Research Agendas in Global Emergency Medicine

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Much data has been gathered regarding the health characteristics of many populations around the world. Less research has been focused internationally on the emergency care and prevention of acute noninfectious illness and injury. In a review of the Cochrane database of systematic reviews and the database of abstracts of reviews of effects, Swingler et al [1] found a paucity of articles on injury research in developing countries compared with what has been done in developed countries. Others have noted a general lack of articles in various domains that may interface with emergency medicine (EM) [2]. According to a World Bank report, only 10% of the annual health research dollars ($60 billion) is spent on problems (defined by various health indicators) that affect the health of 90% of the world population [3]. A United Nations report from 2002 showed that Organization for Economic Cooperation and Development (OECD) countries (United States, European Union, Canada, Japan, Turkey, Mexico, Australia, and New Zealand), the world's richest, spent only 0.3% of total health expenditure on aid to more needy populations [4]. Of that, only a small part would have been directed specifically at research.

The pathophysiologic principles of diseases and the effects of medication and procedural interventions are likely to be similar between low- and middle income countries (LMIC) (see Appendix 1) and high-income countries (HIC). However, it is unrealistic to think of applying many of the systemic approaches to overall patient care developed in nations that

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spend thousands of dollars yearly per capita on health care to countries with annual per capita health care spending of less than $100, calculated after counting international aid [5].

As with the pathophysiology of diseases, the criteria that might be established to define the quality of health care as it relates to achieving the WHO-defined state of "health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [6] might be different in LMIC than in HIC. In the literature discussion of assessing quality of health care, largely focusing on HIC, the definition of quality has been extensively debated from Donabedian's original definition in 1980 to an Institute of Medicine discussion in 1990 and continuing thereafter [7]. In one collection of articles on quality in health care, several articles comparing countries on several criteria dealt only with HIC using criteria that have relatively little meaning in LMIC [8].

Research techniques developed in HIC to assess the systemic issues that affect the quality of health care may have great applicability in LMIC. The New England Journal of Medicine published a series of six articles focusing the various aspects of evaluating quality of health care in the United States [7,9-13]. The series and accompanying commentaries serve as an excellent summary of the foci of health care quality assessment research [14].

The Global Burden of Disease (BOD) report, published in 1996, identified a number of noninfectious disorders as already accounting for a significant proportion of death and disability in 1990 with a major rise predicted over the next 30 years [15] (for more detail on projected burdens, see the article "Hot topics in international emergency medicine" elsewhere in this issue). The global pandemic of HIV has attracted a large percentage of available research and development resources over the last 10 years [16]. Some researchers have questioned the reliance on the BOD report for prioritizing health spending policy, suggesting a classification based on care needs rather than cause [17].

During the 1990s, a number of global events occurred that brought greater appreciation of a place for emergency health care even at the most rudimentary stages of development (ie, refugee camps) [18]. Influencing factors ranged from rapid advances in information access through digital technologies to urbanization and globalization, including dissemination of the United States model of EM via translation and global transmission of the television series "ER."

In July 2003, the Fogarty International Center of the National Institutes of Health (NIH) invited 40 experts from around the globe, many who were active researchers in fields related to trauma and injury, to discuss ways to reduce the burden of trauma and injuries in LMIC. The major topics addressed included research gaps and training needs related to intentional and unintentional injuries in LMIC; basic science and options related to diagnosis and treatment of injury, wound care, wound healing, spinal injury, brain injury, and orthopedics; ethical challenges to performing trauma research; capacity building; and mental health issues related to trauma and
injury [19]. This broad base of interest demonstrates the increasing recognition of the disease burden caused by trauma and injury and the need to promote research and training in the field.

This article reviews some areas where more focused EM-relevant research has taken place and some domains likely to be future directions, based on WHO BOD reports, the Fogarty consultation, and various WHO and World Bank reports cited here and in the "Hot topics" article elsewhere in this issue. We intend for the topics presented here and the references cited to serve as a question-generating foundation for further project development. The reference list is diverse to reflect the breadth of interpretations of emergency health care.

International emergency medicine research fundamentals

Capacity building

Human capacity building is one of the most fundamental areas in which the international health care community can benefit from developed-economy-based research projects. As one searches the medical literature catalogued through the United States National Library of Medicine in various domains involving international health care development, the presence of "local" members of the primary research team, as reflected in authorship rank, seems to have improved over the past 15 years. Many projects use or train local personnel, although this is often at the level of local health workers as opposed to faculty from local universities. Many of the developing country native researcher-authors have worked and written from within United States- or European Union-based programs after immigration following advanced degrees or post-doctoral fellowships, contributing to a "brain drain" from the developing economies. Those who have attempted to foster research from within developing economies have often been hampered by a lack of infrastructure and institutional stagnation [20].

A 1996 report by the World Health Organization (WHO) estimated that 80% of all working scientists in all domains were located in the highly industrialized nations of the United States, Western Europe, and Japan, with a few in other Asian countries [21]. Over the years since that report, several established centers of research have gained wider recognition, and others have been developed more or less de novo. The Indian Institute of Technology, with a seat in Delhi and branches throughout the country, has become well respected in a variety of technologic domains, including the "Transportation Research and Injury Prevention Programme" investigating road traffic safety [22]. Singapore and other cities in Asia have developed "Science Parks" to promote technology development, but as the governments have become more aware of the costs of health, more research is being promoted in the life sciences [23]. Increasingly, collaborative colleagues are "on the ground."
The Fogarty International Center of the National Institutes of Health published a program announcement in April 2004 seeking projects specifically focused on capacity development in low- and middle-income countries through collaborative projects that incorporate the training of researchers from LMIC with the return to their country of origin [24].

