International Outsourcing of Medical Research by High-Income Countries: Changes From 1995 to 2005

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Background: Medical research outsourcing provides a financial benefit to those conducting research and financial incentives to the developing countries hosting the research. Little is known about how frequently outsourcing occurs or the type of research that is outsourced.
Methods: To document changes in medical research outsourcing over a 10-year period, we conducted a cross-sectional comparison of 3 medical journals: *Lancet*, *The New England Journal of Medicine*, and *JAMA: The Journal of the American Medical Association* in the last 6 months of 1995 and 2005. The main outcome measure was the 10-year change in proportion of studies including patients from low-income countries.
Findings: We reviewed 598 articles. During the 10-year period, the proportion of first authors from low-income countries increased from 3% to 6% ($P = 0.21$), whereas studies with participants from low-income countries increased from 8% to 22% ($P = < 0.001$). In 2005, compared with studies conducted exclusively in high-income countries, those including participants from low-income countries were more likely to be randomized trials (55% vs 35%, $P = 0.004$), to study medications (65% vs 34%, $P < 0.001$), to be funded by pharmaceutical companies (33% vs 21%, $P = 0.05$), and to involve pediatric populations (29% vs 8%, $P < 0.001$).
Interpretation: Outsourcing of medical research seems to be increasing. Additional studies are required to know if subjects from low-income countries are being adequately protected.

Key Words: outsourcing, medical research

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Outsourcing, the transfer of the management of a business function to an external service provider,[1] has become increasingly popular over the last decade in business and manufacturing. As globalization has taken hold, increasing economic competition has pushed companies in high-income countries to outsource production and service to countries with lower wages and fewer regulations. Clinical medicine, once thought immune to outsourcing, now includes "nighthawk" radiology services in India and may expand to other fields, including pathology or even intensive care.[2] There are a number of reasons to think that sponsors of medical research may benefit from outsourcing as well. First, the cost of conducting clinical trials in the United States is increasing annually by 10%, and conducting clinical trials overseas could reduce costs by as much as 50%.[3] Second, Americans are becoming less eager to participate in medical research: recent estimates suggest that fewer than 5% of US patients are willing to participate in clinical trials, resulting in 86% of clinical trials being delayed for a mean of 366 days.[4] In contrast, developing countries offer a vast supply of drug-naive patients who are eager to participate in clinical trials. India's huge population, with a diversity of common untreated diseases (40 million asthmatic, 34 million diabetic, and 3 million cancer patients), enables sponsors to recruit subjects more quickly and bring drugs to the market faster.[5] Finally, clinical research in the United States is subject to strict regulations and high safety and compensation standards, all of which increase costs.[4]

Since 2002, the number of Food and Drug Administration (FDA)–regulated investigators based outside the United States has grown by 15% annually, whereas the number of US-based investigators has declined by 5%.[6] Leading destinations for outsourcing of US medical research include Ireland, India, Canada, Singapore, Israel, and China.[7] It has been estimated that by 2010, the major global pharmaceutical companies will invest 1.5 billion dollars in India alone.[4] Such investments can support growth of medical and research infrastructure, provide jobs for local researchers, and offer research subjects both financial compensation and the opportunity to receive therapies that would otherwise be unavailable to them.

At the same time, medical research outsourcing raises a number of concerns. In the United States, outsourcing will lead to job loss. It has been predicted that 3.3 million US jobs will move offshore by 2015; some of those will be in medical research.[7] In low-income countries, foreign-sponsored research may pose threats to patient rights and safety. In 2001, the Department of Health and Human Services found that the FDA receives minimal information on the performance of foreign institutional review boards (IRBs) and therefore could not guarantee the rights and safety of human subjects participating in overseas clinical trials.[7]

Although concerns about outsourcing of both medical care and medical research have captured the attention of editorialists, documentation has been limited.[6,8] One study found that one third of US industry–sponsored phase 3 clinical trials are being conducted outside the United States, which represents a doubling from 10 years earlier.[6] By measuring the types of studies and funding sources, we sought to identify some of the forces behind this trend. We hypothesized that over a 10-year period, we would observe an increase in medical research outsourcing, as evidenced by the inclusion of patients from low-income countries, and that industry-funded clinical trials would be most affected by these changes.

