

Evidence-Based Global Health

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THE EFFECTIVENESS OF MANY INTERVENTIONS TO improve health in poor populations in the developing world remains untested and therefore unproven. It is sometimes assumed that what works is known and that the only challenge is to make interventions widely available to underserved populations worldwide, the so-called know-do gap. However, other than vaccination, few global health interventions are evidence-based.

Evidence-based global health requires use of the evidence from randomized controlled trials and other scientifically valid studies to evaluate global health interventions and to measure progress in improving global health. Randomized controlled trials of global public health interventions are often cluster trials, randomizing groups or communities.^{1,2} When evidence from randomized trials is not available or is difficult to generalize, observational studies provide useful information but must be carefully interpreted.² Global health needs assessment and monitoring also rely on observational studies. This issue of THE JOURNAL illustrates the different approaches used in evidence-based global health research, with 1 individual and 3 cluster randomized controlled trials conducted in resource-poor communities to evaluate essential interventions aimed at preventing diseases and disorders prevalent in the developing world,³⁻⁶ and 4 observational studies measuring or estimating the frequency of specific health problems and associated risk factors for a number of important worldwide public health concerns.⁷⁻¹⁰

When feasible, individual randomization remains the best method available to evaluate an intervention. The report in this issue by Kaul et al⁴ is an example of such a well-conducted trial, illustrating that rigorous evaluations are necessary to determine whether interventions are effective. In this study, monthly antibiotic chemoprophylaxis for sexually transmitted infections (STIs) did not reduce the incidence of human immunodeficiency virus type 1 (HIV-1) infection in Kenyan sex workers, although the frequency of gonorrhea, chlamydia, and trichomoniasis was signifi-

cantly reduced.⁴ Since STIs are associated with acquisition of HIV-1, it was expected that azithromycin prophylaxis would have an impact. Searching for the reasons for this failure to achieve a rational goal will provide insight into the transmission dynamics of HIV-1 and the approaches needed to reduce transmission in a cost-effective manner. Without this type of evaluation, a costly drug could be used without predictable effect, except to select for antibiotic resistance.

Many routine interventions, such as handwashing, are not fully supported by good data. As also reported in this issue, Luby and colleagues³ randomized low-income neighborhoods in Karachi, Pakistan, to evaluate the effect of household handwashing with soap on incidence of diarrhea among children. The investigators found that handwashing is effective and that plain soap is as effective as antibacterial soap. This is not surprising, as it is the mechanical removal of bacteria from the hands that is important; soap facilitates this removal, and antibacterial products add little to the overall effectiveness of soap.¹¹ This report appears to be the first well-conducted trial to provide convincing evidence of the effectiveness of an intervention as simple as household handwashing on reducing diarrhea incidence among infants younger than 1 year.

Large-scale programs of nutritional education are another example of well-established interventions that are often not evidence-based. For example, in another report in this issue, Rivera et al⁵ randomly assigned communities in Mexico to a comprehensive program including fortified nutrition supplements for children and education, health care, and cash transfers to the families, and compared these communities with a control group among other communities in which the introduction of the interventions was delayed for 1 year. The investigators found that the intervention was associated with better growth in height and lower rates of anemia in low-income, rural infants and children. It is essential that other large-scale nutritional intervention studies or monitoring programs are evaluated in a similar rigorous manner in the future. A systematic review identified

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only 2 randomized controlled trials on growth monitoring of children.¹² One trial from India found no difference in nutritional status at 30 months among the children allocated to growth monitoring and the control group.¹³ Another study from Lesotho did show an impact of growth monitoring on mothers' knowledge about nutrition, but the report failed to provide evidence on any impact of the program on the nutritional status of the children.¹⁴

