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## Relation between burden of disease and randomised evidence in sub-Saharan Africa: survey of research

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### Abstract

**Objective** To evaluate whether the amount of randomised clinical research on various medical conditions is related to the burden of disease and health needs of the local populations in sub-Saharan Africa.

**Design** Construction and analysis of comprehensive database of randomised controlled trials in sub-Saharan Africa based on Medline, the Cochrane Controlled Trials Register, and several African databases.

**Setting** Sub-Saharan Africa.

**Main outcome measures** Number of trials and randomised subjects for each category of disease in the global burden of disease taxonomy; ratios of disability adjusted life years (DALYs) per amount of randomised evidence.

**Results** 1179 eligible randomised controlled trials were identified. The number of trials published each year increased over time. Almost half of the trials (n = 565) had been done in South Africa. There was relatively good correlation between the estimated burden of disease at year 2000 and the number of trials performed ( $r = 0.53$ ,  $P = 0.024$ ) and the number of participants randomised ( $r = 0.68$ ,  $P = 0.002$ ). However, some conditions—for example, injuries (over 20 000 DALYs per patient ever randomised)—were more neglected than others.

**Conclusion** Despite recent improvements, few clinical trials are done in sub-Saharan Africa. Clinical research in this part of the world should focus more evenly on the major contributors to burden of disease.

### Introduction

Demand is increasing for research to be prioritised according to the importance of health issues,<sup>1</sup> and burden of disease measures have been proposed to aid this process.<sup>2</sup> There is concern that little medical research is done on diseases affecting people in developing countries.<sup>3</sup> Sub-Saharan Africa is a developing area facing severe, pressing, and often unique health challenges.<sup>4</sup> Its burden of disease per million people is estimated to be five times higher than that of established market economies.<sup>2</sup>

Effective interventions are needed to improve health, and efficacy is best assessed by randomised controlled trials. Randomised controlled trials in Africa have not been comprehensively assessed, and it is not known whether the trials cover the local health needs. We therefore constructed a comprehensive database of randomised controlled trials conducted in sub-Saharan Africa over the past 50 years. We then evaluated whether the amount of randomised evidence relates to the burden of different health problems and whether specific conditions are neglected.

### Methods

#### Eligibility criteria

We considered all randomised controlled trials conducted in sub-Saharan Africa that investigated one or more health problems.<sup>2</sup> We excluded non-randomised and pseudorandomised controlled trials; trials enrolling non-local populations (such as tourists); and trials not in humans. Studies in northern Africa<sup>2</sup> and meeting abstracts, books, and other reports were also excluded.

#### Identification of trials

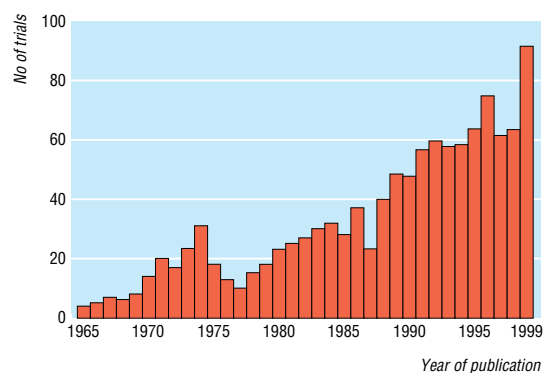
We searched sequentially Medline (to February 2000), the Cochrane Controlled Trials Register (issue 2, 2000), and the African Published Trials Register of the South African Cochrane Center. The African register has been developed and continuously updated over the past three years from seven diverse international and African databases plus hand searching of back years from 12 major African journals. Terms reflecting randomised controlled trials were conjugated with “Africa,” “sub-Saharan Africa,” and specific geographical names.

