

Review Article

Clinical trials in Ghana: evolution and current landscape

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ABSTRACT

A review of published clinical trials from Ghana shows the earliest trials initiated in the 1970s, were mainly trials of interventions against onchocerciasis and childhood Burkitt's lymphoma. Subsequent trials in the 1980s and 1990s were more diverse, comprising of preventive as well as therapeutic interventions against major communicable diseases of the period. In more recent times, trials of interventions against malaria have since 2000, been the most dominant and have included some of the most recently developed vaccines. There has, since the early days of clinical trial history in Ghana, been a consistent presence of trials of reproductive health interventions and surgically-related trials. There have been few trials of tuberculosis, or neonatal-related interventions, and trials against major non-communicable diseases such as hypertension, cardiovascular diseases, and mental health disorders have been virtually non-existent. The clinical trial evolution in Ghana has reflected global health initiatives and external funding exigencies and there is an urgent need for trials that are dynamic and directed towards addressing other significant and especially non-communicable disease causes of morbidity and mortality in Ghana.

Keywords: Clinical trial, Disease burden, Communicable diseases, Non-communicable diseases

INTRODUCTION

Clinical trials have been conducted since ancient times;¹ however, the history of controlled trials is recent, with what is normally considered as the first modern clinical trial being reported in the 1950s.² Ghana is a country located in the West African sub-region along the Gulf of Guinea, bordered on the east by Togo, on the west by Ivory Coast, and on the north and south by Burkina Faso and the Gulf of Guinea and Atlantic Ocean, respectively.

THE DISEASE BURDEN AND RELEVANT HEALTH INDICATORS

The average life expectancy at birth in Ghana was 66 years in 2013, and infant mortality was 39 per 1000 live-births. The leading causes of burden of disease (as % of total DALY's) in 2004 were, malaria (12.3%), HIV

(7.6%), diarrhoeal diseases (6.0%), lower respiratory infections (5.5%), neonatal infections and conditions (5.2%), birth asphyxia and birth trauma (4.4%), prematurity and low birth weight (4.0%), maternal conditions (3.5%), tuberculosis (3.2%), and other unintentional injuries (2.2%). The leading causes of deaths in children under five years of age in 2008 were, malaria (26%), prematurity (12%), birth asphyxia (11%), pneumonia (10%), diarrhoea (9%), neonatal (9%), congenital (4%), HIV/AIDS (3%), measles (2%), and injuries (2%). The major causes of morbidity and mortality are shown (Table 1).

According to the Ghana health service, malaria accounted for 38% of all out-patient consultations and 36% of all admissions to health facilities, and for 33% of all deaths in children under the age of five years in Ghana in 2011. According to national AIDS control programme data, there was an estimated 200000 people (1.3%) infected

with HIV in Ghana in 2012 (estimated average HIV prevalence in 2014 is 0.8%). Other GHS data from 2010 indicates maternal mortality rate as 350/100000 live-births, and under five mortality was 72/1000 births, with an infant mortality rate of 51.8 and neonatal mortality as a percentage of under five deaths being 39. Although infectious diseases still constitute a major cause of the overall morbidity and mortality in Ghana, the burden of non-communicable disease has shown a consistent increasing trend. It has been estimated that currently, non-communicable diseases, constitute up to 42% of overall mortality, mainly from cardiovascular disease. The estimated prevalence of hypertension is 28% among young urban Ghanaian adults³ but may be higher in other communities and the prevalence of diabetes has been estimated to range between 6 and 13%.^{4,5}

Table 1: The major disease and mortality burden in Ghana.

Cause of total deaths	Deaths	%	Age-standardized death rate per 100000 population	Rate
Diarrhoeal diseases	23516	12.53	Diarrhoea diseases	175.69
HIV/AIDS	18465	9.85	Stroke	125.45
Stroke	13780	7.34	Coronary heart disease	120.08
Influenza / pneumonia	13390	7.14	HIV/AIDS	91.00
Coronary heart disease	13086	6.97	Influenza / pneumonia	72.88
Tuberculosis	11738	6.25	Tuberculosis	60.37
Malaria	11300	6.02	Lung disease	42.09
Low birth weight	6056	3.23	Malaria	31.84
Birth trauma	5674	3.02	Road traffic accidents	28.11
Road traffic accidents	5032	2.68	Kidney disease	26.72
Lung disease	4492	2.39	Diabetes mellitus	23.47
Other injuries	3772	2.01	Other injuries	19.89
Violence	3646	1.94	Hypertension	18.91
Kidney disease	3269	1.74	Violence	18.54
Schistosomiasis	2914	1.55	Liver cancer	18.50