Many interventions that have been shown to be efficacious in an industrialized country have not been shown to be similarly effective when carried out in developing countries. In a recent review of the global evidence of community-based interventions for reducing perinatal and neonatal mortality in developing countries, Bhutta et al¹⁵ reported that less than 5% of all randomized trials and systematic reviews of interventions were based on investigations in representative community settings. All communities would not be expected a priori to respond in similar manner to interventions, as there are so many social, cultural, genetic, and infrastructure differences among them. Context may be especially important for behavioral interventions. For example, smoking prevention and cessation programs have been extensively tested in experimental studies in industrialized countries. Such trials demonstrate the efficacy of individual behavioral counseling but show a disappointing lack of effectiveness of community interventions.^{16,17} Because of the implications of these findings in resource-limited settings and the limitations inherent in generalizing these results to developing countries, it is necessary to carry out appropriate trials in the developing world. However, it may not be as simple as it appears to replicate studies in different populations. For example, the report in this issue by Liu and colleagues⁸ shows that the original Framingham study functions overestimated the risk of coronary heart disease in a Chinese population, demonstrating that risk assessment tools also need to be adapted to specific populations. However, the specific risk factors were consistent across countries, suggesting that some studies may not need to be fully replicated to extrapolate results to other countries.

Identifying population- or context-specific features that determine the effectiveness of public health interventions requires more studies at a global level, thereby increasing the potential to both generalize the results and identify features germane to specific locales. Many health problems are shared by industrialized and developing countries and could be studied at a global level if there were common protocols, standardized methods, and funds to conduct comparative trials.¹⁸ Global multicenter studies should thus include countries from as many regions of the world as possible. This is all the more important where local features are likely to influence diseases and interventions. For instance, results from the World Mental Health Survey, also reported in this issue, show that the prevalence of mental disorders and their probability of treatment vary widely from one country to another.⁷

Evidence on sustainability of interventions and their impact following the completion of trials is limited. For example, in carefully controlled trials, insecticide-treated bednets have been shown to reduce malaria transmission, but the sustainability and long-term impact of this intervention is unknown.¹⁹ Reducing exposure to malaria during early infancy could lead to a delay in acquisition of immunity against malaria and to a rebound in morbidity and mortality at later ages, especially if the programs are not sustained or if insecticide resistance becomes a serious problem. In another article in this issue, Lindblade et al⁶ report on their follow-up study of the population involved in a cluster randomized trial of insecticide-treated bednets in an area of intense perennial malaria transmission in Kenya. These researchers showed that in this population, the use of bednets was sustainable and significantly increased in subsequent years, the frequency of anopheline mosquitoes in the household significantly decreased, all-cause mortality decreased in infants, and mortality of older children did not increase during up to 6 years of longitudinal surveillance thus far. But this is still a short-term follow-up. Will it be possible to restudy the same population in a few years to determine the true long-term durability of the effect? Such studies must be funded, the follow-up published, and the results used to develop sound policy that can be translated into effective practice to achieve the full impact of such research.

Other categories of interventions deserve further evaluation. For example, little evidence is available about the effectiveness of population-level interventions aimed at preventing relatively rare events such as maternal death. Testing such interventions in randomized controlled trials requires large sample sizes, greatly increasing the cost and decreasing the likelihood of adequate funding. As such, when the outcome is a rare event, surrogate measures are used by default, leaving open the question of the actual health impact. For example, numerous trials have shown that prenatal iron supplementation increases hemoglobin levels, but the impact on morbidity and mortality is still unknown.²⁰ Evidence of efficacy of maternal mortality reduction programs is also limited.²¹ Multicenter trials are needed to properly evaluate such interventions in different settings but using the same methods and outcome criteria. Such outcome criteria should include rare events but also meaningful surrogate measures such as maternal morbidity. More widespread use of standardized quasi-experimental designs and surveillance systems, including use of verbal autopsies when needed, also would help to provide quality data on rare events in resource-poor areas.

