

Beyond the bedside: A review of translational medicine in global health

Richard S Hoehn, Daniel E Abbott

Richard S Hoehn, Daniel E Abbott, Department of Surgery, University of Cincinnati, Cincinnati, OH 45267, United States

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Correspondence to: Daniel E Abbott, MD, Department of Surgery, University of Cincinnati, 231 Albert Sabin Way, ML 0558, Cincinnati, OH 45267,

United States. abbottde@ucmail.uc.edu

Telephone: +1-513-5587865

Fax: +1-513-5840459

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syndrome, and non-communicable diseases. Laboratory research has excelled in many of these areas and is struggling in a few. Where successful therapies have been discovered there are often problems with appropriate use or dissemination to groups in need. Also, many diseases would be better prevented from a population health approach. This review highlights successes and struggles in the arena of global health, from smallpox eradication to the impending epidemic of cardiovascular disease, in an attempt to illustrate of the various phases of translational research.

Key words: Global health; Human immunodeficiency virus; Translational research; Vaccines; Cancer; Non-communicable diseases

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Core tip: This review summarizes efforts in translational research as applied to the major global health issues of vaccines, human immunodeficiency virus and acquired immunodeficiency syndrome and non-communicable diseases. Historical perspective as well as current efforts are presented in an effort to describe the success and challenges that are concurrent with translational medicine on the international stage.

Abstract

Translational research is a broad field of medicine with several key phases moving from scientific discovery to bench research and the hospital bedside, followed by evidence-based practice and population-level policy and programming. Understanding these phases is crucial when it comes to preventing and treating illness, especially in global health. Communities around the world struggle with a variety of health problems that are at some times similar and at others quite different. Three major world health issues help to outline the phases of translational research: vaccines, human immunodeficiency virus and acquired immunodeficiency

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INTRODUCTION

To address the breadth of translational research, the United States National Institutes of Health has recently endorsed a 5-phase model that describes the process

of moving from scientific discoveries to population health (Figure 1)^[1]. The process starts with scientific discovery of a problem or pathology, termed T0. From there, T1 and T2 encompass the classic “bench to bedside” process of finding a candidate treatment, test, or clinical intervention (T1) and then comparing safety and efficacy of the candidate against a placebo or existing therapy in randomized trials or other study designs (T2). Lastly, T3 research focuses on implementation and dissemination of evidence-based interventions and T4 examines population-level health impact and cost-effectiveness^[2].

The purpose of this review is to describe the impact of the phases of translational research on global health. Communities around the world suffer from health issues that are at times very different but can also be quite similar. Some therapies are readily available in resource-rich countries but scarce in less affluent countries. Other therapies simply do not work in certain parts of the world due to disease specificity or cultural issues. Though there are many blights, three major issues affecting the health of the global population are vaccine development, the human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS), and non-communicable diseases (NCDs). Here we will review the history and current status of research in these areas, highlighting the role of various phases of translational research with respect to their effects on global health.

VACCINES

Early successes

The history of vaccine development and distribution exemplifies translational research. Edward Jenner discovered the smallpox vaccine in the 1790s by treating patients with “matter” from the sores of cowpox^[3]. This technique of sharing the live cowpox virus between patients lasted through the 19th century until the development of a live attenuated vaccine in the early 20th century^[4]. In the coming decades the World Health Organization (WHO) would sponsor a smallpox vaccination program, and eradication of the virus was formally declared in 1980 (the only other disease to be declared eradicated is Rinderpest, an RNA virus that affected cattle and water buffalo, mostly in Africa; vaccines for this virus were developed in the early 20th century and two major attempts at mass vaccination led to eradication in 2011).