#### Database

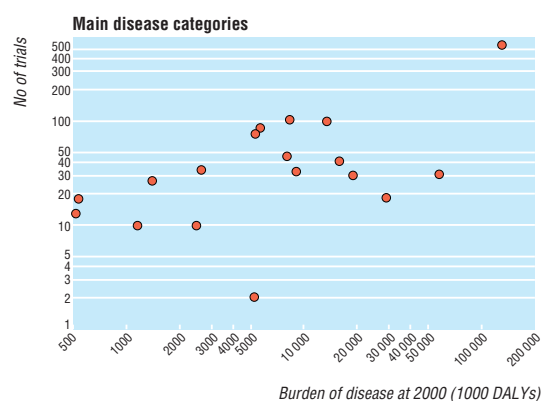
From each article, we extracted the following information: author, journal, year of publication, unit of randomisation (individual or cluster), sample size, disease(s) targeted (and taxonomy in the *Global Burden of Disease*<sup>2</sup>), type of intervention (therapeutic or preventive), and country or countries of recruitment.

#### Analyses

Descriptive analyses include the geographical distribution of trials, number of new trials published, and esti-



**Fig 1** Number of randomised controlled trials in sub-Saharan Africa published during 1965-99. Twelve trials were published during 1949-64 and eight in early 2000



**Fig 2** Correlation between burden of disease and number of randomised trials in sub-Saharan Africa for major disease categories defined in global burden of disease taxonomy. Data on skin diseases are not shown as the burden of disease was small and no exact data were given

mates of the number of trials performed per million people in various countries (1990 population estimates).<sup>5</sup> The main analysis evaluated the number of trials and the number of randomised participants for each category of health problem in the Global Burden of Disease taxonomy.<sup>1 2 6 7</sup> Burden of disease estimates add the number of lost years due to early death plus equivalents of "lost" years due to living with disability from various diseases. The sum is measured in disability adjusted life years (DALYs). For each major disease category we estimated the ratio of burden of disease per each trial and the ratio of burden of disease per participant. We used rank correlation analyses to evaluate whether the number of trials or participants correlated with the DALYs attributed to each health problem.

## Results

We screened 2803 references (Medline 875, Cochrane Clinical Trials Registry 940, South African Cochrane Center Registry 988) and fully scrutinised 1334 articles. Of the 1179 eligible randomised controlled trials, 93 studied two diseases (and were thus counted for both). A total of 795 trials (67%) focused on

treatment rather than prevention. The median sample size was 90 (interquartile range 42-238). Only 535 trials had over 100 participants; 154 trials had over 500 participants; and 79 trials had over 1000.

Publication of randomised controlled trials increased over time (fig 1). Ninety two were published in 1999, more than in any previous year. Almost half of the trials had been done in South Africa (n=565). Four other countries accounted for another quarter (Nigeria=98, Kenya=89, Gambia=56, Tanzania=50). Only 19 countries had more than one trial per million population. South Africa accounted for over 90% of all trials on malignant, respiratory (31/33), digestive (69/76), musculoskeletal (27/27), and congenital (2/2) diseases and 75-90% of trials on diabetes (10/13), endocrine (9/10), cardiovascular (75/99), and genitourinary (29/34) diseases and injuries (26/31), but for only 14% of trials on infectious and parasitic diseases (74/150).

Overall, there was good correlation between burden of disease and randomised evidence (table 1) with modest differences depending on how randomised evidence was measured (table 2). However, good correlation does not ensure a proportional relation (fig 2). For the burden of disease per trial performed, the worst ratios were for congenital anomalies, injuries, respiratory infections, and conditions arising during the perinatal period. The best ratios were for oral conditions, diabetes mellitus, musculoskeletal diseases, maternal conditions, and digestive diseases (table 1).

### Infectious and parasitic diseases

An analysis restricted to infectious and parasitic diseases showed good correlation between the estimated burden of disease and the amount of randomised evidence, with modest differences depending on how randomised evidence was measured (table 2). Despite the good correlation, differences in emphasis were discernible. Least attention had been given to diarrhoeal diseases (834 000 DALYs per trial), childhood cluster diseases (628 000/ trial), and HIV (571 000/trial). Results were similar when we considered DALYs per participant.

