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International Health Alerts 2018-4 Abstracts

Infectious diseases

1. *Am J Trop Med Hyg.* 2018 Oct 29

Housing Characteristics and Leishmaniasis: A Systematic Review

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Leishmaniasis is a major neglected tropical disease associated with high rates of disability and death. This disease is associated with poverty, which can be reflected in housing quality, especially in rural areas. This systematic review found that mud walls with cracks and holes, damp, and dark houses were risk factors for transmission of leishmaniasis. These characteristics create favorable conditions for sand fly breeding and resting as sand flies prefer humidity, warmth, and protection from sunlight during the day. Housing interventions might be a promising research area with a special focus on education as individual and collective protection for the effective control of leishmaniasis.

2. *Am J Trop Med Hyg.* 2018 Nov;99(5):1211-1218

Onchocerciasis-Associated Epilepsy with Head Nodding Seizures-Nodding Syndrome: A Case Series of 15 Patients from Western Uganda, 1994

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Nodding syndrome (NS) is an encephalopathy characterized by the core symptom of epileptic head nodding seizures, affecting children at the age between 3 and 18 years in distinct areas of tropical Africa. A consistent correlation with onchocerciasis was found, but so far, the causation of NS has not been fully clarified. With a systematic analysis of features of a cohort of epilepsy patients examined in the Itwara onchocerciasis focus of western Uganda in 1994, we provide evidence that NS actually occurred in this area at this time, and we demonstrate a correlation between prevalence of NS and that of onchocerciasis in different villages. Following the elimination of onchocerciasis by community-directed treatment with ivermectin and ground larviciding, our data provide a baseline to examine the question whether NS will disappear once its putative cause has been removed.

3. *Am J Trop Med Hyg.* 2018 Nov;99(5):1234-1238

Managing Severe Tetanus without Ventilation Support in a Resource-limited Setting in Bangladesh

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Tetanus, a vaccine-preventable and potentially fatal disease, continues to remain prevalent in low- and middle-income countries. Furthermore, physicians are often unfamiliar with management of severe tetanus without ventilator support. Therefore, we proposed a modified treatment protocol that provides a low-cost and effective solution for the management of severe tetanus in resource-constrained settings. This is an observational study of 42 patients with severe tetanus treated during 2015-2016 at Surya Kanta Hospital, Bangladesh. This facility does not have an intensive care unit (ICU), and patients admitted here were provided treatment with the modified protocol. A total number of 42 patients with severe tetanus were treated with the modified protocol. Among them,

24 (57.1%) recovered completely, six (14.3%) recovered with the sequela, and 12 (28.6%) died. Among those who recovered with the sequela, four needed mechanical support during walking and two had a visual impairment. No significant adverse event was recorded during the treatment period. The results gathered during this case series provide a sustainable, low-cost, and effective solution to management of severe tetanus in resource-constrained settings where ICUs are unavailable.

4. [BMJ 2018;362:k3948](#)

Pandemrix vaccine: why was the public not told of early warning signs?

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Eight years after the pandemic influenza outbreak, a lawsuit alleging that GlaxoSmithKline's Pandemrix vaccine caused narcolepsy has unearthed internal reports suggesting problems with the vaccine's safety. Peter Doshi asks what this means for the future of transparency during public health emergencies

In October 2009, the US National Institutes of Health infectious diseases chief, Anthony Fauci, appeared on YouTube to reassure Americans about the safety of the "swine flu" vaccine. "The track record for serious adverse events is very good. It's very, very, very rare that you ever see anything that's associated with the vaccine that's a serious event," he said.

Four months earlier, the World Health Organization had declared H1N1 influenza a pandemic, and by October 2009 the new vaccines were being rolled out across the world. A similar story was playing out in the UK, with prominent organisations, including the Department of Health, British Medical Association, and Royal Colleges of General Practitioners, working hard to convince a reluctant NHS workforce to get vaccinated. "We fully support the swine flu vaccination programme ... The vaccine has been thoroughly tested," they declared in a joint statement.

Except, it hadn't. Anticipating a severe influenza pandemic, governments around the world had made various logistical and legal arrangements to shorten the time between recognition of a pandemic virus and the production of a vaccine and administration of that vaccine in the population. In Europe, one element of those plans was an agreement to grant licences to pandemic vaccines based on data from pre-pandemic "mock-up" vaccines produced using a different virus (H5N1 influenza). Another element, adopted by countries such as Canada, the US, UK, France, and Germany, was to provide vaccine manufacturers indemnity from liability for wrongdoing, thereby reducing the risk of a lawsuit stemming from vaccine related injury.

5. [BMJ 2018;363:k4431](#)

Maternal-fetal transmission and adverse perinatal outcomes in pregnant women infected with Zika virus: prospective cohort study in French Guiana

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The recent epidemics in French Polynesia and the Americas have confirmed vertical trans-placental transmission of Zika virus and its association with congenital anomalies, particularly severe central nervous system lesions. Nevertheless, the exact burden of disease remains unclear, especially in endemic countries. Similarly to congenital cytomegalovirus and toxoplasmosis infections, vertical transmission is not systematic and does not always lead to fetuses/infants with apparent signs of infection. The risk of congenital Zika virus syndrome (CZS) was estimated, at first, to be higher than 40% in a cohort of women who developed symptomatic Zika virus infection during pregnancy in

Brazil, whereas more recent data from the US Zika pregnancy registry suggest an overall risk of 5% and up to 8% in cases of maternal infection in the first trimester. The lack of fetal/neonatal testing in previous studies has impaired accurate estimations of maternal-fetal transmission and risk of symptomatic congenital infection.

Abstract

Objectives To estimate the rates of maternal-fetal transmission of Zika virus, adverse fetal/neonatal outcomes, and subsequent rates of asymptomatic/symptomatic congenital Zika virus infections up to the first week of life.

Design Cohort study with prospective data collection and subsequent review of fetal/neonatal outcomes.

Settings Referral centre for prenatal diagnosis of the French Guiana Western Hospital.

Participants Pregnant women at any stage of pregnancy with a laboratory confirmed symptomatic or asymptomatic Zika virus infection during the epidemic period in western French Guiana. The cohort enrolled 300 participants and prospectively followed their 305 fetuses/newborns.

Main outcome measures Rate of maternal-fetal transmission of Zika virus (amniotic fluid, fetal and neonatal blood, urine, cerebrospinal fluid, and placentas); clinical, biological, and radiological outcomes (blindly reviewed); and adverse outcomes defined as moderate signs potentially related to congenital Zika syndrome (CZS), severe complications compatible with CZS, or fetal loss. Associations between a laboratory confirmed congenital Zika virus infection and adverse fetal/neonatal outcomes were evaluated.

Results Maternal-fetal transmission was documented in 26% (76/291) of fetuses/newborns with complete data. Among the Zika virus positive fetuses/newborns, 45% (34/76) presented with no signs/complications at birth, 20% (15/76) with moderate signs potentially related to CZS, 21% (16/76) with severe complications compatible with CZS, and 14% (11/76) with fetal loss. Compared with the Zika virus positive fetuses/neonates, those that were identified as negative for Zika virus (215/291) were less likely to present with severe complications (5%; 10/215) or fetal loss (0.5%; 1/215; relative risk 6.9, 95% confidence interval 3.6 to 13.3). Association between a positive Zika virus test and any adverse fetal/neonatal outcome was also significant (relative risk 4.4, 2.9 to 6.6). The population attributable fraction estimates that a confirmed congenital Zika virus infection contributes to 47% of adverse outcomes and 61% of severe adverse outcomes observed.

Conclusion In cases of a known maternal Zika virus infection, approximately a quarter of fetuses will become congenitally infected, of which a third will have severe complications at birth or fetal loss. The burden of CZS might be lower than initially described in South America and may not differ from other congenital infections.

6. Lancet 2018 Oct 6;392(10154):1207-1216. Epub 2018 Jan 18

Single dose moxidectin versus ivermectin for *Onchocerca volvulus* infection in Ghana, Liberia, and the Democratic Republic of the Congo: a randomised, controlled, double-blind phase 3 trial.

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Erratum in Lancet 2018 Oct 6;392(10154):1196.

Comment in Lancet 2018 Oct 6;392(10154):1170-1172.

