Building evidence for improving childhood immunisation coverage in Africa

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Abstract

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The Expanded Programme on Immunisation has the potential to substantially reduce child mortality and contribute to achieving the Millennium Development Goals. We assessed the programme's performance in Africa, the reasons for poor performance, and effective interventions for improving its performance on the continent. We used a combination of methods including systematic reviews, bibliometric analyses, generalised linear models, and grading of the quality of evidence.

We found that African countries have made extraordinary advances since childhood immunisation programmes began in 1974. However, there exist wide inter-country and intra-country differences, and the quality of immunisation data is poor. Besides, vaccines are administered well after the recommended ages in many countries; leaving children exposed to deadly vaccine-preventable diseases for long periods. In addition, Africa's contribution to the global immunisation research output is minimal. There is no association between research productivity and immunisation coverage in Africa, which may signal lack of interactive communication between policymakers and researchers. Furthermore, individual and contextual factors (defined at community and country levels) are independently associated with low immunisation coverage; suggesting that immunisation system strengthening should address people and the communities and societies in which they live. Lastly, we found moderate-to-high quality evidence that interactive educational meetings, audit and feedback, supportive supervision; and use of community health workers, parent reminders, home visits, interactive communication, mass media, and material incentives have the potential to improve childhood immunisation coverage in Africa. We recommend that these proven interventions should be an integral part of national immunisation action plans in Africa; accompanied by rigorous monitoring and evaluation to inform decisions being made. There is also a need for high-quality studies on other potentially useful interventions such as best approaches for integration with other primary care services, public stewardship of the private sector, school-based vaccination, and sustainable programme financing mechanisms in Africa.

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Contents

List of abbreviations

%	Percent
AEFI	Adverse events following immunisation
AIDS	Acquired immune deficiency syndrome
AFRO	African Region of the World Health Organization
AFP	Acute flaccid paralysis
BASICS	Basic Support for Institutionalizing Child Survival
BCG	Bacille Calmette-Guérin
CENTRAL	Cochrane Central Register of Controlled Trials
CBA	Controlled before and after study
CI	Confidence intervals
EPI	Expanded Programme on Immunisation
DHS	Demographic and health survey
DoV	Decade of Vaccines Collaboration
DTP	Diphtheria-tetanus-pertussis vaccine
DTP1	First dose of DTP
DTP3	Third dose of DTP
EBP	Evidence-based practice
EMRO	WHO Eastern Mediterranean Region
EPOC	Cochrane Effective Practice and Organisation of Care Group
GAVI	Global Alliance for Vaccine and Immunisation
GDP	Gross domestic product
GIVS	Global Immunisation Vision and Strategy
GVAP	Global Vaccine Action Plan
HepB	Hepatitis B
Hib	*Haemophilus influenza* type b
HIV	Human immunodeficiency virus
HTA	Health Technology Assessment
ICC	Intra-cluster correlation
IRR	Incidence rate ratio
ITS	Interrupted time series
JRF	Joint Reporting Form
MEASURE DHS	Monitoring and Evaluation to Assess and Use Results (of) Demographic and Health Surveys
MCV1	First dose of measles-containing vaccine
MDGs	Millennium Development Goals
MDG-4	4th Millennium Development Goal
Men A	*Neisseria meningitides* group A
MOR	Median odds ratio
MLM	Mid-Level Management
MVP	Meningitis Vaccine Project
NGO	Non-Governmental Organisation
OPV	Oral polio vaccine

OR	Odds ratio
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
PCV	Pneumococcal conjugate vaccine
PPP	Purchasing power parity
RCT	Randomised controlled trials
RED	Reach Every District
R&D	Research and development
SIAs	Supplementary immunisation activities
SIGLE	System for Information on Grey Literature in Europe
Td	Tetanus toxoid and reduced strength diphtheria
UCI	Universal Childhood Immunisation
UNICEF	United Nations Children Fund
USA	United States of America
USAID	United States Agency for International Development
USD	United States Dollar
WHA	World Health Assembly
WHO	World Health Organisation

CHAPTER 1: General introduction

1.1. About this chapter

In this chapter, we provide general information about childhood immunisation programmes and related international health goals. In addition, we provide a motivation for doing the study and explain the objectives.

1.2. The Expanded Programme on Immunisation

Immunisation is widely acknowledged as one of the most powerful public health interventions available to improve child survival; not only by directly combatting some of the key diseases and causes of child mortality, but also by providing a platform for broader health services.[1-7] The concentrated global effort to use vaccination as a public health intervention began when the World Health Organization (WHO) launched the Expanded Programme on Immunisation (EPI) in 1974, following an immensely successful worldwide smallpox eradication programme.[8] The EPI programme typically consists of regularly scheduled services that reach each new cohort of children less than one year of age with vaccines at health facilities, scheduled outreach sites, or (in special circumstances) from door to door. When the EPI was launched in 1974, WHO recommended a standard immunisation schedule covering six basic antigens i.e. Bacille Calmette-Guérin (BCG), polio, diphtheria-tetanus-pertussis (DTP), and measles. The proportion of children who receive the full series of three doses of the DTP vaccine (DTP3) by 12 months of age is traditionally used as a standard measure of the programme's ability to reach the target population, and is generally accepted to reflect the overall performance of EPI programmes.[8]

The traditional EPI vaccines are estimated to annually prevent 2.5 million child deaths (mainly from measles, pertussis, tetanus, and diphtheria) as well as severe morbidity from devastating diseases such as poliomyelitis and tuberculous meningitis for millions more children around the world.[7, 9, 10] However, immunisation has the potential to do

more. Introducing a portfolio of newly available vaccines (i.e. pneumococcal conjugate, rotavirus, and meningococcal group A conjugate vaccines)[4, 5, 11-15] and under-utilised vaccines (such as Hepatitis B, *Haemophilus influenzae* type b, and yellow fever vaccines)[16-20] into routine immunisation programmes of low and middle-income countries between now and 2015 could save the lives of millions more children. This would lead the world closer to achieving the Millennium Development Goals.[3, 21] Table 1 shows a typical EPI schedule in Africa. Vitamin A supplementation is associated with large reductions in mortality in children aged 6 months to five years in low and middle-income countries; and it is included in the EPI schedule in Africa for this reason, even though it is not a vaccine.[22]

Table 1: A typical EPI schedule in Africa

Vaccine	Doses	Age	Minimum interval
BCG	1	Birth or soon after	Not applicable
OPV	4	Birth, 6,10,14 weeks	4 weeks
DTP	3	6,10,14 weeks	4 weeks
HepB*	3/4	Birth, 6, 10, 14 weeks	4 weeks
Hib	3	6,10,14 weeks	4 weeks
PCV	3	6,10,14 weeks	4 weeks
RV**	2/3	6,10,14 weeks	4 weeks
Measles***	1	9 months	Not applicable
Yellow fever	1	9 months	Not applicable
Vitamin A	2	9, 15 months	6 months

BCG, Bacille Calmette-Guérin; OPV, oral polio vaccine; DTP, diphtheria-tetanus-pertussis vaccine; HepB, Hepatitis B vaccine; Hib, *Haemophilus influenzae* type b vaccine; PCV, pneumococcal conjugate vaccine; RV, rotavirus vaccine.
* Some countries in Africa have a policy of giving a birth dose of the hepatitis B vaccine.
** The Strategic Advisory Group of Experts (SAGE) has removed the maximum age restriction for rotavirus vaccine, but continues to recommend that the first dose be given as soon as possible after 6 weeks of age.
.*** Measles vaccine is now recommended as a two-dose schedule, with the second dose given during the second year of life.