Health care improvement domains

Improvement in health quality depends on working in one of the three assessment spheres originally described by Donabedian: structure (eg, physical plant, beds/population, nurses or doctors/patient visit, educational background of providers, etc.), process (eg, order of events such as whether to place a Foley or obtain pelvis x-ray first in multiple trauma evaluation), and outcome (eg, percent survival to full neurologic recovery of patients of type "1" in structure "A" with process "X", change in score on SF-36, discussed below) [25]. Achieving health care improvement revolves around evaluating outcomes under one paradigm, changing a structural or procedural aspect, and reassessing outcomes. Once optimal outcomes with given patient sets and sociologic constraints are determined, the structural and procedural sets associated with them become benchmarks for developing standards of care.

Two significant caveats exist. First, the same outcome might be possible with different sets of structural or procedural components. Second, process assessment is more sensitive than outcome assessment because errors in process do not always lead to poor outcomes. Questions such as, "Is there an outcome difference of stable blunt trauma patients with abdominal pain evaluated with bedside ultrasound (FAST) exams versus non-contrast CAT scan?" are critical in resource-restricted economies. Equally important and arguably pertinent to a greater percentage of any population are more systemic questions, such as "the impact on trauma morbidity from training township health workers to recognize indicators of domestic violence" in an area with a high incidence of female trauma victims and a culture not supportive of women's independence.

Defining the locus of research

William Haddon's injury evaluation matrix and the underlying principles of the relations between host, vector, and environment are useful constructs to apply when examining and cataloguing domains of research in EM and injury prevention. Runyan has proposed a third dimension to factor in: "value criteria," which includes concepts such as effectiveness, cost, and feasibility for any intervention [26] (Fig. 1).

The majority of research in LMIC health care has been focused on preventive endeavors following reasonable logic that it is less expensive in the long run to prevent virtually any medical conditions than to treat them
A number of the classic scourges of low-income economies are responding to preventive endeavors, primarily those focused on improved sanitation and insect vector control. As predicted in the 1996 WHO Burden of Disease report, the line-up of disorders leading to the greatest burden is shifting toward chronic diseases of more developed economies, mental disorders, and traumatic events, largely related to traffic crashes [27]. As the efforts to decrease burden from infectious diseases did not ignore treatment while working on prevention initiatives, so treatment for the current and future line-up of burden leaders must continue concurrent with developing preventive measures. Because many of these disorders are well represented in the medical literature of the past 30 years, it might seem reasonable that all developing countries need do is to read the literature and implement the same measures. A number of structural factors make this unreasonable, thus creating a need for well-focused research to define solutions relevant to LMIC.

The basics: issues with design and data collection

To define the current situation, identify problems, and set baselines against which innovations can be assessed for effect, it is necessary to gather and assess epidemiologic data. The global, generally population-level, epidemiologic data cited in the various WHO, World Bank, or other transnational organizational reports are generally presented with many explanatory notes discussing the validity of the data in terms of completeness of vital records and assumptions made in developing the final presentation [28,29]. Even the most fundamental of data used in such reports can be inconsistent. For example, in the United Nations urbanization population reports, geographic definitions of urban units, from which would be derived population figures that serve as the denominator for many epidemiologic studies, vary from region to region, if even specified [30,31]. Does New York City have a population of around 7 million or 17 million?
Various investigators have attempted to overcome problems of less than ideal data sets in developing economies, few of which have computerized databases of health or illness information. LaPorte [32], in 1994, proposed a technique commonly used in assessing animal populations: capture-recapture. Although this technique has been used in a number of studies, it has been criticized for methodologic difficulties, particularly in developing country settings [33-35]. In this technique, a database of interest/relevance is extracted, identifying all individuals of interest (eg, a police list of injured persons in motor vehicle crashes). A different list that should catalog the same information is extracted for individuals of interest (hospital ED registrations in the region). Any individuals who appeared in the first sample are identified in the second sample, thus giving some sense of how complete the each list is in capturing a representation of "reality." The exercise may be repeated with any number of lists (databases) that purportedly represent the same phenomenon. There are several limitations. For this to work, the lists should be independent (ie, not getting data from each other in any way), and a subject should have an equal likelihood of ending up on any of the lists, implying that each agency that makes up a list is equally staffed, vigilant, and informed of events to have the same chance to capture an individual, for example, injured in a car crash. The subject must be the same for each list. One study group realized they were having problems and found out that the local population had a socially accepted practice of using different names in different settings or in interacting with different persons/agencies [24].

Financial support for the collection of background epidemiologic data is frequently limited. Because personnel costs are generally the largest single category of any budgeted activity, techniques that increase the efficiency of person-hours allow for more data to be incorporated.

Two-stage cluster sampling is a personnel-efficient method for gathering survey data from larger populations with data access problems (access, cost, etc.). The population in question is divided into clusters, perhaps by geographic (area sampling), administrative (school districts, precincts), or other parameters. A sample of clusters is chosen using a simple random sample or a "probability proportional size"-based or other technique. From these clusters, enough elements (eg, people) of study interest are chosen to meet the required sample size (from prior sample-size calculations).