METHODS

Study Design

We compared studies published in 1995 and 2005 in (the online versions of) the following journals: *Lancet*, *The New*

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England Journal of Medicine (*N Engl J Med*), and *The Journal of the American Medical Association* (*JAMA*). Two investigators (R.K.B. and M.S.W.) extracted data on all original research articles published from July through December 1995 and July through December 2005. Conflicts were resolved by a third investigator (M.B.R.). Articles were categorized into 1 of 4 study designs: randomized controlled trials, meta-analysis, cohort studies, and other. We recorded the country of the institutional affiliation of all authors. Using the World Bank 2007 list of high-income countries (Appendix A), each author affiliation was designated as from a high-income country or not, and the study as a whole was designated as having all high or mixed high-/low-income author affiliations. The number of study subjects, their ages (<18, 18–64, or ≥65 years), and their countries were also recorded. Similarly, the subject countries were designated as high- or low-income using the World Bank list, and the study as a whole was defined as having subjects in high-income or mixed high-/low-income countries. The funding sources were categorized as the National Institutes of Health (NIH), the World Health Organization (WHO), a pharmaceutical industry, foundations/private grants, other governments, and not stated. Studies were also categorized according to medical specialty area (cardiology, pulmonary, gastroenterology, oncology, etc) and study intervention type (medication, device, procedure, and surgery).

TABLE 1. Association of Study Characteristics With Year of Publication (Total, 598)

Study Characteristic		1995 (n = 304), n (column %)	2005 (n = 294), n (column %)	*P*
Design	Cohort	52 (17)	56 (19)	0.0004
	Meta-analysis	6 (2)	9 (3)	
	Randomized trial	79 (26)	116 (39)	
	Other	167 (55)	113 (38)	
Speciality	Cardiology	44 (14)	52 (18)	0.005
	Endocrine	7 (2)	17 (6)	
	Genetics	12 (4)	8 (3)	
	Gastrointestinal	20 (7)	8 (3)	
	Infectious disease	43 (14)	46 (16)	
	Neurology	17 (6)	9 (3)	
	Obstetrics and gynecology	20 (7)	16 (5)	
	Oncology	20 (7)	42 (14)	
	Pediatrics	23 (8)	23 (8)	
	Pulmonary	11 (4)	9 (3)	
	Other	87 (29)	64 (22)	
Study focus	Device	6 (2)	13 (4)	0.023
	Disease	138 (45)	105 (36)	
	Medicine	107 (35)	126 (43)	
	Surgery	16 (5)	7 (2)	
	Test	19 (6)	26 (9)	
	Other	18 (6)	17 (6)	
Funding source	NIH	57 (19)	90 (31)	0.0008
	Pharmaceutical	49 (16)	72 (24)	0.01
	WHO	5 (2)	7 (2)	0.52
	Government	44 (14)	69 (23)	0.005
	Foundation	156 (51)	152 (52)	0.93
	NA	80 (26)	34 (12)	<0.0001
Study size	≤100	91 (31)	28 (10)	<0.0001
	101–300	60 (21)	45 (16)	
	301–1000	53 (18)	63 (23)	
	1001–6000	47 (16)	71 (26)	
	>6000	41 (14)	68 (25)	
No. countries	1	233 (78)	170 (58)	<0.0001
	2	42 (14)	52 (18)	
	3+	24 (8)	70 (24)	
Patient ages	Adult	77 (29)	47 (18)	0.0013
	Adult/geriatric	92 (35)	117 (44)	
	Geriatric	17 (6)	8 (3)	
	Pediatric	30 (11)	34 (13)	
	Pediatric/adult	23 (9)	16 (6)	
	All	24 (9)	42 (16)	

Funding source is yes/no for each type because some studies had multiple sources.

The primary outcome measure was the change in proportion of studies including patients from outside high-income countries from 1995 to 2005. We also examined the change in proportions of first and last authors from outside high-income countries over the same period. Secondary outcomes included the types of trials performed, the area of specialty, the funding sources, the study size, the number of countries participating in the research, the age of the study population, and the type of research being conducted.

Data Analysis

Associations of study characteristics with year of publication were evaluated using χ^2 tests (Table 1). Stratifying on study year, the association of study characteristics with patient countries grouped as only high income versus mixed income (some or all low income) were assessed via the χ^2 statistics. The Fisher exact test was used when cell size criteria for χ^2 were not met. In addition, z tests were used to evaluate differences in proportions of specified study characteristics for high- or mixed-income subjects between years.