1.3. Millennium Development Goals

In the year 2000 the global community made a historic commitment to eradicate extreme poverty and improve the health and welfare of the world's poorest people within 15 years.[23] The commitment is embodied in the United Nations Millennium Declaration, which spells out eight time-bound goals, known as the Millennium Development Goals (MDGs). The eight goals are:

1. To eradicate extreme poverty and hunger;
2. To achieve universal primary education;
3. To promote gender equality and empower women;
4. To reduce child mortality;
5. To improve maternal health;
6. To combat HIV/AIDS, malaria, and other diseases;
7. To ensure environmental sustainability; and
8. To develop a global partnership for development.[23]

The MDGs are increasingly recognised as the over-arching development framework and, as such, are increasingly guiding the policies of low and middle-income countries, international agencies, and research projects; and this thesis is no exception.

1.4. Global Alliance for Vaccines and Immunisation

When EPI was born in 1974, global immunisation coverage hovered around 5%. Through the 1980s, the United Nations Children Fund (UNICEF) and WHO led a successful global campaign to achieve Universal Childhood Immunisation with the six traditional EPI vaccines; by immunising at least 80% of all children by 1990. Unfortunately, other donor priorities overtook EPI in the 1990s and the programme suffered. Low and middle-income countries struggled to maintain childhood immunisation, and pharmaceutical companies had no incentive to invest in supplying vaccines to low-income countries. The outcome was that more than 30 million children were born annually in countries with inadequate or no childhood immunisation programmes.[24] As a result of this failure to reach all children with life-saving vaccines, three million lives were lost each year due to vaccine-preventable diseases. In response to this unacceptable situation, national governments, international agencies, non-governmental organisations, and the private sector came together to create the Global Alliance for Vaccines and Immunisation (GAVI) in 2000.

GAVI's aim is to save children's lives and protect people's health by increasing access to childhood vaccines in low-income countries. National governments of the 72 poorest countries of the world are eligible to apply for GAVI support. The GAVI model is designed to aggregate resources to create results beyond the capability of any single agency or country. It is also designed to make a rapid positive impact, using independent financial and administrative structures to ensure efficient transfer of support from donors to targeted countries. GAVI provides time-limited funding (usually over five years) for the supply of vaccines and other forms of support to strengthen implementing country immunisation services and health systems.[20, 25, 26 27]

1.5. Global Immunisation Vision and Strategy

In 2005, WHO and UNICEF launched the Global Immunisation Vision and Strategy (GIVS).[28, 29] The primary objective of GIVS was to reduce vaccine-preventable disease mortality and morbidity by two-thirds by 2015 compared to 2000, which would be a significant contribution towards achieving the fourth Millennium Development Goal. GIVS presents a unifying vision and strives for a world in 2015 where immunisation would be highly valued and more people would be protected against more diseases. This vision is reflected in the over-arching goals, which relate to immunisation coverage, immunisation safety, sustainability, and disease reduction.

GIVS has four strategic areas, namely:

1. Protecting more people in a changing world;
2. Introducing new vaccines and technology;
3. Integrating immunisation, other linked health interventions, and surveillance in the health systems context; and
4. Immunisation in the context of global interdependence.

One of the targets set forth by GIVS was that all countries will achieve immunisation coverage of at least 90% at national level and 80% in all districts (to be measured by DTP3 coverage) by 2010, and to sustain these achievements through 2015. [28, 29]

1.6. Reach Every District

Immunisation coverage declined or stagnated in the WHO African region (which essentially refers to sub-Saharan Africa) in the 1990's. As a result, sub-Saharan Africa accounted for one-third of the estimated 33.4 million children globally who were un-immunised (defined as children who did not receive at least three doses of the DTP vaccine by 12 months of age) in 2002.[24] To reach these un-immunised children, the WHO African Regional Office and its partners developed the Reach Every District (RED) strategy as an innovative approach to improve childhood immunisation coverage in the region. [30, 31] The RED approach focuses on the district as the operational level and builds capacity at the district, health facility, and community levels to address common obstacles to routine childhood immunisation.

The strategy focuses on five components, namely:

1. Planning and management of resources;
2. Supportive supervision;
3. Re-establishment of outreach services;
4. Community links with service delivery; and
5. Monitoring and use of data for action.

Beginning in late 2002, countries across sub-Saharan Africa were introduced to the RED approach during workshops and technical meetings.[30, 31]

