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International Health Alerts 2020-2 Abstracts

Child Health

Subnational mapping of under-5 and neonatal mortality trends in India: the Global Burden of Disease Study 2000–17

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Background. India has made substantial progress in improving child survival over the past few decades, but a comprehensive understanding of child mortality trends at disaggregated geographical levels is not available. We present a detailed analysis of subnational trends of child mortality to inform efforts aimed at meeting the India National Health Policy (NHP) and Sustainable Development Goal (SDG) targets for child mortality.

Methods. We assessed the under-5 mortality rate (U5MR) and neonatal mortality rate (NMR) from 2000 to 2017 in 5×5 km grids across India, and for the districts and states of India, using all accessible data from various sources including surveys with subnational geographical information. The 31 states and groups of union territories were categorised into three groups using their Socio-demographic Index (SDI) level, calculated as part of the Global Burden of Diseases, Injuries, and Risk Factors Study on the basis of per-capita income, mean education, and total fertility rate in women younger than 25 years. Inequality between districts within the states was assessed using the coefficient of variation. We projected U5MR and NMR for the states and districts up to 2025 and 2030 on the basis of the trends from 2000 to 2017 and compared these projections with the NHP 2025 and SDG 2030 targets for U5MR (23 deaths and 25 deaths per 1000 livebirths, respectively) and NMR (16 deaths and 12 deaths per 1000 livebirths, respectively). We assessed the causes of child death and the contribution of risk factors to child deaths at the state level.

Findings. U5MR in India decreased from 83·1 (95% uncertainty interval [UI] 76·7–90·1) in 2000 to 42·4 (36·5–50·0) per 1000 livebirths in 2017, and NMR from 38·0 (34·2–41·6) to 23·5 (20·1–27·8) per 1000 livebirths. U5MR varied 5·7 times between the states of India and 10·5 times between the 723 districts of India in 2017, whereas NMR varied 4·5 times and 8·0 times, respectively. In the low SDI states, 275 (88%) districts had a U5MR of 40 or more per 1000 livebirths and 291 (93%) districts had an NMR of 20 or more per 1000 livebirths in 2017. The annual rate of change from 2010 to 2017 varied among the districts from a 9·02% (95% UI 6·30–11·63) reduction to no significant change for U5MR and from an 8·05% (95% UI 5·34–10·74) reduction to no significant change for NMR. Inequality between districts within the states increased from 2000 to 2017 in 23 of the 31 states for U5MR and in 24 states for NMR, with the largest increases in Odisha and Assam among the low SDI states. If the trends observed up to 2017 were to continue, India would meet the SDG 2030 U5MR target but not the SDG 2030 NMR target or either of the NHP 2025 targets. To reach the SDG 2030 targets individually, 246 (34%) districts for U5MR and 430 (59%) districts for NMR would need a higher rate of improvement than they had up to 2017. For all major causes of under-5 death in India, the death rate decreased between 2000 and 2017, with the highest decline for infectious diseases, intermediate decline for neonatal disorders, and the smallest decline for congenital birth defects, although the magnitude of decline varied widely between the states. Child and maternal malnutrition was the predominant risk factor, to which 68·2% (65·8–70·7) of under-5 deaths and 83·0% (80·6–

85·0) of neonatal deaths in India could be attributed in 2017; 10·8% (9·1–12·4) of under-5 deaths could be attributed to unsafe water and sanitation and 8·8% (7·0–10·3) to air pollution.

Interpretation. India has made gains in child survival, but there are substantial variations between the states in the magnitude and rate of decline in mortality, and even higher variations between the districts of India. Inequality between districts within states has increased for the majority of the states. The district-level trends presented here can provide crucial guidance for targeted efforts needed in India to reduce child mortality to meet the Indian and global child survival targets. District-level mortality trends along with state-level trends in causes of under-5 and neonatal death and the risk factors in this Article provide a comprehensive reference for further planning of child mortality reduction in India.

2. Lancet 2020;395(10239):1779–801

Mapping geographical inequalities in childhood diarrhoeal morbidity and mortality in low-income and middle-income countries, 2000–17: analysis for the Global Burden of Disease Study 2017

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Background. Across low-income and middle-income countries (LMICs), one in ten deaths in children younger than 5 years is attributable to diarrhoea. The substantial between-country variation in both diarrhoea incidence and mortality is attributable to interventions that protect children, prevent infection, and treat disease. Identifying subnational regions with the highest burden and mapping associated risk factors can aid in reducing preventable childhood diarrhoea.

Methods. We used Bayesian model-based geostatistics and a geolocated dataset comprising 15 072 746 children younger than 5 years from 466 surveys in 94 LMICs, in combination with findings of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017, to estimate posterior distributions of diarrhoea prevalence, incidence, and mortality from 2000 to 2017. From these data, we estimated the burden of diarrhoea at varying subnational levels (termed units) by spatially aggregating draws, and we investigated the drivers of subnational patterns by creating aggregated risk factor estimates.

Findings. The greatest declines in diarrhoeal mortality were seen in south and southeast Asia and South America, where 54·0% (95% uncertainty interval [UI] 38·1–65·8), 17·4% (7·7–28·4), and 59·5% (34·2–86·9) of units, respectively, recorded decreases in deaths from diarrhoea greater than 10%. Although children in much of Africa remain at high risk of death due to diarrhoea, regions with the most deaths were outside Africa, with the highest mortality units located in Pakistan. Indonesia showed the greatest within-country geographical inequality; some regions had mortality rates nearly four times the average country rate. Reductions in mortality were correlated to improvements in water, sanitation, and hygiene (WASH) or reductions in child growth failure (CGF). Similarly, most high-risk areas had poor WASH, high CGF, or low oral rehydration therapy coverage.

Interpretation. By co-analysing geospatial trends in diarrhoeal burden and its key risk factors, we could assess candidate drivers of subnational death reduction. Further, by doing a counterfactual analysis of the remaining disease burden using key risk factors, we identified potential intervention strategies for vulnerable populations. In view of the demands for limited resources in LMICs, accurately quantifying the burden of diarrhoea and its drivers is important for precision public health.

3. NEJM 2020;382(26):2524-33

Hydroxyurea Dose Escalation for Sickle Cell Anemia in Sub-Saharan Africa

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Background. Hydroxyurea has proven safety, feasibility, and efficacy in children with sickle cell anemia in sub-Saharan Africa, with studies showing a reduced incidence of vaso-occlusive events and reduced mortality. Dosing standards remain undetermined, however, and whether escalation to the maximum tolerated dose confers clinical benefits that outweigh treatment-related toxic effects is unknown.

Methods. In a randomized, double-blind trial, we compared hydroxyurea at a fixed dose (approximately 20 mg per kilogram of body weight per day) with dose escalation (approximately 30 mg per kilogram per day). The primary outcome was a hemoglobin level of 9.0 g or more per deciliter or a fetal hemoglobin level of 20% or more after 24 months. Secondary outcomes included the incidences of malaria, vaso-occlusive crises, and serious adverse events.

Results. Children received hydroxyurea at a fixed dose (94 children; mean [±SD] age, 4.6±1.0 years) or with dose escalation (93 children; mean age, 4.8±0.9 years); the mean doses were 19.2±1.8 mg per kilogram per day and 29.5±3.6 mg per kilogram per day, respectively. The data and safety monitoring board halted the trial when the numbers of clinical events were significantly lower among children receiving escalated dosing than among those receiving a fixed dose. At trial closure, 86% of the children in the dose-escalation group had reached the primary-outcome thresholds, as compared with 37% of the children in the fixed-dose group (P<0.001). Children in the dose-escalation group had fewer sickle cell–related adverse events (incidence rate ratio, 0.43; 95% confidence interval [CI], 0.34 to 0.54), vaso-occlusive pain crises (incidence rate ratio, 0.43; 95% CI, 0.34 to 0.56), cases of acute chest syndrome or pneumonia (incidence rate ratio, 0.27; 95% CI, 0.11 to 0.56), transfusions (incidence rate ratio, 0.30; 95% CI, 0.20 to 0.43), and hospitalizations (incidence rate ratio, 0.21; 95% CI, 0.13 to 0.34). Laboratory-confirmed dose-limiting toxic effects were similar in the two groups, and there were no cases of severe neutropenia or thrombocytopenia.

Conclusions. Among children with sickle cell anemia in sub-Saharan Africa, hydroxyurea with dose escalation had superior clinical efficacy to that of fixed-dose hydroxyurea, with equivalent safety.

4. TMIH 2020;25(4):454-66

'Know-Can' gap: gap between knowledge and skills related to childhood diarrhoea and pneumonia among frontline workers in rural Uttar Pradesh, India

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In India, frontline workers (FLWs) – public accredited social health activists (ASHAs) and private rural medical providers (RMPs) – are important for early detection and treatment of childhood diarrhoea and pneumonia. This cross-sectional study aims to measure knowledge and skills, and the gap between the two ('know-can' gap), regarding assessment of childhood diarrhoea with dehydration and pneumonia among FLWs, and to explore factors associated with them.

Methods. We surveyed 473 ASHAs and 447 RMPs in six districts of Uttar Pradesh. We assessed knowledge and skills using face-to-face interviews and video vignettes, respectively, about key signs of both conditions. The 'know-can' gap corresponds to absent skills among FLWs with correct knowledge. We used logistic regression to identify the correlates of knowledge and skills.

Results. FLWs' correct knowledge ranged from 23% to 48% for dehydration signs and 27% to 37% for pneumonia signs. Their skills ranged from 3% to 42% for dehydration and 3% to 18% for pneumonia. There was a significant 'know-can' gap in all the signs, except 'sunken eyes'. Training and supervisory support was associated with better knowledge and skills for diarrhoea with dehydration, but only better knowledge for pneumonia.