BACKGROUND: The morbidity and socioeconomic effects of onchocerciasis, a parasitic disease that is primarily endemic in sub-Saharan Africa, have motivated large morbidity and transmission control programmes. Annual community-directed ivermectin treatment has substantially reduced prevalence. Elimination requires intensified efforts, including more efficacious treatments. We

compared parasitological efficacy and safety of moxidectin and ivermectin. **METHODS:** This double-blind, parallel group, superiority trial was done in four sites in Ghana, Liberia, and the Democratic Republic of the Congo. We enrolled participants (aged ≥ 12 years) with at least 10 *Onchocerca volvulus* microfilariae per mg skin who were not co-infected with *Loa loa* or lymphatic filariasis microfilaraemic. Participants were randomly allocated, stratified by sex and level of infection, to receive a single oral dose of 8 mg moxidectin or 150 $\mu\text{g}/\text{kg}$ ivermectin as overencapsulated oral tablets. The primary efficacy outcome was skin microfilariae density 12 months post treatment. We used a mixed-effects model to test the hypothesis that the primary efficacy outcome in the moxidectin group was 50% or less than that in the ivermectin group. The primary efficacy analysis population were all participants who received the study drug and completed 12-month follow-up (modified intention to treat). This study is registered with ClinicalTrials.gov, number NCT00790998. **FINDINGS:** Between April 22, 2009, and Jan 23, 2011, we enrolled and allocated 998 participants to moxidectin and 501 participants to ivermectin. 978 received moxidectin and 494 ivermectin, of which 947 and 480 were included in primary efficacy outcome analyses. At 12 months, skin microfilarial density (microfilariae per mg of skin) was lower in the moxidectin group (adjusted geometric mean 0.6 [95% CI 0.3-1.0]) than in the ivermectin group (4.5 [3.5-5.9]; difference 3.9 [3.2-4.9], $p < 0.0001$; treatment difference 86%). Mazzotti (ie, efficacy-related) reactions occurred in 967 (99%) of 978 moxidectin-treated participants and in 478 (97%) of 494 ivermectin-treated participants, including ocular reactions (moxidectin 113 [12%] participants and ivermectin 47 [10%] participants), laboratory reactions (788 [81%] and 415 [84%]), and clinical reactions (944 [97%] and 446 [90%]). No serious adverse events were considered to be related to treatment. **INTERPRETATION:** Skin microfilarial loads (ie, parasite transmission reservoir) are lower after moxidectin treatment than after ivermectin treatment. Moxidectin would therefore be expected to reduce parasite transmission between treatment rounds more than ivermectin could, thus accelerating progress towards elimination.

Malaria

7. *Am J Trop Med Hyg.* 2018 Oct 22 [Epub ahead of print]

Evaluation of a Novel Quantitative Test for Glucose-6-Phosphate Dehydrogenase Deficiency: Bringing Quantitative Testing for Glucose-6-Phosphate Dehydrogenase Deficiency Closer to the Patient

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency, a common genetic blood condition, can result in kernicterus at birth, and later in life as severe hemolysis on exposure to certain infections, foods, and drugs. The unavailability of point-of-care tests for G6PD deficiency is a barrier to routine curative treatment of *Plasmodium vivax* malaria with 8-aminoquinolines, such as primaquine. Two quantitative reference tests (Trinity Biotech, Bray, Ireland and Pointe Scientific, MI; Cat No. G7583) and the point-of-care STANDARD™ G6PD test (SD Biosensor, South Korea) were evaluated. The STANDARD G6PD test was evaluated at multiple temperatures, in anticoagulated venous and capillary samples, including 79 G6PD-deficient and 66 intermediate samples and across two laboratories, one in the United States and one in Thailand. The STANDARD test performed equivalently to a reference assay for its ability to diagnose G6PD deficiency ($< 30\%$ normal) with a sensitivity of 100% (0.95 confidence interval [CI]: 95.7-100) and specificity of 97% (0.95 CI: 94.5-98.5), and could reliably identify females with less than 70% normal G6PD activity with a sensitivity of 95.5% (0.95 CI: 89.7-98.5) and specificity of 97% (0.95 CI: 94.5-98.6). The STANDARD G6PD product represents an opportunity to diagnose G6PD deficiency equally for males and females in basic clinical

laboratories in high- and low-resource settings. This quantitative point-of-care diagnostic test for G6PD deficiency can provide equal access to safe radical cure of *P. vivax* cases in high- and low-resource settings, for males and females and may support malaria elimination, in countries where *P. vivax* is endemic.

8. [Am J Trop Med Hyg. 2018 Oct 22 \[Epub ahead of print\]](#)

New Prototype Screened Doors and Windows for Excluding Mosquitoes from Houses: A Pilot Study in Rural Gambia

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Despite compelling evidence that modern housing protects against malaria, houses in endemic areas are still commonly porous to mosquitoes. The protective efficacy of four prototype screened doors and two windows designs against mosquito house entry, their impact on indoor climate, as well as their use, durability and acceptability was assessed in a Gambian village. A baseline survey collected data on all the houses and discrete household units, each consisting of a front and back room, were selected and randomly allocated to the study arms. Each prototype self-closing screened door and window was installed in six and 12 units, respectively, with six unaltered units serving as controls. All prototype doors reduced the number of house-entering mosquitoes by 59-77% in comparison with the control houses. The indoor climate of houses with screened doors was similar to control houses. Seventy-nine percentage of door openings at night occurred from dusk to midnight, when malaria vectors begin entering houses. Ten weeks after installation the doors and windows were in good condition, although 38% of doors did not fully self-close and latch (snap shut). The new doors and windows were popular with residents. The prototype door with perforated concertinaed screening was the best performing door because it reduced mosquito entry, remained fully functional, and was preferred by the villagers. Screened doors and windows may be useful tools for reducing vector exposure and keeping areas malaria-free after elimination, when investment in routine vector control becomes difficult to maintain.

9. [BMJ Glob Health.; 3\(5\): e000999. 2018 Oct 19](#)

Emerging implications of policies on malaria treatment: genetic changes in the *Pfmdr-1* gene affecting susceptibility to artemether–lumefantrine and artesunate–amodiaquine in Africa

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Artemether–lumefantrine (AL) and artesunate–amodiaquine (AS-AQ) are the most commonly used artemisinin-based combination therapies (ACT) for treatment of *Plasmodium falciparum* in Africa. Both treatments remain efficacious, but single nucleotide polymorphisms (SNPs) in the *Plasmodium falciparum* multidrug resistance 1 (*Pfmdr1*) gene may compromise sensitivity. AL and AS-AQ exert opposing selective pressures: parasites with genotype 86Y, Y184 and 1246Y are partially resistant to AS-AQ treatment, while N86, 184 F and D1246 are favoured by AL treatment. Through a systematic review, we identified 397 surveys measuring the prevalence of *Pfmdr1* polymorphisms at positions 86 184 or 1246 in 30 countries in Africa. Temporal trends in SNP frequencies after introduction of AL or AS-AQ as first-line treatment were analysed in 32 locations, and selection coefficients estimated. We examined associations between antimalarial policies, consumption, transmission intensity and rate of SNP selection. 1246Y frequency decreased on average more rapidly in locations where

national policy recommended AL (median selection coefficient(s) of -0.083), compared with policies of AS-AQ or both AL and AS-AQ (median $s = -0.035$ and 0.021 , $p < 0.001$ respectively). 86Y frequency declined markedly after ACT policy introduction, with a borderline significant trend for a more rapid decline in countries with AL policies ($p = 0.055$). However, these trends could also be explained by a difference in initial SNP frequencies at the time of ACT introduction. There were non-significant trends for faster selection of N86 and D1246 in areas with higher AL consumption and no trend with transmission intensity. Recorded consumption of AS-AQ was low in the locations and times Pfmdr1 data were collected. SNP trends in countries with AL policies suggest a broad increase in sensitivity of parasites to AS-AQ, by 7–10 years after AL introduction. Observed rates of selection have implications for planning strategies to cycle drugs or use multiple first-line therapies to maintain drug efficacy.

