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International Health Alerts 2017-1 Abstracts

Child Health

1. Am J TMH 2017;96(1):249-257

Performance of Health Workers Using an Electronic Algorithm for the Management of Childhood Illness in Tanzania: A Pilot Implementation Study

Rambaud-Althaus C et al., Swiss Tropical and Public Health Institute, Basel, Switzerland <clotilde.rambaud@unibas.ch>

In low-resource settings, where qualified health workers (HWs) are scarce and childhood mortality high, rational antimicrobial prescription for childhood illnesses is a challenge. To assess whether smartphones running guidelines, as compared with paper support, improve consultation process and rational use of medicines for children, a pilot cluster-randomized controlled study was conducted in Tanzania. Nine primary health-care facilities (HFs) were randomized into three arms: 1) paper algorithm, 2) electronic algorithm on a smartphone, and 3) control. All HWs attending children aged 2-59 months for acute illness in intervention HFs were trained on a new clinical algorithm for management of childhood illness (ALMANACH) either on 1) paper or 2) electronic support; 4 months after training, consultations were observed. An expert consultation was the reference for classification and treatment. Main outcomes were proportion of children checked for danger signs, and antibiotics prescription rate. A total of 504 consultations (166, 171, and 167 in control, paper, and phone arms, respectively) were observed. The use of smartphones versus paper was associated with a significant increase in children checked for danger signs (41% versus 74%, P = 0.04). Antibiotic prescriptions rate dropped from 70% in the control to 26%, and 25% in paper and electronic arms. The HWs-expert agreement on pneumonia classification remained low (expert's pneumonia identified by HWs in 26%, 30%, and 39% of patients, respectively).Mobile technology in low-income countries is implementable and has a potential to improve HWs' performance. Additional point-of-care diagnostic tests are needed to ensure appropriate management. Improving the rational use of antimicrobial is a challenge that ALMANACH can help to take up.

2. Lancet 2017;389(10065):167-175

A cleaner burning biomass-fuelled cookstove intervention to prevent pneumonia in children under 5 years old in rural Malawi (the Cooking and Pneumonia Study): a cluster randomised controlled trial

Mortimer K et al., Malawi Liverpool Wellcome Trust Programme, Blantyre, Malawi <Kevin.mortimer@lstmed.ac.uk>

Background: WHO estimates exposure to air pollution from cooking with solid fuels is associated with over 4 million premature deaths worldwide every year including half a million children under the age of 5 years from pneumonia. We hypothesised that replacing open fires with cleaner burning biomass-fuelled cookstoves would reduce pneumonia incidence in young children.
Methods: We did a community-level open cluster randomised controlled trial to compare the effects of a cleaner burning biomass-fuelled cookstove intervention to continuation of open fire cooking on pneumonia in children living in two rural districts, Chikhwawa and Karonga, of Malawi. Clusters were randomly allocated to intervention and control groups using a computer-generated randomisation schedule with stratification by site, distance from health centre, and size of cluster. Within clusters, households with a child under the age of 4·5 years were eligible. Intervention households received two biomass-fuelled cookstoves and a solar panel. The primary outcome was WHO Integrated Management of Childhood Illness (IMCI)-defined pneumonia episodes in children under 5 years of age. Efficacy and safety analyses were by intention to treat. The trial is registered with ISRCTN, number ISRCTN59448623.

Findings: We enrolled 10 750 children from 8626 households across 150 clusters between Dec 9, 2013, and Feb 28, 2016. 10 543 children from 8470 households contributed 15 991 child-years of follow-up data to the intention-to-treat analysis. The IMCI pneumonia incidence rate in the intervention group was 15·76 (95% CI 14·89-16·63) per 100 child-years and in the control group 15·58 (95% CI 14·72-16·45) per 100 child-years, with an intervention versus control incidence rate ratio (IRR) of 1·01 (95% CI 0·91-1·13; p=0·80). Cooking-related serious adverse events (burns) were seen in 19 children; nine in the intervention and ten (one death) in the control group (IRR 0·91 [95% CI 0·37-2·23]; p=0·83).
Interpretation: We found no evidence that an intervention comprising cleaner burning biomass-fuelled cookstoves reduced the risk of pneumonia in young children in rural Malawi. Effective strategies to reduce the adverse health effects of household air pollution are needed.

3. TMIH 2017;22(2):139-147
Variability of respiratory rate measurements in children suspected with non-severe pneumonia in north-east Tanzania
Muro F et al., Kilimanjaro Christian Medical University College, Moshi, Tanzania

Objective: Measurement of respiratory rate is an important clinical sign in the diagnosis of pneumonia but suffers from interobserver variation. Here, we assess the use of video recordings as a quality assurance tool that could be useful both in research and in training of staff.
Methods: Respiratory rates (RR) were recorded in children aged 2-59 months presenting with cough or difficulty breathing at two busy outpatient clinics in Tanzania. Measurements were repeated at 10-min intervals in a quiet environment with simultaneous video recordings that were independently reviewed by two paediatricians.
Results: Eight hundred and fifty-nine videos were sent to two paediatricians; 148 (17.2%) were considered unreadable by one or both. For the 711 (82.8%) videos that were readable by both paediatricians, there was perfect agreement for the presence of raised RR with a kappa value (κ) of 0.85 (P < 0.001); and in 476 (66.9%) cases, both paediatricians agreed on the RR within 2 breaths per minute (±2 bpm). A reported illness of 5 days or more was associated with unreadable video recordings (OR = 3.44, CI: 1.5-6.08; P < 0.001). The multilevel model showed that differences between observers accounted for only 13% of the variability in RR.
Conclusion: Video recordings are reliable tools for quality assurance of RR measurements in children with suspected pneumonia. Videos with a clear view of respiratory movements may also be useful in training primary healthcare staff.

Communicable diseases

4. Am J TMH 2017;Jan 23.pii:16-0671
Countrywide Reassessment of Schistosoma mansoni Infection in Burundi Using a Urine-Circulating Cathodic Antigen Rapid Test: Informing the National Control Program
Ortu G et al., Imperial College London, United Kingdom <dcolley@uga.edu>

Following implementation of the national control program, a reassessment of Schistosoma mansoni prevalence was conducted in Burundi to determine the feasibility of moving toward elimination. A countrywide cluster-randomized cross-sectional study was performed in May 2014. At least 25 schools were sampled from each of five eco-epidemiological risk zones for schistosomiasis. Fifty randomly selected children 13-14 years of age per school were included for a single urine-circulating cathodic antigen (CCA) rapid test and, in a subset of schools, for duplicate Kato-Katz slides preparation from a single stool sample. A total of 17,331 children from 347 schools were tested using CCA. The overall prevalence of S. mansoni infection, when CCA trace results were considered negative, was 13.5% (zone range [zr] = 4.6-17.8%), and when CCA trace results were considered positive, it was 42.8% (zr = 34.3-49.9%). In 170 schools, prevalence of this infection determined using Kato-Katz method was 1.5% (zr ==0-2.7%). The overall mean intensity of S. mansoni infection

determined using Kato-Katz was 0.85 eggs per gram (standard deviation = 10.86). A majority of schools (84%) were classified as non-endemic (prevalence = 0) using Kato-Katz; however, a similar proportion of schools were classified as endemic when CCA trace results were considered negative (85%) and nearly all (98%) were endemic when CCA trace results were considered positive. The findings of this nationwide reassessment using CCA rapid test indicate that Schistosoma infection is still widespread in Burundi, although its average intensity is probably low. Further evidence is now needed to determine the association between CCA rapid test positivity and low-intensity disease transmission.

5. EID 2016;22(12) and 2017;23(1)

Information about Zika

Zika Virus Infection in the Central Nervous System and Female Genital Tract (EID 2016 Dec;22(12):2228-2230)
Zika Virus Knowledge among Pregnant Women Who Were in Areas with Active Transmission (EID 2017;23(1):164-166)
Cost-effectiveness of Increasing Access to Contraception during the Zika Virus Outbreak, Puerto Rico (EID 2017;23(1):74-82)
Guillain-Barré Syndrome and Healthcare Needs during Zika Virus Transmission, Puerto Rico (EID 2017;23(1):134-136)
Persistent Zika Virus Detection in Semen in a Traveler Returning to the United Kingdom from Brazil (EID 2017;23(1):137-139)
Prolonged Detection of Zika Virus in Vaginal Secretions and Whole Blood (EID 2017;23(1):99-101)
Low Circulation of Zika Virus, Cambodia, 2007-2016 (EID 2017;23(2):296-299)

6. JAMA 2017;317(2):142-143

Editorial: Global Burden of Raised Blood Pressure

Huffman MD, Lloyd-Jones DM, Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago <dlj@northwestern.edu>

In this issue of JAMA, Forouzanfar and colleagues report updated estimates of the global burden of raised systolic blood pressure (SBP) from 1980 to 2015 using data from 844 reports of nationally representative samples comprising 8.7 million individuals from the Global Burden of Diseases, Injuries, and Risk Factors Study 2015 (GBD 2015).
These data cannot inform clinical practice guidelines regarding appropriate levels for initiation of blood pressure–lowering therapy or goal levels for treatment. However, these data strengthen the case to lower the risk for cardiovascular diseases in those with SBP of 140 mm Hg or higher by all effective means available, including improving uptake of healthy diets, minimizing weight gain or promoting weight loss in overweight and obese individuals, and promoting uptake and adherence to effective blood pressure–lowering drugs as well as management of related cardiovascular risk.
The GBD project continues to evolve and engage the medical community with its impressive scope of data. It is difficult to imagine not having a group performing global-level synthesis to provide the best estimates of disease burden. The project remains relatively new by historical standards, yet has made remarkable progress, including raising the awareness of the importance of data systems to inform and improve health. The project works to be transparent about its complex methods, which remain challenging for most readers, but it also works to encourage global participation, which has increased since the project began. Even if the extensive amounts of data are fuzzy and imperfect, they provide valuable estimates of current global disease burden.