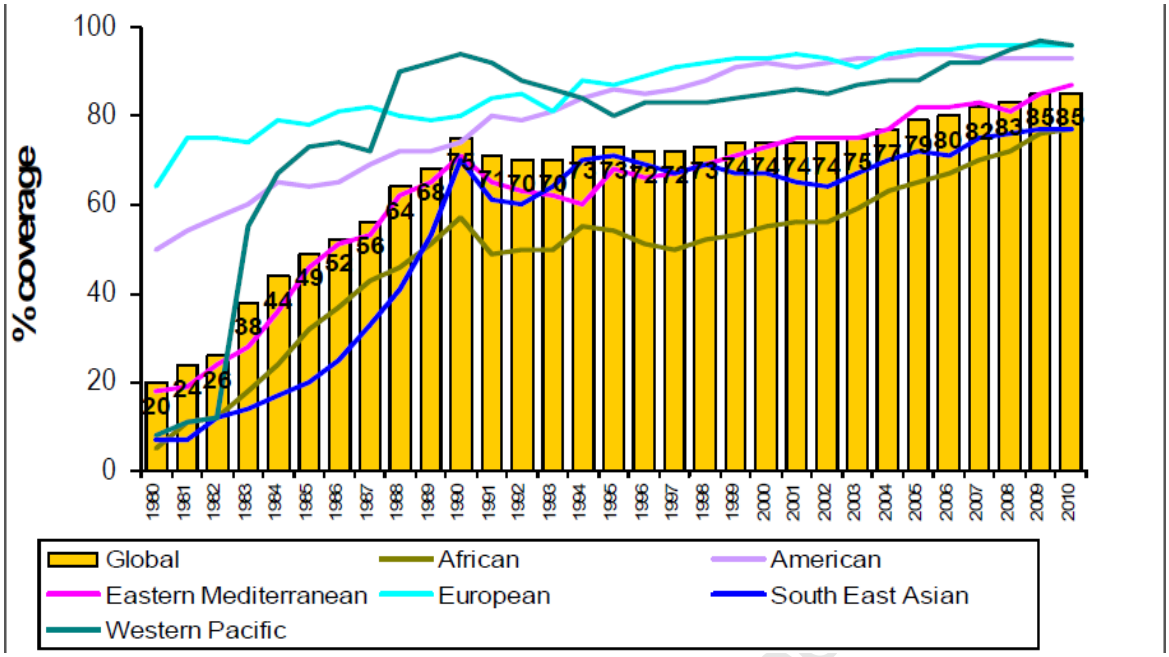
1.7. Decade of Vaccines Collaboration

The Decade of Vaccines Collaboration (DoV) is newly created initiative which envisions a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases.[32] Its mission is to extend the full benefits of immunisation to all people by 2020 and beyond, regardless of where the people are born, who they are, or where they live. The DoV was initially discussed by the 64th World Health Assembly in May 2011 as part of the progress report on the implementation of GIVS. Four Working Groups and a Steering Committee were set up within the DoV to develop the Global Vaccine Action Plan (GVAP). The former consisted of representatives of governments, civil society, health professionals, global development agencies, universities and research institutions, and vaccine manufacturers. The initial drafts of GVAP went through a consultation process that began in May 2011 and included global and regional meetings, dozens of issue-specific gatherings, and online consultations of a wide range of immunisation stakeholders. The final GVAP was endorsed by the 65th World Health Assembly in May 2012 in Geneva.[32]

1.8. Rationale of the project

Through the efforts of national EPI programmes, and the assistance of the global initiatives discussed above, global DTP3 coverage rose from 17% in 1980 to 85% in 2010.[24, 33] However, Africa lags behind the rest of the world. DTP3 coverage in the WHO African Region rose from 5% in 1980 to only 77% in 2010 (Figure 1). [24, 33]

Figure 1: Evolution DTP3 coverage from 1980 to 2010 by WHO Region



Source: WHO [References 24 and 33; data as of July 2011]

We believe that an evidence-based practice (EBP) approach[34, 35] would improve the effectiveness, efficiency and equity of immunisation policies in Africa, and lead African countries to achieve the GIVS targets and eventually MDG-4. EBP, also referred to as evidence-informed policymaking, is the conscientious, explicit and judicious use of the best available research evidence when making healthcare decisions. [34, 35] An EBP approach to improving EPI programmes in Africa and, consequently, reducing child mortality on the continent demands first an understanding of why EPI has failed to reach its maximum potential. And secondly, appropriate corrective interventions to address the observed EPI challenges should be identified and implemented.[36-39] These were the reasons why we set up this project, with the general and specific objectives described below.

1.9. Objectives of the project

The aim of the thesis was to evaluate EPI performance in Africa, the reasons for poor performance, and effective interventions for improving EPI performance on the continent. The project focuses on child immunisation coverage, because the determination of immunisation status is the critical element of EPI performance assessment.[8, 40, 41] The study combines several methods including bibliometric analyses, generalised linear models, systematic reviews, and grading of the quality of evidence of effects.

The specific objectives of the project were:

1. To assess routine childhood immunisation services, accelerated control of priority vaccine-preventable diseases, and introduction of new and underutilised vaccines in Africa (Chapter 2).
2. To evaluate Africa's contribution to the global immunisation research output; and to determine whether immunisation research productivity is associated with immunisation coverage in Africa (Chapter 3).
3. To develop and test a model of childhood immunisation coverage that includes individual, community, and country-level characteristics (Chapter 4).
4. To synthesise the global evidence from systematic reviews and randomised controlled trials of interventions for increasing immunisation coverage; and to discuss their relevance to the EPI programme in Africa (Chapter 5).

CHAPTER 2: The Expanded Programme on Immunisation in Africa

2.1. About this chapter

In this chapter, we report a systematic review of EPI performance in Africa.

2.2. Introduction

The 2015 deadline for the achievement of the Millennium Development Goals (MDGs) is less than five years away. Africa is significantly behind the rest of the world in making good its commitment to reduce child mortality by two-thirds[42]. Africa has the highest under-five mortality rate of all the world's continents, with nearly half of all global deaths in under five year olds occurring in sub-Saharan Africa.[42, 43] Globally, the under-five mortality rate reduced by 26% from 91 deaths per 1000 live births in 1990 to 67 deaths per 1000 live births in 2007; while in sub-Saharan Africa the rate decreased by only 20%, from 181 to 145 over the same period. Vaccine-preventable diseases are a major contributor to high African child mortality rates, partly because of the limited introduction of new vaccines and low uptake of existing vaccines.[44] In 2010, only 77% of African infants received the full series of three doses of the diphtheria-tetanus-pertussis vaccine (DTP3). Overall more than seven million children in Africa did not receive DTP3 by one year of age in 2010.[24, 33] Furthermore, vaccine efficacy tends to be lower in low-income countries than in higher-income countries,[5, 45] thus the need to attain and sustain high and equitable childhood immunisation coverage in sub-Saharan Africa; where most countries are low-income. We assessed the performance of EPI in Africa, with a focus on the determination of immunisation status. There is consensus within the EPI community that the critical element of EPI performance evaluation is routine immunisation coverage.[8, 40, 41] The latter is the output of a system which involves a series of inter-related components; such as training, vaccine delivery, financing, vaccine logistics, and management. We also sought and reported data on these components of the routine

immunisation system as well as progress in the accelerated control of priority vaccine-preventable diseases on the African continent.

2.3. Methods

From July 2011 to July 2012, we searched websites of WHO and other international agencies (as shown in Table 2) for information on the performance of national EPI programmes in Africa. We supplemented this targeted grey literature search with searches of Africa-Wide and PubMed databases, for peer-reviewed data published between 1970 and 2010 on childhood immunisation programmes in Africa. The search strategy used for each database is shown in Table 2.

