risk factors for disease progression (including age ≥ 50 years, diabetes, hypertension, obesity, smoking, conditions associated with immunosuppression, unvaccinated status, or comorbidities such as cancer, cardiovascular, pulmonary, and kidney disorders). Enrolment occurred in 11 cities in Brazil. The primary endpoint was a composite of COVID-19 emergency setting retention for greater than 6 h or hospitalisation (defined as either retention in a COVID-19 emergency setting or transfer to tertiary hospital) from COVID-19 up to 28 days. Using a Bayesian analytical approach, the authors found that the proportion of patients reaching the primary endpoint was lower for the fluvoxamine group compared with placebo (11% vs 16%; relative risk: 0.68; 95% Bayesian credible interval 0.52–0.88), with a probability of superiority of 99.8%.

The TOGETHER trial had low risk of bias. The allocation was concealed, participants, investigators, and caregivers were unaware of treatment assignments, and the main analyses followed the intention-to-treat principle. It should also be noted that TOGETHER constitutes the largest randomised trial completed to date aimed at testing the effect of fluvoxamine for outpatients with COVID-19. Conversely, the main study limitations are related to the lack of event adjudication and to the inconclusive effects on patient-important outcomes such as hospitalisation and mortality.

What are the lessons learned from the TOGETHER trial? From a research perspective, the TOGETHER trial reinforces the concept that it is possible to rapidly generate high-quality, randomised evidence even during a pandemic such as COVID-19. Undeniably, key factors for the success of this initiative rely on the scientific exchange between academic groups from Brazil and Canada and on the use of an adaptive, platform, randomised design. This research methodology allows simultaneous and efficient assessment of different potential therapies for COVID-19. From a clinical practice perspective, the results represent an important step in understanding the role of fluvoxamine for outpatients with COVID-19. In this sense, the study strongly suggests that fluvoxamine constitutes an effective, safe, inexpensive, and relatively well tolerated option for the management of ambulatory patients with COVID-19, which is particularly useful for (but not limited to) low-resource settings.

Despite the important findings from the TOGETHER trial, some questions related to the efficacy and safety of fluvoxamine for patients with COVID-19 remain open. The definitive answer regarding the effects of fluvoxamine on individual outcomes such as mortality and hospitalisations still need addressing. In addition, it remains to be established whether fluvoxamine has an additive effect to other therapies such as monoclonal antibodies⁷ and budesonide,⁸ and what is the optimal fluvoxamine therapeutic scheme. Finally, it is still unclear whether the results from the TOGETHER trial extend to other outpatient populations with COVID-19, including those without risk factors for disease progression, those who are fully vaccinated, and those infected with the delta variant or other variants.

14. Health Policy and Planning, Vol 37 (4), April 2022: 505 – 513

Seroprevalence and risk factors of COVID-19 in healthcare workers from 11 African countries: a scoping review and appraisal of existing evidence

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A better understanding of serological data and risk factors for coronavirus disease 2019 (COVID-19) infection in healthcare workers (HCWs) is especially important in African countries where human resources and health services are more constrained. We reviewed and appraised the evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seroprevalence and its risk factors in HCWs in Africa to inform response and preparedness strategies during the SARS-CoV-2 pandemic. We followed the Preferred Reporting Items for systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines in this scoping review. Databases including PubMed, Embase and preprint servers were searched accordingly from the start of the COVID-19 pandemic to 19 April 2021. Our search yielded 12 peer-reviewed and four pre-print articles comprising data on 9223 HCWs from 11 countries in Africa. Seroprevalence varied widely and ranged from 0% to 45.1%. Seropositivity was associated with older age, lower education, working as a nurse/non-clinical HCW or in gynaecology, emergency, outpatient or surgery departments. Asymptomatic rates were high and half of the studies recommended routine testing of HCWs. This scoping review found a varying but often high SARS-CoV-2 seroprevalence in HCWs in 11 African countries and identified certain risk

factors. COVID-19 public health strategies for policy and planning should consider these risk factors and the potential for high seroprevalence among HCWs when prioritizing infection prevention and control measures and vaccine deployment.

Development Assistance for Health & North-South partnerships

15. Health Policy and Planning, Vol 37 (4), April 2022: 523 – 534

What makes working together work? A scoping review of the guidance on North–South research partnerships

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At their best, research partnerships provide a mechanism to optimize each partner’s strengths, make scientific discoveries and achieve development goals. Each partner stands to gain from the relationship and perceives it to be fair. However, partnerships between institutions in the global North and the global South have been beleaguered by structural inequalities and power imbalances, and Northern stakeholders have been criticized for perpetuating paternalistic or neo-colonial behaviours. As part of efforts to redress imbalances and achieve equity and mutual benefit, various principles, guidelines, frameworks and models for partnership have been developed. This scoping review maps the literature and summarizes key features of the guidelines for North–South research partnerships. The review was conducted between October 2020 and January 2021. Three academic journal databases and Google were searched, and additional resources were identified through a hand search of reference lists and expert recommendation. Twenty-two guidelines were identified published between 1994 and 2021 and originating predominantly in the fields of international development and global health. The themes addressed within the guidelines were aggregated using NVivo qualitative analysis software to code the content of each guideline. Topics featuring most prominently in the guidelines were: partner roles, responsibilities and ways of working; capacity strengthening; motivation and goals; resource contributions; agenda setting and study design; governance structures and institutional agreements; dissemination; respect for affected populations; data handling and ownership; funding and long-term commitments. The current study reinforces many of the themes from two recent scoping reviews specific to the field of global health, but gaps remain, which need to be addressed: Southern stakeholders continue to be under-represented in guideline development, and there is limited evidence of how guidelines are used in practice. Further exploration is needed of Southern stakeholder priorities and whether and how guidelines are operationalized.