A second vaccination “victory” resulted from the work of one of the fathers of bacteriology, Robert Koch, who demonstrated that the bacterium *Bacillus anthracis* was the cause of “wool-sorters’ disease” in 1876^[5]. Anthrax had plagued livestock for millennia, and humans involved in wool and hide processing were at risk of infection. Following this discovery, Louis Pasteur described a randomized controlled trial in which he treated livestock with an attenuated anthrax vaccine prior to inoculating them with a virulent strain

of the bacteria^[6]. The results were dramatic; 48 h after inoculation, all vaccinated sheep survived and all un-vaccinated sheep were dead. Virtual eradication was made possible by livestock quarantining and vaccination, but recent terror attacks using the anthrax spore have generated interest in newer vaccines^[7-9]. While the vaccine is only available for at-risk patients (veterinarians, researchers, certain military personnel, etc.) due to difficulties with production and storage, research is underway to develop a stable, needleless vaccine for widespread use^[10].

Works in progress

Worldwide, diarrheal illness is the second leading cause of death in children under the age of five years (760000 deaths each year)^[11]. There are many causes of diarrhea and a significant portion of the disease burden can be prevented through public health efforts to create safe drinking water and adequate sanitation. Infectious causes are well described, and three major sources have been the focus of vaccination efforts in recent decades.

Rotavirus is a leading cause of child mortality worldwide, especially in low-income regions; in children under the age of five in 2008, 5% of all mortality and over one-third of diarrhea-related mortality were attributable to rotavirus infection. Early experiments led to development of monovalent live-oral vaccines with variable success^[12]. In 1998 the rhesus rotavirus tetravalent vaccine (RRV-TV) was licensed for administration in children after successful trials. However, after several cases of bowel obstruction and intussusception following vaccine administration, the Centers for Disease Control and Prevention advised against using the vaccine and in 1999 the manufacturer withdrew the vaccine from market^[13]. Since that time, three live-attenuated oral vaccines have been approved for use. The monovalent (RV1) and pentavalent (RV5) rotavirus vaccines have been evaluated in several large trials and subsequently approved for use in most countries including the United States and the European Union^[14]. A third, the Lanzhou lamb rotavirus vaccine, has been approved for use in China only^[15].

Another major cause of diarrheal illness is typhoid fever, caused by *Salmonella enterica typhi* (*S. typhi*). Two vaccines, injectable (Vi PS) and oral (Ty21a), have shown efficacy and safety in clinical trials and field settings in Chile, Indonesia, and India, but are not ready for widespread immunization protocols^[16]. The Vi PS vaccine is non-immunogenic in children under 2 years, and many *S. typhi* strains are negative for the Vi polysaccharide. The Ty21a vaccine is not recommended for children under 5 years, and its acid-labile nature creates challenges with oral administration. Several newer typhoid vaccines are currently in phase 1-3 trials worldwide, but not licensed for use^[17].

Cholera, caused by *Vibrio cholerae*, is another area of focus for vaccine manufacturers. Dukoral®, an oral killed whole-cell vaccine, was licensed after

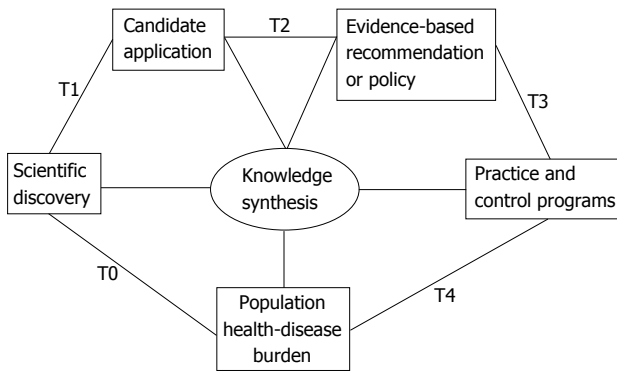


Figure 1 Epidemiology and the phases of translational research. T0: Scientific discovery research; T1: Translational research from discovery to candidate application; T2: Translational research from candidate application to evidence-based recommendation or policy; T3: Translational research from recommendation to practice and control programs; T4: Translational research from practice to population health impact. Source: Khoury *et al.*^[2]

a large randomized controlled trial in Bangladesh in 1990^[18]. The per-dose cost of United States \$5.25 was felt to be prohibitive for use in low-income regions, and subsequent development of Shanchol® at United States \$1.85 per dose was deemed fiscally feasible; Shanchol® use was then adopted after randomized controlled trials in Vietnam and India confirmed safety and immunogenicity^[19,20]. Four single dose, live attenuated oral cholera vaccines are in active clinical programs with hopes to improve efficacy, hasten onset and increase duration of protection^[21].