Table 2: Search strategy for this systematic review

Websites reviewed:

1. http://www.who.int/immunization/aboutus/en/index.html
2. http://www.afro.who.int/en/clusters-a-programmes/ard/immunization-and-vaccines-development.html
3. http://www.emro.who.int/entity/vpi/
4. http://www.unicef.org/
5. http://www.gavialliance.org/
6. http://www.measlesinitiative.org/
7. http://www.polioeradication.org/
8. http://www.meningvax.org/
9. http://www.msf.org/

Search strategy for PubMed:

"Immunization"[Mesh] OR "Vaccination"[Mesh] OR "Immunization, Secondary"[Mesh] OR "Immunization Programs"[Mesh] OR "Immunization Schedule"[Mesh] OR "Immunization, Passive"[Mesh] OR "Mass Vaccination"[Mesh] **AND** ((ALGERIA) OR (ANGOLA) OR (BENIN) OR (BOTSWANA) OR (BURKINA FASO) OR (BURUNDI) OR (CAMEROON) OR (CANARY ISLANDS OR "CANARY ISLANDS") OR ((CAPE VERDE) OR "CAPE VERDE") OR (CENTRAL AFRICAN REPUBLIC) OR (CHAD) OR (COMOROS) OR (CONGO) OR (DEMOCRATIC REPUBLIC CONGO) OR (DJIBOUTI) OR (EGYPT) OR ((EQUATORIAL GUINEA) OR "EQUATORIAL GUINEA") OR (ERITREA) OR (ETHIOPIA) OR (GABON) OR (GAMBIA) OR (GHANA) OR (GUINEA) OR ((GUINEA BISSAU) OR "GUINEA BISSAU") OR (IVORY COAST) OR ((COTE D'IVOIRE) OR "COTE D'IVOIRE") OR (KENYA) OR (LESOTHO) OR (LIBERIA) OR (LIBYA) OR (LIBIA) OR (JAMAHIRIYA) OR (JAMAHIRYIA) OR (MADAGASCAR) OR (MALAWI) OR (MALI) OR (MAURITANIA) OR (MAURITIUS)

OR (MOROCCO) OR (MOZAMBIQUE) OR (MOCAMBIQUE) OR (NAMIBIA) OR (NIGER) OR (NIGERIA) OR (REUNION) OR (RWANDA) OR ((SAO TOME) OR "SAO TOME") OR (SENEGAL) OR (SEYCHELLES) OR ((SIERRA LEONE) OR "SIERRA LEONE") OR (SOMALIA) OR ((SOUTH AFRICA) OR "SOUTH AFRICA") OR ((ST HELENA) OR "ST HELENA") OR (SUDAN) OR (SWAZILAND) OR (TANZANIA) OR (TANGANYIKA) OR (TOGO) OR (TUNISIA) OR (UGANDA) OR ((WESTERN SAHARA) OR "WESTERN SAHARA") OR (ZAIRE) OR (ZAMBIA) OR (ZIMBABWE) OR (AFRICA[MH]) OR (SOUTH* AND AFRICA*) OR (WEST* AND AFRICA*) OR (EAST* AND AFRICA*) OR (NORTH* AND AFRICA*) OR (CENTRAL* AND AFRICA*) OR (SUB SAHARAN AFRICA*) OR (SUBSAHARAN AFRICA*) OR (AFRICA*) NOT (((GUINEA PIG*) OR "GUINEA PIG*") OR ((ASPERGILLUS NIGER) OR "ASPERGILLUS NIGER"))) **AND** ("Infant, Newborn"[Mesh] OR "Infant"[Mesh] OR "Child, Preschool" [Mesh])

Limits: Humans, Publication Date from 1970/01/01 to 2010/12/31

Search strategy for Africa Wide:

KW ("Immunization" OR "Vaccination" OR "Immunization, Secondary" OR "Immunization Programs" OR "Immunization Schedule" OR "Immunization, Passive" OR "Mass Vaccination" OR "Vaccine") AND KW (infant OR newborn OR child*)

Limiters - Scholarly (Peer Reviewed) Journals; Year Published: 1970-2010

We screened the search outputs in duplicate and selected publications which focused on immunisation or the "traditional" vaccine-preventable diseases (measles, diphtheria, tetanus, pertussis, and poliomyelitis), were conducted in an African country, and had human beings as the subject. From the final pool of studies we selected (by consensus) key websites and peer-reviewed publications with relevant data on immunisation coverage, components of the routine immunisation system, accelerated control of priority vaccine-preventable diseases, and introduction of new and under-utilised vaccines in Africa. For immunisation coverage, we conducted quantitative analyses of district and national data as described below. For other aspects of EPI performance, we conducted a narrative synthesis of the information contained in the selected publications. We collected and reported data from all the 53 countries on the African continent, unless in instances where relevant data were only available for the WHO African Region.

We conducted data management and statistical analyses of routine immunisation coverage data using Microsoft Access, STATA 10, and ArcGIS software. We compared national coverage for DTP3, first dose of measles-containing vaccine (MCV1), and BCG from the end of each decade since the onset of EPI in 1974 to 2010. We also used the reported data for the first and third dose of DTP (i.e. DTP1 and DTP3 respectively) to calculate national DTP drop-out rate as ((DTP1-DTP3)/DTP1) x100%. The drop-out rate

measures the proportion of children who received the first dose of a vaccine and failed to come back for the remaining doses. A drop-out rate of less than 10% was considered acceptable. In addition, we used the reported tetanus toxoid coverage data for pregnant women to calculate the proportion of newborns protected from tetanus at birth (PAB). The latter refers to at least 80% coverage with two or more doses of tetanus toxoid (i.e. TT2+) in pregnant women. Furthermore, we used WHO and UNICEF estimates of national immunisation coverage for BCG, DTP1, DTP3, MCV1, and PAB.[46]