RESULTS

We reviewed a total of 598 articles, including 304 published in 1995 and 294 published in 2005. The characteristics of original research articles changed substantially over the 10-year period; most notably, the proportion of randomized trials increased from 26% in 1995 to 39% in 2005. Study size also increased, with 51% of the research studies in 2005 having populations greater than 1000 patients compared with only 30% in 1995. The proportion of multinational studies increased; studies limited to a single country declined from 78% to 58%. Foundations were the most common funding source, funding approximately 51% of studies in both years. At the same time, studies funded by the NIH increased from 19% to 31% and those funded by industry increased from 16% to 24%, whereas studies in which no funding source was identified declined from 26% to 12% ($P \leq 0.001$). The proportion of first authors from low-income countries increased from 3% in 1995 to 6% in 2005 ($P = 0.21$), and that of senior authors also increased from 3% to 5% ($P = 0.12$). During the same period, the percentage of studies including participants from low-income countries increased from 8% to 22% ($P < 0.001$). The fastest growing segment was studies that included patients from low-income countries conducted by investigators from high-income countries (Fig. 1).

Of the 571 studies with identifiable subject countries or world region, only 87 (15%) included subjects, at least in part, in low-income countries. In total, 84 different countries were involved in at least one study. The low-income countries most commonly included were South Africa (12 studies), Brazil and Mexico (11 each), and China and Argentina (10 each). First or last authors from institutions in low-income countries were rare, but authors from low-income countries participated in some form in 80% of the studies that included subjects from low-income countries (73% in 1995 vs 83% in 2005, $P = 0.29$) and 12% of the studies overall (7% in 1995 vs 18% in 2005, $P = 0.0002$). In the 3 journals we examined, studies including low-income countries seemed most often published in *Lancet* (58 studies), followed by *N Engl J Med* (21 studies), and *JAMA* (8 studies).

Research conducted in both high- and low-income countries differed from research conducted exclusively in high-income countries in several ways (Table 2). First, in 2005, randomized controlled trials were more common in studies including subjects in low-income countries, whereas cohort studies were conducted largely in high-income countries. Second, studies including subjects in low-income countries were increasingly focused on infectious disease. Third, research including subjects in low-income countries focused primarily on medications; in contrast, all of the research on medical devices in both years was conducted solely in high-income countries. Funding sources also differed. Pharmaceutical company funding was more common in studies that included patients from low-income countries, and the difference increased over time. In contrast, studies exclusive in high-income countries were more likely to receive funding by the NIH than studies including low-income countries. All the research

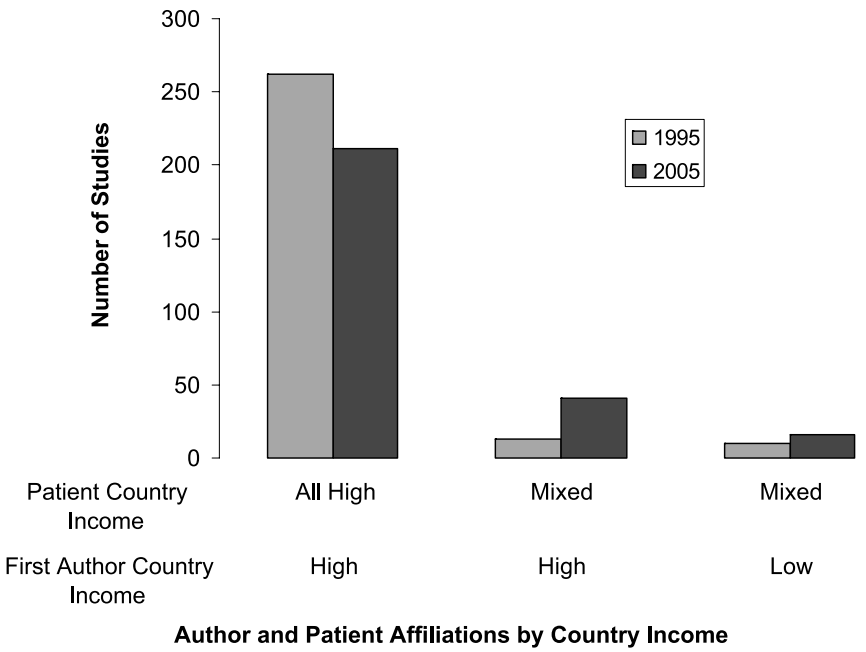

FIGURE 1. Change in author and patient countries from 1995 to 2005.