Ongoing challenges with "the big three"

Despite some vaccination success as a result of collaborative translational research implementation, malaria, tuberculosis (TB), and HIV/AIDS are three of the top ten causes of death worldwide^[22]. As such, much attention and funding has been directed towards finding vaccines for these diseases. Progress has been made, but there are still significant challenges.

There are approximately 250 million reported cases of malaria every year, including almost one million deaths in Sub-Saharan Africa, mostly in children^[23]. Many different vaccines are currently in various trials and they all face a similar challenge; *Plasmodium falciparum*, the causative agent of malaria, has a complex life cycle, with polymorphic antigens expressed in separate phases of the cycle^[24]. The best current vaccine candidate, RTS,S/AS01, is a combination of a portion of the circumsporozoite protein that helps the parasite invade human liver cells and the hepatitis B surface antigen, as well as the liposomal formulation adjuvant AS01. A phase II b trial of the RTS,S malaria vaccine showed safety and efficacy at 20 mo^[25] and phase III trials have demonstrated 31%-56% efficacy for one year, with protection from clinical malaria for at least 3.5 years^[26,27]. However, efficacy of the vaccine wanes with time and also varies based on the age of the vaccinated child^[28]. Despite mediocre results,

RTS,S will likely be the first malaria vaccine to receive regulatory approval^[29].

The bacille Calmette-Guérin (BCG) vaccine for *Mycobacterium TB* is one of the earliest developed vaccines and has been given to over four billion people to date^[30,31]. Despite this fact, TB kills 1.4 million people annually and drug-resistant TB is becoming a major problem^[32]. BCG protects infants from tuberculous meningitis and miliary TB, but is less effective against pulmonary TB in adolescents and adults. There are currently almost twenty candidate vaccines in various phases of clinical trials, all designed to prevent active TB disease^[32,33]. Some of these are live recombinant vaccines that have been genetically engineered for enhanced efficacy and/or safety, meant to replace BCG. Others are proteins or viral vector expressing antigens that are meant to serve as an immune booster following initial treatment with the BCG vaccine^[24]. A common challenge among trials evaluating TB vaccines is that the disease has a long latent period; thus, trialing preventative vaccines is slow and expensive^[31].

HIV kills two million people annually and infects approximately 7000 people per day, making it one of top causes of death worldwide^[34]. Naturally, a significant portion of the world's research dollars are directed toward treating and preventing this disease. Challenges facing researchers looking for a vaccine against HIV include: global variability of HIV, lack of a validated animal model with appropriate immune response, large variety of infected cells that develop as a result of HIV genome integration into the host's DNA, and destruction of immune cells by HIV^[24]. Phase III trials of most vaccines have failed to show efficacy^[35,36] or reduce viral loads^[37,38], and some have actually shown increased HIV infection among vaccine recipients^[39]. The most exciting results are from a randomized controlled trial comparing placebo to a recombinant canarypox vector vaccine (ALVAC-HIV) and two boosters of a recombinant glycoprotein 120 subunit vaccine (AIDSVAX B/E). In a population of greater than 16000 healthy Thai volunteers, this AIDSVAX B/E showed 31% vaccine efficacy vs placebo by reducing the cumulative probability of infection, but did not reduce viral loads^[40]. Nevertheless, finding a safe and effective vaccine against HIV is proving to be one of the most daunting tasks in research today^[41].

Targeted efforts in resource-poor environments

Even when early-phase translational research has found a safe and effective vaccine for a given disease there are still challenges to widespread availability, and the major barrier to vaccine development for low-income regions is cost^[42]. Patients in poor countries cannot afford new, expensive vaccines and pharmaceutical companies are not incentivized to invest capital in developing treatments that will be too expensive for the prospective customers to afford^[43]. Not only that, but the opportunity costs of delaying more profitable projects

are not appealing to industry. To solve this problem, major institutions in global health came together in 1999 to create the Global Alliance for Vaccines and Immunization (GAVI)^[44]. One aim of the alliance is to support new vaccine research, as outlined by their approach to meningitis.