## Discussion

### Strengths and weaknesses

Although the number of trials or enrolled participants is a measure of research activity, it may not reflect the public health emphasis given to a disease. Firstly, trials can vary substantially in size and importance. Nevertheless, analyses limited to studies with over 100 or over 500 participants gave similar results. Secondly, other types of clinical research are also important. However, randomised controlled trials are the standard for therapeutic and preventive interventions, are easy to identify, and provide a measurable surrogate of the intensity of topical clinical research. Thirdly, for some conditions it is more difficult to run trials. For example, war is a major contributor of DALYs in this area. Randomised trials may be almost impossible to implement in war stricken areas, although it is questionable whether medical research is helpless against war and its consequences.<sup>8</sup> Despite this difficulty, other unintentional injuries account for more

**Table 1** Burden of disease and evidence from randomised controlled trials for main categories of human disease in sub-Saharan Africa

Disease category	Burden of disease in 2000 (1000 DALYs)	No of trials (No before 1990)	No of participants	Ratio of burden of disease (1000 DALYs)	
				Per trial	Per participant
Infectious and parasitic diseases	131 327	540 (183)	813 305	243	0.16
Respiratory infections	29 077	18 (7)	52 811	1615	0.55
Maternal conditions	5 691	85 (30)	25 148	67	0.23
Conditions arising during perinatal period	18 700	30 (8)	28 381	623	0.66
Nutritional deficiencies	8 389	105 (37)	111 922	80	0.07
Malignant neoplasms	8 114	46 (30)	128 786	176	0.06
Diabetes mellitus	522	13 (9)	1 276	40	0.41
Endocrine disorders	1 168	10 (8)	287	117	4.07
Neuropsychiatric conditions	15 788	41 (21)	3 580	385	4.41
Sense organ diseases	2 460	10 (2)	607	246	4.05
Cardiovascular diseases	13 390	99 (59)	5 648	135	2.37
Respiratory diseases	9 037	33 (13)	3 320	274	2.72
Digestive diseases	5 418	76 (48)	5 545	71	0.98
Genitourinary diseases	2 651	34 (15)	1 903	78	1.39
Skin diseases	—*	6 (3)	407	—	—
Musculoskeletal diseases	1 404	27 (22)	1 536	52	0.91
Congenital anomalies	5 224	2 (0)	1 321	2612	3.95
Oral conditions	534	18 (8)	3 567	30	0.15
Injuries	58 352	31 (19)	2 887	1882	20.21

\*Burden of disease considered small, no exact data given.

Data are not shown for 48 trials (32 published before 1990) that examined topics such as analgesia and anaesthesia that cannot be categorised under the global burden of disease taxonomy.

DALYs than war and are amenable to preventive interventions.<sup>9</sup> Finally, publication bias may influence if and where African trials are published.<sup>10–11</sup> Nevertheless, our search included local journals and it is therefore unlikely that we missed many published trials.

#### Randomised evidence in other continents

For many diseases relevant randomised controlled trials may have been done in other continents. Systematic screening of all trials worldwide would have been impracticable. In addition, extrapolation of results from other continents to Africa causes problems because interpretation of generalisability would be subjective and the trials would not take into account the important local challenges that often occur when implementing medical interventions in Africa.<sup>12</sup>

Almost a million randomised trials have been done worldwide,<sup>13</sup> but most have been done in countries with an established market economy. Even if we assume that 150 000 trials have been done in such countries (a low estimate), the overall ratio of burden of disease per trial is about 400 times higher in Africa than in established market economies. Estimates are worse if we exclude South Africa, a country with a mixed economic profile.