Because the clusters may vary in the total number of elements contained within each of them, "probability proportional to size" may be used to minimize distortion from the difference in frequency of occurrence of the event under study between clusters (eg, the fact that one cluster may have many more eligible subjects in it than another cluster) [36]. In using two-step sampling, care must be taken to account for intra-cluster grouping similarities of the ultimate study objects (neighborhood household members, school students, hospital patients, etc.). Mock et al [37] used this technique to establish a comparative portrait of trauma systems in
Ghana, Mexico and Seattle, making a strong argument for improving EM capacity in the developing economy setting.

An in-depth discussion of modifications of epidemiologic techniques in the face of questionable data sources is beyond the scope of this article; however, the point being made here is that the researcher working in the international/developing economy settings is best served by looking to a variety of techniques for data acquisition and analysis and by seeking assistance from other researchers experienced in developing country research.

Notwithstanding some of the methodologic difficulties that must be overcome in any population research setting and that are likely to be more vexing in developing countries, locally relevant, rigorously obtained epidemiologic data are critical for assessing pre-event, event, or post-event interventions. Considering the importance of epidemiologic findings in policy development, an epidemiologist or statistician experienced in developing-country research should be consulted at the time of research project planning to help choose the most rigorous methodology practical in the anticipated project setting. Development of locally managed projects through collaboration with developed-economy programs provides necessary background data and develops local research capacity. One such relatively recent project is the joint activity of Umeå University School of Public Health in Sweden and Hanoi Medical University in Vietnam. This project is a community-based epidemiologic surveillance station in northern Vietnam. The results of 2 years of surveillance were published as a series of articles comprising a supplement to the Scandinavian Journal of Public Health [38].

Current state of research in some selected domains

Outcomes research

Because the basic pathophysiology of disease and injury is the same in LMIC and HIC settings, the most significant contributions to improving a population's health will likely come from attempts to reduce the incidence of suboptimal health events or to improve the outcomes when such events occur. Numerous general health and disease-specific instruments exist for measuring outcome in different clinical settings. Evaluation of outcomes of care and interventions based on patients' personal sense of change in the quality of their life addresses the most fundamental rationale for medical care and public health initiatives—optimizing the WHO-defined condition of health. Coordination through the WHO of multi-country efforts to improve emergency care with projects structured similarly to the Integrated Management of Childhood Illness program permits cross-cultural assessments for quality indicators of emergency health care in resource-constrained settings [39]. Outcome evaluation has been proposed as useful and appropriate to apply to evaluating efficacy and quality EM care [40].
Health-related quality of life

In an increasing number of countries, self-reported quality of life (QOL) and health-related QOL are becoming major measures of performance of the health care system at all levels from physician practices to health care delivery systems [41-43]. One of the significant evolutions that have occurred in international health over the past 10 to 15 years has been a shifting of the burden of disease from lethal infant and childhood diseases to chronic disorders characteristic of developed economies. As a population shifts from the pyramidal age distribution of one burdened with high infant and childhood mortality to the more rectangular distribution associated with more chronic diseases, health care outcomes measures shift from questions of survival to questions of quality of existence [44].

Because QOL is an abstract construct, to measure it, it must be defined in terms of a validated, reproducible measure [45,46]. In 1989, the Rand Corporation published the Medical Outcomes Trust Study in which one of the primary study tools was a patient-based questionnaire designed to assess the respondents' QOL in relation to their health [47]. The instrument originally developed for this has been refined to what is now known as the "Short Form-36" or SF-36 [48]. This questionnaire has been rigorously validated in relation to a number of medical problems and in several countries [49,50]. Other instruments have been developed, validated, and translated into many languages, including the Duke Health Profile, the Sickness Impact Profile, and the Nottingham Health Profile [51]. Before these instruments are used in unvalidated settings, ethnographic assessment should be conducted to assure acceptance of survey techniques and to verify that translations of terms representing abstract constructs "mean the same" in the intended population of study. Perceptions of concepts such as "risk" vary greatly between cultures and under different circumstances in the same culture [52].

Unintentional injuries

Road crashes dominate the statistics related to societal burden from unintentional injuries. Researchers around the world have been actively working for a number of years to find locally applicable interventions to decrease the burden of these events. Researchers involved in this field come from a variety of disciplines, including civil engineers, urban planners, psychologists, and physicians. Some resources are listed at the end of this article. The vast majority of research has been directed at the prevention of the event or of injury during the event.

Rivara et al [53] reviewed literature and statistics in the United States related to the national development of regional trauma response systems and concluded that an effect takes several years to become apparent. The implications for developing economies with the increasing burden of traffic...
crash injuries are direct: Research, planning, and policy development/implementation need to occur now to mitigate the effects of coming socio-cultural changes. A view from this perspective is like looking at the beach water receding more than usual in the moments before arrival of a Tsunami. Hopefully, some policy makers will lift their eyes before they are washed away. There is little in the literature regarding low-cost approaches to organized, stratified trauma response in developing economies [54-56].