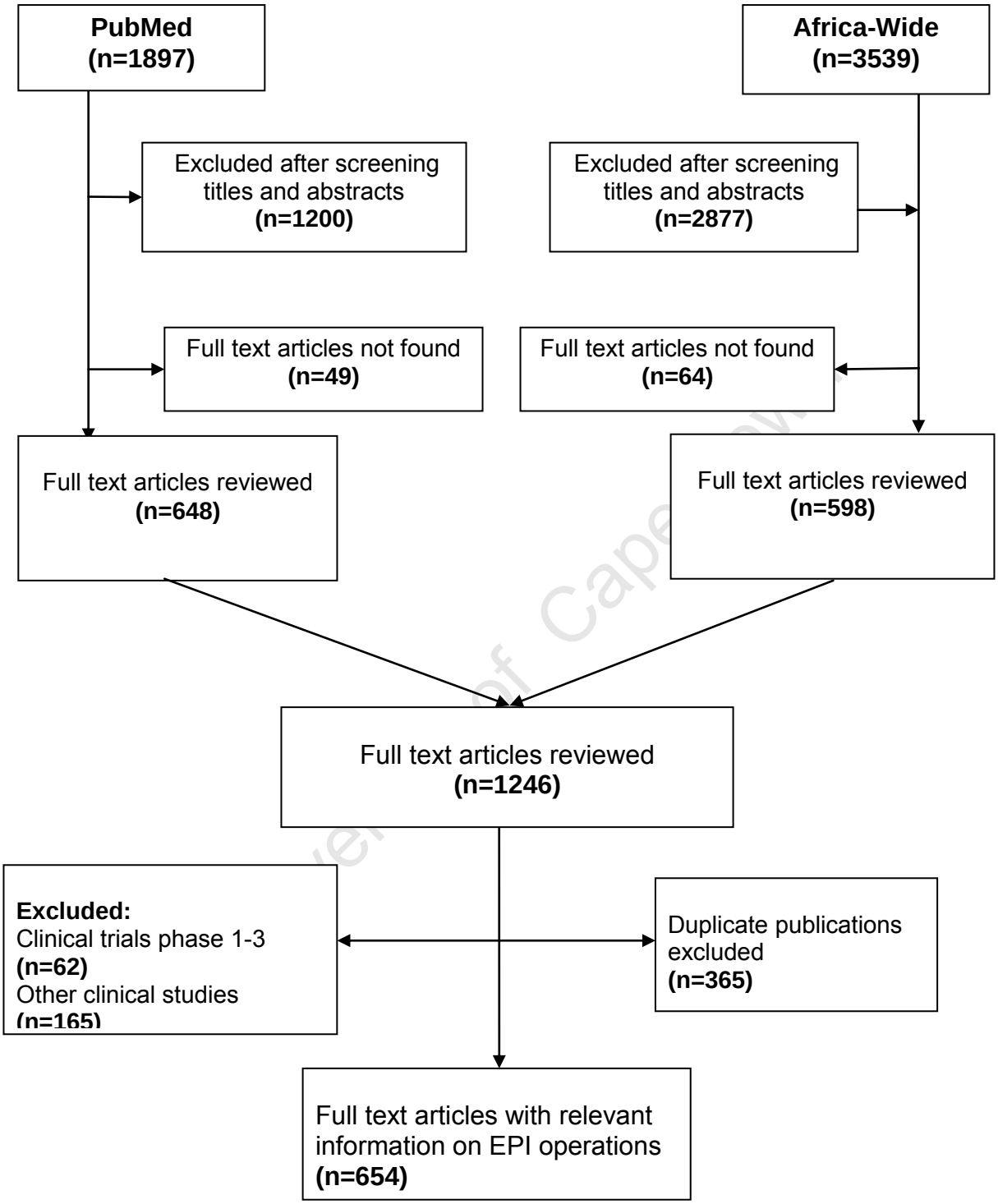
2.4. Results of the peer-reviewed literature search

The search and selection process of peer-reviewed articles on EPI in Africa is shown in Figure 2. We identified 1897 records in PubMed and 3539 records in Africa Wide, published between 1 January 1970 and 31 December 2010. After screening the titles and abstracts, we excluded 1200 articles from PubMed and 2877 articles from Africa Wide; which were clearly not on an operational aspect of childhood immunisation programmes in Africa. Of the remaining 1359 articles, the full text publications of 113 articles were not available and we excluded them from further review. We then reviewed the full text publications of the remaining 1246 articles, from which we excluded 365 duplicate publications and 227 reports of phase 1-3 randomised controlled trials and clinical management of vaccine-preventable diseases; because these were not directly relevant to EPI operations.

The remaining 654 articles contained information on various aspects of the planning, implementation, monitoring, and evaluation of immunisation activities in 47 African countries. The 654 articles were categorised as follows: 334(51%) were on programme management issues, 114(17%) were vaccine effectiveness studies, 101(15%) were epidemiological or burden of disease studies, 82(13%) were on vaccine policy making, and 23 (4%) were on vaccine financing. These studies were published in 156 different scientific journals with citation impact factors ranging from 0 to 53.29; where 62% had an impact factor from 2 to 10, and 11% had an impact factor greater than 10.

The full reference list of the 654 articles is available, on request.

Figure 2: Search and selection of EPI articles from peer-reviewed literature



2.5. Routine childhood immunisation services

2.5.1. Routine childhood immunisation coverage

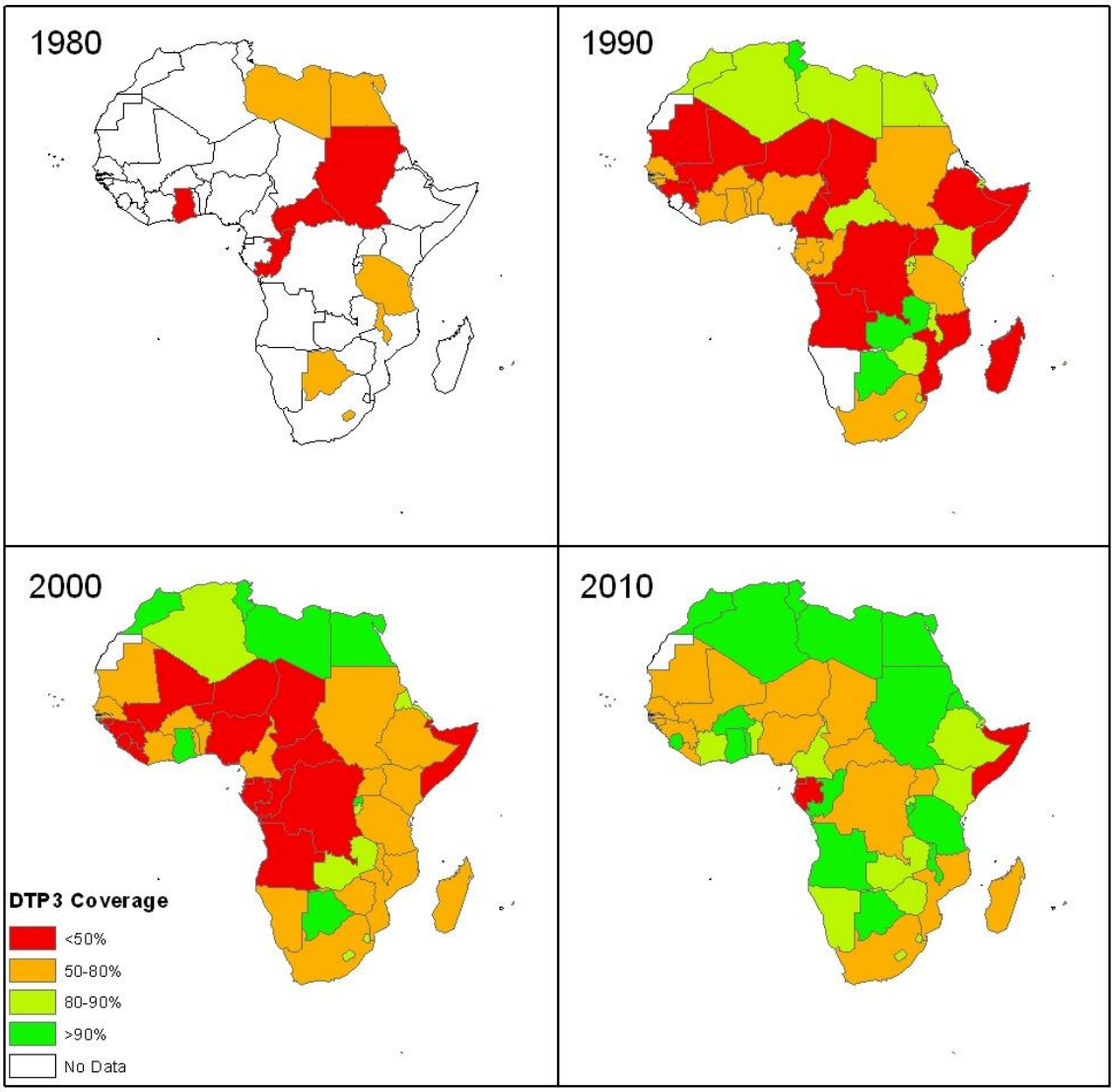
According to WHO and UNICEF coverage estimates (available since 1980),[46] the number of African countries with national DTP3 coverage of at least 90% increased from 0(0%) in 1980, through 7(13%) in 1990 and 9(17%) in 2000, to 22(42%) in 2010.[24] The improvements in national DTP3 coverage between 1980 and 1990 as well as between 2000 and 2010 were significant (all $p<0.001$). However, there were no significant differences in national DTP3 coverage between 1990 and 2000 (probably due to decreased external funding when the Universal Childhood Immunisation campaign ended). Figure 3 shows the evolution in national DTP3 coverage in Africa since 1980. Similar to national DTP3 coverage, we also observed a steady improvement in the proportion of countries having an acceptable DTP drop-out rate (i.e. less than 10%) from 1980 till 1990, stagnation between 1990 and 2000, and a significant ($p=0.0013$) increase between 2000 and 2010.