Conclusions. FLWs are crucial to the Indian health system, and high-quality FLW services are necessary for continued progress against under-five deaths. The gap between FLWs' knowledge and

skills warrants immediate attention. In particular, our results suggest that knowledge-focused trainings are insufficient for FLWs to convert knowledge into appropriate assessment skills.

Communicable Diseases

5. Am J TMH 2020;May 12

Schistosomiasis Consortium for Operational Research and Evaluation: Mission Accomplished
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The Schistosomiasis Consortium for Operational Research and Evaluation (SCORE), a program focusing on schistosomiasis control in sub-Saharan Africa between 2008 and 2019, investigated ways to improve coverage and efficacy of ongoing chemotherapy programs and concluded that because of continued transmission, mass distribution of praziquantel cannot eliminate the disease without complementary control activities. Schistosomiasis Consortium for Operational Research and Evaluation's activities comprised large-scale, multicountry field studies comparing various mass drug administration strategies and some specific research avenues, such as assessment of high-sensitivity diagnostics, identification of hotspots, quantification of the role of the snail host, predictive modeling, and changes in schistosome population genetics under drug pressure. The discoveries made and the insights gained regarding cost-effective strategies for delivering preventive chemotherapy should assist policy makers to develop guidelines for the control and ultimate elimination of schistosomiasis. Other articles in this series:

- Schistosomiasis Consortium for Operational Research and Evaluation: Mission Accomplished
- Schistosomiasis Consortium for Operational Research and Evaluation (SCORE): Its Foundations, Development, and Evolution
- Impact of Different Mass Drug Administration Strategies for Gaining and Sustaining Control of Schistosoma mansoni and Schistosoma haematobium Infection in Africa
- Discovering, Defining, and Summarizing Persistent Hotspots in SCORE Studies
- SCORE Studies on the Impact of Drug Treatment on Morbidity due to Schistosoma mansoni and Schistosoma haematobium Infection
- Challenges in Protocol Development and Interpretation of the Schistosomiasis Consortium for Operational Research and Evaluation Intervention Studies
- Evaluation, Validation, and Recognition of the Point-of-Care Circulating Cathodic Antigen, Urine-Based Assay for Mapping Schistosoma mansoni Infections
- Circulating Anodic Antigen (CAA): A Highly Sensitive Diagnostic Biomarker to Detect Active Schistosoma Infections—Improvement and Use during SCORE
- SCORE Operational Research on Moving toward Interruption of Schistosomiasis Transmission
- Snail-Related Contributions from the Schistosomiasis Consortium for Operational Research and Evaluation Program Including Xenomonitoring, Focal Mollusciciding, Biological Control, and Modeling
- Parasite Population Genetic Contributions to the Schistosomiasis Consortium for Operational Research and Evaluation within Sub-Saharan Africa
- The Schistosomiasis Consortium for Operational Research and Evaluation Rapid Answers Project: Systematic Reviews and Meta-Analysis to Provide Policy Recommendations Based on Available Evidence

- Application of Schistosomiasis Consortium for Operational Research and Evaluation Study Findings to Refine Predictive Modeling of Schistosoma mansoni and Schistosoma haematobium Control in Sub-Saharan Africa
- Lessons Learned in Conducting Mass Drug Administration for Schistosomiasis Control and Measuring Coverage in an Operational Research Setting
- The Schistosomiasis Consortium for Operational Research and Evaluation 2008–2020: Approaches, Experiences, Lessons, and Recommendations
- Contributions of the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) to Schistosomiasis Control and Elimination: Key Findings and Messages for Future Goals, Thresholds, and Operational Research

6. Am J TMH 2020;102(4):711-18

Interactions of Schistosoma and HIV in Sub-Saharan Africa: A Systematic Review
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Schistosomiasis is an acute and chronic parasitic disease caused by blood flukes of the genus Schistosoma. More than 220 million people worldwide were estimated to have active schistosomiasis in 2017, 90% of whom live on the African continent, but only 102 million were reported to have received treatment. Africa is also disproportionately burdened by HIV, with an estimated 26 million people living with HIV in 2017. Given these overlapping epidemics, we conducted a systematic review to ascertain the contribution of schistosomes to HIV acquisition risk, the contribution of HIV to schistosome acquisition, the impact of HIV on schistosomiasis-related morbidity, the impact of schistosomes on HIV disease progression and immune response, the impact of HIV on the efficacy of praziquantel treatment, and the impact of HIV on egg shedding. We reviewed studies of people living in sub-Saharan Africa coinfected with HIV and Schistosoma spp. between January 1996 and July 2018. We found that 1) infection with Schistosoma haematobium increases the risk of HIV acquisition, 2) there is currently a lack of data on whether HIV infection increases the risk of Schistosoma acquisition, 3a) HIV coinfection was not an accelerating factor for adverse Schistosoma outcomes, 3b) schistosomiasis may be an important contributor to immune activation in HIV coinfected people, 4) praziquantel use in coinfected people may improve immune reconstitution on antiretroviral therapy for HIV, and 5) there is evidence that HIV infection reduces egg excretion in individuals infected with Schistosoma mansoni.

7. Am J TMH 2020;102(5):1131-36

Biologics in Leprosy: A Systematic Review and Case Report
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Tumor necrosis factor (TNF)-α inhibitors increase susceptibility to tuberculosis, but the effect of biologics on susceptibility to leprosy has not been described. Moreover, biologics may play a role in treating erythema nodosum leprosum (ENL). The objectives of this systematic review were to determine whether the development of clinical leprosy is increased in patients being treated with

biologics and to assess the use of biologics in treating leprosy reactions. A systematic literature review was completed of patients with leprosy who received treatment with biologics either before or after a diagnosis of leprosy was confirmed. All studies and case reports were included for qualitative evaluation. The search yielded 10 cases (including one duplicate publication) of leprosy diagnosed after initiation of TNF-α inhibitors and four case reports of refractory ENL successfully treated with infliximab or etanercept. An unpublished case of persistent ENL responsive to infliximab is also presented. These data demonstrate that the use of TNF-α inhibitors may be a risk factor for developing leprosy or reactivating subclinical infections. Leprosy can present with skin lesions and arthritis, so leprosy should be considered in patients presenting with these signs before starting treatment with these agents. Leprosy should be considered in patients who develop worsening eruptions and neurologic symptoms during treatment with TNF-α inhibitors. Finally, TNF-α inhibitors appear effective in some cases of refractory ENL.

8. Lancet 2020;395(10229):1063-77
Seminar
Middle East respiratory syndrome
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The Middle East respiratory syndrome coronavirus (MERS-CoV) is a lethal zoonotic pathogen that was first identified in humans in Saudi Arabia and Jordan in 2012. Intermittent sporadic cases, community clusters, and nosocomial outbreaks of MERS-CoV continue to occur. Between April 2012 and December 2019, 2499 laboratory-confirmed cases of MERS-CoV infection, including 858 deaths (34·3% mortality) were reported from 27 countries to WHO, the majority of which were reported by Saudi Arabia (2106 cases, 780 deaths). Large outbreaks of human-to-human transmission have occurred, the largest in Riyadh and Jeddah in 2014 and in South Korea in 2015. MERS-CoV remains a high-threat pathogen identified by WHO as a priority pathogen because it causes severe disease that has a high mortality rate, epidemic potential, and no medical countermeasures. This Seminar provides an update on the current knowledge and perspectives on MERS epidemiology, virology, mode of transmission, pathogenesis, diagnosis, clinical features, management, infection control, development of new therapeutics and vaccines, and highlights unanswered questions and priorities for research, improved management, and prevention.

9. NEJM 2020;382(19):1832-42
Review: Ebola
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Ebola virus (EBOV) was the best-known and most extensively studied member of the Filoviridae family (Mononegavirales order) long before the shattering 2013–2016 West African epidemic. The virologic taxon Filoviridae was defined in 1982 and subsequently amended regularly to accommodate changes. These amendments and the unfortunate renaming of commonly used terms has made the filovirus taxonomy confusing. Today, EBOV refers to the specific member virus of the type species Zaire ebolavirus in the genus ebolavirus. The history of filoviruses largely involves human outbreaks Marburg virus (MARV) was the first filovirus to be discovered, in 1967. EBOV and Sudan virus (SUDV) were codiscovered in 1976 in the Democratic Republic of Congo (DRC) and South Sudan, respectively. Subsequently, two additional ebolaviruses were found to be pathogenic in humans: Taï Forest virus (TAFV) in Côte d'Ivoire in 1994 and Bundibugyo virus (BDBV) in Uganda in 2007.

Reston virus (RESTV), imported into the United States from the Philippines in 1989–1990, has long been the exception, since it appears to infect humans only subclinically. Unexpectedly, it emerged in swine in the Philippines, and RESTV sequences were detected in pigs in China, raising fear about food safety. The zoonotic potential of RESTV remains unclear, and investigation of that potential is urgently needed.

COVID-19

10. Am J TMH 2020;Jun 1
Why is There Low Morbidity and Mortality of COVID-19 in Africa?
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Three months since the detection of the first COVID-19 case in Africa, almost all countries of the continent continued to report lower morbidity and mortality than the global trend, including Europe and North America. We reviewed the merits of various hypotheses advanced to explain this phenomenon, including low seeding rate, effective mitigation measures, population that is more youthful, favorable weather, and possible prior exposure to a cross-reactive virus. Having a youthful population and favorable weather appears compelling, particularly their combined effect; however, progression of the pandemic in the region and globally may dispel these in the coming months.