7. Lancet 2017;389(10069):621-628

Safety and immunogenicity of a recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in Sierra Leone: a single-centre, randomised, double-blind, placebo-controlled, phase 2 trial

Zhu FC et al., Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China
Background: A recombinant adenovirus type-5 vector-based vaccine expressing the glycoprotein of Ebola Zaire Makona variant showed good safety and immunogenicity in a phase 1 trial of healthy Chinese adults. We aimed to assess the safety and immunogenicity of this vaccine in healthy adults in Sierra Leone and to determine the optimal dose.
Methods: We did a single-centre, randomised, double-blind, placebo-controlled, phase 2 clinical trial at Sierra Leone-China Friendship Hospital, Freetown, Sierra Leone. We recruited healthy adults aged 18-50 years who were HIV negative, had no history of Ebola virus infection, and had no previous immunisation with other Ebola vaccine candidates. Participants were sequentially enrolled and randomly assigned (2:1:1), by computer-generated block randomisation (block size of eight), to receive the high-dose vaccine (1·6 × 1011 viral particles), low-dose vaccine (8·0 × 1010 viral particles), or placebo (containing only vaccine excipients, with no viral particles). Participants, investigators, and study staff (except two study pharmacists) were masked from treatment allocation. The primary safety outcome was occurrence of solicited adverse reactions within 7 days of vaccination, analysed by intention to treat. The primary immunogenicity outcome was glycoprotein-specific antibody responses at days 14, 28, and 168 after vaccination, analysed in all vaccinated participants who had blood samples drawn for antibody tests. The trial is registered with the Pan African Clinical Trials Registry, number PACTR201509001259869, and is completed.
Findings: During Oct 10-28, 2015, 500 participants were enrolled and randomly assigned to receive the high-dose vaccine (n=250), low-dose vaccine (n=125), or placebo (n=125). 132 (53%) participants in the high-dose group, 60 (48%) in the low-dose group, and 54 (43%) in the placebo group reported at least one solicited adverse reaction within 7 days of vaccination. Most adverse reactions were mild and self-limiting. Solicited injection-site adverse reactions were significantly more frequent in vaccine recipients (65 [26%] in high-dose group and 31 [25%] in low-dose group) than in those receiving placebo (17 [14%]; p=0·0169). Glycoprotein-specific antibody responses were detected from day 14 onwards (geometric mean titre 1251·0 [95% CI 976·6-1602·5] in low-dose group and 1728·4 [1459·4-2047·0] in high-dose group) and peaked at day 28 (1471·8 [1151·0-1881·8] and 2043·1 [1762·4-2368·4]), but declined quickly in the following months (223·3 [148·2-336·4] and 254·2 [185·0-349·5] at day 168). Geometric mean titres in the placebo group remained around 6·0-6·8 throughout the study period. Three serious adverse events (malaria, gastroenteritis, and one fatal asthma episode) were reported in the high-dose vaccine group, but none was deemed related to the vaccine.
Interpretation: The recombinant adenovirus type-5 vector-based Ebola vaccine was safe and highly immunogenic in healthy Sierra Leonean adults, and 8·0 × 1010 viral particles was the optimal dose.

8. PLoS Med 2017;14(1):e1002203

Zika Virus Infection as a Cause of Congenital Brain Abnormalities and Guillain–Barré Syndrome: Systematic Review

Krauer F et al., and WHO Zika Causality Working Group <hc.ebinu.mpsi@wol.alocin>

Background: The World Health Organization (WHO) stated in March 2016 that there was scientific consensus that the mosquito-borne Zika virus was a cause of the neurological disorder Guillain–Barré syndrome (GBS) and of microcephaly and other congenital brain abnormalities based on rapid evidence assessments. Decisions about causality require systematic assessment to guide public health actions. The objectives of this study were to update and reassess the evidence for causality through a rapid and systematic review about links between Zika virus infection and (a) congenital brain abnormalities, including microcephaly, in the foetuses and offspring of pregnant women and (b) GBS in any population, and to describe the process and outcomes of an expert assessment of the evidence about causality.
Methods and Findings: The study had three linked components. First, in February 2016, we developed a causality framework that defined questions about the relationship between Zika virus infection and each of the two clinical outcomes in ten dimensions: temporality, biological plausibility, strength of association, alternative explanations, cessation, dose–response relationship, animal experiments, analogy, specificity, and consistency. Second, we did a systematic review (protocol number CRD42016036693). We searched multiple online sources up to May 30, 2016 to find studies

that directly addressed either outcome and any causality dimension, used methods to expedite study selection, data extraction, and quality assessment, and summarised evidence descriptively. Third, WHO convened a multidisciplinary panel of experts who assessed the review findings and reached consensus statements to update the WHO position on causality. We found 1,091 unique items up to May 30, 2016. For congenital brain abnormalities, including microcephaly, we included 72 items; for eight of ten causality dimensions (all except dose–response relationship and specificity), we found that more than half the relevant studies supported a causal association with Zika virus infection. For GBS, we included 36 items, of which more than half the relevant studies supported a causal association in seven of ten dimensions (all except dose–response relationship, specificity, and animal experimental evidence). Articles identified nonsystematically from May 30 to July 29, 2016 strengthened the review findings. The expert panel concluded that (a) the most likely explanation of available evidence from outbreaks of Zika virus infection and clusters of microcephaly is that Zika virus infection during pregnancy is a cause of congenital brain abnormalities including microcephaly, and (b) the most likely explanation of available evidence from outbreaks of Zika virus infection and GBS is that Zika virus infection is a trigger of GBS. The expert panel recognised that Zika virus alone may not be sufficient to cause either congenital brain abnormalities or GBS but agreed that the evidence was sufficient to recommend increased public health measures. Weaknesses are the limited assessment of the role of dengue virus and other possible cofactors, the small number of comparative epidemiological studies, and the difficulty in keeping the review up to date with the pace of publication of new research. **Conclusions**: Rapid and systematic reviews with frequent updating and open dissemination are now needed both for appraisal of the evidence about Zika virus infection and for the next public health threats that will emerge. This systematic review found sufficient evidence to say that Zika virus is a cause of congenital abnormalities and is a trigger of GBS.

Essential medicines

9. JAMA 2017;317(5):473-474

Privatized Pharmaceutical Innovation vs Access to Essential Medicines A Global Framework for Equitable Sharing of Benefits

Burci GL, Gostin LO, Georgetown University Law Center, O'Neill Institute for National and Global Health Law, Washington <gostin@law.georgetown.edu>

The effect of the current privatized model of pharmaceutical innovation on the development and affordability of lifesaving vaccines and medicines has been an enduring source of conflict. The need to promote and reward the development of new drugs and devices through patent protection—and the high prices this promotion and protection generate—seem to adversely affect equitable access to essential medicines and the right to health. Throughout the world, even in the United States, the high cost of pharmaceuticals provokes controversy, as is evident with the pricing of the epinephrine injection (EpiPen) and ledipasvir/sofosbuvir (Harvoni).

The global landscape on innovation and access to medicines is fragmented and inequitable. The price of antiretroviral agents to treat human immunodeficiency virus/AIDS, for example, has declined precipitously, but equally important medicines cost far too much for health care systems. For example, in the United States, the price of a standard nondiscounted 12-week course of Harvoni to treat hepatitis C is $84 000. The privatized model for pharmaceutical innovation also is not producing treatments for neglected diseases such as dengue and leishmaniasis, vaccines for diseases with pandemic potential such as Ebola, and new antimicrobials to address the growing problem of drug resistance.

On September 14, the United Nations Secretary-General's High-Level Panel on Access to Medicines sought to close the gap between privatized innovation and affordability of pharmaceuticals. Intense disagreements between public interest organizations and industry—between high- and lower-income countries—revealed the entrenched economic and social interests at stake, with the outcome potentially affecting millions of lives. The disagreements became evident on November 8, when the World Trade Organization (WTO), the international organization managing the global rules of trade and adjudicating trade disputes, discussed the high-level report. The findings of the report were also considered, and generated disagreement and heated discussions, in the UN General Assembly and the

Programme Coordinating Board of UNAIDS, the UN Joint Programme on HIV/AIDS. The report has also been proposed for discussion in the World Health Organization (WHO) Executive Board at the end of January 2017. In this Viewpoint we offer a global framework to foster coherence, enhancing incentives for innovation while ensuring equitable access.