Health systems, Health Systems Financing & Health Policy

16. Health Policy and Planning, Vol 37 (4), April 2022: 429–439

Who is paid in pay-for-performance? Inequalities in the distribution of financial bonuses amongst health centres in Zimbabwe

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Although pay-for-performance (P4P) schemes have been implemented across low- and middle-income countries (LMICs), little is known about their distributional consequences. A key concern is that financial bonuses are primarily captured by providers who are already better able to perform (for example, those in wealthier areas), P4P could exacerbate existing inequalities within the health

system. We examine inequalities in the distribution of pay-outs in Zimbabwe's national P4P scheme (2014–2016) using quantitative data on bonus payments and facility characteristics and findings from a thematic policy review and 28 semi-structured interviews with stakeholders at all system levels. We found that in Zimbabwe, facilities with better baseline access to guidelines, more staff, higher consultation volumes and wealthier and less remote target populations earned significantly higher P4P bonuses throughout the programme. For instance, facilities that were 1 SD above the mean in terms of access to guidelines, earned 90 USD more per quarter than those that were 1 SD below the mean. Differences in bonus pay-outs for facilities that were 1 SD above and below the mean in terms of the number of staff and consultation volumes are even more pronounced at 348 USD and 445 USD per quarter. Similarly, facilities with villages in the poorest wealth quintile in their vicinity earned less than all others—and 752 USD less per quarter than those serving villages in the richest quintile. Qualitative data confirm these findings. Respondents identified facility baseline structural quality, leadership, catchment population size and remoteness as affecting performance in the scheme. Unequal distribution of P4P pay-outs was identified as having negative consequences on staff retention, absenteeism and motivation. Based on our findings and previous work, we provide some guidance to policymakers on how to design more equitable P4P schemes.

HIV

17. *BMJ Global Health* 2022;7:e007641. Original research

Effects of a multimedia campaign on HIV self-testing and PrEP outcomes among young people in South Africa: a mixed-methods impact evaluation of 'MTV Shuga Down South'

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Abstract

Introduction Innovative HIV technologies can help to reduce HIV incidence, yet uptake of such tools is relatively low among young people. To create awareness and demand among adolescents and young adults, a new campaign of the pan-African MTV Shuga series ('Down South 2'; DS2), featured storylines and messages about HIV self-testing (HIVST) and pre-exposure prophylaxis (PrEP) through television, radio and accompanying multimedia activities in 2019–2020.

Methods We conducted a mixed-methods evaluation of the new MTV Shuga series among 15–24 years old in Eastern Cape, South Africa, in 2020. Quantitative and qualitative methods were used to investigate complementary evaluations questions, namely, whether and how the DS2 campaign works. A web-based survey, promoted via social media platforms of schools, universities and communities, assessed exposure to MTV Shuga and knowledge of HIV status; secondary outcomes included awareness and uptake of HIVST and PrEP. We used multivariable logistic regression to estimate associations between exposure to DS2 and each outcome, adjusting for sociodemographic factors, media assets and exposure to other media campaigns. An embedded qualitative evaluation explored mechanisms of DS2's impact through deductive and inductive thematic analysis of in-depth individual and group interviews.

Results Among 3431 online survey participants, 43% had engaged with MTV Shuga and 24% with DS2 specifically. Knowledge of HIV status was higher among those exposed to DS2 (71%) vs those who were not (39%; adjusted OR=2.26 (95% CI 1.78 to 2.87)). Exposure was also associated with increased awareness of HIVST (60% vs 28%; aOR=1.99 (1.61 to 2.47)) and use of HIVST (29% vs 10%; aOR=2.49 (1.95 to 3.19)). One-third of respondents were aware of PrEP, with higher proportions among those exposed versus non-exposed to DS2 (52% vs 27%; aOR=1.90 (1.53 to 2.35)). Qualitative insights identified mechanisms by which DS2 increased awareness, confidence and motivation to use HIVST and PrEP, but had less influence on service access.

Conclusions We found evidence consistent with a positive causal impact of the MTV Shuga DS2 campaign on HIV prevention outcomes among young people in a high-prevalence setting. As diverse testing and PrEP technologies become accessible, an immersive edutainment campaign can help to expand HIV prevention choices and close age and gender gaps in HIV testing and prevention goals.

18. Lancet 2022; 399(10337):1779-89

Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial

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Erratum in: Lancet 2022;399(10337):1778

Background: Oral pre-exposure prophylaxis has been introduced in more than 70 countries, including many in sub-Saharan Africa, but women experience considerable barriers to daily pill-taking, such as stigma, judgement, and the fear of violence. Safe and effective long-acting agents for HIV prevention are needed for women. We aimed to evaluate the safety and efficacy of injectable cabotegravir compared with daily oral tenofovir diphosphate plus emtricitabine (TDF-FTC) for HIV prevention in HIV-uninfected women.

Methods: HPTN 084 was a phase 3, randomised, double-blind, double-dummy, active-controlled, superiority trial in 20 clinical research sites in seven countries in sub-Saharan Africa. Participants were eligible for enrolment if they were assigned female sex at birth, were aged 18-45 years, reported at least two episodes of vaginal intercourse in the previous 30 days, were at risk of HIV infection based on an HIV risk score, and agreed to use a long-acting reversible contraceptive method. Participants were randomly assigned (1:1) to either active cabotegravir with TDF-FTC placebo (cabotegravir group) or active TDF-FTC with cabotegravir placebo (TDF-FTC group). Study staff and participants were masked to study group allocation, with the exception of the site pharmacist who was responsible for study product preparation. Participants were prescribed 5 weeks of daily oral product followed by intramuscular injections every 8 weeks after an initial 4-week interval load, alongside daily oral pills. Participants who discontinued injections were offered open-label daily TDF-FTC for 48 weeks. The primary endpoints of the study were incident HIV infection in the intention-to-treat population, and clinical and laboratory events that were grade 2 or higher in all women who had received at least one dose of study product. This study is registered with ClinicalTrials.gov, NCT03164564.

Findings: From Nov 27, 2017, to Nov 4, 2020, we enrolled 3224 participants (1614 in the cabotegravir group and 1610 in the TDF-FTC group). Median age was 25 years (IQR 22-30); 1755 (54.7%) of 3209 had two or more partners in the preceding month. 40 incident infections were observed over 3898 person-years (HIV incidence 1.0% [95% CI 0.73-1.40]); four in the cabotegravir group (HIV incidence 0.2 cases per 100 person-years [0.06-0.52]) and 36 in the TDF-FTC group (1.85 cases per 100 person-years [1.3-2.57]; hazard ratio 0.12 [0.05-0.31]; $p < 0.0001$; risk difference -1.6% [-1.0% to -2.3%]). In a random subset of 405 TDF-FTC participants, 812 (42.1%) of 1929 plasma samples had tenofovir concentrations consistent with daily use. Injection coverage was 93% of the total number of person-years. Adverse event rates were similar across both groups, apart from injection site reactions, which were more frequent in the cabotegravir group than in the TDF-FTC group (577 [38.0%] of 1519 vs 162 [10.7%] of 1516) but did not result in injection discontinuation. Confirmed pregnancy incidence was 1.3 per 100 person-years (0.9-1.7); no congenital birth anomalies were reported.