The North African “meningitis belt” is an area that includes countries from Senegal to Ethiopia with a population of around 350 million people^[45]. Annual outbreaks in these countries claim hundreds to thousands of lives and are caused mostly by *Neisseria meningitidis* (*N. meningitidis*) serogroup A^[46]. Controlling these outbreaks requires identifying the culprit strain of *N. meningitidis* and producing a specific polysaccharide vaccine to treat the population at risk. These polysaccharide vaccines are poorly immunogenic in young children, do not prime immunologic memory, and do not lead to “herd immunity”^[47]. To combat this problem, in 2001 the Bill and Melinda Gates Foundation gave United States \$70 million to the WHO to establish the Meningitis Vaccine Project^[48]. The goal was to eliminate epidemic meningitis in Africa through the development of a serogroup A meningococcal conjugate vaccine that would cost less than United States \$0.50 per dose. Vaccine development began in 2003, clinical phase 1-3 trials were completed, and in 2010 MenAfriVac™ was licensed for use in populations aged between one and 29 years; large-scale immunization campaigns began immediately. In 2011, no case of meningococcal A disease occurred in a vaccine recipient in Burkina Faso and the percentage of meningococcal infections in Niger due to serogroup A dropped from 98.6% to less than 2%^[49].

The GAVI alliance has also addressed hepatitis B virus (HBV) in China. HBV is a significant problem in low-income countries, and China accounts for up to half of the HBV-related deaths worldwide^[50]. Over 260000 people die annually in China from HBV-related liver cancer and cirrhosis. A full 60% have a history of infection, and around 10% are chronic carriers^[51]. However, because of high costs, vaccination rates were substantially higher in major cities and wealthy provinces in Eastern China. In 2002, China added HBV vaccination to its National Immunization Programme, and at the same time the China Ministry of Health teamed with GAVI to start the China-GAVI project with a goal of providing free HBV vaccination to people in the poor and western provinces of China. From 1997-2003, overall vaccination coverage increased from 70.7% to 89.8% and timely coverage increased from 29.1% to 75.8%. In the 22 provinces targeted by the China-GAVI Project, timely coverage increased from 64% in 2004 to 81% in 2006, and complete coverage increased from 52% in 2001 to 92% in 2006^[52]. National HBV vaccination programs have had similar effects in other countries^[53] and have been shown to greatly reduce the incidence of hepatocellular carcinoma in these populations^[54].

These examples of meningitis and HBV illustrate

the benefit of targeted funding towards developing specific therapies or distributing existing therapies to a population in need. Fifty years after the Sabin and Salk vaccines were developed, polio has been eradicated in much of the world and vaccine campaigns are now addressing the few remaining countries with recently documented cases^[55,56]. The Bill and Melinda Gates Foundation has given United States \$1.5 billion to the Children's Vaccine Program for research initiatives in malaria, TB, diarrheal diseases, measles, hookworm, and meningitis^[56]. GAVI is targeting the 74 poorest countries in the world with a three-fold approach: improving vaccination infrastructure, purchasing necessary vaccines, and supporting research and development^[56].

For many diseases, notably HIV, TB, and malaria, challenges in vaccine development still need to be overcome. For many others, effective vaccines exist and simply need to be distributed effectively. Through this combination of research and distribution it is possible to use discoveries in the lab to prevent and even eliminate the burden caused by these historically tragic diseases.

HIV/AIDS

In 1981 scientists discovered HIV as the causative agent of AIDS, typified by uncommon opportunistic infections in otherwise healthy young men^[57]. Since then, highly active antiretroviral therapy (HAART) has been proven to significantly reduce morbidity and mortality by suppressing HIV replication and improving CD4⁺ T cell counts. Population studies in developed as well as developing countries have shown a significant effect of HAART treatment on reductions in both viral load as well as HIV transmission and new diagnoses^[58-63]. The WHO has made evidence-based recommendations for HIV treatment and prevention^[64] and the international community has contributed substantially through organizations such as Global Fund to Fight AIDS, TB and Malaria and PEPFAR, the President's Emergency Plan for AIDS Relief^[65]. Despite this progress, over two million people per year become newly infected with HIV worldwide^[66].