At a Centers for Disease Control-sponsored symposium on improving statistical information on injuries, reference was made to literature on international occupational deaths with only three articles cited, all using developed economies as the research arena [57]. Emergency medical care providers are frequently the first point of contact for injured workers, whether symptoms become apparent at the work site or later. A solid understanding of unique risks at local work sites often provides critical information for correct diagnosis and treatment planning. Research on local risk factors and training of local health workers in emergency occupational medical principles are underdeveloped on a global basis. A search of the Medline database crossing the medical subheadings "occupational accidents" and "developing countries," limited to English language and Human publications, yielded only 45 articles. "Occupational accidents" yielded 9878 articles. The legions of factory, crafts, agricultural, and other workers in developing economies have not had adequate attention put to defining and controlling their risks or the acute care of their injuries with recognition of the link to occupation. From the ship-breaking beaches of Pakistan to carpet-weaving shops in Srinigar to brothels throughout the world, occupational injuries and illnesses are epidemic, with the most common point of contact to the health care system frequently being the local version of EM.

Childhood injuries carry a high mortality and morbidity in developing countries for a variety of reasons from traditional practices to access to care [58]. Bartlett [59] reviewed the literature on this topic and concluded, "existing research is scanty and is largely limited to hospital-based studies." Childhood injuries are frequently looked upon as "a part of growing up" and thus frequently receiving less attention than deserved even when they are well documented in school settings [60].

Other domains of unintentional injury that have been studied in the HIC, such as falls among elderly persons, need culture-specific research to seek the best setting-specific solutions to decrease the individual morbidity and the societal burden.

Intentional injuries

Interpersonal violence is such an integral part of the domain of emergency health care, particularly in the United States, that it deserves particular study in developing countries. Several researchers in the
international arena have brought up the connection between interpersonal violence and various political issues [61,62]. Oloruntumehin [63] reviews and comments on some of the factors that likely link rapid urbanization in developing countries with increased violence.

The issues of domestic violence and child abuse are recognized to be problems in all countries, although on-site professional training for recognition and acute management of the psycho-social crisis is lacking in most countries. A search of the United Nations Human Rights web site on the topic of child abuse yielded 250 citations, with many of them being individual country declarations to work toward curtailing it. Lachman [64], in a review focused on Africa, points out that it is only in the last few years that a broader definition of child abuse had been used in South Africa but that there are major cultural hurdles, with practices such as female circumcision and corporeal punishment still socially accepted.

Self-inflicted injuries

Depression and associated self-inflicted injuries have been identified as significant and growing contributors to the BOD, with an estimated 1 million successful suicides globally in 2000 (the same number of deaths as from malaria); this has been designated one of the “Grand Challenges.” As in the United States, a significant number of attempts are by young adults and adolescents [65,66]. Although pesticides are the agent of choice for self-injury in most developing economies [67,68], other methods, such as drowning, self-immolation, and hanging are favored in some parts of the world [69]. Preventive and therapeutic endeavors deserve further culture-specific analysis.

The list of injury control and management issues that deserve study as part of the effort to fulfill the UN goal of “health” for all global citizens is large, providing ample opportunities for project development.

Noninfectious diseases

Projections of various population evaluations suggest that the global trend of increasing survival to adulthood noted over the past 20 years will continue, contributing to a global mean population age shift, increasing the proportion of the global population aged 60 and over from 10% in 2000 to 21% in 2050 with 59% of that age group located in the Asia and Pacific region [70]. On a health basis, this translates to an increasing global burden of chronic diseases and acute diseases of aging populations. Although space permits only brief treatment of three high burden of disease priority topics here, the interested reader might consider researching additional topics such as falls in the elderly population, ethics of end-of-life decisions in resource-constrained settings, to mention two at widely different points on the spectrum.
Cardiovascular diseases

In 1999, cardiovascular disease (CVD) accounted for a third of all deaths and 78% of deaths in LMIC, more than any other class of disease [71]. As economies evolve, they harbor different groupings of CVDs, starting when they are less developed with higher incidences of congenital and rheumatic heart disease and progressing to hypertension and ultimately to a state of affairs similar to the United States and Western Europe [72]. Although cost-effectiveness is a theme in CVD treatment research in developed economies, the treatment of these entities is a goal in the United States. Many of the response protocols being developed for that market are likely to entail financial burdens that make direct transfer to a developing economy difficult. For example, are chest pain observation centers and intensive care unit admission for non-Q-wave infarcts reasonable responses in other cultures for sociologic or economic reasons? What are the culture-specific indicators for choosing a level of medical response?

Respiratory illness

Although the United States and increasing numbers of developed countries have successfully campaigned to reduce cigarette smoking, the sales of tobacco products have steadily climbed in the developing world. According to the WHO, as of 2003, around 60% of the estimated 5700 billion cigarettes sold annually and 75% of tobacco users are in developing countries [73]. Tracheal, bronchial, and lung cancers as a group were the tenth leading cause of death worldwide for males in 2000 [74].

Throughout Asia, manufacturing is increasing at a frenzied pace with variable environmental controls. With major shifts of population distribution leading to increased urbanization and the expected increases in particulate pollution from resultant mega-cities, pulmonary disorders such as chronic obstructive pulmonary disease and allergic reactive airway disease will increase in many parts of the world [75]. Although these areas have been heavily studied in the United States, research is needed to find the best management plans in other cultures.