Interpretation: Although both products for HIV prevention were generally safe, well tolerated, and effective, cabotegravir was superior to TDF-FTC in preventing HIV infection in women.

19. TMIH 2022;27(5):479-93

Systematic review: Development of a person-centered care framework within the context of HIV treatment settings in sub-Saharan Africa

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Objectives: Person-centred care (PCC) meets the needs of individuals by increasing convenience, providing supportive and culturally appropriate services to diverse populations, and engaging families, communities, and stakeholders in planning and provision of care. While the evidence demonstrates that PCC approaches can lead to clinical improvements across the HIV care continuum, it is not yet well defined in the context of HIV service delivery.

Methods: A systematic review was conducted to define PCC practices for HIV treatment services in health facilities in sub-Saharan Africa. Data synthesis led to the development of a PCC framework including domain and sub-domain development. The study team used the Effective Public Health Project Practice tool for quantitative studies to assess the quality of the included studies.

Results: Thirty-one studies from 12 countries met the inclusion criteria, including 56,586 study participants (females 42%-100% and males 0%-58%), resulting in three major domains and 11 sub-domains. These include staffing (sub-domains of composition, availability, and competency); service delivery standards (sub-domains of client feedback mechanisms; service efficiency and integration; convenience and access; and digital health worker support tools); and direct client support services (sub-domains of psychosocial services, logistics support, client-agency, and digital client support tools). Twenty-five of the person-centred interventions within these domains resulted in improvements in linkage to care, treatment retention, and/or viral suppression.

Conclusions: The PCC framework can help to provide a more consistent classification of HIV treatment interventions and will support improved assessment of these interventions to ensure that people receive personalised care.

20. TMIH 2022;27(5):537-43

Testing modality associated with fast-track ART initiation in Botswana

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Objectives: The aim of this study was to identify community testing modalities associated with fast-track ART initiation in Botswana.

Methods: We conducted a retrospective cohort study that included all Botswana citizens 15 years or older who were newly identified as HIV-positive from 1 May 2017 to 31 January 2019, in Mahalapye and Southern districts. We used Poisson regression with robust error variance and generalised linear mixed models to control for cluster effects to model risk of ART initiation within 7 and 30 days of HIV diagnosis, testing modality factors.

Results: A total of 1436 individuals were newly identified HIV-positive, with men accounting for 60% across all testing modalities. 22% of all HIV-positive individuals were initiated on ART within 7 days. Clients diagnosed through index testing were more likely to be started on ART within 7 days (adjusted risk ratio [aRR] = 1.38, 95% CI 1.37-1.38) and 30 days (aRR = 1.17, 95% CI 1.09-1.26) than those diagnosed through mobile/outreach testing.

Conclusions: Community HIV testing can complement facility-based testing by reaching individuals who may be less likely to seek HIV services at a facility, such as men. Monitoring ART initiation by testing modalities is critical to identify the optimal ones and to guide continuous programme improvement.

Mental Health

21. BMJ Global Health 2022;7:e007409. Original research

The economic burden of dementia in low- and middle-income countries (LMICs): a systematic review
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Abstract

Introduction More than two-thirds of people with dementia live in low- and middle-income countries (LMICs), resulting in a significant economic burden in these settings. In this systematic review, we consolidate the existing evidence on the cost of dementia in LMICs.

Methods Six databases were searched for original research reporting on the costs associated with all-cause dementia or its subtypes in LMICs. The national-level dementia costs inflated to 2019 were expressed as percentages of each country's gross domestic product (GDP) and summarised as the total mean percentage of GDP. The risk of bias of studies was assessed using the Larg and Moss method.

Results We identified 14 095 articles, of which 24 studies met the eligibility criteria. Most studies had a low risk of bias. Of the 138 LMICs, data were available from 122 countries. The total annual absolute per capita cost ranged from US\$590.78 for mild dementia to US\$25 510.66 for severe dementia. Costs increased with the severity of dementia and the number of comorbidities. The estimated annual total national costs of dementia ranged from US\$1.04 million in Vanuatu to US\$195 billion in China. The average total national expenditure on dementia estimated as a proportion of GDP in LMICs was 0.45%. Indirect costs, on average, accounted for 58% of the total cost of dementia, while direct costs contributed 42%. Lack of nationally representative samples, variation in cost components, and quantification of indirect cost were the major methodological challenges identified in the existing studies.

Conclusion The estimated costs of dementia in LMICs are lower than in high-income countries. Indirect costs contribute the most to the LMIC cost. Early detection of dementia and management of comorbidities is essential for reducing costs. The current costs are likely to be an underestimation due to limited dementia costing studies conducted in LMICs, especially in countries defined as low-income.

22. Health Policy and Planning, Vol 37 (4), April 2022: 492 - 504

Profile of the current psychiatrist workforce in South Africa: establishing a baseline for human resource planning and strategy

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The World Health Organization Global Health Observatory Data Repository reports South Africa with 1.52 psychiatrists per 100 000 of the population among other countries in Africa with 0.01 psychiatrists per 100 000 (Chad, Burundi and Niger) to more than 30 per 100 000 for some countries in Europe. The overall situation, while being cognizant that mental health care is not only provided by specialist psychiatrists and that the current treatment gap may have to be addressed by strategies such as appropriate task sharing, suggests that there are actually too few psychiatrists to meet the country's mental health care needs. To address the need to develop a strategy to increase the local specialist training and examination capacity, a situational review of currently practicing psychiatrists was undertaken by the [BLINDED] and the [BLINDED] using the South African Society of Psychiatrists membership database. The number, distribution and attributes of practicing psychiatrists were compared with international figures on the ratio of psychiatrists per 100 000 population. In April 2019, there were 850 qualified psychiatrists actively practicing in the country and based on the national population figure of 55.6 million people (2016 Census), the psychiatrists per 100 000 ratio was 1.53. This indicates no improvement between 2016 to 2019. From the South African Society of Psychiatrists database, we determined that about 80% of psychiatrists are working in the private sector—a much higher proportion than is usually quoted. As the vast majority of psychiatrists are practicing in urban areas in two provinces, Gauteng (n = 350) and Western Cape (n = 292), the ratio of psychiatrists per 100 000 in these areas is relatively higher at 2.6 and 5.0, respectively, whereas rural areas in South Africa are largely without specialist mental health expertise at a rate of 0.03 per 100 000 population. This investigation provides a discipline-specific situational review of the attributes and distribution of the current workforce of specialists in the country.