**Table 2** Correlation between estimated burden of disease and number of randomised controlled trials and enrolled subjects

	All major categories of disease		Infectious disease category	
	r*	P value	r*	P value
Burden of disease in 2000 and:				
Total No of trials	0.53	0.024	0.85	<0.001
No of trials with n>100	0.64	0.004	0.79	0.001
No of trials with n>500	0.61	0.007	0.78	0.001
Total No of randomised subjects	0.68	0.002	0.25	0.39
Burden of disease in 1990 and:				
No of trials before 1990	0.35	0.15	0.67	0.009
No of trials before 1990 with n>100	0.61	0.009	0.62	0.018

\*Spearman's correlation coefficient.

#### What is already known on this topic

Sub-Saharan Africa has a large burden of disease

Little clinical research is conducted for problems affecting sub-Saharan Africa

#### What this study adds

Only 1179 randomised controlled trials conducted in sub-Saharan Africa in the past 50 years were identified

Correlation between the amount of randomised evidence and the estimated burden of disease was fairly good

However, some disease categories were more neglected than others, with the worst being injuries

#### Implications for policymakers and the future

Most African countries cannot afford to support medical research.<sup>14</sup> In addition, the pharmaceutical industry may be reluctant to sponsor trials in the developing world because the prospects for profit are limited, even if effective treatments are developed.<sup>15–17</sup> Not for profit organisations may also have difficulty supporting such research on their own. They may have difficulty in setting priorities<sup>18</sup> and often prefer to offer practical help rather than foster research.

Despite these limitations, the major health problems of the developing world cannot be set aside. Their consequences also affect the developed world.<sup>19</sup> Success can often be obtained with limited funds. Many diseases in sub-Saharan Africa coexist in vulnerable patient groups, and treatment or prevention of one disease may have a major effect on another (for example, HIV and tuberculosis).<sup>20</sup> Seemingly

expensive interventions can become affordable if there is strong political will and collaboration with the industry.

The pace of clinical research is accelerating in sub-Saharan Africa. The area needs more international support, but this should be provided without fostering just another form of colonisation.<sup>21</sup> African researchers should have a meaningful say in setting research priorities,<sup>22</sup> and outside support should help develop sustainable local research capacity.

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## Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials

John Pickup, Martin Mattock, Sally Kerry

### Abstract

**Objective** To compare glycaemic control and insulin dosage in people with type 1 diabetes treated by continuous subcutaneous insulin infusion (insulin infusion pump therapy) or optimised insulin injections.

**Design** Meta-analysis of 12 randomised controlled trials.

**Participants** 301 people with type 1 diabetes allocated to insulin infusion and 299 allocated to insulin injections for between 2.5 and 24 months.

**Main outcome measures** Glycaemic control measured by mean blood glucose concentration and percentage of glycated haemoglobin. Total daily insulin dose.

**Results** Mean blood glucose concentration was lower in people receiving continuous subcutaneous insulin infusion compared with those receiving insulin injections (standardised mean difference 0.56, 95% confidence interval 0.35 to 0.77), equivalent to a difference of 1.0 mmol/l. The percentage of glycated haemoglobin was also lower in people receiving

insulin infusion (0.44, 0.20 to 0.69), equivalent to a difference of 0.51%. Blood glucose concentrations were less variable during insulin infusion. This improved control during insulin infusion was achieved with an average reduction of 14% in insulin dose (difference in total daily insulin dose 0.58, 0.34 to 0.83), equivalent to 7.58 units/day.

**Conclusions** Glycaemic control is better during continuous subcutaneous insulin infusion compared with optimised injection therapy, and less insulin is needed to achieve this level of strict control. The difference in control between the two methods is small but should reduce the risk of microvascular complications.

### Introduction

Continuous subcutaneous insulin infusion, often called insulin pump therapy, was introduced in the 1970s as a way of achieving and maintaining strict control of blood glucose concentrations in people with type 1 (insulin dependent) diabetes.<sup>1</sup> Short acting insulin is infused subcutaneously from a portable pump at one



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