HIV/TB

10. *Am J Trop Med Hyg.* 2018 Oct 1.. [Epub ahead of print]

The Impact of Acquired Immune Deficiency Syndrome Treatment on Tuberculosis Detection at the National Level in South Africa

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Human immunodeficiency virus/Tuberculosis (HIV/TB) coinfection is particularly prevalent in South Africa, where TB has been the leading cause of death for more than a decade. The 2004-2008 national rollout of antiretroviral therapy (ART) provides a unique opportunity to examine the population-level impact of ART on the TB epidemic. We performed longitudinal regression analysis to follow the evolution of TB outcomes before and after the introduction of ART using a large data set from the National Health Laboratory Service. This is the first study to produce estimates of the impact of the ART rollout by exploiting staggered timing and geographic variation in the rollout. After ART became available in a health facility, 3.7% ($P < 0.0001$) more patients were tested for TB and 3.2% ($P < 0.0001$) more received repeat testing; however, there was a steep rise in testing before the introduction of ART. Although the number of TB-positive patients increased by 4.3% ($P = 0.0002$) in the first year post-ART, the TB rate among tested patients fell by 2% points (8%, $P = 0.001$) after 2 years. Sputum smear testing declined relative to more technologically advanced diagnostics post-ART. Antiretroviral therapy availability increased the attention to TB screening and drew new patients into the health-care system. Small increases in the numbers of repeat patients are indicative of retention in care. The decline in TB rates post-ART suggests that the reduction in TB risk due to improved immune functioning and health-care contact likely outweighed the increased TB risk because of the longer lifespan of ART initiators.

11. *Am J Trop Med Hyg.* 2018 Nov;99(5):1114-1116

To End TB, First-Ever High-Level Meeting on Tuberculosis Must Address Stigma

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World leaders gather to consolidate their commitment to ending tuberculosis (TB). Vital to the success of renewed efforts is an overdue recognition of the pervasive and pernicious influence of TB stigma. TB stigma is sustained in structures, policies, traditions, and norms. Innovative modifications

to infection control, drug dispensing, and surveillance practices are required to increase demand for TB screening and effective therapeutic alliances among those diagnosed. The authors argue that reducing TB stigma requires a scientific and inclusive process, with prominent roles for TB survivors and a willingness to integrate and learn from other stigmatized conditions.

12. [BMJ 2018;362:k2738](#)

Revisiting the timetable of tuberculosis

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Tuberculosis has a much shorter incubation period than is widely thought, say Marcel A Behr and colleagues, and this has implications for prioritising research and public health strategies. Between a quarter and a third of the world's population are estimated to be latently infected with *Mycobacterium tuberculosis*. The 2018 World Health Organization resource page for tuberculosis (TB) states: "On average, 5-10% of those who are infected will develop active TB disease over their lifetime." Other authorities use terms such as "dormant" or "alive but inactive". Because "reactivated" TB is contagious, eradicating latent infection is a cornerstone of global TB control and achieving a better understanding of latent infection is deemed a research priority. The word latent has both biological and medical definitions. The biological concept of latency is that of a resting stage, hidden until circumstances are suitable for development. The medical definition is simply a pathological process in which symptoms are not yet manifest. The TB clinical community has long used the apposition of latent TB infection and reactivation, clearly applying the biological definition.

The importance attached to latency is reflected in a major push from research funding agencies to understand the biology and epidemiology of latent TB infection and to develop drugs that specifically treat latent infection, aiming for global TB eradication (supplementary box 2). Multiple longitudinal epidemiological studies, however, show that the majority of TB disease manifests soon after infection, with disease rarely occurring more than two years after infection. (We use the term "remote infection" to describe infection preceding active TB by more than two years.) The vast burden of global TB is, therefore, from recently transmitted infection. Only in countries with a low TB burden, where ongoing transmission is minimal, is TB from remote infection a substantial contributor to the active TB burden. Importantly, most such TB cases do not generally result in major disease outbreaks, probably as a result of well functioning public health systems.

Appreciating the natural history of infection and disease should help us to strategise for the global eradication of TB and to design vaccine efficacy trials. Furthermore, the natural history of TB does not support the many terms currently used to describe the various phases of TB infection. These terms are not only confusing, but even misleading. We suggest using just three simple terms—tuberculous reactivity, primary infection, and active TB.

13. [BMJ Glob Health. 2018 Sep 7;3\(5\):e000940](#)

The sex gap in neonatal mortality and the AIDS epidemic in sub-Saharan Africa

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The sex gap in early-age death is one of the most important sources of child inequality in all societies, and it carries negative social consequences in the long run. In the absence of gender discrimination in

the allocation of foods and health resources, mortality rates are higher in boys than in girls. Recent studies however suggest that in sub-Saharan Africa, the general improvement in state capacity and the quality of political and democratic institutions has had stronger health benefits for boys, reducing the male-female gap in early-age mortality. Democratic indicators such as political participation, competitiveness in the recruitment of the executive and constraints on executive power substantially improved after 1990. These positive developments led to an improvement in the quality of public health institutions. Mabeu and Pongou's research implies that the health benefits of these positive institutional changes have mostly accrued to boys, in part because these changes have helped constrain the negative influences of the male biological make-up on mortality. But this pattern was likely to be specific to HIV-unexposed children. Among HIV-exposed children, it seems that other forces were at play.

In this editorial, we analyse trends in the sex gap in neonatal death—death occurring within 1 month of birth—during the era of the AIDS epidemic, and argue that they were sensitive to the availability of antiretroviral medicines. Child exposure to HIV (during pregnancy, delivery and breast feeding) reduced the female survival advantage, but this situation was gradually reversed by the availability of antiretroviral treatment. Over the period 1960–2017 for both boys and girls in sub-Saharan Africa neonatal mortality declined substantially over this period for both sexes. However, as shown, the decline was more important for male children, especially between 1980 and 2008, a period corresponding to one in which antiretroviral therapy was either non-existent or low.

14. *International Journal of Epidemiology*, 2018, Vol 47 (5): 1549–1560

What is the true tuberculosis mortality burden? Differences in estimates by the World Health Organization and the Global Burden of Disease study

García-Basteiro AL, Brew J, Williams B, Borgdorff, M, Cobelens, F, Amsterdam Institute for Global Health and Development (AIGHD), Amsterdam alberto.garcia-basteiro@manhica.net

Background: The World Health Organization (WHO) and the Global Burden of Disease (GBD) study at the Institute for Health Metrics and Evaluation (IHME) periodically provide global estimates of tuberculosis (TB) mortality. We compared the 2015 WHO and GBD TB mortality estimates and explored which factors might drive the differences.

Methods: We extracted the number of estimated TB-attributable deaths, disaggregated by age, HIV status, sex and country from publicly available WHO and GBD datasets for the year 2015. We 'standardized' differences between sources by adjusting each country's difference in absolute number of deaths by the average number of deaths estimated by both sources.

Results: For 195 countries with estimates from both institutions, WHO estimated 1 768 482 deaths attributable to TB, whereas GBD estimated 1 322 916 deaths, a difference of 445 566 deaths or 29% of the average of the two estimates. The countries with the largest absolute differences in deaths were Nigeria (216 621), Bangladesh (49 863) and Tanzania (38 272). The standardized difference was not associated with HIV prevalence, prevalence of multidrug resistance or global region, but did show correlation with the case detection rate as estimated by WHO [$r = -0.37$, 95% confidence interval (CI): -0.49 ; -0.24] or, inversely, with case detection rate based on GBD data ($r = 0.44$, 95% CI: 0.31 ; 0.54). Countries with a recent national prevalence survey had higher standardized differences (higher estimates by WHO) than those without ($P = 0.006$). After exclusion of countries with recent prevalence surveys, the overall correlation between both estimates was $r = 0.991$.

Conclusions: A few countries account for the large global discrepancy in TB mortality estimates. The differences are due to the methodological approaches used by WHO and GBD. The use and

interpretation of prevalence survey data and case detection rates seem to play a role in the observed differences.

15. *International Journal of Epidemiology*, 2018, Vol 47 (5): 1645–1657

Development and validation of a predictive ecological model for TB prevalence

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Background: Nationally representative tuberculosis (TB) prevalence surveys provide invaluable empirical measurements of TB burden but are a massive and complex undertaking. Therefore, methods that capitalize on data from these surveys are both attractive and imperative. The aim of this study was to use existing TB prevalence estimates to develop and validate an ecological predictive statistical model to indirectly estimate TB prevalence in low- and middle-income countries without survey data.

Methods: We included national and subnational estimates from 30 nationally representative surveys and 2 district-level surveys in India, resulting in 50 data points for model development (training set). Ecological predictors included TB notification and programmatic data, co-morbidities and socio-environmental factors extracted from online data repositories. A random-effects multivariable binomial regression model was developed using the training set and was used to predict bacteriologically confirmed TB prevalence in 63 low- and middle-income countries across Africa and Asia in 2015.