23. Lancet Psychiatry 2022;9(1):59-71

Clinical Trial

Efficacy and cost-effectiveness of task-shared care for people with severe mental disorders in Ethiopia (TaSCS): a single-blind, randomised, controlled, phase 3 non-inferiority trial
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Background: There have been no trials of task-shared care (TSC) using WHO's mental health Gap Action Programme for people with severe mental disorders (psychosis or affective disorder) in low-income or middle-income countries. We aimed to evaluate the efficacy and cost-effectiveness of TSC compared with enhanced specialist mental health care in rural Ethiopia.

Methods: In this single-blind, phase 3, randomised, controlled, non-inferiority trial, participants had a confirmed diagnosis of a severe mental disorder, recruited from either the community or a local outpatient psychiatric clinic. The intervention was TSC, delivered by supervised, non-physician primary health care workers trained in the mental health Gap Action Programme and working with community health workers. The active comparison group was outpatient psychiatric nurse care augmented with community lay workers (PSY). Our primary endpoint was whether TSC would be non-inferior to PSY at 12 months for the primary outcome of clinical symptom severity using the Brief

Psychiatric Rating Scale, Expanded version (BPRS-E; non-inferiority margin of 6 points).

Randomisation was stratified by health facility using random permuted blocks. Independent clinicians allocated groups using sealed envelopes with concealment and outcome assessors and investigators were masked. We analysed the primary outcome in the modified intention-to-treat group and safety in the per-protocol group. This trial is registered with ClinicalTrials.gov, number NCT02308956.

Findings: We recruited participants between March 13, 2015 and May 21, 2016. We randomly assigned 329 participants (111 female and 218 male) who were aged 25-72 years and were predominantly of Gurage (198 [60%]), Silte (58 [18%]), and Mareko (53 [16%]) ethnicity. Five participants were found to be ineligible after randomisation, giving a modified intention-to-treat sample of 324. Of these, 12-month assessments were completed in 155 (98%) of 158 in the TSC group and in 158 (95%) of 166 in the PSY group. For the primary outcome, there was no evidence of inferiority of TSC compared with PSY. The mean BPRS-E score was 27.7 (SD 4.7) for TSC and 27.8 (SD 4.6) for PSY, with an adjusted mean difference of 0.06 (90% CI -0.80 to 0.89). Per-protocol analyses (n=291) were similar. There were 47 serious adverse events (18 in the TSC group, 29 in the PSY group), affecting 28 participants. These included 17 episodes of perpetrated violence and seven episodes of violent victimisation leading to injury, ten suicide attempts, six hospital admissions for physical health conditions, four psychiatric admissions, and three deaths (one in the TSC group, two in the PSY group). The incremental cost-effectiveness ratio for TSC indicated lower cost of -US\$299.82 (95% CI -454.95 to -144.69) per unit increase in BPRS-E scores from a health care sector perspective at 12 months.

Interpretation: WHO's mental health Gap Action Programme for people with severe mental disorders is as cost-effective as existing specialist models of care and can be implemented effectively and safely by supervised non-specialists in resource-poor settings.

24. [Lancet Psychiatry 2022;9\(2\):137-150](#)

Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019
GBD 2019 Mental Disorders Collaborators

Background: The mental disorders included in the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 were depressive disorders, anxiety disorders, bipolar disorder, schizophrenia, autism spectrum disorders, conduct disorder, attention-deficit hyperactivity disorder, eating disorders, idiopathic developmental intellectual disability, and a residual category of other mental disorders. We aimed to measure the global, regional, and national prevalence, disability-adjusted life-years (DALYs), years lived with disability (YLDs), and years of life lost (YLLs) for mental disorders from 1990 to 2019.

Methods: In this study, we assessed prevalence and burden estimates from GBD 2019 for 12 mental disorders, males and females, 23 age groups, 204 countries and territories, between 1990 and 2019. DALYs were estimated as the sum of YLDs and YLLs to premature mortality. We systematically reviewed PsycINFO, Embase, PubMed, and the Global Health Data Exchange to obtain data on prevalence, incidence, remission, duration, severity, and excess mortality for each mental disorder. These data informed a Bayesian meta-regression analysis to estimate prevalence by disorder, age, sex, year, and location. Prevalence was multiplied by corresponding disability weights to estimate YLDs. Cause-specific deaths were compiled from mortality surveillance databases. The Cause of Death Ensemble modelling strategy was used to estimate death rate by age, sex, year, and location.

The death rates were multiplied by the years of life expected to be remaining at death based on a normative life expectancy to estimate YLLs. Deaths and YLLs could be calculated only for anorexia nervosa and bulimia nervosa, since these were the only mental disorders identified as underlying causes of death in GBD 2019.

Findings: Between 1990 and 2019, the global number of DALYs due to mental disorders increased from 80.8 million (95% uncertainty interval [UI] 59.5-105.9) to 125.3 million (93.0-163.2), and the proportion of global DALYs attributed to mental disorders increased from 3.1% (95% UI 2.4-3.9) to 4.9% (3.9-6.1). Age-standardised DALY rates remained largely consistent between 1990 (1581.2 DALYs [1170.9-2061.4] per 100 000 people) and 2019 (1566.2 DALYs [1160.1-2042.8] per 100 000 people). YLDs contributed to most of the mental disorder burden, with 125.3 million YLDs (95% UI 93.0-163.2; 14.6% [12.2-16.8] of global YLDs) in 2019 attributable to mental disorders. Eating disorders accounted for 17 361.5 YLLs (95% UI 15 518.5-21 459.8). Globally, the age-standardised DALY rate for mental disorders was 1426.5 (95% UI 1056.4-1869.5) per 100 000 population among males and 1703.3 (1261.5-2237.8) per 100 000 population among females. Age-standardised DALY rates were highest in Australasia, Tropical Latin America, and high-income North America.