Mental health

Uni-polar depression has emerged over the past 15 years as one of the top health burdens in all societies. In the United States, depression has been found to be a major cause of work absenteeism, leading to a significant financial burden on businesses [76]. In developing countries, depression has roots in multiple factors, with conflict being a frequent correlate [77,78]. Improving health worker understanding of the correlation between physical symptoms and mental disorders should improve the correct identification and treatment of patients presenting for emergency health care [79].
Health care systems and policy development

As many countries advance economically and develop more formally organized health delivery systems, it is much easier for policy makers to develop the legal and policy framework for an effective, efficient health care system if they operate with strong data. Patching emergency care on after a system has been developed without attention to supporting the unique and critical requirements for locally appropriate, efficient emergency medical systems will likely lead to lost lives and increased cost later when attempting to respond to increasing demand associated with further economic development.

Effective public health policy development and implementation can be difficult for a number of reasons, from special interest group opposition (e.g., from the tobacco and alcohol industries) to restrictions on advertising to public sense of encroachment on personal liberties (e.g., helmet or seat-belt laws). The OECD, an organization primarily of developed economy countries, has declared a focus on corruption as an issue of "major political and economic significance" [80]. This topic is being discussed with increasing openness in international development literature as a reality that, like any other system problem, needs study to characterize it with the goal of attempting to control or eliminate it. Klitgaard et al [81] published a small handbook that covers many of the issues surrounding this topic.

Emergency medicine systems development

Trauma response

Trauma response research in developing societies must address the issue of accessibility to health care resources from the perspectives of geographic and financial factors. In a study of children with burns in Ghana, Forjuoh [58] brought out at least two significant accessibility issues: (1) A number of children did not present until several days after the injury due to financial restrictions or poor transport infrastructure (dirt roads), and (2) 33% of delayed presentations were due to lack of awareness of the burn severity, revealing a need to study methods of public education.

Mock et al [82], in a study of trauma, also in Ghana, found that only approximately 50% of patients with one or more day of disability from a traumatic event sought formal medical care. Forjuoh et al [58] found in their study of burns that a significant number were treated with home remedies that consisted of various natural products from plants to urine and cow dung, frequently complicating the course. These two studies bring up a number of questions that need further evaluation to help delineate the best response in these societies to decrease the burden of these injuries.

Arreola-Rissa et al [56] turned their attention to Latin America in a study evaluating trauma outcomes in Monterey, Mexico in comparison to Seattle.
They found that the most significant difference was in the prehospital domain. Their initial epidemiologic study led to a focused second study to evaluate the effect of low-cost interventions, such as changes in the dispatch paradigm [83]. Ali [84] also addressed the issue of trauma care and found an improvement in trauma mortality after presentation of the American College of Surgeons Advanced Trauma Life Support course in the Caribbean country of Trinidad and Tobago. This study was early in the development of what is now one of the more advanced Emergency Medicine systems in the Caribbean. Evaluation of hospital trauma management using well-validated instruments such as TRISS scoring allows for better interfacility comparison and the creation of larger databanks for further study [85].

Prehospital care

In most LMIC, the most rapid transport to a hospital or emergency health station is not by ambulance or any other form of organized system. Frequently it is by private citizen using whatever means of conveyance is handy, from carrying in the arms to wheelbarrows, animal carts, or taxis. Generally, it would be unrealistic to propose development of a United States- or European-style prehospital system in these settings. The most effective models for different LMIC will be best determined through well-designed outcomes studies examining innovative, context-relevant, cost-sensitive responses that may incorporate principles from HIC systems. In an extensive literature review looking for low-cost interventions to decrease the burden of injuries in developing countries, Mock et al [86] identified three domains encompassing areas that need further assessment: (1) human resources (staffing and training), (2) physical resources (equipment, supplies, and infrastructure), and (3) administration and organization. As with Arreola-Risa's study in Monterey [83], partnerships of LMIC settings with culturally sensitive HIC EM researchers will help reveal cost-effective, locally appropriate solutions.

Other systemic issues, such as effective staffing, site-appropriate triage, and effective management of high volume, have pressing questions that need well-managed projects to help provide a better service. Molyneux [87] found, in a pediatric service in Malawi, that institution of an emergency service with up to 800 patients per day was associated with an in-patient case fatality rate decrease from around 12% to around 6%. Regional and national resources such as poison control centers, disaster response plans, health care worker certification, and continuing education need input from research results to provide the most appropriate local service.

Public education

In many developing economies, access to formal emergency health services is impeded by a number of factors from geography to poverty. Increased awareness by the general public regarding initial management of
A number of health problems will likely assist in limiting the burden on formal health resources while decreasing the incidence of delayed presentations with associated complications, such as those seen by Forjuoh in Ghanian children with burns [58]. Public education in injury and illness recognition and initial management of disease and injury should be a part of the public health system in all countries.

Organized out-of-hospital emergency care systems have been characterized as cost inefficient [88]. These conclusions generally refer to the concept of ambulances staffed with trained medics [89,90]. Building the capacity of local community health workers to understand and implement appropriate emergency care principles may be more appropriate but requires training programs and outcomes research similar to what has been done for the WHO IMCI (Integrated management of childhood illness) program [39].

Funding

Funding for EM-relevant research in LMIC has become more available with increasing international awareness of the importance of injury contribution to the burden of disease [72]. There is a multitude of funding agencies interested in improving the health conditions of people throughout the world. Most have specific mandates from their mission statements that are often purposely broad to allow evolution with the context within which the agency wishes to operate [91]. The World Bank has become the largest financial supporter of health development [92]. World Bank loan-associated policies, such as structural adjustment and a push through the 1990s for privatization, have generated a great deal of controversy [93,94]. Pressure on recipients to follow World Bank programs without adequate attention to fundamental sociologic and ethical issues of access for the poor have at times left a bad impression of HIC-driven health policy projects in LMIC [95].