Results: Out of the 111 ecological predictors considered, 14 were retained for model building (due to incompleteness or collinearity). The final model retained for predictions included five predictors: continent, percentage retreated cases out of all notified, all forms TB notification rates per 100 000 population, population density and proportion of the population under the age of 15. Cross-fold validations in the training set showed very good average fit ($R\text{-sq} = 0.92$).

Conclusion: Predictive ecological modelling is a useful complementary approach to indirectly estimating TB burden and can be considered alongside other methods in countries with limited robust empirical measurements of TB among the general population.

16. *Lancet* 2018 Sep 8;392(10150):821-834

Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

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Comment in *Lancet* 2018 Sep 8;392(10150):797-798. *Lancet* 2018 Sep 8;392(10150):798-800.

BACKGROUND: Treatment outcomes for multidrug-resistant tuberculosis remain poor. We aimed to estimate the association of treatment success and death with the use of individual drugs, and the optimal number and duration of treatment with those drugs in patients with multidrug-resistant tuberculosis. **METHODS:** In this individual patient data meta-analysis, we searched MEDLINE, Embase, and the Cochrane Library to identify potentially eligible observational and experimental studies published between Jan 1, 2009, and April 30, 2016. We also searched reference lists from all systematic reviews of treatment of multidrug-resistant tuberculosis published since 2009. To be eligible, studies had to report original results, with end of treatment outcomes (treatment completion [success], failure, or relapse) in cohorts of at least 25 adults (aged >18 years). We used

anonymised individual patient data from eligible studies, provided by study investigators, regarding clinical characteristics, treatment, and outcomes. Using propensity score-matched generalised mixed effects logistic, or linear regression, we calculated adjusted odds ratios and adjusted risk differences for success or death during treatment, for specific drugs currently used to treat multidrug-resistant tuberculosis, as well as the number of drugs used and treatment duration. **FINDINGS:** Of 12 030 patients from 25 countries in 50 studies, 7346 (61%) had treatment success, 1017 (8%) had failure or relapse, and 1729 (14%) died. Compared with failure or relapse, treatment success was positively associated with the use of linezolid (adjusted risk difference 0·15, 95% CI 0·11 to 0·18), levofloxacin (0·15, 0·13 to 0·18), carbapenems (0·14, 0·06 to 0·21), moxifloxacin (0·11, 0·08 to 0·14), bedaquiline (0·10, 0·05 to 0·14), and clofazimine (0·06, 0·01 to 0·10). There was a significant association between reduced mortality and use of linezolid (-0·20, -0·23 to -0·16), levofloxacin (-0·06, -0·09 to -0·04), moxifloxacin (-0·07, -0·10 to -0·04), or bedaquiline (-0·14, -0·19 to -0·10). Compared with regimens without any injectable drug, amikacin provided modest benefits, but kanamycin and capreomycin were associated with worse outcomes. The remaining drugs were associated with slight or no improvements in outcomes. Treatment outcomes were significantly worse for most drugs if they were used despite in-vitro resistance. The optimal number of effective drugs seemed to be five in the initial phase, and four in the continuation phase. In these adjusted analyses, heterogeneity, based on a simulated I2 method, was high for approximately half the estimates for specific drugs, although relatively low for number of drugs and durations analyses. **INTERPRETATION:** Although inferences are limited by the observational nature of these data, treatment outcomes were significantly better with use of linezolid, later generation fluoroquinolones, bedaquiline, clofazimine, and carbapenems for treatment of multidrug-resistant tuberculosis. These findings emphasise the need for trials to ascertain the optimal combination and duration of these drugs for treatment of this condition. **FUNDING:** American Thoracic Society, Canadian Institutes of Health Research, US Centers for Disease Control and Prevention, European Respiratory Society, Infectious Diseases Society of America.

17. *N Engl J Med* 2018; 379:1672-1674

New Promise for Vaccines against Tuberculosis - Editorial

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Tuberculosis has now exceeded infection with the human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) and malaria as the world's largest cause of death from an infectious disease. The World Health Organization (WHO) estimates that there are 10.4 million new cases and 1.7 million deaths annually, including 0.4 million deaths in people with HIV infection, of which 95% occur in low and middle-income countries. The WHO End TB Strategy has set the ambitious target of reducing the incidence of tuberculosis disease by 90% by 2035. Yet since 2000, although global tuberculosis mortality has declined by 30%, the incidence of disease is being reduced only glacially, by approximately 1 to 2% per year, and the incidence of drug-resistant disease is increasing.

Vaccines represent one of the most cost-effective interventions to prevent death and debility from infectious diseases. In the case of tuberculosis, there has been widespread skepticism in the scientific community that an effective tuberculosis vaccine would be technically feasible and in industry that it can be economically viable. We know that immunologic mechanisms are essential for protection against tuberculosis: the disease develops in only 5 to 10% of persons infected with *Mycobacterium tuberculosis*, but immunodeficiency increases the risk of tuberculosis disease to approximately 8% per year. In studies before the antibiotic era, Heimbeck found that latent tuberculosis infection in nurses in Norway who were entering training provided 97% protection against development of

disease. In later studies, he found that Bacille Calmette–Guérin (BCG) was about half as protective as latent tuberculosis. Since the BCG vaccine, the most widely used vaccine in the world, was introduced in 1921, its value has been a subject of continuing controversy. In a large British Medical Research Council trial involving adolescents, the BCG vaccine was 87% protective against disease and 74% protective at 20 years. In contrast, the largest BCG trial, involving 260,000 people in India followed for 15 years, showed no protection in any age group. The most likely explanation is that a high percentage of South Indian participants, in contrast to British adolescents, had already been exposed to *M. tuberculosis* or nontuberculous mycobacteria, which interfered with the detection of any additional protection provided by the vaccine. Indeed, a retrospective analysis revealed that the subgroup not showing exposure to nontuberculous mycobacteria by skin test with a *M. intracellulare* purified protein derivative showed 37 to 45% protection. A novel trial design that tested whether BCG revaccination could prevent infection by *M. tuberculosis* showed 45% protection against sustained *M. tuberculosis* infection. However, other trials of new vaccines have been disappointing: a killed nontuberculous mycobacteria (*M. obuense*) vaccine given in five doses to HIV-positive participants had a vaccine efficacy of less than 40%, a single *M. tuberculosis* antigen (Ag85A) in modified vaccinia Ankara strain showed no protection, and a new subunit vaccine failed to show meaningful protection. A number of new vaccine candidates are in clinical trials, but no vaccine has yet been shown to be effective in populations that have already been exposed to *M. tuberculosis* or nontuberculous mycobacteria. The report by Van Der Meeren et al. now published in the *Journal* shows significant efficacy in the prevention of clinical tuberculosis by a subunit vaccine among persons already infected with *M. tuberculosis*. The M72/AS01E vaccine consists of a two *M. tuberculosis* proteins given with the AS01E adjuvant, a version of that used in licensed zoster and (in Europe) malaria vaccines. The primary end point was preventing active pulmonary tuberculosis in adults, nearly all of whom had received the BCG vaccine as children. Their exposure to *M. tuberculosis* was established by an interferon- γ release assay measuring T-cell responses to *M. tuberculosis* antigens not present in the BCG vaccine. In the trial involving some 3500 adults in 11 centers in South Africa, Kenya, and Zambia, the incidence of clinical tuberculosis disease was significantly lower in the M72/AS01E group than in the placebo group. The overall vaccine efficacy was 54%, a finding that establishes proof of principle. Curiously, protection was greater in participants 25 years of age or younger than in those older than 25 years of age and greater in men than in women. The greater effectiveness of the M72/AS01E vaccine relative to a previous subunit vaccine suggests that the adjuvant may be critical, an important finding in itself. The results, if generalizable, suggest that the vaccine is likely to be effective when administered to young adults, and modeling has suggested that a vaccine targeted to adolescents and adults would have the most rapid and cost-effective outcome on the global epidemic. In high burden countries, a high percentage of adults has already been exposed to *M. tuberculosis* infection, many of whom have latent infection. In this context, what makes this study particularly remarkable is that it uniquely engendered protection in persons already exposed to and presumably latently infected with *M. tuberculosis*. What will be required to develop the proof of concept of this vaccine, or any other vaccine, into a licensed product that can become a cornerstone of tuberculosis prevention? One critical question, which can be addressed with biobanked samples from a subgroup of the trial participants, is what are the immunologic and gene expression differences between recipients who were protected and those who were not? This has the potential to reveal correlates or biomarkers of protection that currently do not exist, which could greatly reduce the time and costs of future trials. Because it would be ideal to have a single vaccine that is effective in both *M. tuberculosis*-infected and uninfected persons and that is effective in different age and risk groups (e.g., HIV-infected persons), follow-up trials involving these populations will be important for validating and extending the results. The importance of previous BCG vaccination and latent *M. tuberculosis* infection on the efficacy