District immunisation data from WHO/UNICEF Joint Reporting Forms (please see section 2.5.2. below) were available for 2005 and 2010.[24] In 2005, sixteen (30%) African countries reported 80% DTP3 coverage in at least 80% of their districts. District DTP3 coverage data were not available for two countries (Algeria and Djibouti) in 2005. In 2010, no improvement was observed as only 16 (30%) countries reported 80% DTP3 coverage in at least 80% of their districts. District DTP3 coverage data were not available for three countries (Cape Verde, Libya, and Rwanda) in 2010.

In addition, the quality of immunisation data in many African countries is questionable.[47-49] External evaluations have encountered difficulties in verifying vaccine doses administered in health facilities; usually as the result of discrepancies in information between health facilities and their corresponding districts or because completed recording forms were not available at the health facilities visited. Weaknesses in the monitoring of immunisation data are common in most countries. These include inconsistent use of coverage monitoring charts; inadequate monitoring of vaccine stocks, injection supplies, and adverse events following immunisation (AEFI); and poor monitoring of completeness

and timeliness of reporting of data. [47-49] Furthermore, in many African countries, vaccine doses are administered well after the recommended ages; leaving children exposed to deadly vaccine-preventable diseases for long periods. These delays vary widely, between and within countries.[50]

Figure 3: Evolution of national DTP3 coverage in Africa from 1980 to 2010



NB: The maps show North African countries (which belong to the WHO Eastern Mediterranean Region) consistently having GIVS-level coverage, unlike most of sub-Saharan Africa (i.e. the WHO African Region).

2.5.2. Collection of routine childhood immunisation data

In this section, we summarise our understanding of how childhood immunisation data are collected and disseminated; from the remotest rural vaccination centre in Africa to the headquarters of WHO in Geneva and UNICEF in New York. Healthcare workers collect administrative data on the number of vaccinations given, in tally sheets or immunisation registers at the immunisation delivery point, and report to local authorities. These data are aggregated and reported (at regular intervals e.g. monthly or quarterly) to higher administrative levels, up to the central level.[8, 19] Each year, WHO and UNICEF jointly collect the administrative immunisation data from countries through a standard questionnaire known as the WHO/UNICEF Joint Reporting Form. Data collected in the Joint Reporting Form (JRF) include estimates of national immunisation coverage, reported cases of vaccine-preventable diseases, immunisation schedules, and immunisation system performance indicators. Countries send the completed JRF to WHO and UNICEF by April of the following year, and these are available on the web in July.[24, 33]

WHO and UNICEF use the administrative coverage data reported by countries, supplemented by coverage data from surveys reported in peer-reviewed and grey literature, to produce WHO/UNICEF estimates of national immunisation coverage.[46, 51] WHO and UNICEF also consult local experts, especially national EPI managers and WHO/UNICEF regional and national staff, for additional information on the performance of specific immunisation systems. The information is used to derive immunisation coverage estimates through a country-by-country review of available data informed and constrained by a set of heuristics; without applying any statistical or mathematical models. Draft WHO/UNICEF national coverage estimates are sent to national authorities for review and comment, and then modified accordingly. The WHO and UNICEF indicate that while the final immunisation coverage estimates may or may not differ from reported administrative data, the estimates constitute an independent technical assessment of the performance of national immunisation systems by WHO and UNICEF. The two United Nations agencies have been deriving these annually updated country-specific national immunisation coverage estimates since 1980.[46, 51]

2.5.3. Training

Training needs assessments in 14 countries in sub-Saharan Africa in the late 90s referred to the needs for management training, bottlenecks between pre- and in-service training, poor coverage of EPI topics in training curricula, and lack of training of teachers in EPI.[52, 53] This led the WHO African Regional Office to institute the Mid-Level Management (MLM) training courses in the region; to provide EPI managers with new and advanced skills in planning, management, monitoring and evaluation. An external evaluation was conducted in 2005 of the MLM training held between 2000 and 2004 in the African Region, to assess its effectiveness and impact, and its contribution to EPI management. The evaluation consisted of a desk review of the MLM course reports, MLM modules and reference documents; interviews with MLM course participants, facilitators, supervisors, ministry of health officials and country-based partners; and focus group discussions.