On the other side of the coin, many initial incarnations of research ideas can be refined in ways that keep the researcher's interest and possibly serve the population better as they more closely mate with funders' agendas. Funding agencies that rely on individual donations are caught in the "popularity of the moment" trap in that they must keep the attention of their donors. As with domestic United States medical research, the large multilateral funding agencies, such as the United States Agency for International Development, CARE, the World Bank, and others, have core mission statement agendas and shifting priorities based on regional or world political and economic conditions. Michaud and Forjuoh [96] reviewed assistance to the health sector from 1972 through 1990 and concluded that the vast majority of international assistance was directed to infectious disease programs (Table 1). Although their review was for a period of time before the BOD report, many funding sources are still more focused on infectious disease and primary health care principles with much less support of noncommunicable diseases [97].
Table 1

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<th>Topic</th>
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<td>Leprosy, tropical diseases, HIV, STDs</td>
<td>$4/USD/DALY</td>
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<td>Expanded Program on Immunization, malaria, and trachoma</td>
<td>$1/USD/DALY</td>
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<tr>
<td>Acute respiratory infections, noncommunicable diseases, injuries</td>
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Funding by developed nations in 2001 was assessed at around US$53 billion, equivalent to 0.2% of the total combined gross national product (GNP) of donor countries, well below the United Nations guideline level of 0.7%. If all donor countries raised their donation levels to 0.7%, the monetary value would be between US$175 and 200 billion. The UN projected health portion of that would be US$27 billion, although defining which parts assist health development would be difficult [99].

Private donations are a significant factor in health development, whether as small donations or contracts from nongovernmental organizations (NGOs) or as family foundation donations. The Bill and Melinda Gates Foundation, in conjunction with the Foundation for the NIH, commissioned a panel of 20 scientists from developing and developed countries to devise a list of “Grand Challenges” to remove “critical barriers to solving important health problems in the developing world” [97]. The panel decided on a list of seven Goals with 14 Grand Challenges that they felt represented some of the heaviest burdens on the most vulnerable sectors of the poorest, least-developed economies. These challenges are somewhat different from the top 14 projected global burdens of disease (Table 2). In 2003, the Gates Foundation donated $200 million to the Foundation for the NIH to award as grants for study of these 14 Grand Challenges [97].

The UN published an economic analysis overseen by Jeffrey Sachs in 2001 in which a strong case is made for the severe burden of infectious diseases, malnutrition, lack of water, and security, particularly among the poorest of countries [98]. At the same time, the demographic factors that favor diseases from the BOD list are evolving in even the poorest of nations (eg, more motorized transport, urbanization, and economic disparity with attendant violence).

Ethics and institutional review in international projects

There are innumerable EM-relevant questions that need answers to improve global health. In addition to logistic challenges, transnational research and development projects bring forward challenging ethics issues. Such ethics questions can be seen as related to the structure of the project or to the enrollment of subjects to study or “serve.” Both aspects have relevance in the international setting, particularly when projects are
### Grand Challenges versus Global Burden of Disease

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<tr>
<td>GOAL: To improve childhood vaccines</td>
<td>1. Ischemic heart disease</td>
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<tr>
<td>GC#1: Create effective single-dose vaccines that can be used soon after birth</td>
<td>2. Unipolar depression</td>
</tr>
<tr>
<td>GC#2: Prepare vaccines that do not require refrigeration</td>
<td>3. Road traffic accidents</td>
</tr>
<tr>
<td>GC#3: Develop needle-free delivery systems for vaccines</td>
<td>4. Cerebrovascular diseases</td>
</tr>
<tr>
<td>GOAL: To create new vaccines</td>
<td>5. Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>GC#4: Devise reliable tests in model systems to evaluate live attenuated vaccines</td>
<td>6. Lower respiratory infection</td>
</tr>
<tr>
<td>GC#5: Solve how to design antigens for effective, protective immunity</td>
<td>7. Tuberculosis</td>
</tr>
<tr>
<td>GC#6: Learn which immunologic responses provide protective immunity</td>
<td>8. War</td>
</tr>
<tr>
<td>GOAL: To control insects that transmit agents of disease</td>
<td></td>
</tr>
<tr>
<td>GC#7: Develop a genetic strategy to deplete or incapacitate a disease-transmitting insect population</td>
<td></td>
</tr>
<tr>
<td>GC#8: Develop a chemical strategy to deplete or incapacitate a disease-transmitting insect population</td>
<td></td>
</tr>
<tr>
<td>GOAL: To improve nutrition to promote health</td>
<td>9. Diarrheal diseases</td>
</tr>
<tr>
<td>GC#9: Create a full range of optimal, bioavailable nutrients in a single staple plant species</td>
<td></td>
</tr>
<tr>
<td>GOAL: To improve drug treatment of infectious diseases</td>
<td>10. HIV</td>
</tr>
<tr>
<td>GC#10: Discover drugs and delivery systems that minimize the likelihood of drug-resistant micro-organisms</td>
<td></td>
</tr>
<tr>
<td>GOAL: To cure latent and chronic infections</td>
<td>11. Perinatal disorders</td>
</tr>
<tr>
<td>GC#11: Create therapies that can cure latent infections</td>
<td>12. Violence</td>
</tr>
<tr>
<td>GC#12: Create immunologic methods that can cure chronic infections</td>
<td></td>
</tr>
<tr>
<td>GOAL: To measure disease and health status accurately and economically in developing countries</td>
<td></td>
</tr>
<tr>
<td>GC#13: Develop technologies that permit quantitative assessment of population health status</td>
<td>13. Congenital anomalies</td>
</tr>
<tr>
<td>GC#14: Develop technologies that allow assessment of individuals for multiple conditions or pathogens at point-of-care</td>
<td>14. Self-inflicted injuries</td>
</tr>
</tbody>
</table>
primarily based in a HIC with the target population in a LMIC [99]. Many projects have been developed without input from the target populations. Ethical considerations in international research have recently been discussed in the literature as having not been well addressed in an organized fashion and not involving input from the developing countries being studied [100].