10. Lancet 2017;389(10067):403-476

Essential medicines for universal health coverage

Wirtz VJ 1, Hogerzeil HV2, et al., 1Department of Global Health/Center for Global Health and Development, Boston University School of Public Health, Boston, MA, USA <vwirtz@bu.edu> 2Global Health Unit, University Medical Centre Groningen, University of Groningen, Groningen, Netherlands

Essential medicines satisfy the priority health-care needs of the population. Essential medicines policies are crucial to promoting health and achieving sustainable development. Sustainable Development Goal 3.8 specifically mentions the importance of "access to safe, effective, quality and affordable essential medicines and vaccines for all" as a central component of Universal Health Coverage (UHC), and Sustainable Development Goal 3.b emphasises the need to develop medicines to address persistent treatment gaps.

The recognition of the importance of essential medicines is not new. At the 1985 Nairobi Conference on the Rational Use of Drugs, government representatives and other stakeholders proposed a comprehensive set of essential medicines policies. 30 years later, The Lancet's Commission on Essential Medicines Policies convened to explore these questions: what progress has been achieved? What challenges remain to be addressed? Which lessons have been learned to inform future approaches? And how can essential medicines policies be harnessed to promote UHC and contribute to the global sustainable development agenda? This report addresses these questions, with the intent to reposition essential medicines policies on the global development agenda.

The Commission identified five areas that are crucial to essential medicines policies: paying for a basket of essential medicines, making essential medicines affordable, assuring the quality and safety of medicines, promoting quality use of medicines, and developing missing essential medicines. The Commission located essential medicines policies within the context of current global debates about balancing trade and intellectual property policies with human rights, assuring health security, strengthening people-centred health systems, and advancing access to essential technologies. In all policy areas, particular attention was paid to furthering equity in access, strengthening relevant institutions, and creating accountability. For each policy area, the Commission made actionable recommendations, thereby reaffirming essential medicines policies as a central pillar of the global health and development agenda.

A future of accountability for essential medicines policies

The Commission is confident that new endeavours to create an independent accountability system, supported by the global community, will ensure that crucial actions are taken to protect investments made in essential medicines, and that these investments translate into health and development for all. Without essential medicines, no health system can ensure that the population it serves progressively realises its right to health. Yet essential medicines policies have received insufficient attention since the Nairobi conference in 1985. In this report the Commission presents practical recommendations that will enable a new era of equity, strengthened institutions, and accountability to ensure that essential medicines policies support UHC and sustainable development in the 21st century.

Health Policy / Health Financing

11. BMJ 2017;356:i6699 Research

Cost effectiveness of a government supported policy strategy to decrease sodium intake: global analysis across 183 nations

Webb M et al., Correspondence to Mozaffarian D <dariush.mozaffarian@tufts.edu>

Objective To quantify the cost effectiveness of a government policy combining targeted industry agreements and public education to reduce sodium intake in 183 countries worldwide.
Design Global modeling study.
Setting 183 countries.
Population Full adult population in each country.
Intervention A "soft regulation" national policy that combines targeted industry agreements, government monitoring, and public education to reduce population sodium intake, modeled on the recent successful UK program. To account for heterogeneity in efficacy across countries, a range of scenarios were evaluated, including 10%, 30%, 0.5 g/day, and 1.5 g/day sodium reductions achieved over 10 years. We characterized global sodium intakes, blood pressure levels, effects of sodium on blood pressure and of blood pressure on cardiovascular disease, and cardiovascular disease rates in 2010, each by age and sex, in 183 countries. Country specific costs of a sodium reduction policy were estimated using the World Health Organization Noncommunicable Disease Costing Tool. Country specific impacts on mortality and disability adjusted life years (DALYs) were modeled using comparative risk assessment. We only evaluated program costs, without incorporating potential healthcare savings from prevented events, to provide conservative estimates of cost effectiveness Main outcome measure Cost effectiveness ratio, evaluated as purchasing power parity adjusted international dollars (equivalent to the country specific purchasing power of US$) per DALY saved over 10 years.
Results Worldwide, a 10% reduction in sodium consumption over 10 years within each country was projected to avert approximately 5.8 million DALYs/year related to cardiovascular diseases, at a population weighted mean cost of I$1.13 per capita over the 10 year intervention. The population weighted mean cost effectiveness ratio was approximately I$204/DALY. Across nine world regions, estimated cost effectiveness of sodium reduction was best in South Asia (I$116/DALY); across the world's 30 most populous countries, best in Uzbekistan (I$26.08/DALY) and Myanmar (I$33.30/DALY). Cost effectiveness was lowest in Australia/New Zealand (I$880/DALY, or 0.02×gross domestic product (GDP) per capita), although still substantially better than standard thresholds for cost effective (<3.0×GDP per capita) or highly cost effective (<1.0×GDP per capita) interventions. Most (96.0%) of the world's adult population lived in countries in which this intervention had a cost effectiveness ratio <0.1×GDP per capita, and 99.6% in countries with a cost effectiveness ratio <1.0×GDP per capita.
Conclusion A government "soft regulation" strategy combining targeted industry agreements and public education to reduce dietary sodium is projected to be highly cost effective worldwide, even without accounting for potential healthcare savings.

12. HPP 2016;31(10):1515–1529

Models of public–private engagement for health services delivery and financing in Southern Africa: a systematic review

Whyle EB et al., School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa < eleanorbethwhyle@gmail.com>

In low- and middle-income countries (LMICs), the private sector—including international donors, non-governmental organizations, for-profit providers and traditional healers—plays a significant role in health financing and delivery. The use of the private sector in furthering public health goals is increasingly common. By working with the private sector through public–private engagement (PPE), states can harness private sector resources to further public health goals. PPE initiatives can take a variety of forms and understanding of these models is limited. This paper presents the results of a Campbell systematic literature review conducted to establish the types and the prevalence of PPE projects for health service delivery and financing in Southern Africa. PPE initiatives identified through the review were categorized according to a PPE typology. The review reveals that the full range of PPE models, eight distinct models, are utilized in the Southern African context. The distribution of the available evidence—including significant gaps in the literature—is discussed, and key considerations for researchers, implementers, and current and potential PPE partners are presented. It was found that the literature is disproportionately representative of PPE initiatives located in South Africa, and of

those that involve for-profit partners and international donors. A significant gap in the literature identified through the study is the scarcity of information regarding the relationship between international donors and national governments. This information is key to strengthening these partnerships, improving partnership outcomes and capacitating recipient countries. The need for research that disaggregates PPE models and investigates PPE functioning in context is demonstrated.

13. HPP 2016;31(10):1530–1547

A scoping review of cost benefit analysis in reproductive, maternal, newborn and child health: What we know and what are the gaps?

Maitra C et al., School of Economics, The University of Queensland, St Lucia Campus, Brisbane, Australia <c.maitra@uq.edu.au> <chandana.maitra@uqconnect.edu.au>

Growing evidence suggests that early life investments in health are associated with improved human capital and economic outcomes. Various recent global studies have simulated the expected economic returns from alternative packages of interventions in reproductive, maternal, newborn and child health (RMNCH). However, very little is known about the comparability of estimates of the economic returns of RMNCH interventions across studies in low and middle income countries. Our study aims to fill this gap. We performed a comprehensive scoping review of the recent literature (2000- 2013) on the economic returns (i.e. benefit-cost ratios) of RMNCH-related interventions, conducted in low and middle income countries. A total of 36 studies were identified. They were read in full and information was abstracted on both the estimates of benefit-cost ratios, the methodological approach and assumptions used. The estimated economic returns fluctuated considerably across settings as the associated costs of disease patterns, social behaviours and health systems varied. Yet, greater sources of variation stemmed from differences in methodology. The observed methodological inconsistencies limit the accuracy and comparability of the estimated returns across various contexts. The reviewed studies suggest that the benefit-cost ratios are favourable in the majority of cases, providing further support to a growing body of economic literature that suggests investments early in life, such as those interventions related to RMNCH, are good investments. Beyond advocacy purposes, for the reviewed literature to be used by policymakers to inform their decisions on investments, a consistent methodological approach should be adopted.

14. HPP 2017;32(2):236–247

Delivery fee exemption and subsidy policies: how have they affected health staff? Findings from a four-country evaluation

Witter S et al., Institute for Global Health and Development, Queen Margaret University, Musselburgh, Edinburgh <switter@qmu.ac.uk>

Many countries, especially in Africa, have in recent years introduced fee exemptions or subsidies targeting deliveries and emergency obstetric care. A number of aspects of these policies have been studied but there are few studies which look at how staff have been affected and how they have responded. This article focuses on this question, comparing data from Benin, Burkina Faso, Mali and Morocco. It is nested in wider evaluation of the policies. The article analyses responses to a health worker survey, carried out in 2012 on 683 health staff (doctors, nurses, midwives and others such as auxiliaries) across the four countries. The survey focused on working hours, workloads, pay, motivation and perceptions of the policies, as well as reported changes in workload and remuneration over the period of policy introduction. Self-reported staff output ratios suggest that midwives are over-worked across all settings, but facility data presents lower estimates, making it hard to judge the adequacy of workforces. Staff are generally positive about the policies' effects on the health system (increasing supervised delivery rates, benefiting the poor, improving access to medicines and supplies and improving quality of care). In personal terms, staff in Mali and Burkina Faso report increased satisfaction with work as a result of the policies, while in Benin, there is little change and in Morocco a deterioration (which correlated with recommendations about extending exemption policies in future). Awareness of policies was high amongst staff but only a small minority had received any written

guides or training on policy implementation. It is crucial that planned health financing changes engage with their implications for staffing—estimating whether specific cadres can absorb increase demand, for example, as well as how to engage them in the policy implementation such that their personal needs are met and their professionalism enhanced.