11. BMJ 2020;369:m2018
Editorials
Lack of efficacy of hydroxychloroquine in covid-19
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Studies in mild-to-moderate cases as well as severe disease leave us still searching for a magic pill. Some have trumpeted the 4-aminoquinoline antimalarial drugs, chloroquine and hydroxychloroquinine, for the treatment of covid-19, based on the (literally) incredible results of efficacy in reported uncontrolled trials. Two linked studies, however, add to an increasing body of evidence that these drugs lack virological or clinical efficacy in the treatment of covid-19, and might even be harmful.

Because 4-aminoquinolines block endosomal acidification, this drug class has long been looked at for potential antiviral effect. Didier Raoult and colleagues in Marseilles used uncontrolled observations to claim that hydroxychloroquine (whether or not combined with the antibacterial azithromycin) is effective in treating covid-19. Further, Raoult has asserted that using placebo controls is unethical in times of plague and pestilence.

Picking up on such themes, politicians with no expertise in science, medicine, or public health, supported by certain media, have picked up on the use of antimalarials as magic pills for the covid-19 pandemic. Rick Bright, former director of the US Department of Health and Human Services' Biomedical Advanced Research and Development Authority, was moved from his post after resisting calls for widespread immediate dissemination of such drugs.

The two new studies in The BMJ do not support the use of 4-aminoquinolines in covid-19. The first, an open label randomized trial of high dose hydroxychloroquine in mildly to moderately ill patients with covid-19 admitted to 16 government hospitals in China, showed no difference in virological endpoint at 28 days between groups treated with hydroxychloroquine versus standard care. The endpoint was time to negative conversion of SARS-CoV-2 on real time reverse transcription polymerase chain reaction (RT-PCR) tests on either an upper or lower respiratory sample (not

specified), but viral loads were not quantified. No patients died and adverse effects were reported as minimal (electrocardiographic details were not provided).

The second study was an observational controlled study of patients with radiographically demonstrated covid-19 pneumonia requiring oxygen in French hospitals. Hydroxychloroquine was dosed at 600 mg daily and the primary outcome was transfer to intensive care. Survival at 21 days with or without acute respiratory distress syndrome did not differ between the groups treated with hydroxychloroquine versus standard care. Eight of 84 patients receiving hydroxychloroquine had the drug stopped because of electrocardiogram changes. These authors concluded that hydroxychloroquine in moderately ill patients with covid-19 was not useful, perhaps even harmful.

12. BMJ GH 2020-002967

Voices from the frontline: findings from a thematic analysis of a rapid online global survey of maternal and newborn health professionals facing the COVID-19 pandemic

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Introduction. The COVID-19 pandemic has substantially impacted maternity care provision worldwide. Studies based on modelling estimated large indirect effects of the pandemic on services and health outcomes. The objective of this study was to prospectively document experiences of frontline maternal and newborn healthcare providers.

Methods. We conducted a global, cross-sectional study of maternal and newborn health professionals via an online survey disseminated through professional networks and social media in 12 languages. Information was collected between 24 March and 10 April 2020 on respondents' background, preparedness for and response to COVID-19 and their experience during the pandemic. An optional module sought information on adaptations to 17 care processes. Descriptive statistics and qualitative thematic analysis were used to analyse responses, disaggregating by low-income and middle-income countries (LMICs) and high-income countries (HICs).

Results. We analysed responses from 714 maternal and newborn health professionals. Only one-third received training on COVID-19 from their health facility and nearly all searched for information themselves. Half of respondents in LMICs received updated guidelines for care provision compared with 82% in HICs. Overall, 47% of participants in LMICs and 69% in HICs felt mostly or completely knowledgeable in how to care for COVID-19 maternity patients. Facility-level responses to COVID-19 (signage, screening, testing and isolation rooms) were more common in HICs than LMICs. Globally, 90% of respondents reported somewhat or substantially higher levels of stress. There was a widespread perception of reduced use of routine maternity care services, and of modification in care processes, some of which were not evidence-based practices.

Conclusions. Substantial knowledge gaps exist in guidance on management of maternity cases with or without COVID-19. Formal information-sharing channels for providers must be established and mental health support provided. Surveys of maternity care providers can help track the situation, capture innovations and support rapid development of effective responses.

13. BMJ GH 2020-00278

Commentary

Oxygen provision to fight COVID-19 in sub-Saharan Africa

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Summary box
- The adequate provision of medical oxygen is going to make the difference between life and death for the majority of patients with COVID-19 in Africa.
- Sub-Saharan African countries lack affordable and reliable oxygen supply.
- There is evidence from sub-Saharan Africa for why medical oxygen provision must be made a regional urgent priority.
- Efforts being made in some African countries demonstrate how oxygen provision can be scaled up through innovative cheap technologies.

Introduction. Oxygen saves lives. Its provision is a critical component of emergency respiratory resuscitation around the world, and it consequently features on the WHO's list of essential medicines. Oxygen therapy is not just used for pneumonia and other lung diseases. It is also crucial for treating various non-respiratory conditions that result in hypoxaemia, such as sepsis, severe malaria, trauma and cardiovascular diseases. It is equally essential for surgical care and anaesthesia.

In Western countries, the reaction to the COVID-19 pandemic has been to increase hospital capacity and to provide more intensive care units (ICUs) and more ventilators. There had been little discussion of the provision of oxygen as this is a standard clinical tool widely available in hospitals. This is not the case in sub-Saharan Africa (SSA). There is a shortage of oxygen in health centres in SSA. When it comes to prioritising medical resources, SSA needs to save the maximum number of lives during the COVID-19 pandemic; arguably, two things should be atop of that list before ICUs and ventilators. These are personal protective equipment (PPE) for frontline health workers and oxygen for the patients. The need for PPE is a global issue and one whose importance has been highlighted in the different health systems as it is critical to ensure frontline health workers are protected from COVID-19 infection and that they are not infection conduits within hospitals.

Oxygen, on the other hand, has received less attention, and yet it is the second most important aspect of the COVID-19 response. Critically, pneumonia is a predominant clinical feature of COVID-19, and adequate ventilation support is essential for patient survival. It has been indicated that supplemental oxygen is a first essential step for the treatment of patients with severe COVID-19 with hypoxaemia and should be a primary focus in resource-limited settings. In China, a study of 1099 hospitalised patients with laboratory-confirmed COVID-19 this year found that 41.3% needed supplemental oxygen and 2.3% needed invasive mechanical ventilation. Therefore, investing in supplementary oxygen would strengthen the response to COVID-19 in African countries and save lives.

14. Lancet 2020;395(10241):1883
Editorial
Global governance for COVID-19 vaccines

The COVID-19 pandemic has uncovered serious gaps in the health-care systems of many nations. In particular, it exposes a fragmented global governance system that does not have the structures to coordinate the pooling and sharing of resources needed to combat pandemics. Since the early days of the pandemic, medical protectionism has emerged as nations scrambled for their own stocks of personal protective equipment and ventilators. COVID-19 vaccines could be the next example. Already there is a danger of a vaccine bidding war, with governments competing for a limited number of doses, well before a vaccine even reaches the market.

There is a urgent need for new arrangements at the global level to facilitate the development, finance, production, and equitable distribution of COVID-19 vaccines. Controlling the pandemic demands global cooperation. The nationalist and competitive approaches taken by a few high-income countries to get hold of a small supply of vaccines could result in excessive casualties in other parts of the

world. Global solidarity is needed instead, and resources must be pooled and shared. Gavi Covax is a step in the right direction.

It is imperative that more governments and pharmaceutical companies agree to shoulder the costs of vaccine research and manufacturing, and to share data and technologies. They need to commit to WHO allocation guidelines and cooperate globally to distribute vaccines fairly to those at greatest risk. A pandemic vaccine needs strong global governance behind it.

Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis

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Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 and is spread person- to-person through close contact. We aimed to investigate the effects of physical distance, face masks, and eye protection on virus transmission in health-care and non-health-care (eg, community) settings.

Methods. We did a systematic review and meta-analysis to investigate the optimum distance for avoiding person-to- person virus transmission and to assess the use of face masks and eye protection to prevent transmission of viruses. We obtained data for SARS-CoV-2 and the betacoronaviruses that cause severe acute respiratory syndrome, and Middle East respiratory syndrome from 21 standard WHO-specific and COVID-19-specific sources. We searched these data sources from database inception to May 3, 2020, with no restriction by language, for comparative studies and for contextual factors of acceptability, feasibility, resource use, and equity. We screened records, extracted data, and assessed risk of bias in duplicate. We did frequentist and Bayesian meta-analyses and random-effects meta- regressions. We rated the certainty of evidence according to Cochrane methods and the GRADE approach. This study is registered with PROSPERO, CRD42020177047.

Findings. Our search identified 172 observational studies across 16 countries and six continents, with no randomized controlled trials and 44 relevant comparative studies in health-care and non-health-care settings (n=25 697 patients). Transmission of viruses was lower with physical distancing of 1 m or more, compared with a distance of less than 1 m (n=10 736, pooled adjusted odds ratio [aOR] 0·18, 95% CI 0·09 to 0·38; risk difference [RD] –10·2%, 95% CI –11·5 to –7·5; moderate certainty); protection was increased as distance was lengthened (change in relative risk [RR] 2·02 per m; p =0·041; moderate certainty). Face mask use could result in a large reduction in risk of interaction infection (n=2647; aOR 0·15, 95% CI 0·07 to 0·34, RD –14·3%, –15·9 to –10·7; low certainty), with stronger associations with N95 or similar respirators compared with disposable surgical masks or similar (eg, reusable 12–16-layer cotton masks; pinteraction=0·090; posterior probability >95%, low certainty). Eye protection also was associated with less infection (n=3713; aOR 0·22, 95% CI 0·12 to 0·39, RD –10·6%, 95% CI –12·5 to –7·7; low certainty). Unadjusted studies and subgroup and sensitivity analyses showed similar findings.