The fundamental structure of research studies, particularly double-blind, randomized, controlled studies, has been cited frequently in the discussion of research ethics when applied to studies involving developing country populations as raising significant ethical dilemmas [101]. The focal point for much of the more recent discussion has been the use of placebo-controlled studies and the choice of regimen being tested in clinical trials of HIV treatment regimens in the developing world, particularly in prevention of vertical (maternal-fetal) transmission. The question is whether it is unethical to trial an unknown, usually less expensive, method in an LMIC population when it is not being trialed in an HIC population or to test various prevention strategies without a therapeutic arm to the study [102-104]. The guiding principles found in the Nurnemberg Code [105], the Helsinki Declaration [106], the International Ethical Guidelines for Biomedical Research Involving Human Subjects (published by WHO in cooperation with the Council for International Organizations of Medical Sciences [107]), and other documents on human rights and medical research (Box 1) are called upon to be at the foundation of research design and implementation.

The construct of "ethical" involves some fundamental characteristics relevant to all populations while being socio-culturally sensitive. It is a concept that has evolved with greater scrutiny and as new situations have demanded review. The Helsinki Declaration has been revised twice since it was put forth in 1964 by the World Medical Association. The last planned revision was tabled amid concerns of inadequate input from LMIC representatives [108]. The principles apply to development projects as well, particularly when new approaches are being instituted.

All studies and projects are dependent on recruiting subjects. In LMIC and HIC, providing small compensation to research subjects has been an accepted practice. Whether the activity is responding to a survey or bringing a child for vaccination in a displaced persons camp, many international projects use "token" compensation. In addition to posing the ethical question of "rewarding" (even with a bar of soap) someone to participate, such schemes can backfire; Renne [109] reports that bouillon cubes being given in thanks for family planning survey respondents were rumored to be adulterated with sterility drugs. The local population in this case felt offended by the offering of compensation because participation was something they gave freely [109]. As with many such studies and projects, ethnographic groundwork is frequently limited due to a combination of time and funding issues [109,110].

In EM research, specialty-specific issues have arisen, such as research in critical care prehospital settings. Even for topics that have achieved
Box 1. Documents outlining research ethics

- The Nuremberg Code [105]: The foundation for modern attitudes toward the use of humans as experimental subjects. Developed in response to experiments performed during World War II by German Nazi physicians; put forth 1947. (www.ohsr.od.nih.gov/guidelines/nuremberg.html)
- Declaration of Helsinki: "Ethical Principles for Medical Research Involving Human Subjects" drawn up by the World Medical Association in 1964 with amendments over several following years. It is more of a guide for use of the Nuremberg Code. A proposal to revise in 1997 was tabled amid wide criticism [108]. (www.wma.net/e/policy/b3.htm or www.ohsr.od.nih.gov/guidelines/helsinki.html)
- Guidelines for Conduct of research involving Human Subjects at NIH (Gray Booklet): The NIH policies and procedures for using human research subjects. (www.ohsr.od.nih.gov/guidelines/45cfr46.html)
- Department of Health and Human Services, National Institutes of Health: Office for Protection from Research Risks - Part 46 - Protection of Human Subjects: Primary federal law governing the use of human subjects. International guidelines are located at paragraph 46.101(c), effectively stating that guidelines need to "afford protection at least equivalent to those provided in Volume 45 of the Code of Federal Regulations (45 CFR 46 ff)."
- International Ethical Guidelines for Biomedical Research Involving Human Subjects: Published by the Council for International Organizations of Medical Sciences, in a joint effort with the WHO. Originally promulgated in 1982 as "Proposed guidelines . . ." from WHO and quoted as such in the literature before 1993.

societal- or court-based approval in an HIC, assumption of acceptance in LMICs is presumptive of the comparability of the cultural ethos and disrespectful of the "subject" population because they have not been party to the discussions leading to acceptance in the HIC.

As Annas [111] has stated, "informed consent is a process" in which the potential subject must be given enough appropriate information to allow an informed choice. Many people in developing societies have little or no familiarity with research studies. Ethnographic study to assess the perception of risk within a culture can be helpful in formulating an analogous construct that might be used in community information meetings.
to introduce a study or project [52,112]. Innovative processes may be more applicable in such settings, such as used by a French team who developed what they dubbed "triple media recording" to consent illiterate Paraguayan Indians using voice, video, and still photographic recording of the consent process [113].