observed will also need to be defined. The durability of protection by a subunit vaccine will be important to determine as well, because revaccination may be required. A further question is whether the 54% efficacy of a vaccine containing two antigens in the AS01E adjuvant could be increased by the inclusion of additional *M. tuberculosis* antigens. Finally, because of the wide variation in the efficacy of the BCG vaccine in different parts of the world, it will ultimately be important to carry out phase 3 trials involving multiple geographic populations. Vaccine efficacy trials are expensive, but these costs are small relative to the costs of tuberculosis to the global economy. To sustain the momentum, it is clear that major additional international and domestic funding to support the development and testing of tuberculosis vaccines will be required. Historically, all vaccine development has been an iterative process. The work presented represents an important step forward toward developing an effective immunization against tuberculosis; it is probably not the final iteration. The results reinforce the importance of international collaborations, set the stage for testing additional candidates, and offer renewed hope that effective new vaccines can be developed for tuberculosis.

Mother and Child Health

18. *BMJ Glob Health*. 3(5): e000747. 2018 Oct 15

Creation of the WHO Indicators of Infant and Young Child Development (IYCD): metadata synthesis across 10 countries

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Background Renewed global commitment to the improvement of early child development outcomes, as evidenced by the focus of the United Nations Sustainable Development Goal 4, highlights an increased need for reliable and valid measures to evaluate preventive and interventional efforts designed to affect change. Our objective was to create a new tool, applicable across multicultures, to measure development from 0 to 3 years through metadata synthesis.

Methods Fourteen cross-sectional data sets were contributed on 21 083 children from 10 low/middle-income countries (LMIC), assessed using seven different tools (caregiver reported or directly assessed). Item groups, measuring similar developmental skills, were identified by item mapping across tools. Logistic regression curves displayed developmental trajectories for item groups across countries and age. Following expert consensus to identify well-performing items across developmental domains, a second mapping exercise was conducted to fill any gaps across the age range. The first version of the tool was constructed. Item response analysis validated our approach by putting all data sets onto a common scale.

Results 789 individual items were identified across tools in the first mapping and 129 item groups selected for analysis. 70 item groups were then selected through consensus, based on statistical performance and perceived importance, with a further 50 items identified at second mapping. A tool comprising 120 items (23 fine motor, 23 gross motor, 20 receptive language, 24 expressive language, 30 socioemotional) was created. The linked data sets on a common scale showed a curvilinear trajectory of child development, highlighting the validity of our approach through excellent coverage by age and consistency of measurement across contributed tools, a novel finding in itself.

Conclusions We have created the first version of a prototype tool for measuring children in the early years, developed using novel easy to apply methodology; now it needs to be feasibility tested and piloted across several LMICs.

19. *BMJ Glob Health*. 3(5): e000934. 2018 Oct 31

Disability status, intimate partner violence and perceived social support among married women in three districts of the Terai region of Nepal

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Introduction Women living with disabilities are disproportionately vulnerable to intimate partner violence (IPV). Existing research on the topic largely takes place in high-income settings and treats disability as a dichotomous experience—an individual either has a disability or does not. Disability experiences, however, are diverse such that some individuals face minimal impairment, while for others impairment can be severe. With this spectrum in mind, this study sought to examine the associations between severity of disability impairment, past-year IPV, past-year in-law violence and perceived social support among married women in Nepal.

Methods Baseline data (2016) from a randomised controlled trial aiming to reduce IPV among women aged 18–49 (n=1800) were analysed using generalised estimating equations logistic regressions to assess associations.

Results Women with severe impairment reported higher levels of physical and/or sexual, emotional, economic and in-law violence than women without a disability (adjusted OR (AOR)=1.68, 95% CI 1.04 to 2.72; AOR=1.65, 95% CI 1.03 to 2.65; AOR=1.75, 95% CI 1.02 to 3.02; AOR=2.80, 95% CI 2.53 to 5.11, respectively). Differences in IPV between women reporting some impairment versus no disability were observed for economic (AOR=1.47, 95% CI 1.11 to 1.94) and in-law violence (AOR=1.50, 95% CI 1.07 to 2.10). Women with severe or some impairment versus no disability were less likely to perceive their in-laws as supportive.

Conclusion Disability status was associated with increased vulnerability to IPV. A gradient was observed; the highest levels of IPV were experienced by women with severe impairment, followed by some impairment. Future research should examine the mechanisms driving such observations.

20. *Health Policy and Planning*, 33, 2018 (8): 928 - 936

International Journal of Epidemiology, 2018, Vol 47 (5): 1465–1474

Significant cognitive delay among 3- to 4-year old children in low- and middle-income countries: prevalence estimates and potential impact of preventative interventions

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Background: We sought to: (i) estimate the prevalence of significant cognitive delay (a marked delay in the development of general cognitive functioning) among nationally representative samples of young children in middle- and low-income countries; (ii) estimate the total number of children under 5 years of age with significant cognitive delay living in low- and middle-income countries; and (iii) estimate the potential impact of five preventative interventions.

Methods: Secondary analysis of data collected in Rounds 4 and 5 of UNICEF's Multiple Cluster Indicators Surveys in 51 countries involving 163 293 3- to 4-year-old children. Adjusted population-attributable fractions were used to estimate the potential impact of five interventions based on Sustainable Development Goals (SDGs).

Results: The prevalence of significant cognitive delay in 3- to 4-year-old children in middle- and low-income countries was 10.1% (95% confidence interval 9.7–10.4%). Prevalence was strongly inversely related to country economic wealth. The estimated total number of children under 5 with significant cognitive delay living in low- and middle-income countries was just under 55 million. This number

could be reduced by over 60% if three separate SDGs were achieved; every mother had secondary-level education, every household had access to improved water and sanitation, and every child had an acceptable level of home stimulation.

Conclusions: Our results provide additional evidence in support of a range of specific preventative interventions in early childhood to reduce the loss of developmental potential among children in low- and middle-income countries.

21. [Lancet 2018 Sep 8;392\(10150\):857-865.. Epub 2018 Aug 30](#)

Armed conflict and child mortality in Africa: a geospatial analysis

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Comment in [Lancet 2018 Sep 8;392\(10150\):804-805](#).

BACKGROUND: A substantial portion of child deaths in Africa take place in countries with recent history of armed conflict and political instability. However, the extent to which armed conflict is an important cause of child mortality, especially in Africa, remains unknown. **METHODS:** We matched child survival with proximity to armed conflict using information in the Uppsala Conflict Data Program Georeferenced Events Dataset on the location and intensity of armed conflict from 1995 to 2015 together with the location, timing, and survival of infants younger than 1 year (primary outcome) in 35 African countries. We measured the increase in mortality risk for infants exposed to armed conflicts within 50 km in the year of birth and, to study conflicts' extended health risks, up to 250 km away and 10 years before birth. We also examined the effects of conflicts of varying intensity and chronicity (conflicts lasting several years), and effect heterogeneity by residence and sex of the child. We then estimated the number and portion of deaths of infants younger than 1 year related to conflict. **FINDINGS:** We identified 15 441 armed conflict events that led to 968 444 combat-related deaths and matched these data with 1.99 million births and 133 361 infant deaths (infant mortality of 67 deaths per 1000 births) between 1995 and 2015. A child born within 50 km of an armed conflict had a risk of dying before reaching age 1 year of 5.2 per 1000 births higher than being born in the same region during periods without conflict (95% CI 3.7-6.7; a 7.7% increase above baseline). This increased risk of dying ranged from a 3.0% increase for armed conflicts with one to four deaths to a 26.7% increase for armed conflicts with more than 1000 deaths. We find evidence of increased mortality risk from an armed conflict up to 100 km away, and for 8 years after conflicts, with cumulative increase in infant mortality two to four times higher than the contemporaneous increase. In the entire continent, the number of infant deaths related to conflict from 1995 to 2015 was between 3.2 and 3.6 times the number of direct deaths from armed conflicts. **INTERPRETATION:** Armed conflict substantially and persistently increases infant mortality in Africa, with effect sizes on a scale with malnutrition and several times greater than existing estimates of the mortality burden of conflict. The toll of conflict on children, who are presumably not combatants, underscores the indirect toll of conflict on civilian populations, and the importance of developing interventions to address child health in areas of conflict. **FUNDING:** The Doris Duke Charitable Foundation, and the Centre for Global Child Health at the Hospital for Sick Children.