Another category of seldom-evaluated interventions includes those at the health system level, such as integrated health services. A review of randomized trials, controlled before-and-after studies, and interrupted time series analyses of integration strategies in primary health care services in low- and middle-income countries identified only 4 relevant studies.²² The authors of this review concluded that

there was no consistent pattern of benefit and predictably concluded that more studies were needed. New approaches such as cluster or group randomization of population-based or health system interventions are feasible and should be conducted more often.¹

The ultimate irony is that interventions that have been shown to be efficacious are not used in practice. To illustrate, in an analysis of the evidence of currently available interventions for child health, the Bellagio Child Survival Study Group²³ estimated that almost 55% of global deaths in children younger than 5 years could be prevented by providing these interventions at scale. There is some support for the concept that behavioral interventions can effectively be used to diffuse evidence-based practices among clinicians in industrialized countries.²⁴⁻²⁶ Whether this can be shown in resource-poor developing countries is not known. The few trials that have been performed in developing countries to evaluate the effectiveness of educational interventions promoting the evidence-based treatment of diarrhea have resulted in inconclusive findings.^{27,28} While more trials of such behavioral interventions are needed at a global level, it is also time as well to identify and test new strategies.

The practice of clinical medicine has been deeply transformed by the evidence-based medicine movement.²⁹ Many clinical interventions have now been tested in appropriately designed randomized controlled trials. It is time to launch a similar effort to evaluate global health interventions and to develop an evidence-based global health movement. The recent call for a large effort to include more global health topics in the Cochrane Database of Systematic Reviews is a positive sign.³⁰ However, the need is great, and commitment of multiple national science agencies to work together, coupled with significantly increased investment from national governments, development agencies, and other donors will be essential to ensure that the move toward evidence-based global health is feasible. It is time to establish a global health research collaborative to promote and support this work.³¹⁻³³ International collaboration and support for such efforts are needed to provide the infrastructure for rigorous studies and to generate the sound evidence necessary to improve global health.