TABLE 2. Comparison of Published Research in Countries Designated as All High Versus Studies Including Low-Income Countries Stratified by Year of Publication (Total, 571)

Study Characteristic	Year of Publication		Studies Including Low-Income Countries, n (%)	All High Income, n (%)	*P*
Journal	1995	*JAMA*	1 (4)	79 (30)	0.0003
		N Engl J Med	7 (26)	104 (37)	
		Lancet	19 (70)	88 (33)	
	2005	*JAMA*	7 (12)	91 (43)	<0.0001
		N Engl J Med	14 (23)	75 (36)	
		Lancet	39 (65)	45 (21)	
Design	1995	Cohort	3 (11)	49 (19)	0.0026*
		Meta-analysis	3 (11)	1 (0.4)	
		Randomized trial	10 (37)	67 (25)	
		Other	11 (41)	147 (56)	
	2005	Cohort	4 (7)	52 (25)	0.0006*
		Meta-analysis	2 (3)	1 (0.5)	
		Randomized trial	33 (55)	72 (35)	
		Other	21 (35)	84 (39)	
Specialty	1995	Cardiology	3 (11)	39 (15)	0.12*
		Endocrine	1 (4)	6 (2)	
		Genetics	1 (4)	10 (4)	
		Gastrointestinal	0 (0)	20 (8)	
		Infectious disease	9 (33)	32 (12)	
		Neurology	2 (7)	15 (6)	
		Obstetrics and gynecology	0 (0)	20 (8)	
		Oncology	3 (11)	15 (6)	
		Pediatrics	2 (7)	19 (7)	
		Pulmonary	0 (0)	11 (4)	
		Other	6 (22)	77 (29)	
	2005	Cardiology	4 (7)	43 (20)	0.0003
		Endocrine	3 (3)	12 (6)	
		Genetics	1 (2)	6 (3)	
		Gastrointestinal	1 (2)	6 (3)	
		Infectious disease	23 (38)	22 (10)	
		Neurology	1 (2)	8 (4)	
		Obstetrics and gynecology	5 (8)	11 (5)	
		Oncology	8 (13)	28 (13)	
		Pediatrics	3 (5)	18 (9)	
		Pulmonary	3 (5)	6 (3)	
		Other	9 (15)	51(24)	
Study focus	1995	Device	0 (0)	6 (2)	0.58*
		Disease	11 (41)	122 (46)	
		Medication	13 (48)	88 (33)	
		Surgery	2 (7)	14 (5)	
		Test	0 (0)	17 (6)	
		Other	1 (4)	17 (6)	
	2005	Device	0 (0)	13 (6)	0.0002*
		Disease	18 (30)	82 (39)	
		Medication	39 (65)	72 (34)	
		Surgery	1 (2)	6 (3)	
		Test	2 (3)	22 (10)	
		Other	0 (0)	16 (8)	
Funding source	1995	NIH	4 (15)	52 (20)	0.54
		Pharmaceutical industry	4 (15)	42 (16)	1.00*
		WHO	4 (15)	1 (0.4)	0.0003*
		Government	4 (15)	38 (14)	0.95

(continued on next page)

TABLE 2. *(Continued)*

Study Characteristic	Year of Publication		Studies Including Low-Income Countries, n (%)	All High Income, n (%)	*P*
		Foundation	16 (59)	134 (51)	0.40
		No grant funding	6 (22)	72 (27)	0.57
	2005	NIH	9 (15)	72 (34)	0.0043
		Pharmaceutical industry	20 (33)	45 (21)	0.055
		WHO	7 (11)	0 (0)	<0.0001*
		Government	16 (27)	49 (23)	0.58
		Foundation	36 (60)	105 (50)	0.16
		No grant funding	5 (8)	24 (11)	0.50
Subject ages	1995	Adult	5 (28)	72 (30)	0.40*
		Adult/geriatric	4 (22)	84 (35)	
		Geriatric	1 (6)	15 (6)	
		Pediatric	4 (22)	25 (11)	
		Pediatric/adult	3 (17)	19 (8)	
		All ages	1 (6)	23 (10)	
	2005	Adult	9 (16)	36 (19)	0.0013
		Adult/geriatric	17 (31)	88 (46)	
		Geriatric	0 (0)	7 (4)	
		Pediatric	16 (29)	16 (8)	
		Pediatric/adult	2 (4)	14 (7)	
		All ages	11 (20)	29 (15)	