THE GHANAIAAN HEALTH SYSTEM

Health care in Ghana is mainly provided by the government and administered by the Ministry of Health (MOH) through the Ghana Health Service (GHS). The healthcare system has five levels of providers: i) health posts; ii) health centres and clinics; iii) district hospitals;

iv) regional hospitals; and v) tertiary hospitals. There are over 200 hospitals in Ghana and an estimated 15 doctors and 93 nurses per 100000 population in 2010. A national health insurance scheme was introduced in 2006. There are three MOH/GHS health research centres situated in each of the three epidemiological zones. The majority of clinical trials are conducted in these facilities usually in collaboration with university-affiliated investigators. The history of western medicine in Ghana dates to the 19th century activities of Christian missionaries. Subsequently, the colonial government introduced a pre-medical department and public health ordinance in 1878, preceding the introduction of a formal medical system in the 1880s.

A large proportion of Ghanaians still resort to traditional medicine even though the western medical establishment exhibits a mainly skeptical attitude towards its evidential claims. Although traditional medical practitioners may provide detailed accounts on disease conditions and expert guidance on remedies, usually emphasizing spiritual as well as physical dimensions of healing, the therapeutic descriptions are often based on direct observations and experience and there is no documentation on controlled trials by either traditional medicine or western medical practitioners in the colonial period.

HISTORICAL OVERVIEW OF CLINICAL TRIALS IN GHANA

The earliest PUBMED reported intervention study was by Beausoleil (in 1968),⁴ who investigated possible emergence of chloroquine resistant malaria in a Axim, a coastal city in Ghana. In the study, school children were assigned standard chloroquine doses and followed up according to a pre-specified schedule. Although this study had certain features such as a rigorous reporting standard, the assigned treatments non-randomly allocated and a comparison group was not described, making it a probable a quasi-experimental study.

EARLY CLINICAL TRIALS (1970’S-1989)

The earliest clinical trials were results of studies initiated in the 1970s and reported in the early 1980s. These early trials are classifiable into only a few identifiable categories, i.e., i) onchocerciasis; ii) cancer; iii) vaccine-related; and, iv) reproductive health-related trials (Figure 1).

The initial onchocerciasis trials evaluated the efficacy of diethylcarbamazine⁶ (DEC) and subsequently evaluated safety and efficacy of DEC in comparison with metrifonate.⁷ The early studies showed DEC to be efficacious and the drug was affirmed as the reference microfilaricide at the time. However, because of tolerability and safety concerns of metrifonate, further studies were designed to compare different durations of metrifonate treatment with respect to safety. Subsequent

studies initially reported data on the safety of ivermectin⁸ and later studies compared newer drugs such as mebendazole/levamisole,⁹ and DEC versus ivermectin.⁸ The initial oncology trials evaluated the efficacy of cyclophosphamide against Burkitt's lymphoma in children.¹⁰⁻¹³ Subsequent trials evaluated adjunct therapies such as Epstein-Barr Virus-specific transfer factor treatment on relapse occurrence in Burkitt's lymphoma.^{14,15}

Within the field of reproductive health, a reported study compared the effectiveness of vaginal tablets containing various spermicide doses for pregnancy prevention.¹⁶

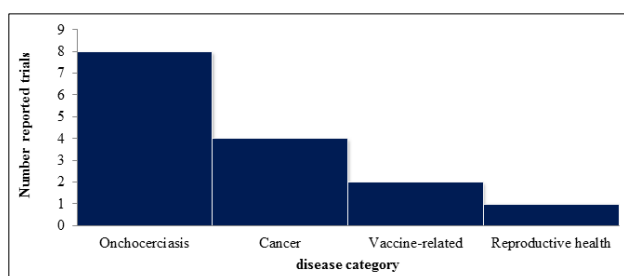


Figure 1: Pubmed published clinical trials from Ghana (1970-1989) - number of trials versus Disease category.