A major barrier to defeating HIV is the highly mutagenic and drug-resistant nature of the virus^[64]. The availability of fixed-dose combination pills and simplified treatment schedules can decrease resistance development by increasing adherence to HAART regimens, but resistance is still developing and can be difficult to monitor^[67]. Genotypic testing and viral load monitoring are often not available in resource-limited settings due to cost-constraints and lack of adequate technology. As such, in resource-limited settings the WHO recommends monitoring early warning signs associated with developing drug-resistance: adherence to first-line regimens, changing regimens, inconsistent filling of prescriptions, and missing appointments^[67]. Diagnosis of drug resistance in resource-limited settings is a clinical observation and research is now investigating empiric second- and third-line HAART

options for patients with suspected resistance^[64].

Ultimately, prevention will be the only way to definitively eradicate HIV. Efforts in vaccine development were discussed previously, but another strategy being investigated is prompt treatment of exposed or at-risk individuals with HAART to prevent viral transmission^[66]. Treatment of mothers and children in the peri-natal period has been demonstrated to safely and effectively reduce HIV transmission at birth and during breastfeeding^[68-70]. HIV post-exposure prophylaxis (PEP) taken within 72 h of an occupational exposure has been shown to prevent transmission in the great majority of cases^[71]. Animal trials and observational studies in humans also demonstrate a benefit for non-occupational exposures such as sexual encounters and intravenous drug use^[72]. There is promise of using antiretroviral therapy as pre-exposure prophylaxis for certain high-risk groups, but phase I - III trials have shown variable protection from HIV transmission, likely due to poor drug adherence^[73]. Potential problems with widespread availability of HIV PEP include increased drug resistance, risky behavior, and decreased cost-effectiveness^[66]. To address these issues, dozens of trials in a variety of countries are either planned or ongoing^[74].

NCD EPIDEMIC

In the year 1900, the three leading causes of death in the United States were pneumonia, TB, and diarrhea/enteritis. These diseases caused one third of all deaths, of which 40% were among children under five years of age. Over the next century scientists would discover microorganisms and their role in infectious disease as well as determine ways to treat them. Subsequently the burden of disease has shifted; pneumonia, influenza, and HIV were responsible for 4.5% of deaths in the United States in 1997. Conversely, 54.7% of deaths in that year were a result of heart disease and cancer^[75].

This shift in disease burden is not unique to the United States or even wealthy, industrialized countries. The incidence of many NCDs such as cardiovascular disease (CVD), cancer, and diabetes is growing so fast in developing countries that many have called it an epidemic^[76,77]. From 1909 to 1999, global mortality caused by cancer and CVD increased from 15% to 53%^[78]. In China, for example, the percentage of mortality attributable to CVD tripled from 1957-1990^[79]. The causes are many and include a worldwide surge in life expectancy, lifestyle changes, urbanization, altered diets, increased tobacco use, poor fetal and childhood nutrition, and diminished physical activity^[77].

Epidemiological studies in developing countries have highlighted the substantial presence of risk factors for CVD, many of which are modifiable^[80-83]. These risk factors are less prevalent in developing countries than in developed nations and the incidence of NCDs is lower as well. Nonetheless, incidence is increasing and developing nations are also at risk of a NCD epidemic^[84]. This provides a unique opportunity to halt disease

progression in these regions. Research from developed countries highlights the benefits of preventative medicine in population-based interventions^[85], and national public health programs have successfully improved population health in developed as well as developing countries by disseminating information regarding risk factors^[86,87]. Social education is especially necessary to confront cultural misconceptions in areas where health professionals are distrusted and obesity is seen as a sign of affluence^[88].

When prevention fails, management of affected or high-risk individuals will always be necessary. While there are many known treatments for diabetes, hypertension, hypercholesterolemia, and other chronic diseases, the incidence of these diseases continues to increase both in the United States and worldwide^[89-91].