Interpretation. The findings of this systematic review and meta-analysis support physical distancing of 1 m or more and provide quantitative estimates for models and contact tracing to inform policy. Optimum use of face masks, respirators, and eye protection in public and health-care settings should be informed by these findings and contextual factors. Robust randomised trials are needed to better inform the evidence for these interventions, but this systematic appraisal of currently best available evidence might inform interim guidance.

// Our comprehensive systematic review provides the best available information on three simple and common interventions to combat the immediate threat of COVID-19, while new evidence on

pharmacological treatments, vaccines, and other personal protective strategies is being generated. Physical distancing of at least 1 m is strongly associated with protection, but distances of up to 2 m might be more effective. Although direct evidence is limited, the optimum use of face masks, in particular N95 or similar respirators in health-care settings and 12–16-layer cotton or surgical masks in the community, could depend on contextual factors; action is needed at all levels to address the paucity of better evidence. Eye protection might provide additional benefits. Globally collaborative and well conducted studies, including randomised trials, of different personal protective strategies are needed regardless of the challenges, but this systematic appraisal of currently best available evidence could be considered to inform interim guidance.

16. Preliminary Report

Effect of Dexamethasone in Hospitalized Patients with COVID-19

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Background: Coronavirus disease 2019 (COVID-19) is associated with diffuse lung damage. Corticosteroids may modulate immune-mediated lung injury and reducing progression to respiratory failure and death.

Methods: The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial is a randomized, controlled, open-label, adaptive, platform trial comparing a range of possible treatments with usual care in patients hospitalized with COVID-19. We report the preliminary results for the comparison of dexamethasone 6 mg given once daily for up to ten days vs. usual care alone. The primary outcome was 28-day mortality.

Results: 2104 patients randomly allocated to receive dexamethasone were compared with 4321 patients concurrently allocated to usual care. Overall, 454 (21.6%) patients allocated dexamethasone and 1065 (24.6%) patients allocated usual care died within 28 days (age- adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; P<0.001). The proportional and absolute mortality rate reductions varied significantly depending on level of respiratory support at randomization (test for trend p<0.001): Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs.

13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14).

Conclusions: In patients hospitalized with COVID-19, dexamethasone reduced 28-day mortality among those receiving invasive mechanical ventilation or oxygen at randomization, but not among patients not receiving respiratory support.

17. BMJ 2020;369:m2512

Covid-19: Demand for dexamethasone surges as RECOVERY trial publishes preprint
Mahase E.

Production of dexamethasone must be rapidly ramped up to meet global demand for the drug, the World Health Organization has said. The call came as the University of Oxford's RECOVERY trial published its much anticipated preprint paper on the drug's effect on covid-19. The paper states that the drug cuts deaths in ventilated patients by one third and deaths in other admitted patients receiving

oxygen by only one fifth. The headline findings of the trial were reported by the investigators on 16 June and were adopted into UK practice the same day through an alert sent to doctors.

WHO's director general, Tedros Adhanom Ghebreyesus, said, "The next challenge is to increase production and rapidly and equitably distribute dexamethasone worldwide, focusing on where it is needed most. Demand has already surged following the UK trial results."

Limitations and follow-up. John Fletcher, research editor at The BMJ who screened the preprint for MedRxiv, said that the trial was useful but that there were "limitations and cause for caution."

He said, "The authors have used relative reductions and chosen the subgroup with the biggest benefit to generate a headline of a one third reduction in deaths. The subgroup analysis was not specified in the trial registry and may be misleading."

Fletcher also noted that the final outcome was unknown for at least 28% of people entered in the trial, as 1807 were still in hospital at 28 days, the endpoint of the trial.

Carl Heneghan, director of the Centre for Evidence Based Medicine at the University of Oxford, said, "Given the fact this is a cheap available drug, and given the size of the effect, to me it is clear there is strong evidence to make this treatment available to the right patients admitted to intensive care units. We have seen a lot of poor quality evidence, but this is towards the spectrum of high quality evidence."

Heneghan added that he would like to see follow-up of the patient group beyond 28 days and additional analysis to see whether the drug could harm patients with mild to moderate disease.

Health Policy

18. HPP 2020;35(3):354-63
The prominent role of informal medicine vendors despite health insurance: a weekly diaries study in rural Nigeria
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In sub-Saharan Africa, accessibility to affordable quality care is often poor and health expenditures are mostly paid out of pocket. Health insurance, protecting individuals from out-of-pocket health expenses, has been put forward as a means of enhancing universal health coverage. We explored the utilization of different types of healthcare providers and the factors associated with provider choice by insurance status in rural Nigeria. We analysed year-long weekly health diaries on illnesses and injuries (health episodes) for a sample of 920 individuals with access to a private subsidized health insurance programme. The weekly diaries capture not only catastrophic events but also less severe events that are likely underreported in surveys with longer recall periods. Individuals had insurance coverage during 34% of the 1761 reported health episodes, and they consulted a healthcare provider in 90% of the episodes. Multivariable multinomial logistic regression analyses showed that insurance coverage was associated with significantly higher utilization of formal health care: individuals consulted upgraded insurance programme facilities in 20% of insured episodes compared with 3% of uninsured episodes. Nonetheless, regardless of insurance status, most consultations involved an informal provider visit, with informal providers encompassing 73 and 78% of all consultations among insured and uninsured episodes, respectively, and individuals spending 54% of total annual out-of-pocket health expenditures at such providers. Given the high frequency at which individuals consult informal providers, their position within both the primary healthcare system and health insurance schemes should be reconsidered to reach universal health coverage.

HIV / AIDS

19. Lancet 2020; 395(10231):1195–207
Treatment of advanced AIDS-associated Kaposi sarcoma in resource-limited settings: a three-arm, open-label, randomised, non-inferiority trial
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Background. Optimal treatment regimens for AIDS-associated Kaposi sarcoma, a frequent contributor to morbidity and mortality among people with HIV, have not been systematically evaluated in low-income and middle-income countries, where the disease is most common. In this study, we aimed to investigate optimal treatment strategies for advanced stage disease in areas of high prevalence and limited resources.

Methods. In this open-label, non-inferiority trial, we enrolled people with HIV and advanced stage AIDS-associated Kaposi sarcoma attending 11 AIDS Clinical Trials Group sites in Brazil, Kenya, Malawi, South Africa, Uganda, and Zimbabwe. Eligible participants were randomly assigned (1:1:1) with a centralised computer system to receive either intravenous bleomycin and vincristine or oral etoposide (the investigational arms), or intravenous paclitaxel (the control arm), together with antiretroviral therapy (ART; combined efavirenz, tenofovir disoproxil fumarate, and emtricitabine). The primary outcome was progression-free survival (PFS) at week 48, using a 15% non-inferiority margin to compare the investigational groups against the active control group. Safety was assessed in all eligible treated study participants. The study was registered with ClinicalTrials.gov, NCT01435018.

Findings. 334 participants were enrolled between Oct 1, 2013, and March 8, 2018, when the study was closed early due to inferiority of the bleomycin and vincristine plus ART arm, as per the recommendations of the Data and Safety Monitoring Board (DSMB). The etoposide plus ART arm also closed due to inferiority in March, 2016, following a DSMB recommendation. Week-48 PFS rates were higher in the paclitaxel plus ART arm than in both investigational arms. The absolute differences in PFS were –30% (95% CI –52 to –8) for the comparison of paclitaxel plus ART (week 48 PFS 50%, 32 to 67; n=59) and etoposide plus ART (20%, 6 to 33; n=59), and –20% (–33% to –7%) for the comparison of paclitaxel plus ART (64%, 55 to 73; n=138) and bleomycin and vincristine plus ART (44%, 35 to 53; n=132). Both CIs overlapped the non-inferiority margin. The most common adverse events, in 329 eligible participants who began treatment, were neutropenia (48 [15%]), low serum albumin (33 [10%]), weight loss (29 [9%]), and anaemia (28 [9%]), occurring at similar frequency across treatment arms.

Interpretation. Non-inferiority of either investigational intervention was not shown, with paclitaxel plus ART showing superiority to both oral etoposide plus ART and bleomycin and vincristine plus ART, supporting its use in treating advanced AIDS-associated Kaposi sarcoma in resource-limited settings.

Malaria

20. Am J TMH 2020;May 18
The Impact of Control Interventions on Malaria Burden in Young Children in a Historically High-Transmission District of Uganda: A Pooled Analysis of Cohort Studies from 2007 to 2018
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There is limited evidence on whether malaria elimination is feasible in high-transmission areas of Africa. Between 2007 and 2018, we measured the impact of malaria control interventions in young children enrolled in three clinical trials and two observational studies in Tororo, Uganda, a historically

high-transmission area. Data were pooled from children aged 0.5-2 years. Interventions included individually assigned chemoprevention and repeated rounds of indoor residual spraying (IRS) of insecticide. All children received long-lasting insecticidal nets (LLINs) and treatment for symptomatic malaria with artemisinin-based combination therapy. Malaria incidence was measured using passive surveillance and parasite prevalence by microscopy and molecular methods at regular intervals. Poisson's generalized linear mixed-effects models were used to estimate the impact of various control interventions. In total, 939 children were followed over 1,221.7 person years. In the absence of chemoprevention and IRS (reference group), malaria incidence was 4.94 episodes per person year and parasite prevalence 47.3%. Compared with the reference group, implementation of IRS was associated with a 97.6% decrease (95% CI: 93.3-99.1%, P = 0.001) in the incidence of malaria and a 96.0% decrease (95% CI: 91.3-98.2%, P < 0.001) in parasite prevalence (both measured after the fifth and sixth rounds of IRS). The addition of chemoprevention with monthly dihydroartemisinin-piperaquine to IRS was associated with a 99.5% decrease (95% CI: 98.6-99.9%, P < 0.001) in the incidence of malaria. In a historically high-malaria burden area of Uganda, a combination of LLINs, effective case management, IRS, and chemoprevention was associated with almost complete elimination of malaria in young children.