REFERENCES

1. Ukoumunne OC, Gulliford M, Chinn S, Sterne J, Burney P, Donner A. Evaluation of health interventions at area and organization level. *BMJ*. 1999;319:376-379.
2. Victora C, Habicht JP, Bryce J. Evidence-based public health: moving beyond randomized trials. *Am J Public Health*. 2004;94:400-405.
3. Luby SP, Agboatwalla M, Painter J, Altaf A, Billhimer WL, Hoekstra RM. Effect of intensive handwashing promotion on childhood diarrhea in high-risk communities in Pakistan: a randomized controlled trial. *JAMA*. 2004;291:2547-2554.
4. Kaul R, Kimani J, Nagelkerke N, et al, for the Kibera HIV Study Group. Monthly antibiotic chemoprophylaxis and incidence of sexually transmitted infections and HIV-1 infection in Kenyan sex workers: a randomized controlled trial. *JAMA*. 2004;291:2555-2562.
5. Rivera JA, Sotres-Alvarez D, Habicht J-P, Shamah T, Villalpando S. Impact of the Mexican Program for Education, Health, and Nutrition (Progres) on growth and anemia in infants and young children: a randomized effectiveness study. *JAMA*. 2004;291:2563-2570.
6. Lindblade KA, Eisele TP, J. E. Gimnig, et al. Sustainability of reductions in malaria transmission and infant mortality in western Kenya with use of insecticide-treated bednets: 4 to 6 years of follow-up. *JAMA*. 2004;291:2571-2580.
7. The WHO World Mental Health Survey Consortium. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. *JAMA*. 2004;291:2581-2590.
8. Liu J, Hong Y, D'Agostino RB Sr, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-provincial Cohort Study. *JAMA*. 2004;291:2591-2599.
9. de Onis M, Blössner M, Borghi E, Frongillo EA, Morris R. Estimates of global prevalence of childhood underweight in 1990 and 2015. *JAMA*. 2004;291:2600-2606.
10. Vollaard AM, Ali S, van Asten HAGH, et al. Risk factors for typhoid and paratyphoid fever in Jakarta, Indonesia. *JAMA*. 2004;291:2607-2615.
11. Larson EL, Lin SX, Gomez-Pichardo C, Della-Latta P. Effect of antibacterial home cleaning and handwashing products on infectious disease symptoms: a randomized, double-blind trial. *Ann Intern Med*. 2004;140:321-329.
12. Panpanich R, Garner P. Growth monitoring in children. *Cochrane Database Syst Rev*. 2000;2:CD001443.
13. George SM, Latham MC, Abel R, Ethirajan N, Frongillo EA. Evaluation of effectiveness of good growth monitoring in South Indian villages. *Lancet*. 1993;342:348-352.
14. Ruel MT, Habicht JP, Olson C. Impact of a clinical-based growth monitoring programme on maternal nutrition knowledge in Lesotho. *Int J Epidemiol*. 1992;21:59-65.
15. Bhutta ZA, Darmstadt GL, Ransom EI. *Using Evidence to Save Newborn Lives*. Washington, DC: Population Reference Bureau; 2003.
16. Lancaster T, Stead LF. Individual behavioural counseling for smoking cessation. *Cochrane Database Syst Rev*. 2002;3:CD001292.
17. Secker-Walker RH, Gnich W, Platt S, Lancaster T. Community interventions for reducing smoking among adults. *Cochrane Database Syst Rev*. 2002;3:CD001745.
18. Institute of Medicine. *America's Vital Interest in Global Health*. Washington, DC: National Academy Press; 1997.
19. Lengeler C. Insecticide-treated bednets and curtains for preventing malaria. *Cochrane Database Syst Rev*. 2004;2:CD000363.
20. Mahomed K. Iron supplementation in pregnancy. *Cochrane Database Syst Rev*. 2000;2:CD000117.
21. Miller S, Sloan N, Winikoff B, Langer A, Fikree F. Where is the "E" in MCH? the need for an evidence-based approach in safe motherhood. *J Midwifery Womens Health*. 2003;48:10-18.
22. Briggs CJ, Capdegelle P, Garner P. Strategies for integrating primary health services in middle- and low-income countries. *Cochrane Database Syst Rev*. 2001;4:CD003318.
23. Jones G, Steketee R, Black R, Bhutta Z, Morris S; Bellagio Child Survival Study Group. How many child deaths can we prevent this year? *Lancet*. 2003;362:65-71.
24. Oxman AD, Thomson MA, Davis DA, Haynes RB. No magic bullets: a systematic review of 102 trials of interventions to help health care professionals deliver services more effectively or efficiently. *CMAJ*. 1995;153:1423-1431.
25. Grol R. Beliefs and evidence in changing clinical practice. *BMJ*. 1997;315:418-421.
26. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA; the Cochrane Effective Practice and Organization of Care Review Group. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. *BMJ*. 1998;317:465-468.
27. Santoso B, Suryawati S, Prawaitasari JE. Small group intervention vs formal seminar for improving appropriate drug use. *Soc Sci Med*. 1996;42:1163-1168.
28. Ross-Degnan D, Soumerai S, Goel PK, et al. The impact of face-to-face educational outreach on diarrhoea treatment in pharmacies. *Health Policy Plan*. 1996;11:308-318.
29. Sackett D, Rosenberg W, Muir Gray J, Haynes RB, Richardson W. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312:71-72.
30. Richards T. Poor countries lack relevant health information, says Cochrane editor. *BMJ*. 2004;328:310.
31. Bhutta ZA. Practicing just medicine in an unjust world. *BMJ*. 2003;327:1000-1001.
32. Commission on Macroeconomics and Health. *Macroeconomics and health: investing in health for economic development*. Available at: <http://www.cmhealth.org>. Accessed April 28, 2004.
33. Keusch GT, Medlin CA. Tapping the power of small institutions. *Nature*. 2003;422:561-562.