CLINICAL TRIALS IN THE PERIOD 1990-1999

The diversity as well as the quantum of reported trials increased substantially although onchocerciasis trials were still dominant. There was a substantial increase in trials of supplementation agents against nutritional deficiencies and major vaccine-preventable diseases, as well as trials of interventions against communicable diseases such as malaria and guinea worm (Figure 2). The earliest surgically-related trial reported in Ghana was a trial of intra-operative 5-fluorouracil as adjunct for reducing intraocular pressure in advanced glaucoma during trabeculectomy.¹⁷ Early reproductive health-related trials reported during the period include a trial that compared oral nifedipine with hydralazine for controlling blood pressure in severe pre-eclampsia,¹⁸ and a trial that evaluated Norplant as a contraceptive method.¹⁹

The supplementation trials against nutritional disorders included studies that evaluated vitamin A supplementation against childhood malaria or morbidity.^{20,21} Other supplementation trials include comparisons of standard oral rehydration solution with what was described as the more culturally acceptable fermented-maize based local solutions for acute diarrhoea in childhood,²² and those that compared various fermented and non-fermented maize-soybean porridges on increased nutrient density with fermented maize-only porridge on catch up growth in children with acute diarrhoea.²³ Other surgically-related supplementation trials include evaluation of dietary fibre load on colonic metabolism and pH.^{24,25}

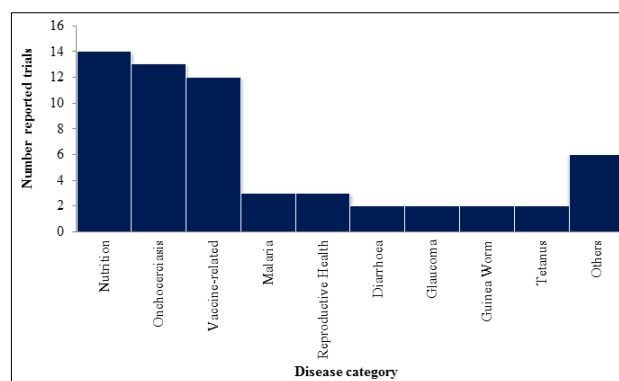


Figure 2: Pubmed published clinical trials from Ghana (1990-1999) - number of trials versus disease category.

The vaccine-related trials reported during the period include a study that compared acellular pertussis vaccine combined with diphtheria and tetanus toxoids with whole cell pertussis-diphtheria-tetanus vaccine for primary childhood immunization,²⁶ and an evaluation of the effect of vitamin A supplementation on immune responses to specific vaccines and the efficacy of the trivalent oral poliovirus vaccine.²⁷ There were several comparative onchocerciasis trials that evaluated drugs such as levamisole with mebendazole,²⁸ albendazole and amorazone, and suramin.²⁹⁻³¹ There were trials of interventions such as ivermectin,³² and dual-antibiotic or antibiotic-hydrocortisone ointments on healing of secondary infections in guinea worm patients,³³ on effectiveness of cotrimoxazole on buruli ulcer,³⁴ permethrin-impregnated bed nets on childhood mortality,³⁵ oral versus intramuscular chloroquine for cerebral malaria,³⁶ and trials that evaluated the effects of ivermectin and albendazole alone and in combination on *Wuchereria bancrofti* microfilaraemia lymphatic filariasis.³⁷⁻⁴⁰

CLINICAL TRIALS IN THE PERIOD 2001-2009

The majority of the reported trials in this period were interventions against malaria (Figure 3): these ranged from drug therapy for acute malaria, of older antimalarials such as chloroquine and sulphadoxine-pyrimethamine,⁴¹⁻⁴⁴ and subsequently, of artemisinin combination therapies,⁴⁵⁻⁴⁸ various interventions for intermittent preventive treatment in infants and pregnant women,^{49,50} and more recently, of the RTS,S vaccine.⁵¹

HIV trials of the decade 2000-2009

The initial HIV-related trials include studies such as the multi-centre phase 2 trial of tenofovir compared with placebo, a trial of a vaginal microbicide gel (SAVVY) for preventing male to female vaginal HIV transmission high risk women,⁵² and related trials such as those comparing acyclovir plus selected antibacterials for episodic herpes treatment on HIV infection progression.