15. HPP 2017;32(2):267–276

Indonesia's road to universal health coverage: a political journey

Pisani E, Kok MO et al., <m.o.kok@vu.nl>

In 2013 Indonesia, the world's fourth most populous country, declared that it would provide affordable health care for all its citizens within seven years. This crystallised an ambition first enshrined in law over five decades earlier, but never previously realised. This paper explores Indonesia's journey towards universal health coverage (UHC) from independence to the launch of a comprehensive health insurance scheme in January 2014. We find that Indonesia's path has been determined largely by domestic political concerns – different groups obtained access to healthcare as their socio-political importance grew. A major inflection point occurred following the Asian financial crisis of 1997. To stave off social unrest, the government provided health coverage for the poor for the first time, creating a path dependency that influenced later policy choices. The end of this programme coincided with decentralisation, leading to experimentation with several different models of health provision at the local level. When direct elections for local leaders were introduced in 2005, popular health schemes led to success at the polls. UHC became an electoral asset, moving up the political agenda. It also became contested, with national policy-makers appropriating health insurance programmes that were first developed locally, and taking credit for them. The Indonesian experience underlines the value of policy experimentation, and of a close understanding of the contextual and political factors that drive successful UHC models at the local level. Specific drivers of success and failure should be taken into account when scaling UHC to the national level. In the Indonesian example, UHC became possible when the interests of politically and economically influential groups were either satisfied or neutralised. While technical considerations took a back seat to political priorities in developing the structures for health coverage nationally, they will have to be addressed going forward to achieve sustainable UHC in Indonesia.

16. Lancet 2017;Jan 6:pii:S0140-6736(16)32586-7

Levers for addressing medical underuse and overuse: achieving high-value health care

Elshaug AG et al., Menzies Centre for Health Policy, The University of Sydney, Australia <elshaug@sydney.edu.au>

The preceding papers in this Series have outlined how underuse and overuse of health-care services occur within a complex system of health-care production, with a multiplicity of causes. Because poor care is ubiquitous and has considerable consequences for the health and wellbeing of billions of people around the world, remedying this problem is a morally and politically urgent task. Universal health coverage is a key step towards achieving the right care. Therefore, full consideration of potential levers of change must include an upstream perspective-ie, an understanding of the system-level factors that drive overuse and underuse, as well as the various incentives at work during a clinical encounter. One example of a system-level factor is the allocation of resources (eg, hospital beds and clinicians) to meet the needs of a local population to minimise underuse or overuse. Another example is priority setting using tools such as health technology assessment to guide the optimum diffusion of safe, effective, and cost-effective health-care services. In this Series paper we investigate a range of levers for eliminating medical underuse and overuse. Some levers could operate effectively (and be politically viable) across many different health and political systems (eg, increase patient activation with decision support) whereas other levers must be tailored to local contexts (eg, basing coverage decisions on a particular cost-effectiveness ratio). Ideally, policies must move beyond the purely incremental; that is, policies that merely tinker at the policy edges after underuse or overuse arises. In this regard, efforts to increase public awareness, mobilisation, and empowerment hold promise as

universal methods to reset all other contexts and thereby enhance all other efforts to promote the right care.
Other papers of this Series in the Lancet 2017; Jan 6:

- Drivers of poor medical care
- Evidence for overuse of medical services around the world Lancet
- Evidence for underuse of effective medical services around the world
- Addressing overuse and underuse around the world

17. Lancet 2017;389(10068):559-570

Improving the health and welfare of people who live in slums

Lilford RJ et al., Warwick Centre for Applied Health Research and Delivery, University of Warwick, Coventry, UK <r.j.lilford@warwick.ac.uk>

In the first paper in this Series we assessed theoretical and empirical evidence and concluded that the health of people living in slums is a function not only of poverty but of intimately shared physical and social environments. In this paper we extend the theory of so-called neighbourhood effects. Slums offer high returns on investment because beneficial effects are shared across many people in densely populated neighbourhoods. Neighbourhood effects also help explain how and why the benefits of interventions vary between slum and non-slum spaces and between slums. We build on this spatial concept of slums to argue that, in all low-income and-middle-income countries, census tracts should henceforth be designated slum or non-slum both to inform local policy and as the basis for research surveys that build on censuses. We argue that slum health should be promoted as a topic of enquiry alongside poverty and health.
The first paper in this Series: Lancet 2017;389(10068):547-558
The history, geography, and sociology of slums and the health problems of people who live in slums

18. TMIH 2017;22(1):12-20

Household experience and costs of seeking measles vaccination in rural Guinea-Bissau

Byberg S et al., Bandim Health Project, Indepth Network, Bissau, Guinea-Bissau

Objectives: Children younger than 12 months of age are eligible for childhood vaccines through the public health system in Guinea-Bissau. To limit open vial wastage, a restrictive vial opening policy has been implemented; 10-dose measles vaccine vials are only opened if six or more children aged 9-11 months are present at the vaccination post. Consequently, mothers who bring their child for measles vaccination can be told to return another day. We aimed to describe the household experience and estimate household costs of seeking measles vaccination in rural Guinea-Bissau.
Methods: Within a national sample of village clusters under demographic surveillance, we interviewed mothers of children aged 9-21 months about their experience with seeking measles vaccination. From information about time and money spent, we calculated household costs of seeking measles vaccination.
Results: We interviewed mothers of 1308 children of whom 1043 (80%) had sought measles vaccination at least once. Measles vaccination coverage was 70% (910/1308). Coverage decreased with increasing distance to the health centre. On average, mothers who had taken their child for vaccination took their child 1.4 times. Mean costs of achieving 70% coverage were 2.04 USD (SD 3.86) per child taken for vaccination. Half of the mothers spent more than 2 h seeking vaccination and 11% spent money on transportation.
Conclusions: We found several indications of missed opportunities for measles vaccination resulting in suboptimal coverage. The household costs comprised 3.3% of the average monthly income and should be taken into account when assessing the costs of delivering vaccinations.

19. TMIH 2017;22(1):74-81

Costs of diarrhoea and acute respiratory infection attributable to not handwashing: the cases of India and China
Townsend J et al., Department of Social and Environmental Health Research, London School of Hygiene and Tropical Medicine, UK

Objective: To estimate the national costs relating to diarrhoea and acute respiratory infections from not handwashing with soap after contact with excreta and the costs and benefits of handwashing behaviour change programmes in India and China.
Methods: Data on the reduction in risk of diarrhoea and acute respiratory infection attributable to handwashing with soap were used, together with World Health Organization (WHO) estimates of disability-adjusted life years (DALYs) due to diarrhoea and acute respiratory infection, to estimate DALYs due to not handwashing in India and China. Costs and benefits of behaviour change handwashing programmes and the potential returns to investment are estimated valuing DALYs at per capita GDP for each country.
Results: Annual net costs to India from not handwashing are estimated at US$ 23 billion (16-35) and to China at US$ 12 billion (7-23). Expected net returns to national behaviour change handwashing programmes would be US$ 5.6 billion (3.4-8.6) for India at US$ 23 (16-35) per DALY avoided, which represents a 92-fold return to investment, and US$ 2.64 billion (2.08-5.57) for China at US$ 22 (14-31) per DALY avoided - a 35-fold return on investment.
Conclusion: Our results suggest large economic gains relating to decreases in diarrhoea and acute respiratory infection for both India and China from behaviour change programmes to increase handwashing with soap in households.

20. TMIH 2017;22(1):92-102
Improving quality of care through payment for performance: examining effects on the availability and stock-out of essential medical commodities in Tanzania
Binyaruka P et al., Ifakara Health Institute, Dar es Salaam, Tanzania

Objective: To evaluate the effects of payment for performance (P4P) on the availability and stock-out rate of reproductive, maternal, newborn and child health (RMNCH) medical commodities in Tanzania and assess the distributional effects.
Methods: The availability of RMNCH commodities (medicines, supplies and equipment) on the day of the survey, and stock-outs for at least one day in the 90 days prior to the survey, was measured in 75 intervention and 75 comparison facilities in January 2012 and 13 months later. Composite scores for each subgroup of commodities were generated. A difference-in-differences linear regression was used to estimate the effect of P4P on outcomes and differential effects by facility location, level of care, ownership and socio-economic status of the catchment population.
Results: We estimated a significant increase in the availability of medicines by 8.4 percentage points (P = 0.002) and an 8.3 percentage point increase (P = 0.050) in the availability of medical supplies. P4P had no effect on the availability of functioning equipment. Most items with a significant increase in availability also showed a significant reduction in stock-outs. Effects were generally equally distributed across facilities, with effects on stock-outs of many medicines being pro-poor, and greater effects in facilities in rural compared to urban districts.
Conclusion: P4P can improve the availability of medicines and medical supplies, especially in poor, rural areas, when these commodities are incentivised at both facility and district levels, making services more acceptable, effective and affordable, enhancing progress towards universal health coverage.