Interpretation: GBD 2019 showed that mental disorders remained among the top ten leading causes of burden worldwide, with no evidence of global reduction in the burden since 1990. The estimated YLLs for mental disorders were extremely low and do not reflect premature mortality in individuals with mental disorders. Research to establish causal pathways between mental disorders and other fatal health outcomes is recommended so that this may be addressed within the GBD study. To reduce the burden of mental disorders, coordinated delivery of effective prevention and treatment programmes by governments and the global health community is imperative.

25. Lancet Public Health 2022;7(2):e105-e125

Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019
GBD 2019 Dementia Forecasting Collaborators

Background: Given the projected trends in population ageing and population growth, the number of people with dementia is expected to increase. In addition, strong evidence has emerged supporting the importance of potentially modifiable risk factors for dementia. Characterising the distribution and magnitude of anticipated growth is crucial for public health planning and resource prioritisation. This study aimed to improve on previous forecasts of dementia prevalence by producing country-level estimates and incorporating information on selected risk factors.

Methods: We forecasted the prevalence of dementia attributable to the three dementia risk factors included in the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 (high body-mass index, high fasting plasma glucose, and smoking) from 2019 to 2050, using relative risks and forecasted risk factor prevalence to predict GBD risk-attributable prevalence in 2050 globally and by world region and country. Using linear regression models with education included as an additional predictor, we then forecasted the prevalence of dementia not attributable to GBD risks. To assess the relative contribution of future trends in GBD risk factors, education, population growth, and population ageing, we did a decomposition analysis.

Findings: We estimated that the number of people with dementia would increase from 57.4 (95% uncertainty interval 50.4-65.1) million cases globally in 2019 to 152.8 (130.8-175.9) million cases in

2050. Despite large increases in the projected number of people living with dementia, age-standardised both-sex prevalence remained stable between 2019 and 2050 (global percentage change of 0.1% [-7.5 to 10.8]). We estimated that there were more women with dementia than men with dementia globally in 2019 (female-to-male ratio of 1.69 [1.64-1.73]), and we expect this pattern to continue to 2050 (female-to-male ratio of 1.67 [1.52-1.85]). There was geographical heterogeneity in the projected increases across countries and regions, with the smallest percentage changes in the number of projected dementia cases in high-income Asia Pacific (53% [41-67]) and western Europe (74% [58-90]), and the largest in north Africa and the Middle East (367% [329-403]) and eastern sub-Saharan Africa (357% [323-395]). Projected increases in cases could largely be attributed to population growth and population ageing, although their relative importance varied by world region, with population growth contributing most to the increases in sub-Saharan Africa and population ageing contributing most to the increases in east Asia.

Interpretation: Growth in the number of individuals living with dementia underscores the need for public health planning efforts and policy to address the needs of this group. Country-level estimates can be used to inform national planning efforts and decisions. Multifaceted approaches, including scaling up interventions to address modifiable risk factors and investing in research on biological mechanisms, will be key in addressing the expected increases in the number of individuals affected by dementia.

26. Lancet Glob Health 2022;10(4):e457-e458

Comment: Addressing the complex needs of people with severe mental health disorders in low-resource settings

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Schizophrenia is a severe mental health disorder, responsible for 12.2% of disability-adjusted life years caused by mental health and substance use disorders globally, it is a cause of individual suffering and of caregiver burden. It is what is commonly understood as mental health disorder in much of the lay population in sub-Saharan Africa because it interferes with the attainment of major life goals such as educational attainment, career development, and establishing lifelong supportive relationships, and people with the condition are exposed to human rights abuses and stigma. Most people with schizophrenia will need long-term care that includes appropriate pharmacological treatment and adjunctive psychosocial interventions. Many sub-Saharan African countries are unable to provide such a response due to a combination of a shortage of specialist mental health services and inadequately trained front-line health providers able to deliver integrated services for severe mental health disorders. Unfortunately, the response of the research community in low and middle-income countries (LMICs), and in sub-Saharan Africa in particular, to the unique needs of people with severe mental health disorders has been inadequate. Thus, although considerable attention has been placed on how to expand services for people with common mental health disorders, such as depression and anxiety, through the integration of services into primary health or community-based platforms, severe mental health disorders, and schizophrenia in particular, have received less focus.

In The Lancet Global Health Article by Laura Asher and colleagues, the authors describe a study designed to address some of the gaps in the literature about how to respond to the needs of people with schizophrenia living in a low-income country. Conducted in the rural Sodo district of Ethiopia, the RISE trial was designed to compare the effectiveness of routine facility-based care with a

combination of facility-based care and community-based rehabilitation. The patient cohort consisted of people with schizophrenia who had been in facility-based care for at least six months before the trial, including those who did not fully engage with this service, or who had not been in facility-based care but were identified through key informants. The primary outcome was disability measured with the proxy-version of the 36-item WHO Disability Assessment Scale at 12 months. A range of equally important secondary outcomes, including clinic attendance, adherence to treatment, symptom level, experience of discrimination and physical restraint, and employment were also assessed.

Overall, the results of the trial at 12-month follow-up suggest a modest effect of the facility-based care plus community-based rehabilitation approach. Although the intervention group had less overall disability at 12 months, better global clinical improvement, and less caregiver burden, the effect of the intervention was not evident on several other domains of disability, including work, self-care, symptom level, experience of discrimination, and employment. The difference between the intervention and control groups was modest, and it is possible that if correction for chance findings had been applied to the results of the multiple comparisons, the few reported differences between the groups might have been further reduced. Given that the RISE trial cohort consisted of some people who had engaged poorly with mental health services, the trial effects were not substantially different from what was reached in the PRIME task-shared facility-based cohort study in the same setting, which raises questions about the specific additional benefits of the RISE trial on the major rehabilitation needs of this vulnerable group of patients.