21. Am J TMH 2020;102(5):1048-55
Asymptomatic Submicroscopic Plasmodium Infection Is Highly Prevalent and Is Associated with Anemia in Children Younger than 5 Years in South Kivu/Democratic Republic of Congo
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One of the most important problems in controlling malaria is the limited access to effective and accurate diagnosis of malaria parasitemia. In the Democratic Republic of Congo (DRC), malaria is one of the leading causes of morbidity and mortality. The purpose of this study was to assess the prevalence of anemia and the relationship with asymptomatic submicroscopic Plasmodium infection. A cross-sectional study was carried out among 1,088 apparently healthy children aged between 6 and 59 months selected at random in the health zone of Miti Murhesa in South Kivu/DRC. Capillary blood was obtained for hemoglobin (Hb) concentration measurement by Hemocue® Hb 301. Malaria detection was performed by microscopy and the loop-mediated isothermal amplification (LAMP) assay. Anemia was defined as Hb < 11g/dL. We applied the chi-square test for comparisons, and multiple logistic regression was used to identify the risk factors for anemia and submicroscopic Plasmodium infection. The prevalence of anemia was 39.6%, and the prevalence of parasitemia was 15.9% and 34.0% using microscopy and LAMP test, respectively. Submicroscopic Plasmodium infection was found in 22.3% of the children. The independent risk factors for anemia are Plasmodium infection, children younger than 24 months, low middle-upper arm circumference, and history of illness two weeks before. Otherwise, children with submicroscopic malaria infection have a significantly increased risk for anemia, with a need of transfusion. The prevalence of malaria infection was underestimated, when microscopy was used to diagnose malaria. Children with low parasitemia detected by LAMP but not by microscopy showed a significantly increased prevalence of anemia.

22. Am J TMH 2020;May 18
The WorldWide Antimalarial Resistance Network Clinical Trials Publication Library: A Live, Open-Access Database of Plasmodium Treatment Efficacy Trials
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Parasite resistance to antimalarial drugs poses a serious threat to malaria control. The WorldWide Antimalarial Resistance Network (WWARN) aims to provide a collaborative platform to support the

global malaria research effort. Here, we describe the "WWARN clinical trials publication library," an open-access, up-to-date resource to streamline the synthesis of antimalarial safety and efficacy data. A series of iteratively refined database searches were conducted to identify prospective clinical trials assessing antimalarial drug efficacy with at least 28 days of follow-up. Of approximately 45,000 articles screened, 1,221 trials published between 1946 and 2018 were identified, representing 2,339 treatment arms and 323,819 patients. In trials from endemic locations, 75.7% (787/1,040) recruited patients with Plasmodium falciparum, 17.0% (177/1,040) Plasmodium vivax, 6.9% (72/1,040) both, and 0.4% (4/1,040) other Plasmodium species; 57.2% (585/1,022) of trials included under-fives and 5.3% (55/1,036) included pregnant women. In Africa, there has been a marked increase in both P. falciparum and P. vivax studies over the last two decades. The WHO-recommended artemisinin-based combination therapies alone or with a gametocidal drug were assessed in 39.5% (705/1,783) of P. falciparum treatment arms and 10.5% (45/429) of P. vivax arms, increasing to 78.0% (266/341) and 22.9% (27/118), respectively, in the last five years. The library is a comprehensive, open-access tool that can be used by the malaria community to explore the collective knowledge on antimalarial efficacy (available at https://www.wwarn.org/tools-resources/literature-reviews/wwarn-clinical-trials-pu blication-library). It is the first of its kind in the field of global infectious diseases, and lessons learnt in its creation can be adapted to other infectious diseases.

23. Lancet 2020;395(10233):1345–60

Triple artemisinin-based combination therapies versus artemisinin-based combination therapies for uncomplicated Plasmodium falciparum malaria: a multicentre, open-label, randomised clinical trial
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Background. Artemisinin and partner-drug resistance in Plasmodium falciparum are major threats to malaria control and elimination. Triple artemisinin-based combination therapies (TACTs), which combine existing co-formulated ACTs with a second partner drug that is slowly eliminated, might provide effective treatment and delay emergence of antimalarial drug resistance.
Methods. In this multicentre, open-label, randomised trial, we recruited patients with uncomplicated P falciparum malaria at 18 hospitals and health clinics in eight countries. Eligible patients were aged 2–65 years, with acute, uncomplicated P falciparum malaria alone or mixed with non-falciparum species, and a temperature of 37·5°C or higher, or a history of fever in the past 24 h. Patients were randomly assigned (1:1) to one of two treatments using block randomisation, depending on their location: in Thailand, Cambodia, Vietnam, and Myanmar patients were assigned to either dihydroartemisinin–piperaquine or dihydroartemisinin–piperaquine plus mefloquine; at three sites in Cambodia they were assigned to either artesunate–mefloquine or dihydroartemisinin–piperaquine plus mefloquine; and in Laos, Myanmar, Bangladesh, India, and the Democratic Republic of the Congo they were assigned to either artemether–lumefantrine or artemether–lumefantrine plus amodiaquine. All drugs were administered orally and doses varied by drug combination and site. Patients were followed-up weekly for 42 days. The primary endpoint was efficacy, defined by 42-day PCR-corrected adequate clinical and parasitological response. Primary analysis was by intention to treat. A detailed assessment of safety and tolerability of the study drugs was done in all patients randomly assigned to treatment. This study is registered at ClinicalTrials.gov, NCT02453308, and is complete.
Findings. Between Aug 7, 2015, and Feb 8, 2018, 1100 patients were given either dihydroartemisinin–piperaquine (183 [17%]), dihydroartemisinin–piperaquine plus mefloquine (269 [24%]), artesunate–mefloquine (73 [7%]), artemether–lumefantrine (289 [26%]), or artemether–lumefantrine plus amodiaquine (286 [26%]). The median age was 23 years (IQR 13 to 34) and 854 (78%) of 1100 patients were male. In Cambodia, Thailand, and Vietnam the 42-day PCR-corrected efficacy after

dihydroartemisinin–piperaquine plus mefloquine was 98% (149 of 152; 95% CI 94 to 100) and after dihydroartemisinin–piperaquine was 48% (67 of 141; 95% CI 39 to 56; risk difference 51%, 95% CI 42 to 59; p<0·0001). Efficacy of dihydroartemisinin–piperaquine plus mefloquine in the three sites in Myanmar was 91% (42 of 46; 95% CI 79 to 98) versus 100% (42 of 42; 95% CI 92 to 100) after dihydroartemisinin–piperaquine (risk difference 9%, 95% CI 1 to 17; p=0·12). The 42-day PCR corrected efficacy of dihydroartemisinin–piperaquine plus mefloquine (96% [68 of 71; 95% CI 88 to 99]) was non-inferior to that of artesunate–mefloquine (95% [69 of 73; 95% CI 87 to 99]) in three sites in Cambodia (risk difference 1%; 95% CI –6 to 8; p=1·00). The overall 42-day PCR-corrected efficacy of artemether–lumefantrine plus amodiaquine (98% [281 of 286; 95% CI 97 to 99]) was similar to that of artemether–lumefantrine (97% [279 of 289; 95% CI 94 to 98]; risk difference 2%, 95% CI –1 to 4; p=0·30). Both TACTs were well tolerated, although early vomiting (within 1 h) was more frequent after dihydroartemisinin– piperaquine plus mefloquine (30 [3·8%] of 794) than after dihydroartemisinin–piperaquine (eight [1·5%] of 543; p=0·012). Vomiting after artemether–lumefantrine plus amodiaquine (22 [1·3%] of 1703) and artemether– lumefantrine (11 [0·6%] of 1721) was infrequent. Adding amodiaquine to artemether–lumefantrine extended the electrocardiogram corrected QT interval (mean increase at 52 h compared with baseline of 8·8 ms [SD 18·6] vs 0·9 ms [16·1]; p<0·01) but adding mefloquine to dihydroartemisinin–piperaquine did not (mean increase of 22·1 ms [SD 19·2] for dihydroartemisinin–piperaquine vs 20·8 ms [SD 17·8] for dihydroartemisinin– piperaquine plus mefloquine; p=0·50).

Interpretation. Dihydroartemisinin–piperaquine plus mefloquine and artemether–lumefantrine plus amodiaquine TACTs are efficacious, well tolerated, and safe treatments of uncomplicated P falciparum malaria, including in areas with artemisinin and ACT partner-drug resistance.

24. Lancet 2020;395(10233):1361–73
Effectiveness of reactive focal mass drug administration and reactive focal vector control to reduce malaria transmission in the low malaria-endemic setting of Namibia: a cluster-randomised controlled, open-label, two-by-two factorial design trial

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Background. In low malaria-endemic settings, screening and treatment of individuals in close proximity to index cases, also known as reactive case detection (RACD), is practised for surveillance and response. However, other approaches could be more effective for reducing transmission. We aimed to evaluate the effectiveness of reactive focal mass drug administration (rfMDA) and reactive focal vector control (RAVC) in the low malaria-endemic setting of Zambezi (Namibia).