HIV / AIDS

21. TMIH 2017;22(2):161-170

Retention in care and reasons for discontinuation of lifelong antiretroviral therapy in a cohort of Cameroonian pregnant and breastfeeding HIV-positive women initiating 'Option B+' in the South West Region

Atanga PN et al., Department of Public Health and Hygiene, University of Buea, Cameroon

Objective: To assess linkage and retention in care along the PMTCT cascade in HIV-positive pregnant and breastfeeding women initiating Option B+ in Cameroon.
Methods: We prospectively determined uptake of HIV testing and counselling (HTC), uptake of ART and retention in care after Option B+ initiation between October 2013 and December 2014 in pregnant and breastfeeding women from five sites within the Kumba Health District. Retention in care was assessed over at least 12 months follow-up and estimated by Kaplan-Meier analysis. During follow-up, tracing outcomes and reasons for discontinuing treatment were documented.
Results: The uptake of HTC of 5813 women with unknown HIV status was 98.5%, 251 (4.4%) were newly diagnosed HIV positive, and ART uptake in women eligible to start Option B+ was 96.8%. We enrolled 268 women initiating lifelong ART in the follow-up. Overall, 65 (24.3%) discontinued treatment, either defined by loss to follow-up (44.6%) or actively stopped treatment (55.8%). Retention in care was 88.0% and 81.1% at 6 and 12 months, respectively. Discontinuation was significantly associated in multivariate analysis with small sites and high staff turnover [aOR 2.5 (95% CI 1.6, 3.9), P < 0.001]. Main reasons for stopping treatment were HIV status denial and stigma (52.8%), religious reasons (25.0%) and lack of transport fare (11.1%).
Conclusion: We observed good uptake of HTC, ART and retention in care, which declined over time. Discontinuation of Option B+ was highest at small sites with a high staff turnover. Improved staffing, adequate task shifting and community interventions to track defaulters including reducing stigma and religious beliefs may improve Option B+ retention.

22. TMIH 2017;22(2):221-231

Treatment outcomes of over 1000 patients on second-line, protease inhibitor-based antiretroviral therapy from four public-sector HIV treatment facilities across Johannesburg, South Africa

Shearer K et al., Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Objectives: To report predictors of outcomes of second-line ART for HIV treatment in a resource-limited setting.
Methods: All adult ART-naïve patients who initiated standard first-line treatment between April 2004 and February 2012 at four public-sector health facilities in Johannesburg, South Africa, experienced virologic failure and initiated standard second-line therapy were included. We assessed predictors of attrition (death and loss to follow-up [≥3 months late for a scheduled visit]) using Cox proportional hazards regression and predictors of virologic suppression (viral load <400 copies/ml ≥3 months after switch) using modified Poisson regression with robust error estimation at 1 year and ever after second-line ART initiation.
Results: A total of 1236 patients switched to second-line treatment in a median (IQR) of 1.9 (0.9-4.6) months after first-line virologic failure. Approximately 13% and 45% of patients were no longer in care at 1 year and at the end of follow-up, respectively. Patients with low CD4 counts (<50 vs. ≥200, aHR: 1.85; 95% CI: 1.03-3.32) at second-line switch were at greater risk for attrition by the end of follow-up. About 75% of patients suppressed by 1 year, and 85% had ever suppressed by the end of follow-up.
Conclusions: Patients with poor immune status at switch to second-line ART were at greater risk of attrition and were less likely to suppress. Additional adherence support after switch may improve outcomes.

23. TMIH 2017;22(2):241-251

Tenofovir stock shortages have limited impact on clinic- and patient-level HIV treatment outcomes in public sector clinics in South Africa

Brennan AT et al., Boston University School of Public Health, USA

Objective: Using data from four public sector clinics in South Africa, we sought to investigate provider- and patient-level outcomes, to understand how the 2012 tenofovir stock shortage affected the HIV care and monitoring of ART patients.
Methods: Prospective cohort analysis of ART-naïve, non-pregnant, HIV-infected patients >18 years initiating first-line ART between 1 July 2011-31 March 2013. Linear regression was used for all outcomes (number of ART initiates, days between pharmacy visits, transfers, single-drug substitutions, treatment interruptions, missed pharmacy visits, loss to follow-up and elevated viral load). We fit splines to smooth curves with knots at the beginning (1 February 2012) and end (31 August 2012) of the stock shortage and displayed results graphically by clinic. Difference-in-difference models were used to evaluate the effect of the stock shortage on outcomes.
Results: Results suggest a potential shift in the management of patients during the shortage, mainly fewer average days between visits during the shortage vs. before or after at all four clinics, and a significant difference in the proportion of patients missing visits during vs. before (RD: 1.2%; 95% CI: 0.5%, 2.0%). No significant difference was seen in other outcomes.
Conclusion: While South Africa has made great strides to extend access to ART and increase the quality of the health services provided, patient care can be affected when stock shortages/outs occur. While our results show little effect on treatment outcomes, this most likely reflects the clinics' ability to mitigate the crisis by continuing to keep patient care and treatment as consistent as possible.

Malaria

24. Am J TMH 2016;95(6):1228-1238

Plasmodium falciparum Resistance to Artemisinin Derivatives and Piperaquine: A Major Challenge for Malaria Elimination in Cambodia

Duru V et al., Malaria Molecular Epidemiology Unit, Institut Pasteur in Cambodia, Phnom Penh, Cambodia <dmenard@pasteur-kh.org>

Artemisinin-based combination therapies (ACTs) are the cornerstone of current strategies for fighting malaria. Over the last decade, ACTs have played a major role in decreasing malaria burden. However, this progress is being jeopardized by the emergence of artemisinin-resistant Plasmodium falciparum parasites. Artemisinin resistance was first detected in western Cambodia in 2008 and has since been observed in neighboring countries in southeast Asia. The problem of antimalarial drug resistance has recently worsened in Cambodia, with reports of parasites resistant to piperaquine, the latest generation of partner drug used in combination with dihydroartemisinin, leading to worrying rates of clinical treatment failure. The monitoring and the comprehension of both types of resistance are crucial to prevent the spread of multidrug-resistant parasites outside southeast Asia, and particularly to Africa, where the public health consequences would be catastrophic. To this end, new tools are required for studying the biological and molecular mechanisms underlying resistance to antimalarial drugs and for monitoring the geographic distribution of the resistant parasites. In this review, we detail the major advances in our understanding of resistance to artemisinin and piperaquine and define the challenges that the malaria community will have to face in the coming years.

25. Am J TMH 2016;95(6 Suppl):52-61

Attacking Plasmodium vivax. Costs and Cost-Effectiveness of Plasmodium vivax Control

White MT et al., Imperial College London, United Kingdom < m.white08@imperial.ac.uk>

Epidemiology, Imperial College London, London, United Kingdom. m.white08@imperial.ac.uk.

The continued success of efforts to reduce the global malaria burden will require sustained funding for interventions specifically targeting Plasmodium vivax The optimal use of limited financial resources necessitates cost and cost-effectiveness analyses of strategies for diagnosing and treating P. vivax and vector control tools. Herein, we review the existing published evidence on the costs and cost-effectiveness of interventions for controlling P. vivax, identifying nine studies focused on diagnosis and treatment and seven studies focused on vector control. Although many of the results from the much more extensive P. falciparum literature can be applied to P. vivax, it is not always possible to extrapolate results from P. falciparum-specific cost-effectiveness analyses. Notably, there is a need for additional studies to evaluate the potential cost-effectiveness of radical cure with primaquine for the prevention of P. vivax relapses with glucose-6-phosphate dehydrogenase testing.

Mental Health

26. Lancet 2016;388(10063):3074-3084

The magnitude of and health system responses to the mental health treatment gap in adults in India and China

Patel V et al., London School of Hygiene & Tropical Medicine, London, UK

This Series paper describes the first systematic effort to review the unmet mental health needs of adults in China and India. The evidence shows that contact coverage for the most common mental and substance use disorders is very low. Effective coverage is even lower, even for severe disorders such as psychotic disorders and epilepsy. There are vast variations across the regions of both countries, with the highest treatment gaps in rural regions because of inequities in the distribution of mental health resources, and variable implementation of mental health policies across states and provinces. Human and financial resources for mental health are grossly inadequate with less than 1% of the national health-care budget allocated to mental health in either country. Although China and India have both shown renewed commitment through national programmes for community-oriented mental health care, progress in achieving coverage is far more substantial in China. Improvement of coverage will need to address both supply-side barriers and demand-side barriers related to stigma and varying explanatory models of mental disorders. Sharing tasks with community-based workers in a collaborative stepped-care framework is an approach that is ripe to be scaled up, in particular through integration within national priority health programmes. India and China need to invest in increasing demand for services through active engagement with the community, to strengthen service user leadership and ensure that the content and delivery of mental health programmes are culturally and contextually appropriate.