People with schizophrenia living in resource-limited settings will have a range of needs. Indeed, the authors of the RISE trial identified some of these needs in the rural setting of Ethiopia, which include family conflict, difficulty participating in work and community life, and stigma. Therefore, rehabilitation efforts in such settings should pay particular attention to how these needs might be met. The authors were aware of this and indicated that one goal of the trial was to enhance community support for people with schizophrenia and shape their social environment, and they had therefore aimed to provide employment assistance and raise community awareness. Therefore, it is disappointing that there was no benefit to employment in the facility-based care plus community-based rehabilitation group. We speculate that perhaps suboptimal community engagement activities and the apparent non-engagement with family groups was responsible for this absence of impact in some of the desired areas.

Nevertheless, it is gratifying that there seems to be a growing interest in attending to the neglect of designing and testing of evidence-based interventions for severe mental health disorders in sub-Saharan Africa. The needs of people with these conditions are complex and often go beyond those of people with common mental health disorders, which have received considerably more research attention. The valiant efforts of the RISE investigators need to be complemented by other researchers working in LMICs, particularly those working in sub-Saharan Africa where mental health resources are sparse. The RISE trial provides a good opportunity for learning about the challenges of designing and testing interventions that utilise a range of local resources to address the rehabilitation needs of people with schizophrenia. Future efforts should strive for more community mobilisation and involvement of families, and thereby will hopefully be more impactful in core areas of rehabilitation.

Non Communicable Diseases

27. [BMJ Global Health 2022;7:e008275](#). Analysis

‘Implementability’ matters: using implementation research steps to guide and support non-communicable disease national planning in low-income and middle-income countries

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Abstract

The 'implementation gap' between national plans and successful implementation is a central theme in addressing non-communicable diseases (NCDs). It is a factor that has undermined Sustainable Development Goal 3.4, which aims to achieve a one-third reduction in premature mortality from four major NCDs by 2030. Responding to the potential of implementation research to support low-income and middle-income countries to effectively advance their strategies, we describe ways to make NCD plans more robust by including implementation steps. These steps are (1) choosing some (but not all) effective and cost-effective options; (2) tailoring interventions and their scale-up to national capacity; and (3) making the priorities implementable. We illustrate with examples from several countries.

28. *Health Policy and Planning*, Vol 37 (4), April 2022: 452 - 460

Addressing severe chronic NCDs across Africa: measuring demand for the Package of Essential Non-communicable Disease Interventions-Plus (PEN-Plus)

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Severe chronic non-communicable diseases (NCDs) pose important challenges for health systems across Africa. This study explores the current availability of and demand for decentralization of services for four high-priority conditions: insulin-dependent diabetes, heart failure, sickle cell disease, and chronic pain. Ministry of Health NCD Programme Managers from across Africa (N = 47) were invited to participate in an online survey. Respondents were asked to report the status of clinical care across the health system. A care package including diagnostics and treatment was described for each condition. Respondents were asked whether the described services are currently available at primary, secondary and tertiary levels, and whether making the service generally available at that level is expected to be a priority in the coming 5 years. Thirty-seven (79%) countries responded. Countries reported widespread gaps in service availability at all levels. We found that just under half (49%) of respondents report that services for insulin-dependent diabetes are generally available at the secondary level (district hospital); 32% report the same for heart failure, 27% for chronic pain and 14% for sickle cell disease. Reported gaps are smaller at tertiary level (referral hospital) and larger at primary care level (health centres). Respondents report ambitious plans to introduce and decentralize these services in the coming 5 years. Respondents from 32 countries (86%) hope to make all services available at tertiary hospitals, and 21 countries (57%) expect to make all services available at secondary facilities. These priorities align with the Package of Essential NCD Interventions-Plus. Efforts will require strengthened infrastructure and supply chains, capacity building for staff and new monitoring and evaluation systems for efficient implementation. Many countries will need targeted financial assistance in order to realize these goals. Nearly all (36/37) respondents request technical assistance to organize services for severe chronic NCDs.

Sexual Reproductive Health

29. *BMJ Global Health* 2022;7:e008913. Commentary

How to use heat-stable carbetocin and tranexamic acid for the prevention and treatment of postpartum haemorrhage in low-resource settings

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Summary box

Heat-stable carbetocin, a uterotonic used for postpartum haemorrhage (PPH) prevention and tranexamic acid, an antifibrinolytic indicated for PPH treatment, are recently recommended medications.

The growing number of medications in the PPH prevention and treatment toolkit can challenge policymakers, programme managers and clinicians operating in resource-constrained settings in deciding where and how to invest limited resources to achieve the best possible maternal health outcomes.

This paper argues that there is no one-size-fits-all approach to implementing international PPH prevention and treatment guidance.

A programmatic strategy tailored to the different levels of maternity care and the availability of skilled providers and cold chain systems is proposed.

Background

The least developed countries, which include those affected by fragility and humanitarian crises, account for 44% of all maternal deaths globally. Postpartum haemorrhage (PPH) is a leading cause of maternal mortality in these low-resource settings. Because uterine atony accounts for approximately two-thirds of PPH cases, WHO recommends that every woman receives a prophylactic uterotonic immediately after birth to prevent PPH as part of the active management of the third stage of labour. Some PPH prevention and treatment medicines are well evidenced with a long implementation history, including oxytocin, misoprostol and ergometrine. Heat-stable carbetocin (HSC), a uterotonic recommended for PPH prevention and tranexamic acid (TXA), an antifibrinolytic recommended for PPH treatment, were recently added to the core list of reproductive health medicines in the 2019 Model List of Essential Medicines by the WHO. Since 2021, both medications have been made available at public sector pricing through the Product Catalogue of the United Nations Population Fund. Unlike heat-sensitive oxytocin or ergometrine, HSC and TXA have the operational advantage of overcoming the logistic costs and challenges inherent to ensuring a cold chain system. Therefore, they could play a critical role in resource-challenged and warm climate settings, where cold chain transport and storage is often not available, which compromises the quality of oxytocin.