Health Systems

22. *BMJ Glob Health*. 2018; 3(1): e000664

Performance-based financing in low-income and middle-income countries: isn't it time for a rethink?

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This paper questions the view that performance-based financing (PBF) in the health sector is an effective, efficient and equitable approach to improving the performance of health systems in low-income and middle-income countries (LMICs). PBF was conceived as an open approach adapted to specific country needs, having the potential to foster system-wide reforms. However, as with many strategies and tools, there is a gap between what was planned and what is actually implemented. This paper argues that PBF as it is currently implemented in many contexts does not satisfy the promises. First, since the start of PBF implementation in LMICs, concerns have been raised on the basis of empirical evidence from different settings and disciplines that indicated the risks, cost and perverse effects. However, PBF implementation was rushed despite insufficient evidence of its effectiveness. Second, there is a lack of domestic ownership of PBF. Considering the amounts of time and money it now absorbs, and the lack of evidence of effectiveness and efficiency, PBF can be characterised as a donor fad. Third, by presenting itself as a comprehensive approach that makes it possible to address all aspects of the health system in any context, PBF monopolises attention and focuses policy dialogue on the short-term results of PBF programmes while diverting attention and resources from broader processes of change and necessary reforms. Too little care is given to system-wide and long-term effects, so that PBF can actually damage health services and systems. This paper ends by proposing entry points for alternative approaches.

23. *BMJ Glob Health*. 2018 Sep 17;3(5):e001041

Creating a specialist physician workforce in low-resource settings: reflections and lessons learnt from the East African Training Initiative

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Many African countries have extremely low ratios of physicians to population, and there are very, very few specialists. This leaves most patients without access to specialised care, and importantly also leaves many countries with insufficient expertise to properly evaluate the burden of illness and the needs of the population overall. The challenges to training a specialised physician workforce in resource-limited settings are many, and they go far beyond the (relatively simple) task of transmission of clinical skills. We initiated a capacity-building programme to train pulmonary physicians in Ethiopia, a country of 105 million persons with a high burden of lung disease that had no prior existing training programme in pulmonary medicine. Using volunteer faculty from the USA and Europe, we have provided high-quality training and established a cohort of pulmonary specialists there. We have identified several components of training that go beyond clinical skills development but which we feel are crucial to sustainability. These components include the delineation of viable career pathways that allow professional growth for subspecialist physicians and that support the permanent establishment of a local faculty; the development of important non-clinical skills, including leadership and pedagogical techniques; training in clinical research methodologies; and the development of mechanisms to amplify the impact of a still relatively small number of specialised physicians to address the needs of the population generally. Our programme, the East African

Training Initiative, has successfully addressed many of these challenges and we hope that it can be replicated elsewhere.

24. *BMJ Glob Health*. 2018 Oct 1;3(5):e000976

Integrated health system strengthening can generate rapid population impacts that can be replicated: lessons from Rwanda to Madagascar

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At the turn of the century, the Millennium Development Goals (MDGs) set targets to dramatically improve human welfare by 2015. These ambitious aims included reducing extreme poverty by 50%, under-5 mortality by 66% and maternal mortality by 75%, and were accompanied by international support. Now, most African countries have international funding and policy commitments to treat HIV, tuberculosis (TB) and malaria, provide contraceptives to women, vaccines for children, and implement WHO-recommended treatment guidelines for maternal and child health, supported by front-line community health workers (CHWs).

Why then, if the treatments are known, affordable at scale and supported by standard policies, did only a few countries achieve their health-related MDGs and what does that mean for the prospects of the Sustainable Development Goals? One answer is that even simple technologies require complex delivery systems—a value chain of staff, stuff, systems and space—to align at the point of care and serve each individual patient. The recognition of this challenge has led to a growing movement towards health system strengthening (HSS) based on WHO's six building blocks—personnel, supplies, finance, leadership, services and information systems.

Those who see the global health challenge primarily through the lens of scale—including policymakers, international stakeholders and social ventures—point out that the HSS building blocks do not actually guide implementers, as they consist of many dimensions that are difficult to prescribe. The result is an enduring tendency for the international community to invest in uncoordinated vertical efforts, often undermined by challenges with integration into local health systems that are unable to adequately support them. Such vertical approaches can be easily measured through process indicators (such as quantity of services delivered), but rarely demonstrate population-level impacts such as on coverage or mortality rates.

In contrast, an alternative paradigm is to integrate HSS initiatives with clinical programmes at multiple levels of the system within a geographically targeted unit. While these have traditionally lacked a strong evidence base, two recent papers in *BMJ Global Health* show that rapid and rigorously evaluated population-level impacts can result from HSS in different political and economic contexts.

25. *BMJ Glob Health*. 2018; 3(5): e001036

Towards constructive rethinking of PBF: perspectives of implementers in sub-Saharan Africa

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- As implementers of Performance Based Financing (PBF) in various countries in Africa, we have seen first-hand its benefits—but we acknowledge that there are challenges that require ongoing improvements, and that debates and critical analyses are opportunities to both question and strengthen the PBF approach.

- However, constructive debates must be based on facts, value the large set of experiences and require that all parties listen attentively and objectively to the arguments of stakeholders, especially those with local knowledge and diversified institutional affiliations.
- Notably, PBF was initiated in Rwanda, jointly by African and European experts—but we acknowledge that in our countries, PBF benefits from financial and technical leadership by the World Bank and other exogenous actors, and while exogeneity can raise problems, this is far from axiomatic.
- PBF is an evolving strategy, with innovation and amendments by national actors based on their context—in Democratic Republic of Congo (a tool for a fair sharing of bonuses), Rwanda (community verification), Cameroon (urban PBF), Burundi (exemption of user fees), Burkina Faso (focus on indigents), Nigeria (coupling PBF with demand-side financing approaches) and Zimbabwe (risk-based verification to reduce administrative costs).
- We see the value of PBF in its system-wide effects, such as improving coordination, decentralisation accountability and overall governance in the health system (including community engagement in health system governance), and completeness and timeliness of health information system data.

26. *BMJ Glob Health* 3(5): e001007. 2018 Oct 25

‘They care rudely!’: resourcing and relational health system factors that influence retention in care for people living with HIV in Zambia

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Introduction Despite access to free antiretroviral therapy (ART), many HIV-positive Zambians disengage from HIV care. We sought to understand how Zambian health system ‘hardware’ (tangible components) and ‘software’ (work practices and behaviour) influenced decisions to disengage from care among ‘lost-to-follow-up’ patients traced by a larger study on their current health status.

Methods We purposively selected 12 facilities, from 4 provinces. In-depth interviews were conducted with 69 patients across four categories: engaged in HIV care, disengaged from care, transferred to another facility and next of kin if deceased. We also conducted 24 focus group discussions with 158 lay and professional healthcare workers (HCWs). These data were triangulated against two consecutive days of observation conducted in each facility. We conducted iterative multilevel analysis using inductive and deductive reasoning.

Results Health system ‘hardware’ factors influencing patients’ disengagement included inadequate infrastructure to protect privacy; distance to health facilities which costs patients time and money; and chronic understaffing which increased wait times. Health system ‘software’ factors related to HCWs’ work practices and clinical decisions, including delayed opening times, file mismanagement, drug rationing and inflexibility in visit schedules, increased wait times, number of clinic visits, and frustrated access to care. While patients considered HCWs as ‘mentors’ and trusted sources of information, many also described them as rude, tardy, careless with details and confidentiality, and favouring relatives. Nonetheless, unlike previously reported, many patients preferred ART over alternative treatment (eg, traditional medicine) for its perceived efficacy, cost-free availability and accompanying clinical monitoring.

Conclusion Findings demonstrate the dynamic effect of health system ‘hardware’ and ‘software’ factors on decisions to disengage. Our findings suggest a need for improved: physical resourcing and structuring of HIV services, preservice and inservice HCWs and management training and mentorship programmes to encourage HCWs to provide ‘patient-centered’ care and exercise ‘flexibility’ to meet patients’ varying needs and circumstances.