27. Lancet 2017;389(10065):176-185

The Healthy Activity Program (HAP), a lay counsellor-delivered brief psychological treatment for severe depression, in primary care in India: a randomised controlled trial

Patel V et al., Sangath Centre, Socorro Village, Bardez-Goa, Goa, India <vikram.patel@lshtm.ac.uk>

Background: Although structured psychological treatments are recommended as first-line interventions for depression, only a small fraction of people globally receive these treatments because of poor access in routine primary care. We assessed the effectiveness and cost-effectiveness of a brief psychological treatment (Healthy Activity Program [HAP]) for delivery by lay counsellors to patients with moderately severe to severe depression in primary health-care settings.
Methods: In this randomised controlled trial, we recruited participants aged 18-65 years scoring more than 14 on the Patient Health Questionnaire 9 (PHQ-9) indicating moderately severe to severe depression from ten primary health centres in Goa, India. Pregnant women or patients who needed urgent medical attention or were unable to communicate clearly were not eligible. Participants were randomly allocated (1:1) to enhanced usual care (EUC) alone or EUC combined with HAP in randomly sized blocks (block size four to six [two to four for men]), stratified by primary health centre and sex, and allocation was concealed with use of sequential numbered opaque envelopes. Physicians

providing EUC were masked. Primary outcomes were depression symptom severity on the Beck Depression Inventory version II and remission from depression (PHQ-9 score of <10) at 3 months in the intention-to-treat population, assessed by masked field researchers. Secondary outcomes were disability, days unable to work, behavioural activation, suicidal thoughts or attempts, intimate partner violence, and resource use and costs of illness. We assessed serious adverse events in the per-protocol population. This trial is registered with the ISRCTN registry, number ISRCTN95149997.
Findings: Between Oct 28, 2013, and July 29, 2015, we enrolled and randomly allocated 495 participants (247 [50%] to the EUC plus HAP group [two of whom were subsequently excluded because of protocol violations] and 248 [50%] to the EUC alone group), of whom 466 (95%) completed the 3 month primary outcome assessment (230 [49%] in the EUC plus HAP group and 236 [51%] in the EUC alone group). Participants in the EUC plus HAP group had significantly lower symptom severity (Beck Depression Inventory version II in EUC plus HAP group 19·99 [SD 15·70] vs 27·52 [13·26] in EUC alone group; adjusted mean difference -7·57 [95% CI -10·27 to -4·86]; p<0·0001) and higher remission (147 [64%] of 230 had a PHQ-9 score of <10 in the HAP plus EUC group vs 91 [39%] of 236 in the EUC alone group; adjusted prevalence ratio 1·61 [1·34-1·93]) than did those in the EUC alone group. EUC plus HAP showed better results than did EUC alone for the secondary outcomes of disability (adjusted mean difference -2·73 [-4·39 to -1·06]; p=0·001), days out of work (-2·29 [-3·84 to -0·73]; p=0·004), intimate partner physical violence in women (0·53 [0·29-0·96]; p=0·04), behavioural activation (2·17 [1·34-3·00]; p<0·0001), and suicidal thoughts or attempts (0·61 [0·45-0·83]; p=0·001). The incremental cost per quality-adjusted life-year gained was $9333 (95% CI 3862-28 169; 2015 international dollars), with an 87% chance of being cost-effective in the study setting. Serious adverse events were infrequent and similar between groups (nine [4%] in the EUC plus HAP group vs ten [4%] in the EUC alone group; p=1·00).
Interpretation: HAP delivered by lay counsellors plus EUC was better than EUC alone was for patients with moderately severe to severe depression in routine primary care in Goa, India. HAP was readily accepted by this previously untreated population and was cost-effective in this setting. HAP could be a key strategy to reduce the treatment gap for depressive disorders, the leading mental health disorder worldwide.

28. Lancet 2017;389(10065):186-195
Counselling for Alcohol Problems (CAP), a lay counsellor-delivered brief psychological treatment for harmful drinking in men, in primary care in India: a randomised controlled trial
Nadkarni A et al., Sangath Centre, Socorro Village, Bardez-Goa, Goa, India

Background: Although structured psychological treatments are recommended as first-line interventions for harmful drinking, only a small fraction of people globally receive these treatments because of poor access in routine primary care. We assessed the effectiveness and cost-effectiveness of Counselling for Alcohol Problems (CAP), a brief psychological treatment delivered by lay counsellors to patients with harmful drinking attending routine primary health-care settings.
Methods: In this randomised controlled trial, we recruited male harmful drinkers defined by an Alcohol Use Disorders Identification Test (AUDIT) score of 12-19 who were aged 18-65 years from ten primary health centres in Goa, India. We excluded patients who needed emergency medical treatment or inpatient admission, who were unable to communicate clearly, and who were intoxicated at the time of screening. Participants were randomly allocated (1:1) by trained health assistants based at the primary health centres to enhanced usual care (EUC) alone or EUC combined with CAP, in randomly sized blocks of four to six, stratified by primary health centre, and allocation was concealed with use of sequential numbered opaque envelopes. Physicians providing EUC and those assessing outcomes were masked. Primary outcomes were remission (AUDIT score of <8) and mean daily alcohol consumed in the past 14 days, at 3 months. Secondary outcomes were the effect of drinking, disability score, days unable to work, suicide attempts, intimate partner violence, and resource use and costs of illness. Analyses were on an intention-to-treat basis. We used logistic regression analysis for remission and zero-inflated negative binomial regression analysis for alcohol consumption. We assessed serious adverse events in the per-protocol population. This trial is registered with the ISCRTN registry, number ISRCTN76465238.

Findings: Between Oct 28, 2013, and July 29, 2015, we enrolled and randomly allocated 377 participants (188 [50%] to the EUC plus CAP group and 190 [50%] to the EUC alone group [one of whom was subsequently excluded because of a protocol violation]), of whom 336 (89%) completed the 3 month primary outcome assessment (164 [87%] in the EUC plus CAP group and 172 [91%] in the EUC alone group). The proportion with remission (59 [36%] of 164 in the EUC plus CAP group vs 44 [26%] of 172 in the EUC alone group; adjusted prevalence ratio 1·50 [95% CI 1·09-2·07]; p=0·01) and the proportion abstinent in the past 14 days (68 [42%] vs 31 [18%]; adjusted odds ratio 3·00 [1·76-5·13]; p<0·0001) were significantly higher in the EUC plus CAP group than in the EUC alone group, but we noted no effect on mean daily alcohol consumed in the past 14 days among those who reported drinking in this period (37·0 g [SD 44·2] vs 31·0 g [27·8]; count ratio 1·08 [0·79-1·49]; p=0·62). We noted an effect on the percentage of days abstinent in the past 14 days (adjusted mean difference [AMD] 16·0% [8·1-24·1]; p<0·0001), but no effect on the percentage of days of heavy drinking (AMD -0·4% [-5·7 to 4·9]; p=0·88), the effect of drinking (Short Inventory of Problems score AMD-0·03 [-1·93 to 1·86]; p=0.97), disability score (WHO Disability Assessment Schedule score AMD 0·62 [-0·62 to 1·87]; p=0·32), days unable to work (no days unable to work adjusted odds ratio 1·02 [0·61-1·69]; p=0.95), suicide attempts (adjusted prevalence ratio 1·8 [-2·4 to 6·0]; p=0·25), and intimate partner violence (adjusted prevalence ratio 3·0 [-10·4 to 4·4]; p=0·57). The incremental cost per additional remission was $217 (95% CI 50-1073), with an 85% chance of being cost-effective in the study setting. We noted no significant difference in the number of serious adverse events between the two groups (six [4%] in the EUC plus CAP group vs 13 [8%] in the EUC alone group; p=0·11).
Interpretation: CAP delivered by lay counsellors plus EUC was better than EUC alone was for harmful drinkers in routine primary health-care settings, and might be cost-effective. CAP could be a key strategy to reduce the treatment gap for alcohol use disorders, one of the leading causes of the global burden among men worldwide.

Sexual Reproductive Health

29. Lancet 2016;388(10061):2811-2824

Reproductive, maternal, newborn, and child health: key messages from Disease Control Priorities 3rd Edition

Black RE et al., Johns Hopkins Bloomberg School of Public Health, Baltimore, USA <rblack1@jhu.edu>

As part of Disease Control Priorities 3rd Edition, the World Bank will publish a volume on Reproductive, Maternal, Newborn, and Child Health that identifies essential cost-effective health interventions that can be scaled up to reduce maternal, newborn, and child deaths, and stillbirths. This Review summarises the volume's key findings and estimates the effect and cost of expanded implementation of these interventions. Recognising that a continuum of care from the adolescent girl, woman, or mother to child is needed, the volume includes details of preventive and therapeutic health interventions in integrated packages: Maternal and Newborn Health and Child Health (along with folic acid supplementation, a key reproductive health intervention). Scaling up all interventions in these packages from coverage in 2015 to hypothetically immediately achieve 90% coverage would avert 149 000 maternal deaths, 849 000 stillbirths, 1 498 000 neonatal deaths, and 1 515 000 additional child deaths. In alternative calculations that consider only the effects of reducing the number of pregnancies by provision of contraceptive services as part of a Reproductive Health package, meeting 90% of the unmet need for contraception would reduce global births by almost 28 million and consequently avert deaths that could have occurred at 2015 rates of fertility and mortality. Thus, 67 000 maternal deaths, 440 000 neonatal deaths, 473 000 child deaths, and 564 000 stillbirths could be averted from avoided pregnancies. Particularly effective interventions in the Maternal and Newborn Health and Child Health packages would be management of labour and delivery, care of preterm births, and treatment of serious infectious diseases and acute malnutrition. Nearly all of these essential interventions can be delivered by health workers in the community or in primary health centres, which can increase population access to needed services. The annual incremental cost of immediately scaling

up these essential interventions would be US$6·2 billion in low-income countries, $12·4 billion in lower-middle-income countries, and $8·0 billion in upper-middle-income countries. With the additional funding, greater focus on high-effect integrated interventions and innovations in service delivery, such as task shifting to other groups of health workers and supply and demand incentives, can help rectify major gaps in accessibility and quality of care. In recent decades, reduction of avoidable maternal and child deaths has been a global priority. With continued priority and expansion of essential reproductive, maternal, newborn, and child health interventions to high coverage, equity, and quality, as well as interventions to address underlying problems such as women's low status in society and violence against women, these deaths and substantial morbidity can be largely eliminated in another generation. <DCP-3.org>