Studies including low-income countries include studies with subjects from at least 1 low-income country. Funding source is yes/no for each type because some studies had multiple sources.

**P* value from the Fisher exact test.

supported by the WHO in 2005 included low-income countries. Finally, the percentage of research focused on children increased dramatically outside high-income countries. In 1995, 14% of pediatric studies included low-income countries, whereas in 2005, the proportion had climbed to 50% ($P = 0.003$).

The 13 pediatric studies conducted in low-income countries appear in Table 3. The studies were primarily focused on infectious diseases occurring in the developing world. They included studies of vaccines and antibiotics. All but one were funded by foundations, governments, or the WHO. The remaining study, of Japanese encephalitis virus, was funded by a pharmaceutical company. Most had local IRB oversight, and about half also had oversight by the sponsoring institution. Nearly one quarter, however, did not report who approved the study. All but one were published in *Lancet*.

In contrast, Table 4 shows pharmaceutical company–sponsored randomized trials that included low-income countries. Studies mostly included new therapies such as medications (eg, zoledronic acid) and monoclonal antibodies (eg, gefitinib) that were likely to be unaffordable to patients in low-income countries. All documented IRB approval. Most IRBs were located in the country where the study took place, but in 2 studies, they were located in the authors' countries instead.

DISCUSSION

In this review of nearly 600 articles from 3 leading medical journals, we found that outsourcing of medical research, which we defined as research conducted by investigators from high-income countries that enrolled patients from lower-income countries, is not only taking place but has increased substantially over a 10-year period. During the same period, randomized controlled trials increased in prevalence and size (and presumably, cost). As a result, almost all published studies in 2005 reported external funding, most commonly from foundations but increasingly from pharmaceutical companies. Pharmaceutical companies were most likely to shift their funding over time, seeking subjects outside high-income countries. Finally, outsourced research mostly involved medications and was disproportionately focused on infectious diseases and children. Nevertheless, despite a tripling of studies conducted either entirely or mostly in low-income countries, more than three fourths of all studies were still conducted exclusively in high-income countries.

The pattern we observed could represent attempts to save money or circumvent regulation, but other considerations, such as humanitarian attempts to address the diseases of poorer patients, may also play a role. Our data support both hypotheses. In the pediatric studies we examined, the humanitarian aspect seemed to dominate. These studies focused on the treatment using inexpensive therapies such as BCG and zinc to treat infectious diseases and malnutrition. They were also funded primarily by foundations, governments, and the WHO. In contrast, the magnitude of outsourcing in pharmaceutical company trials and the study foci implied that economic incentives may have played a larger role in determining these studies' locations.

A number of authors have commented on the growing trend of outsourcing medical research to developing countries, especially India.[4,8–11] The most commonly voiced concerns relate to study quality, patient protection, and equity for subjects in developing countries. Other concerns include the potential loss of research jobs in high-income countries and diminished opportunities for patients from high-income countries to participate in clinical trials or receive potentially life-saving experimental treatments. This lost opportunity may be felt especially keenly during the current economic downturn, as the number