27. *Health Policy and Planning*, 33, 2018 (8): 920-927

The impact of an mHealth monitoring system on health care utilization by mothers and children: an evaluation using routine health information in Rwanda

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Maternal and child mortality rates remain unacceptably high globally, particularly in sub-Saharan Africa. A popular approach to counter these high rates is interventions delivered using mobile phones (mHealth). However, few mHealth interventions have been implemented nationwide and there has been little evaluation of their effectiveness, particularly at scale. Therefore, we evaluated the Rwanda RapidSMS programme—one of the few mHealth programmes in Africa that is currently operating nationwide. Using interrupted time series analysis and monthly data routinely reported by public health centres (n = 461) between 2012 and 2016, we studied the impact of RapidSMS on four indicators: completion of four antenatal care visits, deliveries in a health facility, postnatal care visits and malnutrition screening. We stratified all analyses based on whether the district received concurrent additional supports, including staff and equipment (10 out of 30 Districts). We found that community health workers in Rwanda sent more than 9.3 million messages using RapidSMS, suggesting the programme was successfully implemented. We found that the implementation of the RapidSMS system combined with additional support including training, supervision and equipment provision increased the use of maternal and child health services. In contrast, implementing the RapidSMS system alone was ineffective. This suggests that mHealth programmes alone may be insufficient to improve the use of health services. Instead, they should be considered as a part of more comprehensive interventions that provide the necessary equipment and health system capacity to support them.

28. *Health Policy and Planning*, 33, 2018 (8): 948 - 956

The impact of reducing and eliminating user fees on facility-based delivery: a controlled interrupted time series in Burkina Faso

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User fee reduction and removal policies have been the object of extensive research, but little rigorous evidence exists on their sustained effects in relation to use of delivery care services, and no evidence exists on the effects of partial reduction compared with full removal of user fees. We aimed to fill these knowledge gaps by assessing sustained effects of both partial reduction and complete removal of user fees on utilization of facility-based delivery. Our study took place in four districts in the Sahel region of Burkina Faso, where the national user fee reduction policy (SONU) launched in 2007 (lowering fees at point of use by 80%) co-existed with a user fee removal pilot launched in 2008. We used Health Management Information System data to construct a controlled interrupted time-series analysis and examine both immediate and sustained effects of SONU and the pilot from January 2004 to December 2014. We found that both SONU and the pilot led to a sustained increase in the use of facility-based delivery. SONU produced an accumulative increase of 31.4% (P < 0.01) over 8 years in the four study districts. The pilot further enhanced utilization and produced an additional increase of 23.2% (P < 0.001) over 6 years. These increasing trends did not continue to reach full coverage, i.e. ensuring that all women had a facility-based delivery. Instead, they stabilized 3 years and 4 years after the onset of SONU and the pilot, respectively. Our study provides further evidence that user fee reduction and removal policies are effective in increasing service use in the

long term. However, they alone are not sufficient to achieve full coverage. This calls for the need to implement additional measures, targeting for instance geographical barriers and knowledge gaps, to achieve the target of all women delivering in the presence of a skilled attendant.

29. [Lancet 2018 Sep 5. pii: S0140-6736\(18\)31668-4. \[Epub ahead of print\]](#)

Mortality due to low-quality health systems in the universal health coverage era: a systematic analysis of amenable deaths in 137 countries

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Erratum in Lancet 2018 Sep 20;

BACKGROUND: Universal health coverage has been proposed as a strategy to improve health in low-income and middle-income countries (LMICs). However, this is contingent on the provision of good-quality health care. We estimate the excess mortality for conditions targeted in the Sustainable Development Goals (SDG) that are amenable to health care and the portion of this excess mortality due to poor-quality care in 137 LMICs, in which excess mortality refers to deaths that could have been averted in settings with strong health systems. **METHODS:** Using data from the 2016 Global Burden of Disease study, we calculated mortality amenable to personal health care for 61 SDG conditions by comparing case fatality between each LMIC with corresponding numbers from 23 high-income reference countries with strong health systems. We used data on health-care utilisation from population surveys to separately estimate the portion of amenable mortality attributable to non-utilisation of health care versus that attributable to receipt of poor-quality care. **FINDINGS:** 15·6 million excess deaths from 61 conditions occurred in LMICs in 2016. After excluding deaths that could be prevented through public health measures, 8·6 million excess deaths were amenable to health care of which 5·0 million were estimated to be due to receipt of poor-quality care and 3·6 million were due to non-utilisation of health care. Poor quality of health care was a major driver of excess mortality across conditions, from cardiovascular disease and injuries to neonatal and communicable disorders. **INTERPRETATION:** Universal health coverage for SDG conditions could avert 8·6 million deaths per year but only if expansion of service coverage is accompanied by investments into high-quality health systems.

30. [Lancet 2018 Oct 20;392\(10156\):1461-1472](#)

Revisiting Alma-Ata: what is the role of primary health care in achieving the Sustainable Development Goals?

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The Sustainable Development Goals (SDGs) are now steering the global health and development agendas. Notably, the SDGs contain no mention of primary health care, reflecting the disappointing implementation of the Alma-Ata declaration of 1978 over the past four decades. The draft Astana declaration (Alma-Ata 2·0), released in June, 2018, restates the key principles of primary health care and renews these as driving forces for achieving the SDGs, emphasising universal health coverage. We use accumulating evidence to show that countries that reorient their health systems towards primary care are better placed to achieve the SDGs than those with hospital-focused systems or low investment in health. We then argue that an even bolder approach, which fully embraces the Alma-Ata vision of primary health care, could deliver substantially greater SDG progress, by addressing the

wider determinants of health, promoting equity and social justice throughout society, empowering communities, and being a catalyst for advancing and amplifying universal health coverage and synergies among SDGs.

Global Health

31. *BMJ* 2018;363:k3794

Cities for global health

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In the first of a new series of articles on the role of cities in health, Majid Ezzati and colleagues call for greater action to reduce health inequalities within cities

The number of people, and proportion of the world population, living in cities has increased steadily, with 4.2 billion urban residents now accounting for 55% of the world's population. That urban living influences health is well recognised and increasingly included in broader discussions about cities and sustainable human development. The general tone of such discourse, however, tends towards the negative aspects of infectious outbreaks, vehicular pollution, waste disposal, and unhealthy lifestyles rather than the "positive and progressive aspects of cities . . . recognised by historians, economists, and other social scientists."

The concentration of knowledge and innovation, economic activity, healthcare, education, and other public services endows cities with the potential to deliver substantial improvements to the health and wellbeing of their residents and those of other parts of the country. Further, the local politics in cities, whereby politicians and citizens live side by side as members of the same community, provide an opportunity to avoid and resist the exclusionary and austerity trends seen in national politics and economics around the world and to make health inequalities the central focus of urban health policies. A challenge to this, described a century ago by Chapin and equally relevant today, is the fragmented administrative and technocratic systems in cities. When coupled with pressure from various interest groups, these can easily lead to either continuing cities' own past choices or replicating those elsewhere. To overcome this inertia and harness the health enhancing potential of cities requires using the cross sectoral roles of mayors and city councils to build health and health equity in all policies. Beyond individual cities, global and regional city networks (such as United Cities and Local Governments <https://www.uclg.org/> and the C40 network <https://www.c40.org/>) provide an opportunity for shared learning and coordinated experimentation of innovative policies and how these can be adapted to contemporary local social, demographic, and economic conditions. Building on this thinking, The BMJ is launching a series of articles on important themes in urban health, such as emerging economies and technologies; extreme events and emergencies; housing; migration; and water resource management. The series will focus on actions that cities can take to reduce health inequalities and deliver on their potential to create better and healthier lives for all.