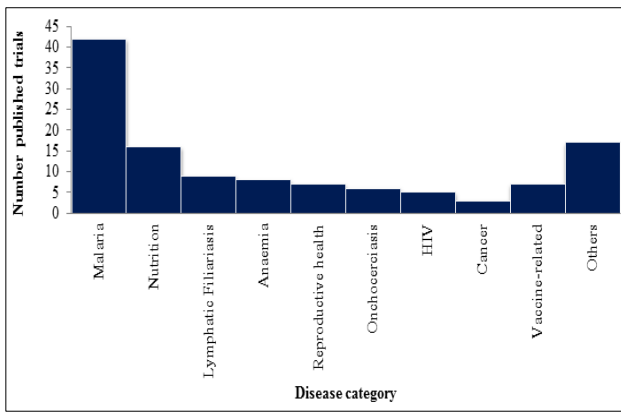


Figure 3: Pubmed published clinical trials from Ghana (2000-2009) - number of trials versus disease category.

Trials against other communicable diseases in the decade 2000-2009

Several notable trials of interventions against other neglected diseases, including a trial that evaluated the effect of albendazole on oesophagostomiasis,⁵³ or different interventions on buruli ulcer,⁵⁴ and notably, a trial of the pentavalent rotavirus vaccine against childhood diarrhoea.⁵⁵

Anaesthesiology and surgical trials of the decade 2000-2009

A notable study within the field of anaesthesiology was a trial that evaluated peri-operative analgesic efficacy of caudal ketamine with or without bupivacaine in children undergoing lower abdominal surgery that showed that ketamine was a safe adjuvant for prolonging caudal analgesia duration.⁵⁶

There was also a study that sought to determine the optimum passive post-mastectomy drainage time by comparing early to late drainage removal,⁵⁷ a trial of diode-laser transcleral cyclophotocoagulation as primary surgical treatment for lowering intraocular pressure for primary open angle glaucoma,⁵⁸ and a trial comparing the effectiveness of vaginal versus sublingual misoprostol for labour induction in women with intrauterine foetal death.⁵⁹

CLINICAL TRIALS 2010-2014

There have been further trials of vaccines against rotavirus diarrhoea,⁶⁰ and further safety trials of the RTS,S vaccine in relation to other EPI vaccines in children⁶¹. There have also been several reproductive health-related trials,^{62,63} as well as trials focused on improving newborn survival.^{64,65} Notably, the only reported trial of artemisinin combination therapy for malaria treatment in Sickle Cell Disease (SCD), has recently been reported⁶⁶ (Figure 4).

The reproductive health-related trials include comparative evaluation of misoprostol versus manual vacuum aspiration (MVA) for managing incomplete abortion,⁶² studies on the effect of extending oxytocin use in the community on prevention of maternal mortality due to post-partum haemorrhage,^{67,68} and the effect of different caesarean section surgical techniques on maternal morbidity, mortality and other outcomes.⁶⁹

Notable among recent trials is a study that evaluated home visits as a strategy to improve neonatal survival,⁶⁵ within which was nested trial which showed that home visits also influenced uptake of skin-to-skin care among low birth-weight infants in rural areas and on neonatal survival.⁷⁰

In relation to other childhood illness was a study that evaluated immediate versus delayed (by one hour) application of Continuous Positive Airways Pressure (CPAP) procedure for childhood acute respiratory distress that showed that immediate CPAP administration resulted in significant decrease in respiratory rate.⁷¹

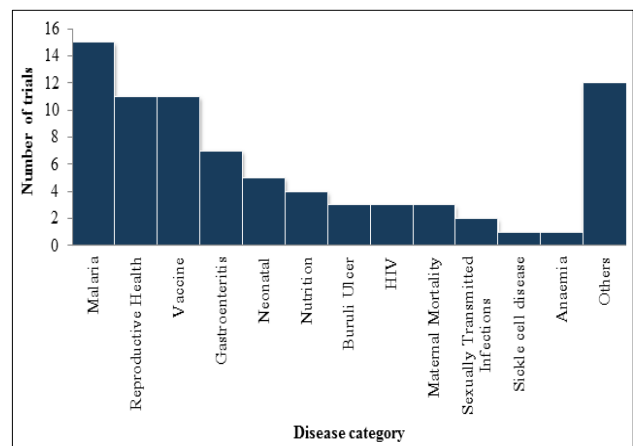


Figure 4: Pubmed published clinical trials from Ghana (2010-2014) - number of trials versus disease category.