TABLE 3. Pediatric Studies Conducted in Low-Income Countries in 2005

Journal	Year	Countries Included	Study Design	Disease Studied	Intervention	Sponsor	IRB Approval
JAMA	2005	Kenya	Cohort	Estimating malnutrition	Measuring mid upper arm circumference	Wellcome Trust	Local
Lancet	2005	Mozambique	Randomized controlled trial	Malaria	Vaccine	Malaria Vaccine Initiative, Spanish Agency for International Cooperation, and Ministry of Health (Spain)	Local + sponsor
Lancet	2005	South Africa	Randomized controlled trial	Human immunodeficiency virus	Zinc supplementation	The US Agency for International Development	Local + sponsor
Lancet	2005	Bangladesh, Benin, Cambodia, and Eritrea	Other	Child survival	Survival interventions, BCG, tetanus, vitamin A, and safe water	Not stated	Not stated
Lancet	2005	Turkey	Cohort	Tuberculosis	BCG vaccine	United Nations Children's Fund/United Nations Development Programme/ World Bank/WHO and the Wellcome Trust	Local + sponsor
Lancet	2005	Nepal	Other	Japanese encephalitis	SA 14-14-2 vaccine	Glovax Company	Local
Lancet	2005	Brazil	Randomized controlled trial	Tuberculosis	BCG vaccine	Department for International Development (UK) and the National Health Foundation, Brazil.	Local + sponsor
Lancet	2005	Bangladesh	Randomized controlled trial	Cholera	Antibiotics	Bayer AG, the National Institute of Allergy and Infectious Diseases, and Wellcome Trust	Local + sponsor
Lancet	2005	Bangladesh	Randomized controlled trial	Pneumonia and diarrhea	Zinc supplementation	US Agency for International Development, Swiss Development Corporation, and Centre for Health and Population Research	Sponsor
Lancet	2005	Africa	Other	Measles	Immunizations	WHO	Not stated
Lancet	2005	China	Randomized trial	Capillary leak syndrome in children	C4A-rich plasma priming	National Natural Science Foundation of China	Local
Lancet	2005	Gambia	Other	*Haemophilus influenzae*	Vaccine	WHO Department of Vaccines and Biologicals and the Medical Research Council	Local + sponsor
Lancet	2005	Vietnam	Randomized trial	Dengue fever and shock	Fluid resuscitation	Wellcome trust	Not stated

of individuals willing to participate in paid trials has increased dramatically, with one research company reporting that its patient database has doubled from 9000 one year ago to 16,000 today.[9]

Given its appearance in 3 of the world's leading medical journals, there is little doubt that outsourced research can be of high quality, although we could not assess the average quality of outsourced research. Concerns about the exploitation of poor subjects in the developing world also have merit and parallel concerns about privately conducted research involving low-income individuals in high-income countries.[10] Developing countries have generally lagged the United States in institutional protection of patients through IRBs. When investigators are in one country and participants are in another, investigators report that institutional review is frequently absent in the participants' country and may be absent altogether.[11] When review occurs, IRBs in investigator countries may fail to respect cultural differences, socioeconomic circumstances, national laws, and administrative structures, whereas IRBs in developing countries are frequently underfunded, understaffed, or undertrained and may fail to uphold high ethical standards.[12] Most of the pharmaceutical industry studies we examined relied exclusively on local IRB oversight, the quality of which is unknown.

The Declaration of Helsinki on the conduct of biochemical studies states that "Medical research is only justified if there is reasonable likelihood that the populations in which the research is carried out stand to benefit from the research."[13] Proving the effectiveness of drugs may not benefit the local population if the drug is priced beyond their reach.[13] We found that pharmaceutical company–sponsored research conducted in low-income countries often involved expensive new drugs that may not be affordable to

TABLE 4. Pharmaceutical Industry–Sponsored Randomized Controlled Trials in Mixed-Income Countries