The evaluation revealed that during 2000-2004, eleven MLM courses were held and 642 participants trained. The latter included 416 EPI managers, 110 lecturers from institutions that train health workers, 114 WHO/UNICEF immunisation focal persons, and others. The 110 academic staff who received MLM training went back to their institutions and introduced change in EPI teaching, based on new developments and strategies in EPI (such as GIVS and RED). Through perception of users and country-based EPI stakeholders, satisfaction index results and observations in the field during the external evaluation, it was evident to the evaluators that the MLM training had increased the performance of the trained staff and therefore contributed to the improvement of EPI coverage in the African Region. Using DTP3 as an indicator, immunisation coverage in the African Region increased from 53% in 2001 to 69% in 2004.

Other collateral benefits of the MLM course included development of capacity building plans by country teams during the course of training; development by the host country of a solid pool of facilitators for national EPI and other MLM courses; extra-regional participation and use of MLM modules developed by the WHO African Region by the

other WHO regions. All MLM modules were scored very highly by course participants and facilitators. However, the evaluation found that the MLM courses were predominantly vertical, and that follow-up of trained managers or facilitators was not consistent. The evaluation team also observed that there was a lack of a reliable database on EPI training activities to keep the institutional memory on training and support capacity building analysis by EPI programme management. Furthermore, there was insufficient involvement and use of the private sector in MLM training. [40, 41]

2.5.4. Vaccine delivery

We describe here the implementation of the RED approach in the WHO African Region, as a proxy for the status of immunisation service delivery in Africa. Implementation of the RED approach began in early 2003 through the provision of technical and financial support to several countries.[30, 31] In June 2005, an external evaluation of RED was conducted in a convenience sample of five countries (Democratic Republic of Congo, Ethiopia, Kenya, Madagascar, and Zimbabwe).[30] At that time, 26 countries were implementing the RED approach in the WHO African Region. The evaluation revealed that the implementation of RED in each country started with training and micro-planning. All five RED components were implemented to some degree in the five countries. Some of the common implementation factors included development of plans, expanding outreach services (defined as services provided in sites outside fixed immunisation sites), planning of supervisory visits, and efforts to link with communities and utilise community health workers. Monitoring tools such as wall charts and maps were observed and reportedly used.

In 2007, a further and more extensive RED evaluation was conducted throughout the year.[31, 53] The nine countries visited were Benin, Cameroon, Democratic Republic of Congo, Ethiopia, Ghana, Madagascar, Sierra Leone, Togo, and Uganda. These countries differed in how quickly they expanded RED, with a few of them rolling-out nationally and others starting with a few priority districts and phasing-in new districts gradually. By 2006, 90% of districts in the nine countries had introduced RED. Although all countries

introduced RED as a package, the emphasis in each country was different. In 80% of the 68 districts visited, outreach was the component mentioned most often by the staff in describing what RED meant in their districts. The most notable changes since the introduction of the RED approach, as noted by district staff, were additional outreach sites and community meetings.

Regarding planning and resource management, annual EPI action plans were available in all countries at the central level, in most districts and in half of the 133 health facilities visited. Only half of district micro-plans indicated hard-to-reach populations and strategies for reaching them. Vaccine stock-outs occurred within the last year at the district and health facility levels in eight of the nine countries visited. Training and managerial capacity gaps were found in a majority of districts. Few district or health facility staff had received recent immunisation training and there was a rapid turnover of staff in several countries, resulting in an increasing proportion of untrained EPI staff. Regarding supportive supervision, two-thirds of districts included supervision in their annual work plans. However, only a third of the districts reported that they had received supervisory visits from the central level in the three months preceding the evaluation. Supervisory visits from districts to health facilities occurred more frequently; two-thirds of health facilities reported receiving supervisory visits in the three months preceding the evaluation. Supervisory checklists were commonly used (four-fifths of health facilities) and supervision of EPI was integrated with that of other health services in six of the nine countries. While four-fifths of health facilities reported receiving immediate verbal feedback, written supervisory feedback was documented in only one-third of the health facilities. District review meetings occurred in almost all districts. Regarding outreach activities, district and health facility staff identified outreach sessions as a positive contributor to immunisation service delivery. Most countries reported an increase in the number of outreach sessions planned and held since the introduction of RED, and outreach was commonly linked to other maternal and child health interventions. Regarding community links with service delivery, the RED evaluation showed that community health workers were active in all countries; assisting with defaulter tracking, outreach, and community education. Two-thirds of health facilities reported holding regular meetings with the community, and four-fifths of health facilities reported that

community health workers had been trained to assist with EPI activities. Half of the health facilities reported that the community health workers were provided with material incentives such as training or re-imbursement of transport costs. Regarding monitoring for action, immunisation monitoring charts were displayed in the majority of districts and health facilities, and most were correct and up-to-date. Health workers in two-thirds of facilities with monitoring charts were able to explain their facility's performance. Ninety five percent of districts reported that they conducted review meetings with their health facilities during the 12 months preceding the evaluation, at which they discussed immunisation data. The problems identified by this RED evaluation have been reported by EPI managers in other African countries.[54]

2.5.5. Financing of childhood immunisation services

By 2010, 96% of African countries had developed comprehensive multiyear immunisation plans with appropriate costing.[24, 53] Eighty-five percent of sub-Saharan African countries had a specific line in their national budget for procurement of vaccines used in routine EPI.[23, 41] The proportion of government funding of the overall expenditure on EPI vaccines in sub-Saharan Africa rose from 48% in 2000 to 53% in 2006. However, the proportion of government funding of overall routine EPI expenditure remained virtually the same at 43-45% between 2000 and 2006.

In 2005, according to information reported in the Joint Reporting Form,[24] 49% (26/53) of African countries reported that at least half of the costs of their routine vaccines were funded by their respective governments.[24] However in 2008, only about 15% of the 34 USD per infant needed for routine EPI was met from government funds.[23] This shortfall is due to rising EPI costs, which pose significant challenges to governments. The cost of fully immunising a child today actually exceeds the total *per capita* government spending on all health care in a majority of African countries. External donor support has helped many African countries to keep pace with rising EPI costs.[26] Adding newly available and under-utilised vaccines (as discussed below) to national routine immunisation programmes will reduce mortality, but at a much higher cost; beyond the affordability of

many African countries.[26] The 2007 evaluation of the RED Approach in the WHO African Region indicated that countries have used WHO and UNICEF grants, support from Non-Governmental Organisations (NGOs), GAVI funds, and national and district health budgets to finance EPI activities.[30, 31] However, the funding (from the various sources) was still not sufficient to meet all EPI needs.