Another challenge to curbing this epidemic is delivery of appropriate therapy. For example, the results of the β -Blocker Heart Attack Trial were published in the United States in 1981, and 15 years later only 62.5% of patients who had had a myocardial infarction were appropriately being prescribed beta-blockers^[92]. Despite wide availability of an inexpensive, safe, efficacious intervention, less than two-thirds of patients receive appropriate treatment.

Studies in United States have shown health benefits using one-on-one lifestyle teaching^[93] and even text and email reminders^[94] to encourage patients to exercise, modify diet, and take medications as instructed. However, these tactics may not apply to resource-limited countries with insufficient supplies of doctors and medicines^[95]. As is the case with vaccines, governments in these countries can improve health by investing in cost-effective initiatives to develop and provide medications for their citizens at an affordable price^[96-98]. Developing regions have had success improving the management of NCDs by focusing on primary care systems improvements and non-physician-led community initiatives^[95,99-102].

Prevention and management of NCDs is a complicated problem, and the challenges faced by developing and developed countries are both similar and different. There is a unique opportunity in the developing world to prevent an epidemic that is currently evolving^[84]. Risk factors are increasing, but the prevalence of NCDs in developing countries is still quite low, and research has shown that prevention, risk factor modification, and policy change can prevent the NCD epidemic from equaling others the world is currently battling.

Ethical issues

The considerations regarding ethical translational research in global health are diverse. Clearly, the exploitation of economically disadvantaged individuals is egregious, but there are many nuances to consider. When a resource-rich country funds research in a resource-poor country, how do you define the standard of care? Is it wrong to inject live malaria parasites into HIV-positive patients to study the effect CD4⁺ T cell counts, even in an area where malaria is endemic^[103]?

Is it fair to randomly assign some malnourished men to receive vitamin-fortified bread and others standard bread when they normally would not have the fortified option anyway^[104]? When conducting HIV vaccine trials in high-risk populations, is it necessary to provide condoms or safe-sex counseling^[105]? Is it ethical to test a new therapy against subjects who go untreated because they cannot afford medicine which is standard of care^[106]? Early-phase translational research has the potential to harm subjects, and that risk increases when crossing international boundaries^[107].

Another ethical conundrum is the notion of disproportionate profiting from discoveries made in resource-poor countries host^[107]. Not only does it seem wrong to expose patients to a potentially life-altering treatment they could never afford, but such discoveries can further exacerbate international disparities in health, as well as create inequalities in care within the host country^[107]. However, international research partnerships can also improve the quality of care in host nations. For over 30 years Cornell has collaborated with the Haitian Ministry of Health on research that started with AIDS and TB but has since expanded to include maternal-child health, family planning, cancer prevention and treatment, immunization, and education. In that time they have successfully reduced rates of HIV and other sexually transmitted infections, increased the number of patients on HAART, and trained thousands of medical personnel, all the while enjoying uninterrupted NIH support since 1983 and generated more than 150 peer-reviewed publications^[108]. By funding symbiotic partnerships it is possible not only to generate research data but also to improve population health and reduce the "implementation gap" that plagues global health^[109].

CONCLUSION

The history and current struggles of research in vaccine development, HIV, and NCDs emphasize the importance of the five phases of translational research. Many vaccines have been successfully discovered and their effectiveness proven, some are works in progress, and all must have the potential to be efficiently delivered to populations in need. Treatment for HIV has evolved rapidly and become increasingly effective, but HIV is far from eradicated. Therapies for NCDs are well studied in the developed world, but there is much work to be done in prevention and population health in both developing and developed countries. Moving from clinical observation to bench research to bedside intervention is a hallmark of academic medicine in resource-rich countries. However, stopping at the bedside will not improve population health. Region-specific epidemiologic research can highlight needs, opportunities, and challenges that vary due to economic and cultural differences between communities, and goal-directed funding and research can find solutions to these problems. Research in developing countries can inform policy in developed countries, and vice-versa. As

the field of global health grows, research and resources will be shared more efficiently and the successes of smallpox and polio will be translated to HIV and cardiovascular disease.

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