Journal	Year	Non–High-Income Countries Included	No. Countries	Study Size	Patient Ages	Disease Studied	Intervention	IRB Approval
N Engl J Med	1995	China	1	312	Adult and geriatric	Stroke	Low–molecular weight heparin	Sponsor
N Engl J Med	1995	Mexico	8	994	Adult and geriatric	Osteoporosis	Alendronate	Local
Lancet	2005	Mozambique	1	2022	Pediatric	Malaria	Vaccine	Local + sponsor
Lancet	2005	China	1	45852	Adult and geriatric	Acute myocardial infarction	Metoprolol	Local + sponsor
Lancet	2005	China	1	45852	Adult and geriatric	Acute myocardial infarction	Plavix	Local + sponsor
Lancet	2005	Latvia, Argentina, Brazil, Bulgaria, Estonia, Greece, Hungary, India, and Lithuania	13	1692	Adult and geriatric	Non–small cell lung cancer	Gefitinib	Local
Lancet	2005	Argentina, India, Malaysia, Mexico, Panama, Philippines, Poland, Slovak Republic, South Africa, South Korea, Taiwan, and Thailand	23	422	Adult, geriatric, and pediatric	Candidemia	Voriconazole, amphotericin B, and fluconazole	Local
Lancet	2005	Hungary	2	418	Adult and geriatric	Surgical wound infection	Nitrous oxide	Local
Lancet	2005	Bangladesh	1	180	Pediatric	Cholera	Ciprofloxacin and erythromycin	Sponsor
Lancet	2005	Hungary and South Africa	11	1411	Adult and geriatric	Chronic obstructive pulmonary disease	Roflumilast	Local
Lancet	2005	Pakistan	1	4691	Pediatric	Childrens' health	Handwashing	Local + sponsor
N Engl J Med	2005	Argentina, Brazil, Chile, Mexico, Romania, Thailand, and South Africa	14	731	Adult and geriatric	Non–small cell lung cancer	Erlotinib	Local
N Engl J Med	2005	South Africa	4	357	Adult and geriatric	Paget disease	Zoledronic acid	Local
N Engl J Med	2005	Brazil, Chile, Lebanon, Mexico, Philippines, Denmark, Egypt, Finland, Romania, and Russia	21	2440	Adult and geriatric	Sepsis	Xigris	Local
N Engl J Med	2005	South Africa	11	3387	Adult and geriatric	Breast cancer	Trastuzumab	Local
N Engl J Med	2005	South Africa	16	905	Adult	Crohn disease	Natalizumab	Local
N Engl J Med	2005	Mexico and South Africa	8	278	Adult and geriatric	Pulmonary arterial hypertension	Sildenafil	Local
N Engl J Med	2005	Chile, Hungary, Peru, South Africa, Argentina, Poland, Russia, Uruguay, and Turkey	24	8010	Adult and geriatric	Breast cancer	Letrozole	Local

the populations of some study countries. In addition, although infectious diseases remain the most common causes of death in the developing world, none of the pharmaceutically funded adult trials conducted in low-income countries studied infectious diseases.

There were several limitations to this study. First, data collection was limited to 3 journals: *Lancet*, *N Engl J Med*, and *JAMA*. We cannot know to what extent the outsourcing seen in our study is representative of research as a whole. Because of the high standards used by these journals, it is possible that a higher proportion of research seen in other journals would be outsourced and an even higher proportion may go unpublished. To the extent that these are true, our findings likely represent only the tip of the iceberg. Future studies using ClinicalTrials.gov may offer a broader view of this phenomenon. Second, our data represent studies published no later than 2005. Given the lag time between study inception and publication, current rates of outsourcing may be higher than we report. Third, our income definition in both years was based on 2007 classifications, so countries with rapid income acceleration during the study period

may have been misclassified in 1995. Finally, we classified authors according to institutional affiliation. Authors from low-income countries could have been misclassified if they had high-income affiliations as visiting researchers.

The advent of globalization, characterized by a free flow of labor, ideas, and goods between countries at great distance, is the result of rapid advances in communication and transportation over the past 20 years. While first, manufacturing and, later, service industries have moved overseas, there are concerns for both the livelihoods of displaced workers in high-income countries and the rights and safety of workers in low-income countries. Medical research is similar to other industries. Rising costs have pushed researchers to seek subjects in places with lower costs and fewer regulations. Private industry seems most vulnerable to these pressures. However, judging by the small number of studies conducted that included low-income countries, this trend is still in its infancy. Just as consumer outcry has prompted some US companies to provide greater safeguards in their overseas factories,[14] the US pharmaceutical industry may face pressure to ensure the consistent application of ethical standards in trials conducted overseas. How this will happen is not yet clear. In 2001, the Department of Health and Human Services recommended that the FDA help build the capacity of foreign IRBs and monitor their performance; however, between 2000 and 2005, the FDA monitored less than 1% of all clinical trials, and three fourths of the inspections took place after the trials were completed.[15]

Over time, while developing nations such as China have become wealthier, working conditions in other industries have improved and wages have begun to rise, prompting both US and Chinese companies to seek investment opportunities in even lower-income countries. Medical research conditions may also improve while developing nations foster their own medical research infrastructure. Studying and reporting on this process is an important first step to ensure that the transition occurs with minimal risk to research subjects.

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