Methods. We did a cluster-randomised controlled, open-label trial using a two-by-two factorial design of 56 enumeration area clusters in the low malaria-endemic setting of Zambezi (Namibia). We randomly assigned these clusters using restricted randomisation to four groups: RACD only, rfMDA only, RAVC plus RACD, or rfMDA plus RAVC. RACD involved rapid diagnostic testing and treatment with artemether-lumefantrine and single-dose primaquine, rfMDA involved presumptive treatment with artemether-lumefantrine, and RAVC involved indoor residual spraying with pirimiphos-methyl. Interventions were administered within 500 m of index cases. To evaluate the effectiveness of interventions targeting the parasite reservoir in humans (rfMDA vs RACD), in mosquitoes (RAVC vs no RAVC), and in both humans and mosquitoes (rfMDA plus RAVC vs RACD only), an intention-to-treat analysis was done. For each of the three comparisons, the primary outcome was the cumulative incidence of locally acquired malaria cases. This trial is registered with ClinicalTrials.gov, number NCT02610400.

Findings. Between Jan 1, 2017, and Dec 31, 2017, 55 enumeration area clusters had 1118 eligible index cases that led to 342 interventions covering 8948 individuals. The cumulative incidence of locally acquired malaria was 30·8 per 1000 person-years (95% CI 12·8–48·7) in the clusters that received rfMDA versus 38·3 per 1000 person-years (23·0–53·6) in the clusters that received RACD; 30·2 per 1000 person-years (15·0–45·5) in the clusters that received RAVC versus 38·9 per 1000 person-years (20·7–57·1) in the clusters that did not receive RAVC; and 25·0 per 1000 person-years (5·2–44·7) in the clusters that received rfMDA plus RAVC versus 41·4 per 1000 person-years (21·5–61·2) in the clusters that received RACD only. After adjusting for imbalances in baseline and implementation factors, the incidence of malaria was lower in clusters receiving rfMDA than in those receiving RACD (adjusted incidence rate ratio 0·52 [95% CI 0·16–0·88], p=0·009), lower in clusters receiving RAVC than in those that did not (0·48 [0·16–0·80], p=0·002), and lower in clusters that received rfMDA plus RAVC than in those receiving RACD only (0·26 [0·10–0·68], p=0·006). No serious adverse events were reported.

Interpretation. In a low malaria-endemic setting, rfMDA and RAVC, implemented alone and in combination, reduced malaria transmission and should be considered as alternatives to RACD for elimination of malaria.

Pharmaceuticals

25. BMJ GH 2020-002446
Commentary
Mass azithromycin administration: considerations in an increasingly resistant world
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Summary box
Recent studies have shown that mass administration of azithromycin in some areas can lead to reduction in childhood mortality, which in turn has led to additional large-scale trials in many parts of the world.

We provide evidence for the emergence of novel azithromycin resistance mechanisms in common bacterial pathogens like Salmonella, arguing that the appealing positive effects of mass drug administration might diminish with increasing azithromycin resistance.

While a silver bullet against childhood mortality is highly desirable, given the alarming rise in antimicrobial resistance and the drying pipeline of novel drugs, the opportunity costs of mass administration should be considered with utmost caution.

Future studies and trials of mass azithromycin administration should include methods for early detection of azithromycin resistance such that preventative measures can be implemented, in case azithromycin resistance begins to spread.

Azithromycin is an oral macrolide discovered in 1980 and approved for medical use in 1988. This relatively inexpensive antibiotic is often deemed as a wonder drug due to its safety and effectiveness against parasitic and helminth infections, in addition to a wide range of bacterial infections. In the early 2000s, biannual administration of azithromycin (mass drug administration, MDA) for trachoma control was found to reduce all-cause mortality by almost 49%. These encouraging results, presumably due to reduction in respiratory and diarrhoeal infections and malaria, led to the placebo-controlled, double-blinded, cluster-randomised MORDOR-I trial (Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance) in Niger, Malawi and Tanzania covering 190 238 children. An overall 13.5% reduction in child mortality was observed in azithromycin versus placebo communities; however, the effect was largely driven by findings in Niger (18.1%), with minimal impact in Malawi (5.7%) and Tanzania (3.4%). While the mechanism of azithromycin's effect on childhood mortality is

not fully understood, the overall success of the MORDOR-I trial has led to additional trials in various other countries, including follow-up trials in Niger and Burkina Faso (NCT03676751). Notably, there are ongoing clinical trials in Pakistan (NCT03564652 and NCT04012177) and a large-scale trial that will provide azithromycin to all children at risk of diarrhoea in seven countries including Pakistan, India and Bangladesh (NCT03130114).

Public Health Emergencies

26. Lancet 2020;395(10232):1305-14

Fangcang shelter hospitals: a novel concept for responding to public health emergencies

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Fangcang shelter hospitals are a novel public health concept. They were implemented for the first time in China in February, 2020, to tackle the coronavirus disease 2019 (COVID-19) outbreak. The Fangcang shelter hospitals in China were large-scale, temporary hospitals, rapidly built by converting existing public venues, such as stadiums and exhibition centres, into health-care facilities. They served to isolate patients with mild to moderate COVID-19 from their families and communities, while providing medical care, disease monitoring, food, shelter, and social activities. We document the development of Fangcang shelter hospitals during the COVID-19 outbreak in China and explain their three key characteristics (rapid construction, massive scale, and low cost) and five essential functions (isolation, triage, basic medical care, frequent monitoring and rapid referral, and essential living and social engagement). Fangcang shelter hospitals could be powerful components of national responses to the COVID-19 pandemic, as well as future epidemics and public health emergencies.

Sexual and Reproductive Health

27. BMJ GH 2020-002371

Original research

The cost of maternal health services in low-income and middle-income countries from a provider's perspective: a systematic review

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Introduction. Maternal health services are effective in reducing the morbidity and mortality associated with pregnancy and childbirth. We conducted a systematic review on costs of maternal health services in low-income and middle-income countries from the provider's perspective.

Methods. We searched multiple peer-reviewed databases (including African Journal Online, CINAHL Plus, EconLit, Popline, PubMed, Scopus and Web of Science) and grey literature for relevant articles published from year 2000. Articles meeting our inclusion criteria were selected with quality assessment done using relevant cost-focused criteria of the Consolidated Health Economic Evaluation Reporting Standards checklist. For comparability, disaggregated costs data were inflated to 2019 US$ equivalents. Costs and cost drivers were systematically compared. Where heterogeneity was observed, narrative synthesis was used to summarise findings.

Results. Twenty-two studies were included, with most studies costing vaginal and/or caesarean delivery (11 studies), antenatal care (ANC) (9) and postabortion care (PAC) (8). Postnatal care (PNC) has been least costed (2). Studies used different methods for data collection and analysis. Quality of peer-reviewed studies was assessed average to high while all grey literature studies were assessed as

low quality. Following inflation, estimated provision cost per service varied (ANC (US$7.24–US$31.42); vaginal delivery (US$14.32–US$278.22); caesarean delivery (US$72.11–US$378.940; PAC (US$97.09–US$1299.21); family planning (FP) (US$0.82–US$5.27); PNC (US$5.04)). These ranges could be explained by intercountry variations, variations in provider type (public/private), facility type (primary/secondary) and care complexity (simple/complicated). Personnel cost was mostly reported as the major driver for provision of ANC, skilled birth attendance and FP. Economies of scale in service provision were reported.

Conclusion. There is a cost savings case for task-shifting and encouraging women to use lower level facilities for uncomplicated services. Going forward, consensus regarding cost component definitions and methodologies for costing maternal health services will significantly help to improve the usefulness of cost analyses in supporting policymaking towards achieving Universal Health Coverage.

28. HPP 2020;35(5):577-86
Providers' perceptions of disrespect and abuse during childbirth: a mixed-methods study in Kenya
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Disrespect and abuse during childbirth are violations of women's human rights and an indicator of poor-quality care. Disrespect and abuse during childbirth are widespread, yet data on providers' perspectives on the topic are limited. We examined providers' perspectives on the frequency and drivers of disrespect and abuse during facility-based childbirth in a rural county in Kenya. We used data from a mixed-methods study in a rural county in Western Kenya with 49 maternity providers (32 clinical and 17 non-clinical) in 2016. Providers were asked structured questions on disrespect and abuse, followed by open-ended questions on why certain behaviours were exhibited (or not). Most providers reported that women were often treated with dignity and respect. However, 53% of providers reported ever observing other providers verbally abuse women and 45% reported doing so themselves. Observation of physical abuse was reported by 37% of providers while 35% reported doing so themselves. Drivers of disrespect and abuse included perceptions of women being difficult, stress and burnout, facility culture and lack of accountability, poor facility infrastructure and lack of medicines and supplies, and provider attitudes. Provider bias, training and women's empowerment influenced how different women were treated. We conclude that disrespect and abuse are driven by difficult situations in a health system coupled with a facilitating sociocultural environment. Providers resorted to disrespect and abuse as a means of gaining compliance when they were stressed and feeling helpless. Interventions to address disrespect and abuse need to tackle the multiplicity of contributing factors. These should include empowering providers to deal with difficult situations, develop positive coping mechanisms for stress and address their biases. We also need to change the culture in facilities and strengthen the health systems to address the system-level stressors.

29. NEJM 2020;382(21):2023–32
Review
Emerging and Reemerging Sexually Transmitted Infections
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The 21st century has seen a global resurgence of sexually transmitted infections (STIs). From a nadir in the 1990s, the rates of gonorrhea, syphilis, and chlamydia infections have increased substantially in highincome countries, with particular increases among men who have sex with men (MSM).