30. HPP 2016;31(10):1479–1491

Effectiveness of interventions to provide culturally appropriate maternity care in increasing uptake of skilled maternity care: a systematic review

Coast E et al., London School of Economics and Political Science, London <e.coast@lse.ac.uk>

Addressing cultural factors that affect uptake of skilled maternity care is recognized as an important step in improving maternal and newborn health. This article describes a systematic review to examine the evidence available on the effects of interventions to provide culturally appropriate maternity care on the use of skilled maternity care during pregnancy, for birth or in the postpartum period. Items published in English, French and/or Spanish between 1 January 1990 and 31 March 2014 were considered. Fifteen studies describing a range of interventions met the inclusion criteria. Data were extracted on population and intervention characteristics; study design; definitions and data for relevant outcomes; and the contexts and conditions in which interventions occurred. Because most of the included studies focus on antenatal care outcomes, evidence of impact is particularly limited for care seeking for birth and after birth. Evidence in this review is clustered within a small number of countries, and evidence from low- and middle-income countries is notably lacking. Interventions largely had positive effects on uptake of skilled maternity care. Cultural factors are often not the sole factor affecting populations' use of maternity care services. Broader social, economic, geographical and political factors interacted with cultural factors to affect targeted populations' access to services in included studies. Programmes and policies should seek to establish an enabling environment and support respectful dialogue with communities to improve use of skilled maternity care. Whilst issues of culture are being recognized by programmes and researchers as being important, interventions that explicitly incorporate issues of culture are rarely evaluated.

31. HPP 2017;32(1):68–78

Incidence and determinants of hysterectomy in a low-income setting in Gujarat, India

Desai S., C-9 Maharani Bagh, New Delhi 110065, India <sapna.i.desai@gmail.com>

Hysterectomy is a leading reason for use of health insurance amongst low-income women in India, but there are limited population-level data available to inform policy. This paper reports on the findings of a mixed-methods study to estimate incidence and identify predictors of hysterectomy in a low-income setting in Gujarat, India. The estimated incidence of hysterectomy, 20.7/1000 woman- years (95% CI: 14.0, 30.8), was considerably higher than reported from other countries, at a relatively low mean age of 36 years. There was strong evidence that among women of reproductive age, those with lower income and at least two children underwent hysterectomy at higher rates. Nearly two-thirds of women undergoing hysterectomy utilized private hospitals, while the remainder used government or other non-profit facilities. Qualitative research suggested that weak sexual and reproductive health services, a widespread perception that the post-reproductive uterus is dispensable and lack of knowledge of side effects have resulted in the normalization of hysterectomy. Hysterectomy appears to be promoted as a first or second-line treatment for menstrual and gynaecological disorders that are actually amenable to less invasive procedures. Most women sought at least two medical opinions prior to hysterectomy, but both public and private providers lacked equipment, skills and motivation to offer alternatives. Profit

and training benefits also appeared to play a role in some providers' behaviour. Although women with insecure employment underwent the procedure knowing the financial and physical implications of undergoing a major surgery, the future health and work security afforded by hysterectomy appeared to them to outweigh risks. Findings suggest that sterilization may be associated with an increased risk of hysterectomy, potentially through biological or attitudinal links. Health policy interventions require improved access to sexual and reproductive health services and health education, along with surveillance and medical audits to promote high-quality choices for women through the life cycle.

32. HPP 2017;32(2): 215–224

When the baby remains there for a long time, it is going to die so you have to hit her small for the baby to come out: justification of disrespectful and abusive care during childbirth among midwifery students in Ghana

Rominski SD, <sarahrom@umich.edu>

Despite global attention, high levels of maternal mortality continue to plague many low- and middle-income settings. One important way to improve the care of women in labour is to increase the proportion of women who deliver in a health facility. However, due to poor quality of care, including being disrespected and abused, women are reluctant to come to facilities for delivery care. The current study sought to examine disrespectful and abusive treatment towards labouring women from the perspective of midwifery students who were within months of graduation. For this study, we conducted focus groups with final year midwifery students at 15 public midwifery training colleges in all 10 of Ghana's regions. Focus group discussions were recorded and transcribed. A multi-disciplinary team of researchers from the US and Ghana analysed the qualitative data. While students were able to talk at length as to why respectful care is important, they were also able to recount times when they both witnessed and participated in disrespectful and abusive treatment of labouring women. The themes which emerged from these data are: 1) rationalization of disrespectful and abusive care; 2) the culture of blame and; 3) no alternative to disrespect and abuse. Although midwifery students in Ghana's public midwifery schools highlight the importance of providing high-quality, patient-centred respectful care, they also report many forms of disrespect and abuse during childbirth. Without better quality care, including making care more humane, the use of facility-based maternity services in Ghana is likely not to improve. This study provides an important starting point for educators, researchers, and policy makers to re-think how the next generation of healthcare providers needs to be prepared to provide high-quality, respectful care to women during labour and delivery in low-resource settings.

33. PLoS Med 2017;14(1): e1002229

Editorial (abridged): Defining Abnormal Fetal Growth and Perinatal Risk: Population or Customized Standards?

Stock SJ and Myers J, <sarah.stock@ed.ac.uk>

Appropriate fetal growth and development in utero is essential for newborn health and lifelong well-being. Both fetal growth restriction (in which the fetus does not achieve its growth potential, usually because of placental insufficiency) and macrosomia (excessive in utero growth, frequently associated with maternal obesity and/or diabetes), are associated with stillbirth, neonatal morbidity and mortality, and long-term risks to health. An aim of obstetric care is to detect fetuses at risk of complications from fetal growth disorders and intervene to reduce the risk. In reality, the only current effective intervention to prevent stillbirth is delivery of the fetus at a point when the risks of continuing the pregnancy are thought to outweigh the risks of birth. It is presumed, although not proven, that timely delivery also minimizes neonatal and longer-term morbidities and mortality.

There is substantial variation in the fetal and newborn growth charts used to detect growth deviations. Although there is broad recognition that appropriate unified standards are needed, two different approaches to fetal and neonatal growth assessment have been advocated. One is based on the premise that fetal growth is strongly influenced by genetic factors and adjusts for this by creation of growth

charts customized for specific phenotypic traits such as maternal ethnicity, height, and weight. The other is to define optimal fetal growth standards at a population level. This is based on the theory that growth potential is similar across populations, and deviation from this norm indicates deprivation or other environmental influences rather than inherent biological differences. Although there are enthusiasts for each approach, they have yet to be directly compared in a clinical trial, and it is not clear if either is superior for detecting the fetus or infant at risk of morbidity because of growth disorders. We are thus reliant on evidence from observational studies. Two articles published in *PLOS Medicine* contribute to the evidence base regarding the use of population charts for detection of fetal growth disorders and how best to determine risk of complications.

That fetal growth has a genetic component is not in question—the fact that fetal sex is a determinant of growth potential illustrates this. However, the amount by which obstetricians can (and should) adjust for genetic variation across populations when assessing fetal growth is unclear. Both of the papers in this issue support the concept that robustly developed population growth standards are appropriate for the diagnosis of fetal growth disorders but that thresholds of risk that are relevant to local populations should be considered. Whatever method is used, the benefits of detecting fetal growth disorders can only be realized if we can effectively reduce risk of complications. At the moment, delivery is the only way of doing this. Even using optimized charts and thresholds, we are likely to overintervene in many normal cases to prevent complications in the few. Ultrasound assessment of fetal growth has limitations, and better methods of risk prediction are needed to prevent death and disability in babies.

34. PLoS Med 2017;14(1):e1002220

The World Health Organization Fetal Growth Charts: A Multinational Longitudinal Study of Ultrasound Biometric Measurements and Estimated Fetal Weight

Kiserud T et al., <on.biu@duresik.divrot>

Background: Perinatal mortality and morbidity continue to be major global health challenges strongly associated with prematurity and reduced fetal growth, an issue of further interest given the mounting evidence that fetal growth in general is linked to degrees of risk of common noncommunicable diseases in adulthood. Against this background, WHO made it a high priority to provide the present fetal growth charts for estimated fetal weight (EFW) and common ultrasound biometric measurements intended for worldwide use.

Methods and Findings: We conducted a multinational prospective observational longitudinal study of fetal growth in low-risk singleton pregnancies of women of high or middle socioeconomic status and without known environmental constraints on fetal growth. Centers in ten countries (Argentina, Brazil, Democratic Republic of the Congo, Denmark, Egypt, France, Germany, India, Norway, and Thailand) recruited participants who had reliable information on last menstrual period and gestational age confirmed by crown–rump length measured at 8–13 wk of gestation. Participants had anthropometric and nutritional assessments and seven scheduled ultrasound examinations during pregnancy. Fifty-two participants withdrew consent, and 1,387 participated in the study.

At study entry, median maternal age was 28 y (interquartile range [IQR] 25–31), median height was 162 cm (IQR 157–168), median weight was 61 kg (IQR 55–68), 58% of the women were nulliparous, and median daily caloric intake was 1,840 cal (IQR 1,487–2,222).