32. *Health Policy and Plan* Vol 333,8 1 Oct p 928-936

Civil society participation in global public private partnerships for health

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The growth of global public-private partnerships for health has opened up new spaces for civil society participation in global health governance. Such participation is often justified by the claim that civil society organizations, because of their independence and links to communities, can help address

democratic deficits in global-level decision-making processes. This article examines the notion of 'civil society engagement' within major public-private partnerships for health, where civil society is often said to play a particularly important role in mediating between public and private spheres. How do major global health partnerships actually define 'civil society', who represents civil society within their global-level decision-making bodies, and what formal power do civil society representatives hold relative to other public and private-sector partners? Based on a structured analysis of publicly available documents of 18 of the largest global public-private partnerships for health, we show that many of them make laudatory claims about the value of their 'civil society engagement'. Most use the term 'civil society' to refer to non-governmental organizations and communities affected by particular health issues, and state that they expect these actors to represent the needs and interests of specific populations in global-level decisions about strategies, funding models and policies. Yet, such civil society actors have a relatively low level of representation within the partnerships' boards and steering committees, especially compared with private-sector actors (10.3 vs 23.7%). Moreover, there is little evidence of civil society representatives' direct and substantial influence within the partnerships' global-level governing bodies, where many decisions affecting country-level programmes are made. Rather, their main role within these partnerships seems to be to implement projects and advocate and raise funds, despite common discourses that emphasise civil society's watchdog function and transformative power. The findings suggest the need for in-depth research into the formal and informal power of civil society within global health governance processes.

33. *Lancet* 2018 Oct 20;392(10156):1482-1486. doi: 10.1016/S0140-6736(18)32332-8

Building the case for embedding global health security into universal health coverage: a proposal for a unified health system that includes public health

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In the wake of the recent west African Ebola epidemic, there is global consensus on the need for strong health systems; however, agreement is less apparent on effective mechanisms for establishing and maintaining these systems, particularly in resource-constrained settings and in the presence of multiple and sustained stresses (eg, conflict, famine, climate change, and globalisation). The construction of the International Health Regulations (2005) guidelines and the WHO health systems framework, has resulted in the separation of public health functions and health-care services, which are interdependent in actuality and must be integrated to ensure a continuous, unbroken national health system. By analysing efforts to strengthen health systems towards attaining universal health coverage and investments to improve global health security, we examine areas of overlap and offer recommendations for construction of a unified national health system that includes public health. One way towards achieving universal health coverage is to broaden the definition of a health system.

Non Communicable Diseases

34. *BMJ Glob Health*. 3(5): e001057. 2018 Oct 15

Do current guidelines for waist circumference apply to black Africans? Prediction of insulin resistance by waist circumference among Africans living in America

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Background To lower the risk of diabetes and heart disease in Africa, identification of African-centred thresholds for inexpensive biomarkers of insulin resistance (IR) is essential. The waist circumference (WC) thresholds that predicts IR in African men and women have not been established, but investigations recently conducted in Africa using indirect measures of IR suggest IR is predicted by WC of 80–95 cm in men and 90–99 cm in women. These WC cannot be used for guidelines until validated by direct measurements of IR and visceral adipose tissue (VAT). Therefore, we determined in a group of African-born black people living in America (A) the WC, which predicts IR and (B) the influence of abdominal fat distribution on IR.

Methods The 375 participants (age 38 ± 10 years (mean \pm SD), 67% men) had IR determined by HOMA-IR and Matsuda index. VAT and subcutaneous adipose tissue (SAT) were measured by abdominal CT scans. Optimal WC for the prediction of IR was determined in sex-specific analyses by area under the receiver operating characteristic (AUC-ROC) and Youden index.

Results Women had more SAT (203 ± 114 vs 128 ± 74 cm²) and less VAT than men (63 ± 48 vs 117 ± 72 cm², $p<0.001$). Optimal WC for prediction of IR in men and women were: 91 cm (AUC-ROC: 0.80 ± 0.03 (mean \pm SE)) and 96 cm (AUC-ROC: 0.81 ± 0.08), respectively. Regression analyses revealed a significant sex–VAT interaction ($p<0.001$). Therefore, for every unit increase in VAT, women had a 0.94 higher unit increase in SAT and 0.07 higher unit increase in WC than men.

Conclusion Working with a group of African-born black people living in America, we accessed technology, which validated observations made in Africa. Higher SAT at every level of VAT explained why the WC that predicted IR was higher in women (96 cm) than men (91 cm). For Africans to benefit from WC measurements, convening a panel of experts to develop evidence-based African-centred WC guidelines may be the way forward.

35. [Lancet 2018 Sep 22;392\(10152\):1072-1088](#). [Epub 2018 Sep 20](#)

NCD Countdown 2030: worldwide trends in non-communicable disease mortality and progress towards Sustainable Development Goal target 3.4

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The third UN High-Level Meeting on Non-Communicable Diseases (NCDs) on Sept 27, 2018, will review national and global progress towards the prevention and control of NCDs, and provide an opportunity to renew, reinforce, and enhance commitments to reduce their burden. NCD Countdown 2030 is an independent collaboration to inform policies that aim to reduce the worldwide burden of NCDs, and to ensure accountability towards this aim. In 2016, an estimated 40.5 million (71%) of the 56.9 million worldwide deaths were from NCDs. Of these, an estimated 1.7 million (4% of NCD deaths) occurred in people younger than 30 years of age, 15.2 million (38%) in people aged between 30 years and 70 years, and 23.6 million (58%) in people aged 70 years and older. An estimated 32.2 million NCD deaths (80%) were due to cancers, cardiovascular diseases, chronic respiratory diseases, and diabetes, and another 8.3 million (20%) were from other NCDs. Women in 164 (88%) and men in 165 (89%) of 186 countries and territories had a higher probability of dying before 70 years of age from an NCD than from communicable, maternal, perinatal, and nutritional conditions combined. Globally, the lowest risks of NCD mortality in 2016 were seen in high-income countries in Asia-Pacific, western Europe, and Australasia, and in Canada. The highest risks of dying from NCDs were observed in low-income and middle-income countries, especially in sub-Saharan Africa, and, for men, in central Asia and eastern Europe. Sustainable Development Goal (SDG) target 3.4—a one-third reduction, relative to 2015 levels, in the probability of dying between 30 years and 70 years of age from cancers, cardiovascular diseases, chronic respiratory diseases, and diabetes by 2030—will be achieved in 35 countries (19%) for women, and 30 (16%) for men, if these

countries maintain or surpass their 2010-2016 rate of decline in NCD mortality. Most of these are high-income countries with already-low NCD mortality, and countries in central and eastern Europe. An additional 50 (27%) countries for women and 35 (19%) for men are projected to achieve such a reduction in the subsequent decade, and thus, with slight acceleration of decline, could meet the 2030 target. 86 (46%) countries for women and 97 (52%) for men need implementation of policies that substantially increase the rates of decline. Mortality from the four NCDs included in SDG target 3.4 has stagnated or increased since 2010 among women in 15 (8%) countries and men in 24 (13%) countries. NCDs and age groups other than those included in the SDG target 3.4 are responsible for a higher risk of death in low-income and middle-income countries than in high-income countries. Substantial reduction of NCD mortality requires policies that considerably reduce tobacco and alcohol use and blood pressure, and equitable access to efficacious and high-quality preventive and curative care for acute and chronic NCDs.

Sexual and Reproductive Health and Rights

36. *BMJ Glob Health*; 3(5): e000825. 2018 Oct 19

Preventing violence against refugee adolescent girls: findings from a cluster randomised controlled trial in Ethiopia

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Introduction Interpersonal violence is a critical public health concern in humanitarian contexts, but evidence of effective violence prevention programmes targeting adolescent girls is lacking. We investigated the efficacy of a life skills and safe spaces programme to reduce adolescent girls' experiences of interpersonal violence in a refugee setting.

Methods In this two-arm, single-blinded, cluster randomised controlled trial, we recruited 919 Sudanese and South Sudanese girls ages 13–19 years residing in refugee camps in Ethiopia. Girls were divided into 31 clusters, with 457 and 462 participants assigned to the intervention and control arms, respectively. Intervention clusters received 30 life skills sessions delivered in safe spaces and 8 complementary sessions for caregivers. The primary outcome was exposure to sexual violence in the previous 12 months. Secondary outcomes included disaggregated forms of sexual violence, physical violence, emotional violence, transactional sex, child marriage, feelings of safety, attitudes around rites of passage and perceptions of social support. Intent-to-treat analysis was used.

Results At 12-month follow-up, the intervention was not significantly associated with reduction in exposure to sexual violence (adjusted OR =0.96, 95% CI 0.59 to 1.57), other forms of violence, transactional sex or feelings of safety. The intervention was associated with improvements in attitudes around rites of passage and identified social supports. Additionally, the intervention showed a decrease in reported child marriage among girls who were married at baseline.

Conclusion While the intervention impacted key markers along the causal pathway to violence reduction, further research and programmatic adaptations are needed to prevent violence towards adolescents in humanitarian contexts.