Getting into the topic

Those who are serious about becoming involved in the international domains of medicine must broaden their search criteria in terms of places to look for information. Much literature on international health issues exists in domains that are not cataloged in MEDLINE. Whether the source is a journal that is not in the collection or a report generated by an NGO, think tank, or university-based program, performing term-based searches with various Internet-based search engines is frequently time consuming and yields number of "hits" that are not of high quality. Even when armed with the exact reference, many medical schools in the United States are likely to not have subscriptions to some of the more obscure journals. At times one is able to find the e-mail contact for authors. This author has had no refusals to requests for copies of articles through e-mail contact of other authors.

The reader is encouraged to follow the reference trail. Many of the authors are cited here, and although the majority addresses non-emergency medicine, numerous other publications are cited (see Appendix 2). Their references lead one further down the research question-generating path. We are hopeful that this article will stimulate the interested reader to help answer some of the questions on that path.

Summary

As the global culture moves forward into the 21st century with increasing interaction of populations through direct contact and electronic interchange, those citizens of our planet who have not benefited from the material gains that have been realized in the "mature economy" countries will increasingly seek equity on all levels, beginning with the most fundamental aspect of health care. There is a need to develop a capacity for treatment of urgent and emergent health conditions globally, a need that will only increase with advancing global economic development.

Acknowledgments

The authors thank Karen Hofman, MD, for her review and helpful comments on this article.
Appendix 1. Definition of terms

LMIC—Low- and middle income countries. The World Bank classifies countries by income according to gross national income (GNI) per capita with the GNI calculated by the Atlas method (see below). For 2003, the groups were: Low-income, $765 or less; lower- to middle-income, $766 to $3035; upper middle income, $3036 to $9,385; and high income, $9386 or more (www.worldbank.yclass/countryclass.html).

GNP—Gross national product. GNP equals the gross domestic product (GDP is defined as the total market value of all final goods and services produced in a country in a given year, equal to total consumer, investment, and government spending, plus the value of exports, minus the value of imports) plus the income earned by domestic residents as a result of investments abroad, minus the income earned in domestic markets accruing to foreigners abroad.


GNI—Gross national income. "The aggregate value of the gross balances of primary incomes for all sectors." GNI is equal to GDP less taxes (less subsidies) on production and imports, compensation of employees, and property income payable to the rest of the world plus the corresponding items receivable from the rest of the world. Thus GNI at market prices is the sum of gross primary incomes receivable by resident institutional units/sectors. It is commonly denominated as GNP. In contrast to GDP, GNI is not a concept of value added but is a concept of income (United Nations; Statistics Division: unstats.un.org/unsd/cdb/cdb_dict_xrxx.asp?def_code=326).

Appendix 2. Additional resources

Foreign aid in the national interest: www.usaid.gov/fani/cover.htm. [Official USAID web site presenting the United States foreign aid policy from the agency perspective.]

Forjuoh SN, Li G. A review of successful transport and home injury interventions to guide developing countries. Soc Sci Med 1996;43:1551-60. [Although this article focuses on strategies to prevent traumatic events, it is an excellently referenced discussion of potential areas of intervention in developing economies. Dr. Forjuoh has authored numerous papers on injury issues in sub-Saharan Africa. It is useful to search Index Medicus for his name to gain an appreciation of the developing country injury literature.]

Global Forum for Health Research: www.globalforumhealth.org/pages/index.asp?ThePage=page1_000500040001_1.htm&Nav=000500040001. [A multilateral organization formed in 1998 to address the "10/90 gap" in
health research spending. Supported by several major developed country supporters of international health research. The Forum attempts to bring together relevant parties from different sectors (government, university, private, researchers, funders) to seek the most cost-effective means to develop research on global health issues. Annual reports are available in pdf format and include reports on global funding and agendas for research.

Human Rights Center at the University of Minnesota: http://www1.umn.edu/humanrts/center/default.html. [Electronic resources including links to most of the major documents that form the foundation for discussions of human rights and ethical issues in health care, particularly internationally. A number of the documents are available in pdf format.]


Research Ethics Training Curriculum: Family Health International: www.fhi.org/en/RH/Training/trainmat/ethicscurr/index.htm. [This on-line training manual is a comprehensive discussion of the topic, relevant whether performing United States-based or international research. In addition to the curriculum, the texts of the United States code for treatment of human subjects and the 1993 version of the International Ethical Guidelines for Biomedical Research Involving Human Subjects from the Council for International Organizations of Medical Sciences (2003 version available in hard copy from CIOM in Geneva) are included.]


Rivara FP, Grossman DC, Cummings P. Injury prevention: second of two parts. N Engl J Med 1997;337:613-8. [These two articles are directed at the United States; however, much of the discussion has universal applicability, and there are a number of references to international studies. Dr. Rivara has published extensively on the domestic and international aspects of injury management and prevention.]

Rivara FP, Cummings P, Koepsell TD, et al, editors. Injury control: a guide to research and program evaluation. Cambridge: Cambridge University Press; 2001. p.304. [The chapters are generally short and written at a practical level, useful for novice researchers in the field and researchers with experience in other fields. For example, one reviewer commented on the chapter on qualitative methods as presenting a convincing argument for the merits of this type of research model, particularly in injury control research.]

Third World Network: www.twnside.org.sg. [A reputable resource of contacts and information from the perspective of developing countries. Offers an alternative view at times from that of other transnational development organizations.]
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