The median pregnancy duration was 39 wk (IQR 38–40) although there were significant differences between countries, the largest difference being 12 d (95% CI 8–16). The median birthweight was 3,300 g (IQR 2,980–3,615). There were differences in birthweight between countries, e.g., India had significantly smaller neonates than the other countries, even after adjusting for gestational age. Thirty-one women had a miscarriage, and three fetuses had intrauterine death.

The 8,203 sets of ultrasound measurements were scrutinized for outliers and leverage points, and those measurements taken at 14 to 40 wk were selected for analysis. A total of 7,924 sets of ultrasound measurements were analyzed by quantile regression to establish longitudinal reference intervals for fetal head circumference, biparietal diameter, humerus length, abdominal circumference, femur length and its ratio with head circumference and with biparietal diameter, and EFW. There was asymmetric

distribution of growth of EFW: a slightly wider distribution among the lower percentiles during early weeks shifted to a notably expanded distribution of the higher percentiles in late pregnancy.
Male fetuses were larger than female fetuses as measured by EFW, but the disparity was smaller in the lower quantiles of the distribution (3.5%) and larger in the upper quantiles (4.5%). Maternal age and maternal height were associated with a positive effect on EFW, particularly in the lower tail of the distribution, of the order of 2% to 3% for each additional 10 y of age of the mother and 1% to 2% for each additional 10 cm of height. Maternal weight was associated with a small positive effect on EFW, especially in the higher tail of the distribution, of the order of 1.0% to 1.5% for each additional 10 kg of bodyweight of the mother. Parous women had heavier fetuses than nulliparous women, with the disparity being greater in the lower quantiles of the distribution, of the order of 1% to 1.5%, and diminishing in the upper quantiles. There were also significant differences in growth of EFW between countries. In spite of the multinational nature of the study, sample size is a limiting factor for generalization of the charts.
Conclusions: This study provides WHO fetal growth charts for EFW and common ultrasound biometric measurements, and shows variation between different parts of the world.

Miscellaneous

35. Am J TMH 2017;96(2):488-492
The Impact of Systematic Point-of-Care Ultrasound on Management of Patients in a Resource-Limited Setting
Stanley A et al., London School of Hygiene and Tropical Medicine, United Kingdom <alastair.stanley@nhs.net>

Although target point-of-care (POC) ultrasonography has been shown to benefit patients in resource-limited settings, it is not clear whether a systematic POC ultrasound assessment in these settings can also lead to similar changes in patient management. A predefined systematic set of POC ultrasound scans were performed on inpatients at a tertiary referral hospital in Tanzania to see if this resulted in changes to patient management. Of the 55 patients scanned, an abnormality was detected in 75% (N = 41), and a change in patient management was recommended or implemented on the basis of POC ultrasound findings in 53% (N = 29). The main impact was earlier initiation of treatment due to more rapid and accurate diagnosis. Further research is warranted to determine whether systematic POC ultrasonography would result in improved patient outcomes in resource-limited settings.

36. BMJ 2017;356:i6534 Practice Pointer
An approach to hypopigmentation
Hill JP et al., <jeremy.hill@gp-c84124.nhs.uk>

What you need to know.
In many cases, non-specialists can form a working diagnosis for hypopigmentation from the history and examination alone.
Common causes include vitiligo, post-inflammatory hypopigmentation, pityriasis versicolor, pityriasis alba, and halo naevi.
Take time to understand how skin changes affect confidence as well as work and home life
Around 1 in 20 people have at least one hypopigmented macule. Patients may worry about pale patches and links to other disease. Hypopigmentation can be upsetting, particularly if visible. For people with darker skin, hypopigmentation may also result in stigma. Most causes of hypopigmentation are not serious, can be diagnosed clinically and may be treatable. This article aims to help non-specialists assess and treat patients with hypopigmented patches, focusing on the commonest conditions and mentioning rarer but important conditions where specialist referral may be necessary.
What features in the history and examination should I focus on?
Consider demographics:

Age—Pityriasis alba typically affects children, pityriasis versicolor usually affects young adults, vitiligo affects people of any age but commonly starts before the age of 30 years.
Race—Hypopigmented patches occur in all racial groups but are much more noticeable in those with darker skin; post-inflammatory hypopigmentation (occurring after a rash has resolved) is also more common in people with darker skin. Leprosy should be considered in patients from areas of the world where it is still prevalent.

37. BMJ 2017;356:i6583 Research

Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data

Martineau AR et al., <a.martineau@qmul.ac.uk>

Objectives: To assess the overall effect of vitamin D supplementation on risk of acute respiratory tract infection, and to identify factors modifying this effect.
Design: Systematic review and meta-analysis of individual participant data (IPD) from randomised controlled trials.
Data sources: Medline, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov, and the International Standard Randomised Controlled Trials Number registry from inception to December 2015.
Eligibility criteria for study selection: Randomised, double blind, placebo controlled trials of supplementation with vitamin D3 or vitamin D2 of any duration were eligible for inclusion if they had been approved by a research ethics committee and if data on incidence of acute respiratory tract infection were collected prospectively and prespecified as an efficacy outcome.
Results: 25 eligible randomised controlled trials (total 11 321 participants, aged 0 to 95 years) were identified. IPD were obtained for 10 933 (96.6%) participants. Vitamin D supplementation reduced the risk of acute respiratory tract infection among all participants (adjusted odds ratio 0.88, 95% confidence interval 0.81 to 0.96; P for heterogeneity <0.001). In subgroup analysis, protective effects were seen in those receiving daily or weekly vitamin D without additional bolus doses (adjusted odds ratio 0.81, 0.72 to 0.91) but not in those receiving one or more bolus doses (adjusted odds ratio 0.97, 0.86 to 1.10; P for interaction=0.05). Among those receiving daily or weekly vitamin D, protective effects were stronger in those with baseline 25-hydroxyvitamin D levels <25 nmol/L (adjusted odds ratio 0.30, 0.17 to 0.53) than in those with baseline 25-hydroxyvitamin D levels ≥25 nmol/L (adjusted odds ratio 0.75, 0.60 to 0.95; P for interaction=0.006). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (adjusted odds ratio 0.98, 0.80 to 1.20, P=0.83). The body of evidence contributing to these analyses was assessed as being of high quality.
Conclusions: Vitamin D supplementation was safe and it protected against acute respiratory tract infection overall. Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.

38. BMJ 2017;356:j456 Editorials

Do vitamin D supplements help prevent respiratory tract infections?

Bolland MJ, Avenell A, <a.avenell@abdn.ac.uk>

A clinically useful effect remains uncertain despite hints in a new analysis
Vitamin D supplementation is a hot topic, provoking passionate arguments for and against widespread supplementation. Recently in The BMJ we discussed the evidence, concluding that vitamin D supplements should not be taken by adults to prevent non-musculoskeletal disease. Three months later comes a meta-analysis by Martineau and colleagues (doi:10.1136/bmj.i6583), concluding that prevention of acute respiratory tract infection is a "major new indication for vitamin D supplementation." Given the short time between articles, why are the conclusions so different? Is this really a major new development, providing the long sought reliable evidence of benefits of vitamin D on a non-skeletal outcome in the general population? Or is it yet another hypothesis about vitamin D supplementation that needs testing in adequately powered randomised controlled trials?

Should these results change clinical practice? Probably not. The results are heterogeneous and not sufficiently applicable to the general population. We think that they should be viewed as hypothesis generating only, requiring confirmation in well designed adequately powered randomised controlled trials. Several very large such randomised controlled trials of vitamin D supplements will report on the effects on respiratory infections within the next few years. These trials have not targeted individuals with very low serum concentrations of vitamin D, and there is still a need for trials in these population groups. We consider that current evidence does not support the use of vitamin D supplementation to prevent disease, except for those at high risk of osteomalacia, currently defined as 25-hydroxyvitamin D levels less than 25 nmol/L.

39. NEJM 2017;376:548-560 Review article

Approach to Fever in the Returning Traveler

Thwaites GE et al.

Fever in the returning traveler is a common clinical scenario that often leads to hospitalization and may be the only symptom of a serious or life-threatening illness. Three percent of 784 Americans who traveled abroad for short periods reported an episode of febrile illness, and fever was the chief symptom in 28% of 24,920 ill travelers who presented to travel clinics on their return home. The absolute number of travelers is large and rising, with the International Tourism Organization reporting 1.2 billion trips in 2015, an increase of 4.4% from the previous year. The challenge presented by returning travelers with febrile illnesses is changing for two reasons. First, increasing numbers of travelers are older than 60 years of age or are seeking health care elsewhere (“medical tourists”), and these travelers are more likely than others to have clinically significant coexisting conditions and consequently increased morbidity from infections. Second, the likelihood of multidrug resistance in the infecting organisms is increasing. The recent Ebola epidemic in West Africa, the emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV), and the reemergence of Zika and chikungunya viruses have highlighted the importance of being alert to the possibility that an emerging pathogen is causing a febrile episode.

Fever in the returning traveler is an evolving clinical challenge, with respect to both the infections responsible for the fever and the sources and quality of information available to assist the physician. We review available sources of global information on outbreaks and the epidemiologic features of infectious diseases and offer a practical approach to emerging or transmissible infectious diseases that may pose a life-threatening risk to patients, as well as clinicians and laboratory workers.