Concurrent with the increase in these established STIs are emerging epidemics and outbreaks of "nonclassical" sexually transmissible pathogens that cause a wide range of clinical syndromes. These pathogens include enteric pathogens (e.g., shigella and hepatitis A virus), those spread by close contact (e.g., Neisseria meningitidis), and recently characterized pathogens that can spread through sexual contact (e.g., Zika virus). Furthermore, increases in antimicrobial resistance have heightened concern about ever more limited treatment options for STIs, particularly gonorrhea and Mycoplasma genitalium infection. The factors contributing to sustained transmission of STIs within populations are multiple, complex, and context specific. In principle, these factors include the probability of transmission, the rate of change in sexual partners, and the duration of infectiousness. Examples of factors that have enhanced STI transmission include unprecedented connectivity between persons, facilitated by global travel and online social networking, and increasing use of preexposure prophylaxis against human immunodeficiency virus (HIV) infection. The multitude of socioeconomic and structural variables that impede access to testing and treatment are important in sustaining epidemics of curable STIs. In this review, we provide an overview of major pathogens that have emerged or reemerged as STIs over the past decade. We discuss epidemiologic features of these infections, including insights provided by genomic technologies, diagnostic approaches, and practical issues relating to treatment and control.

30. TMIH 2020;25(4):442-53
Variation in competent and respectful delivery care in Kenya and Malawi: a retrospective analysis of national facility surveys
Arsenault C et al.

Objective. Although substantial progress has been made in increasing access to care during childbirth, reductions in maternal and neonatal mortality have been slower. Poor-quality care may be to blame. In this study, we measure the quality of labour and delivery services in Kenya and Malawi using data from observations of deliveries and explore factors associated with levels of competent and respectful care.
Methods. We used data from nationally representative health facility assessment surveys. A total of 1100 deliveries in 392 facilities across Kenya and Malawi were observed and quality was assessed using two indices: the quality of the process of intrapartum and immediate postpartum care (QoPIIPC) index and a previously validated index of respectful maternity care. Data from standardised observations of care were analysed using descriptive statistics and multivariable random-intercept regression models to examine factors associated with variation in quality of care. We also quantified the variance in quality explained by each domain of covariates (patient-, provider- and facility-level and subnational divisions).
Results. Only 61–66% of basic elements of competent and respectful care were performed. In adjusted models, better-staffed facilities, private hospitals and morning deliveries were associated with higher levels of competent and respectful care. In Malawi, younger, primipara and HIV-positive women received higher-quality care. Quality also differed substantially across regions in Kenya, with a 25 percentage-point gap between Nairobi and the Coast region. Quality was also higher in higher-volume facilities and those with caesarean section capacity. Most of the explained variance in quality was due to regions in Kenya and to facility, and patient-level characteristics in Malawi.
Conclusions. Our findings suggest considerable scope for improvement in quality. Increasing staffing and shifting births to higher-volume facilities – along with promotion of respectful care in these facilities – should be considered in sub-Saharan Africa to improve outcomes for mothers and newborns.

Systematic Review
Health Workers' Views on Audit in Maternal and Newborn Healthcare in LMICs: A Qualitative Evidence Synthesis

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Objectives: To identify and summarise health workers' views on the use of audit as a method to improve the quality of maternal and newborn healthcare in low- and middle-income countries (LMICs).
Methods: We conducted a qualitative evidence synthesis. PubMed, CINAHL and Global Health databases were searched using keywords, synonyms and MeSH headings for 'audit', 'views' and 'health workers' to find papers that used qualitative methods to explore health workers' views on audit in LMICs. Titles and abstracts were then screened for inclusion. The remaining full-text papers were then screened. The final included papers were quality assessed using the Critical Appraisal Skills Programme tool for qualitative research. Data on audit type and health workers' perceptions were extracted and analysed using thematic synthesis.
Results: Nineteen papers were included in the review, most from sub-Saharan Africa. Health workers generally held favourable views of audit and expressed dedication to the process. Similarly, they described positive experiences conducting audit. The main barriers to implementing audit were the presence of a blame culture, inadequate training and the lack of time and resources to conduct audit. Health workers' motivation and dedication to the audit process helped to overcome such barriers.
Conclusions: Health workers are dedicated to the process of audit, but must be supported with training, leadership and adequate resources to use it. Decision-makers and technical partners supporting audit should focus on improving audit training and finding ways to conduct audit without requiring too much staff time.

Maternal Mortality Due to Cardiac Disease in Low- And Middle-Income Countries

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Objectives: To assess the frequency of maternal death (MD) due to cardiac disease in low- and middle-income countries (LMIC).
Methods: Systematic review searching Medline, EMBASE, Web of Science, Cochrane Library, Emcare, LILACS, African Index Medicus, IMEMR, IndMED, WPRIM, IMSEAR up to 01/Nov/2017. Maternal mortality reports from LMIC reviewing all MD in a given geographical area were included. Hospital-based reports or those solely based on verbal autopsies were excluded. Numbers of MD and cardiac-related deaths were extracted. We calculated cardiac disease MMR (cMMR, cardiac-related MD/100 000 live births) and proportion of cardiac-related MDs among all MDs. Frequency of cardiac MD was compared with the MMR of the country.
Results: Forty-seven reports were included, which reported on 38,486 maternal deaths in LMIC. Reported cMMR ranged from 0/100 000 live births (Moldova, Ghana) to 31.9/100 000 (Zimbabwe). The proportion of cardiac-related MD ranged from 0% (Moldova, Ghana) to 24.8% (Sri Lanka). In countries with a higher MMR, cMMR was also higher. However, the proportion of cardiac-related MD was higher in countries with a lower MMR.
Conclusions: The burden of cardiac-related mortality is difficult to assess due limited availability of mortality reports. The proportion of cardiac deaths among all MD appeared to be higher in countries

with a lower MMR. This is in line with what has been called 'obstetric transition': pre-existing medical diseases including cardiac disease are becoming relatively more important where the MMR falls.

Tuberculosis

33. Lancet.2020;395(10228):973-84

The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis

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Background: Tens of millions of children are exposed to Mycobacterium tuberculosis globally every year; however, there are no contemporary estimates of the risk of developing tuberculosis in exposed children. The effectiveness of contact investigations and preventive therapy remains poorly understood.

Methods: In this systematic review and meta-analysis, we investigated the development of tuberculosis in children closely exposed to a tuberculosis case and followed for incident disease. We restricted our search to cohort studies published between Jan 1, 1998, and April 6, 2018, in MEDLINE, Web of Science, BIOSIS, and Embase electronic databases. Individual-participant data and a pre-specified list of variables were requested from authors of all eligible studies. These included characteristics of the exposed child, the index case, and environmental characteristics. To be eligible for inclusion in the final analysis, a dataset needed to include: (1) individuals below 19 years of age; (2) follow-up for tuberculosis for a minimum of 6 months; (3) individuals with household or close exposure to an individual with tuberculosis; (4) information on the age and sex of the child; and (5) start and end follow-up dates. Studies assessing incident tuberculosis but without dates or time of follow-up were excluded. Our analysis had two primary aims: (1) estimating the risk of developing tuberculosis by time-period of follow-up, demographics (age, region), and clinical attributes (HIV, tuberculosis infection status, previous tuberculosis); and (2) estimating the effectiveness of preventive therapy and BCG vaccination on the risk of developing tuberculosis. We estimated the odds of prevalent tuberculosis with mixed-effects logistic models and estimated adjusted hazard ratios (HRs) for incident tuberculosis with mixed-effects Poisson regression models. The effectiveness of preventive therapy against incident tuberculosis was estimated through propensity score matching. The study protocol is registered with PROSPERO (CRD42018087022).

Findings: In total, study groups from 46 cohort studies in 34 countries-29 (63%) prospective studies and 17 (37%) retrospective-agreed to share their data and were included in the final analysis. 137 647 tuberculosis-exposed children were evaluated at baseline and 130 512 children were followed for 429 538 person-years, during which 1299 prevalent and 999 incident tuberculosis cases were diagnosed. Children not receiving preventive therapy with a positive result for tuberculosis infection had significantly higher 2-year cumulative tuberculosis incidence than children with a negative result for tuberculosis infection, and this incidence was greatest among children below 5 years of age (19·0% [95% CI 8·4-37·4]). The effectiveness of preventive therapy was 63% (adjusted HR 0·37 [95% CI 0·30-0·47]) among all exposed children, and 91% (adjusted HR 0·09 [0·05-0·15]) among those with a positive result for tuberculosis infection. Among all children <5 years of age who developed tuberculosis, 83% were diagnosed within 90 days of the baseline visit.

Interpretation: The risk of developing tuberculosis among exposed infants and young children is very high. Most cases occurred within weeks of contact investigation initiation and might not be

preventable through prophylaxis. This suggests that alternative strategies for prevention are needed, such as earlier initiation of preventive therapy through rapid diagnosis of adult cases or community-wide screening approaches.