30. Lancet 2022;399(10327):803-13

Global, regional, and national prevalence estimates of physical or sexual, or both, intimate partner violence against women in 2018

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Background: Intimate partner violence against women is a global public health problem with many short-term and long-term effects on the physical and mental health of women and their children. The Sustainable Development Goals (SDGs) call for its elimination in target 5.2. To monitor governments' progress towards SDG target 5.2, this study aimed to provide global, regional, and country baseline estimates of physical or sexual, or both, violence against women by male intimate partners.

Methods: This study developed global, regional, and country estimates, based on data from the WHO Global Database on Prevalence of Violence Against Women. These data were identified through a systematic literature review searching MEDLINE, Global Health, Embase, Social Policy, and Web of Science, and comprehensive searches of national statistics and other websites. A country consultation process identified additional studies. Included studies were conducted between 2000 and 2018, representative at the national or sub-national level, included women aged 15 years or

older, and used act-based measures of physical or sexual, or both, intimate partner violence. Non-population-based data, including administrative data, studies not generalisable to the whole population, studies with outcomes that only provided the combined prevalence of physical or sexual, or both, intimate partner violence with other forms of violence, and studies with insufficient data to allow extrapolation or imputation were excluded. We developed a Bayesian multilevel model to jointly estimate lifetime and past year intimate partner violence by age, year, and country. This framework adjusted for heterogeneous age groups and differences in outcome definition, and weighted surveys depending on whether they were nationally or sub-nationally representative. This study is registered with PROSPERO (number CRD42017054100).

Findings: The database comprises 366 eligible studies, capturing the responses of 2 million women. Data were obtained from 161 countries and areas, covering 90% of the global population of women and girls (15 years or older). Globally, 27% (uncertainty interval [UI] 23-31%) of ever-partnered women aged 15-49 years are estimated to have experienced physical or sexual, or both, intimate partner violence in their lifetime, with 13% (10-16%) experiencing it in the past year before they were surveyed. This violence starts early, affecting adolescent girls and young women, with 24% (UI 21-28%) of women aged 15-19 years and 26% (23-30%) of women aged 19-24 years having already experienced this violence at least once since the age of 15 years. Regional variations exist, with low-income countries reporting higher lifetime and, even more pronouncedly, higher past year prevalence compared with high-income countries.

Interpretation: These findings show that intimate partner violence against women was already highly prevalent across the globe before the COVID-19 pandemic. Governments are not on track to meet the SDG targets on the elimination of violence against women and girls, despite robust evidence that intimate partner violence can be prevented. There is an urgent need to invest in effective multisectoral interventions, strengthen the public health response to intimate partner violence, and ensure it is addressed in post-COVID-19 reconstruction efforts.

31. TMIH 2022 doi: 10.1111/tmi.13756. Online ahead of print

The Impact of Option B+ on Mother to Child Transmission of HIV in Africa: A Systematic Review
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Objective: In 2015, WHO released new guidelines to reduce mother to child transmission (MTCT) of HIV. The recommendations, known as Option B+, included initiation of lifelong Highly Active Antiretroviral Therapy regardless of CD4 count for all HIV positive pregnant and breastfeeding mothers. For infants, exclusive breastfeeding for 6 months and antiviral therapy was sanctioned. Targets of <5% transmission in breastfeeding populations and <2% in non-breastfeeding populations were set. This review evaluated the impact of Option B+ on MTCT in African countries.

Methods: Using the PRISMA guidelines, a systematic search of PubMed and Google Scholar databases was conducted to identify relevant studies published between 2015 and 2021. All studies meeting inclusion criteria were evaluated.

Results: Of the 687 references screened, 22 studies from 11 countries (Cameroon, Ethiopia, Lesotho, Malawi, Rwanda, South Africa, Swaziland, Tanzania, Uganda, Zambia, and Zimbabwe) met inclusion criteria. Six studies reported MTCT rates of <2%, 16 studies reported rates of 2-5%, and two studies (Uganda and Zambia) reported 6% or more. Rates varied within the same study at different time

points postpartum, and among studies from the same country. Overall, reported MTCT rates appear to be close to WHO targets. However, diverse study designs, selection bias, extensive loss to follow-up, and undocumented adherence rates to Option B+ protocols may significantly underestimate MTCT rates of HIV in Africa.

Conclusions: Standardized protocols for impact evaluation must be established to provide evidenced-based data on the efficacy of Option B+ in Africa.

32. TMIH 2022;27(3):236-43

Where and why do we lose women from the continuum of care in maternal health? A mixed-methods study in Southern Benin

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Objective: Continuum of care (CoC) in maternal health is built on evidence suggesting that the integration of effective interventions across pregnancy, childbirth, and the postnatal period leads to better perinatal health outcomes. We explored gaps along the CoC in maternal health in Benin.

Methods: A mixed-methods study triangulating results from a qualitative study in southern Benin with a quantitative analysis of Benin Demographic and Health Survey (BDHS) data on the use of services along the CoC was conducted.

Results: Benin Demographic and Health Survey analysis showed that although 89% of women reported at least one antenatal care (ANC) visit, only half initiated ANC in the first trimester and completed 4 or more visits. 85% reported facility-based childbirth and 69% a postnatal check within 48 h after childbirth. Our qualitative study confirms early initiation of ANC and the transition from facility-based childbirth to postnatal care are important gaps along the CoC and reveals late arrival at health facility for childbirth as an additional gap. These gaps interact with spiritual and alternative care practices that aim to safeguard pregnancy and prevent complications. Structural factors related to poverty and disrespectful care in health facilities compounded to limit the utilisation of formal healthcare.

Conclusions: The combined use of BDHS and qualitative data contributed to highlighting critical gaps along the maternal CoC. A lack of integration of spiritual or alternative aspects of care into biomedical services, as well as structural factors, impeded access to healthcare in Benin.

33. TMIH 2022;27(5):468-78

Female genital mutilation and cutting in the Arab League and diaspora: A systematic review of preventive interventions

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Objectives: Female Genital Mutilation and Cutting (FGM/C) is an act of gender-based violence (GBV) and a global public health issue with well-documented adverse outcomes. With the rise in global migration, there is an increasing prevalence of FGM/C among Arab diaspora living in the West and Global South. What remains unclear is how to reduce the practice. This study was designed to identify interventions exerting an effect on reducing the practice of FGM/C.