ONGOING REGISTERED TRIALS

An overview of ongoing trials registered at the website of the Ghanaian Regulatory Authority (Food and Drugs Authority) showed that the most registered studies were vaccine-related trials.

There were also drug-related trials against a range of conditions, as well as nutrient supplementation trials on neonatal and maternal survival (Table 2).

An overview of the US-based clinical trials registry (www.clinicaltrials.gov) showed the majority of registered trials to be trials of interventions against malaria, and reproductive health-related trials.

Table 2: Ongoing trials currently registered at the food and drugs authority website.

Disease category	Intervention	Trial phase	Date of commencement	Duration
Meningitis	Meningococcal conjugate A vaccine	II	October 2008	42 months
Onchocerciasis	Moxidectin	III	July 2010	25 months
Severe malaria	Artimist versus quinine	III	March 2012	5 months
Severe malaria	Intravenous versus intramuscular artesunate	III	August 2011	60 months
Malaria in pregnancy	Artemisinin combination treatments	Not stated	February 2011	60 months
Malaria vaccine	RTS, S/AS01E	III	August 2009	60 months
Malaria vaccine	EBA 175 RII-NG	I	May 2010	18 months
Malaria vaccine	GM2 Z	II	May 2011	27 months
Tuberculosis	Rifampicin versus isoniazid	III	August 2011	60 months
Postpartum haemorrhage	Tranexamic acid	III	October 2011	41 months
Human papillomavirus infection	Gardasil	Not stated	August 2011	18 months
Extended programme on immunization	RTS, S/AS01E	III	May 2012	52 months
Gastroenteritis	Rotarix (rotavirus vaccine)	Not stated	September 2012	7 months
Reproductive health	Oxytocin	Not stated	April 2011	12 months
Reproductive health	Micronutrient supplementation	Not stated	June 2013	48 months
Neonatal survival	Vitamin A	Not stated	August 2011	36 months
Haemoglobin diagnostic accuracy	Pronto versus Pronto7 versus Hemocue 201+ versus haematology analyzer	Not stated	July 2013	2 months

DISCUSSION

The early clinical trials in Ghana (from the 1970's) were conducted relatively quickly after the first modern international clinical trial reports from more developed countries. Although onchocerciasis trials were dominant in the initial two decades of trial history diverse trials focused on the major communicable diseases of the period were done in later years. Subsequently trials of interventions against malaria have been the commonest, possibly reflecting global health initiatives and funding mechanisms that were made available following the emergence of chloroquine resistance and associated increase in childhood mortality. Although the number of trials of interventions against major communicable diseases evolved in response to either increased incidence or increased awareness of the diseases, trials of interventions against major non-communicable diseases, whose contribution to overall morbidity and mortality in Ghana is consistently increasing, are few or virtually non-existent. This worrying trend possibly reflects unavailable financial resources, low commitment, or availability and use of alternative means rather than clinical trials for addressing this phenomenon. The near-absence of reported trials against tuberculosis and

neonatal conditions, which together constitute a significant contributor to the morbidity and mortality burden may also reflect similar situation as described for non-communicable diseases. There has been near-absence of trials of interventions against sickle cell disease, despite the high prevalence of condition in Ghana and associated morbidity. The majority of trials, except those against onchocerciasis have been phase III trials. Although relatively few, reproductive health-related and surgical trials have been done since the earliest days of clinical trial history in Ghana.

CONCLUSION

Trials of interventions against onchocerciasis and Burkitt's lymphoma were the initially reported trials from Ghana. Onchocerciasis chemotherapy trials were dominant in the early decades while malaria trials were dominant in the latter period. There has been a consistent presence of reproductive health-related and surgical trials but near-absence of trials of interventions against major non-communicable diseases such as hypertension, diabetes, cardiovascular diseases and sickle cell disease. Trials of interventions against non-communicable diseases are needed in view of the increasing morbidity

and mortality burden associated with these conditions. There is the need for enhanced clinical-trial related training.

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