Editorial
Empirical Antituberculosis Therapy in Advanced HIV Disease — Too Much, Too Late
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Despite the extraordinary advances in treating human immunodeficiency virus (HIV) infection during the past two decades, mortality, especially in resource-limited areas, remains unacceptably high. The leading killer of persons with HIV infection in these areas is tuberculosis, which accounted for more than a quarter of a million deaths in 2018. Among persons with low CD4+ T-cell counts who start antiretroviral therapy (ART) in low- and middle-income countries, the risk of tuberculosis developing within 6 months after starting therapy is as high as 20%, which exacts a heavy burden in terms of suffering and death. Diagnosing tuberculosis in such patients is often difficult, because the clinical manifestations are protean and diagnostic tests have poor sensitivity. As a result, some clinicians have reasoned that administering empirical antituberculosis treatment to patients with advanced HIV infection who do not yet have tuberculosis could lower the risk of death. In this issue of the Journal, Blanc and colleagues report the results of the well-done STATIS (Systematic vs. Test-Guided Antituberculosis Treatment Impact in Severely Immunosuppressed HIV-Infected Adults Initiating Antiretroviral Therapy with CD4 Cell Counts <100/mm3) trial, which showed that the strategy of providing empirical antituberculosis treatment to patients with established and advanced HIV infection who were beginning ART did not improve survival or prevent bacterial infections as compared with treating only patients who had positive tests for tuberculosis. Patients with CD4 cell counts below 100 cells per cubic millimeter and no evidence of active tuberculosis were randomly assigned to receive either four-drug antituberculosis therapy or regular screening for tuberculosis by means of enhanced diagnostic testing that included chest radiography, rapid molecular diagnostic sputum examinations, and urinary lipoarabinomannan tests. All the participants also received ART and were offered prophylaxis with trimethoprim–sulfamethoxazole.
/// What can be done to reduce tuberculosis incidence and mortality in patients with HIV infection, particularly those with advanced immunosuppression? Rather than empirically treating tuberculosis disease in this population, a better approach might be to incorporate an algorithm established by the World Health Organization in which populations at risk of latent tuberculosis are identified, screened, and offered preventive therapy. The REALITY (Reduction of Early Mortality in HIV-Infected Adults and Children Starting Antiretroviral Therapy) trial evaluated a package of preventive therapies for tuberculosis and other infections in patients with advanced HIV disease beginning ART and showed a significant improvement in survival with the combination prevention package as compared with standard care. The most effective way to prevent both tuberculosis and death from advanced HIV disease, however, may be to diagnose HIV infection before severe immunodeficiency develops and provide these patients with both ART and tuberculosis preventive therapy. The START (Strategic Timing of Antiretroviral Therapy) trial showed that beginning ART before immunosuppression occurs reduces the risk of serious HIV complications, including tuberculosis, and the TEMPRANO trial showed that the combination of tuberculosis preventive therapy and ART lowers the risk of HIV complications, tuberculosis, and death. Continued concerted efforts to diagnose HIV infection as early as possible and initiate antiretroviral and tuberculosis preventive treatment are essential to diminishing the burden of HIV and tuberculosis globally.

For persons with severe immunodeficiency when HIV infection is diagnosed, the best approach may be to promptly start ART and tuberculosis preventive therapy and monitor them closely for opportunistic illnesses. But it is now clear that empirical antituberculosis therapy for persons with advanced HIV infection is a pound of cure that is worse than an ounce of prevention.

35. TMIH 2020;25(5):624-34
Patient-incurred Cost of Inpatient Treatment for Tuberculosis in Rural Malawi
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Objectives: To mitigate the economic burden of tuberculosis (TB), it is important to fully understand the costs of TB treatment from the patient perspective. We therefore sought to quantify the patient-incurred cost of TB treatment in rural Malawi, with specific focus on costs borne by patients requiring inpatient hospitalisation.
Methods: We conducted a cross-sectional survey of 197 inpatients and 156 outpatients being treated for TB in rural Malawi. We collected data on out-of-pocket costs and lost wages, including costs to guardians. Costs for inpatient TB treatment were estimated and compared to costs for outpatient TB treatment. We then explored the equity distribution of inpatient TB treatment cost using concentration curves.
Results: Despite free government services, inpatients were estimated to incur a mean of $137 (standard deviation: $147) per initial TB episode, corresponding to >50% of annual household spending among patients in the lowest expenditure quintile. Non-medical hospitalisation costs accounted for 88% of this total. Patients treated entirely as outpatients incurred estimated costs of $25 (standard deviation: $15) per episode. The concentration curves showed that, among individuals hospitalised for an initial TB episode, poorer patients shouldered a much greater proportion of inpatient TB treatment costs than wealthier ones (concentration index: -0.279).
Conclusion: Patients hospitalised for TB in resource-limited rural Malawi experience devastating costs of TB treatment. Earlier diagnosis and treatment must be prioritised if we are to meet goals of effective TB control, avoidance of catastrophic costs and provision of appropriate patient-centred care in such settings.

Miscellaneous

36. Am J TMH 2020;Jun 1
Why is There Low Morbidity and Mortality of COVID-19 in Africa?
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Three months since the detection of the first COVID-19 case in Africa, almost all countries of the continent continued to report lower morbidity and mortality than the global trend, including Europe and North America. We reviewed the merits of various hypotheses advanced to explain this phenomenon, including low seeding rate, effective mitigation measures, population that is more youthful, favorable weather, and possible prior exposure to a cross-reactive virus. Having a youthful population and favorable weather appears compelling, particularly their combined effect; however, progression of the pandemic in the region and globally may dispel these in the coming months.

37. Lancet 2020; 395(10231):1167
Editorial
The status of nursing and midwifery in the world

Two reports mark the International Year of the Nurse and the Midwife, and World Health Day, April 7, in honour of their vital work providing health services. State of the World's Nursing 2020, released today, is a comprehensive analysis of nursing around the world, produced by WHO with the International Council of Nurses and Nursing Now. The third global State of the World's Midwifery, building on 2011 and 2014 editions, is due in 2021, and will be foreshadowed by a May, 2020, forum for action organised by WHO, the International Confederation of Midwives, and the International Council of Nurses. These evidence-based reports are essential tools to inform international, regional, and national policy dialogues about where and how to invest in the nursing and midwifery workforces to improve primary health care, strengthen emergency response and resilience, and achieve health for all.

State of the World's Nursing and State of the World's Midwifery are essential reports—they give foundation to global conversations about caring, well-being, the value of work, and equality. Investing in nurses and midwives will deliver the health that is needed. Giving nursing and midwifery the status they deserve is long overdue.

Variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 high-income, middle-income, and low-income countries (PURE): a prospective cohort study

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Background: Some studies, mainly from high-income countries (HICs), report that women receive less care (investigations and treatments) for cardiovascular disease than do men and might have a higher risk of death. However, very few studies systematically report risk factors, use of primary or secondary prevention medications, incidence of cardiovascular disease, or death in populations drawn from the community. Given that most cardiovascular disease occurs in low-income and middle-income countries (LMICs), there is a need for comprehensive information comparing treatments and outcomes between women and men in HICs, middle-income countries, and low-income countries from community-based population studies.

Methods: In the Prospective Urban Rural Epidemiological study (PURE), individuals aged 35-70 years from urban and rural communities in 27 countries were considered for inclusion. We recorded information on participants' sociodemographic characteristics, risk factors, medication use, cardiac investigations, and interventions. 168 490 participants who enrolled in the first two of the three phases of PURE were followed up prospectively for incident cardiovascular disease and death.

Findings: From Jan 6, 2005 to May 6, 2019, 202 072 individuals were recruited to the study. The mean age of women included in the study was 50·8 (SD 9·9) years compared with 51·7 (10) years for men. Participants were followed up for a median of 9·5 (IQR 8·5-10·9) years. Women had a lower cardiovascular disease risk factor burden using two different risk scores (INTERHEART and Framingham). Primary prevention strategies, such as adoption of several healthy lifestyle behaviours and use of proven medicines, were more frequent in women than men. Incidence of cardiovascular disease (4·1 [95% CI 4·0-4·2] for women vs 6·4 [6·2-6·6] for men per 1000 person-years; adjusted hazard ratio [aHR] 0·75 [95% CI 0·72-0·79]) and all-cause death (4·5 [95% CI 4·4-4·7] for women vs 7·4 [7·2-7·7] for men per 1000 person-years; aHR 0·62 [95% CI 0·60-0·65]) were also lower in women. By contrast, secondary prevention treatments, cardiac investigations, and coronary revascularisation were less frequent in women than men with coronary artery disease in all groups of countries. Despite this, women had lower risk of recurrent cardiovascular disease events (20·0 [95%

CI 18·2-21·7] versus 27·7 [95% CI 25·6-29·8] per 1000 person-years in men, adjusted hazard ratio 0·73 [95% CI 0·64-0·83]) and women had lower 30-day mortality after a new cardiovascular disease event compared with men (22% in women versus 28% in men; p<0·0001). Differences between women and men in treatments and outcomes were more marked in LMICs with little differences in HICs in those with or without previous cardiovascular disease.

Interpretation: Treatments for cardiovascular disease are more common in women than men in primary prevention, but the reverse is seen in secondary prevention. However, consistently better outcomes are observed in women than in men, both in those with and without previous cardiovascular disease. Improving cardiovascular disease prevention and treatment, especially in LMICs, should be vigorously pursued in both women and men. FUNDING: Full funding sources are listed at the end of the paper (see Acknowledgments).

39. TMIH 2020;25(6):660-65
Review.
Tropical Pyomyositis: An Update

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Tropical pyomyositis (TP) is a life-threatening bacterial infection of the skeletal muscle that occurs particularly among children, young adults and those with immunocompromised conditions.

The appropriate diagnosis and treatment are often delayed due to its non-specific signs, leading to fatal consequences. Staphylococcus aureus, especially methicillin-susceptible S. aureus, is responsible for most TP cases. However, other bacteria (i.e. streptococci, Pseudomonas aeruginosa, Escherichia coli, Klebsiella spp., Candida spp., Mycobacterium spp.) have been reported. This narrative review provides an update on the epidemiology and clinical course of TP. A special focus is laid on the role of toxins (i.e. Panton-Valentine Leucocidin and α-toxin) in the pathogenesis of TP and their implication for the clinical management of infection.