Methods: A systematic review of peer-reviewed articles was conducted on interventions targeting individuals and/or the broader community to prevent FGM/C within the Arab League and its diaspora, up to December 2021. Databases searched included PubMed, Medline, Web of Science, PsycINFO, EMBASE, CINAHL, BIOSIS, ASSIA and Scopus. Quality assessment used the Mixed Methods Appraisal Tool (MMAT) 2018.

Results: Twelve of 896 studies met the inclusion criteria. Eight interventions relied entirely on education with short-term gains but unchanged practices. Three interventions used social marketing and mixed media. Only one study took a multi-sectoral approach.

Conclusions: At a macro level, opportunities to reduce or to end the practice of FGM/C exist through legislation, policy, a public health approach grounded in gender equality and human rights. Using multi-sectoral actions that consider the social context and challenge social norms at macro, meso and micro levels appears more effective than individual-level interventions. Promoting advocacy and developing supportive environments to reduce GBV, enhance gender equality and empower communities is crucial for interventions to succeed and achieve the Sustainable Development Goal target of FGM/C abandonment by 2030.

34. TMIH 2022;27(5):494-509

Interventions to improve obstetric emergency referral decision making, communication and feedback between health facilities in sub-Saharan Africa: A systematic review

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Objective: The objective of the study was to review the evidence on interventions to improve obstetric emergency referral decision making, communication and feedback between health facilities in sub-Saharan Africa (SSA).

Methods: A systematic search of PubMed, Embase, Cochrane Register and CINAHL Plus was conducted to identify studies on obstetric emergency referral in SSA. Studies were included based on pre-defined eligibility criteria. Details of reported referral interventions were extracted and categorised. The Joanna Biggs Institute Critical Appraisal checklists were used for quality assessment of included studies. A formal narrative synthesis approach was used to summarise findings guided by the WHO's referral system flow.

Results: A total of 14 studies were included, with seven deemed high quality. Overall, 7 studies reported referral decision-making interventions including training programmes for health facility and community health workers, use of a triage checklist and focused obstetric ultrasound, which resulted in improved knowledge and practice of recognising danger signs for referral. 9 studies reported on referral communication using mobile phones and referral letters/notes, resulting in increased communication between facilities despite telecommunication network failures. Referral decision making and communication interventions achieved a perceived reduction in maternal mortality. 2 studies focused on referral feedback, which improved collaboration between health facilities.

Conclusion: There is limited evidence on how well referral interventions work in sub-Saharan Africa, and limited consensus regarding the framework underpinning the expected change. This review has led to the proposition of a logic model that can serve as the base for future evaluations which robustly expose the (in)efficiency of referral interventions.

Other

35. Lancet 2022;399(10331):1266–78

NCD Countdown 2030: efficient pathways and strategic investments to accelerate progress towards the Sustainable Development Goal target 3.4 in low-income and middle-income countries
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Most countries have made little progress in achieving the Sustainable Development Goal (SDG) target 3.4, which calls for a reduction in premature mortality from non-communicable diseases (NCDs) by a third from 2015 to 2030. In this Health Policy paper, we synthesise the evidence related to interventions that can reduce premature mortality from the major NCDs over the next decade and that are feasible to implement in countries at all levels of income. Our recommendations are intended as generic guidance to help 123 low-income and middle-income countries meet SDG target 3.4; country-level applications require additional analyses and consideration of the local implementation and utilisation context. Protecting current investments and scaling up these interventions is especially crucial in the context of COVID-19-related health system disruptions. We show how cost-effectiveness data and other information can be used to define locally tailored packages of interventions to accelerate rates of decline in NCD mortality. Under realistic implementation constraints, most countries could achieve (or almost achieve) the NCD target using a combination of these interventions; the greatest gains would be for cardiovascular disease mortality. Implementing the most efficient package of interventions in each world region would require, on average, an additional US\$18 billion annually over 2023–30; this investment could avert 39 million deaths and generate an average net economic benefit of \$2.7 trillion, or \$390 per capita. Although specific clinical intervention pathways would vary across countries and regions, policies to reduce behavioural risks, such as tobacco smoking, harmful use of alcohol, and excess sodium intake, would be relevant in nearly every country, accounting for nearly two-thirds of the health gains of any locally tailored NCD package. By 2030, ministries of health would need to contribute about 20% of their budgets to high-priority NCD interventions. Our report concludes with a discussion of financing and health system implementation considerations and reflections on the NCD agenda beyond the SDG target 3.4 and beyond the SDG period.

Panel 1: Key messages

- Most low-income and middle-income countries are off track to reach SDG target 3.4 for NCD mortality. To help countries get back on track, we propose a framework for NCD investment that is centred around a model package of 21 interventions that are feasible to implement and can form the backbone of national NCD strategies.
- Implementing these interventions could result in a reduction of a third or more in mortality by 2030 for several specific NCDs, especially cardiovascular diseases. Although most of these interventions are cost-effective in nearly all world regions, national governments could further tailor this package by scaling up the most cost-effective subset of interventions that addresses the top NCD causes locally.
- Under ambitious but realistic implementation conditions, the intervention strategy would allow low-income and middle-income countries to achieve SDG target 3.4, including nearly all world regions and 55% of countries; other countries might fall short of the target because of especially unfavourable recent trends and health system constraints.

- Achieving SDG target 3.4 worldwide would require US\$140 billion in new spending over 2023–30, an average of \$18 billion annually, but 39 million deaths could be averted over this period and \$2.7 trillion in net economic benefits could be generated, with benefits outweighing costs nineteen-to-one. These costs would comprise a considerable share of the health budget (median value of 20% by 2030); mobilisation of additional resources would be required in low-income and lower-middle-income countries.
- Although countries exhibit wide variation in NCD epidemiology and health system capacity, cross-cutting intersectoral policies on tobacco, alcohol, and unhealthy diet are relevant and essential in all countries, contribute two-thirds of the total mortality impact of the package, and can reduce need for costly clinical services.
- We conclude with a summary of non-financial challenges that health planners need to consider when developing their NCD strategies; health workforce development is among the most important of these. As such, advocates and policy makers need to have a long-term approach to NCDs that emphasises feasibility and sustainability and is aligned with national health system strengthening and universal health coverage agendas.

NCDs=non-communicable diseases. SDG=Sustainable Development Goal.