2.5.6. Other priority routine immunisation issues in Africa

With regards to vaccine safety, in 2005, 40(77%) African countries reported having adequate national supplies of auto-disable syringes (the recommended vaccine delivery method).[24, 55] This figure had not changed by 2010. Again in 2005, 42(79%) African countries reported having a medical waste management system in place; and 87% (46/53) reported national distribution of safety boxes. In 2010, we observed an increase in the proportion of countries that reported national distribution of safety boxes to 89%, but there was no change for medical waste management.[24]

Integration of health services brings together common functions within and between organisations to solve common problems, developing a commitment to a shared vision and goals, and using common technologies and resources to achieve these goals.[3,6, 55] The RED evaluation indicated that the provision of immunisation with other maternal and child health services were common in health facilities and outreach sessions. Other authors have also provided evidence of limited integration of other interventions to EPI services in African countries.[3, 7] Co-administered interventions included Vitamin A supplementation, family planning, antenatal care, distribution of insecticide-treated bednets, deworming of children, growth monitoring, and curative care.

In many countries there is an inadequate infrastructure, an insufficient number of healthcare workers to administer vaccines, and a lack of appropriate EPI training.[53, 54] The inadequate infrastructure includes lack of cold chain equipment, transportation logistics and inadequate road system; which are present in various degrees in most countries. Some countries also report insufficient numbers of health facilities, resulting in long distances that parents travel to seek immunisation services.

2.6. Accelerated control of vaccine-preventable diseases

Based on the success of the smallpox eradication programme and increasing global routine immunisation coverage, specific disease control objectives were added to the EPI by WHO global and regional governing bodies. Accelerated vaccination strategies for attaining these objectives included high routine immunisation coverage, mass vaccination campaigns (also referred to as supplementary immunisation activities), and active case-based surveillance with laboratory confirmation.[7, 8, 10, 45, 56, 57]

2.6.1. Eradication of poliomyelitis

Since the Global Poliomyelitis Eradication Initiative was launched in 1988, there has been significant progress in the interruption of wild poliovirus circulation; with certification of eradication in WHO Regions of the Americas in 1994, Western Pacific in 2000, and Europe in 2002.[58] However in African countries, the eradication of poliomyelitis is not yet as successful as in the Americas, Western Pacific, or Europe.

Poliomyelitis caused by the wild poliovirus was endemic in 12 African countries in 2000. Between 2000 and 2002, the number of endemic countries decreased to two; and reported new cases of polio declined by 89% from 1863 to 208. [48] Following cessation of polio vaccination in northern Nigeria in September 2003 amidst speculation that the oral polio vaccine was contaminated with contraceptive and infectious particles, wild polio virus spread from Nigeria to eight other African countries by the end of 2003.[10, 59] In total, from 2003 to 2011 wild polio virus was imported from Nigeria into 29 previously polio-free African countries. However, intensified efforts at country and continental levels in Africa since 2010 have resulted in the number of reported wild polio virus cases on the continent dropping by 47% from 657 in 2010 to 350 in 2011.[53, 58, 60] Despite this significant improvement, in 2011, polio was still endemic in one country (Nigeria), had re-established transmission in three countries (Angola, Chad, and Democratic Republic of Congo), and was imported to ten others (Central African Republic, Congo, Cote d'Ivoire, Gabon, Guinea, Kenya, Liberia, Mali, Niger, and Uganda).[58] A previously polio-free country is said to have re-established transmission if active wild poliovirus transmission persists for more than 12 months following an importation.[58] In 2012, there has been

significant progress towards polio eradication in Africa. From January to July 2012, two re-established transmission countries (Angola and Democratic Republic of Congo) and four importation countries (Niger, Mali, Liberia, and Cote d'Ivoire) did not report any new cases of paralysis due to the wild poliovirus.[53]

Case-based surveillance in the context of polio eradication consists of surveillance of acute flaccid paralysis (AFP), which has been established in all African countries. The two main surveillance indicators (non-polio AFP rate of at least 2 per 100,000 inhabitants below 15 years of age, and stool specimen collection rate of at least 80% within 14 days from date of onset of paralysis) are consistently met at national level in the majority of countries. However, sub-optimal surveillance performance is commonplace at district level, and inadequate capacity to conduct high-quality outbreak investigations still pose challenges to achieving polio eradication in Africa.

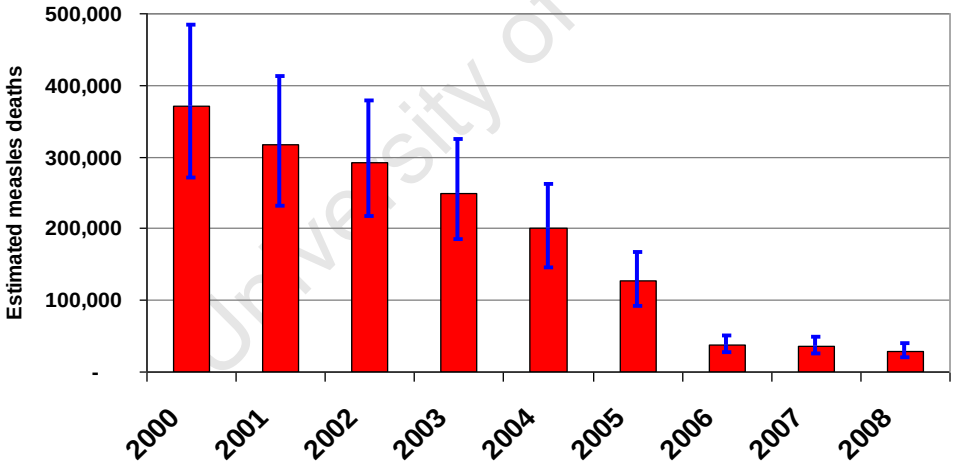
2.6.2. Accelerated control and elimination of measles

Routine vaccination with the first dose of a measles-containing vaccine (MCV1) at nine months of age was implemented in most African countries by 1980. However because of sub-optimal MCV1 coverage, measles outbreaks remained widespread. Nearly one million children died from measles worldwide annually, half of them in Africa. This led the World Health Assembly (WHA) in 1989 and the World Summit for Children in 1990 to set the goal for measles mortality reduction of 95%, compared with pre-vaccine levels.[53, 56, 61, 62] The key strategies of the measles mortality reduction goal were: vaccination through routine health services (MCV1); nationwide catch-up supplementary immunisation activities (SIAs) among children aged 9 months to 15 years of age; follow-up SIAs every 3-4 years among children aged 9-59 months; improved management of measles cases; and case-based measles surveillance with laboratory confirmation to monitor and assess the impact of the vaccination activities.

From 1996 to 2000, seven southern African countries (Namibia, Botswana, South Africa, Zimbabwe, Malawi, Swaziland, and Lesotho) implemented the recommended measles mortality reduction strategies.[63] An estimated 24 million children were vaccinated during

the catch-up measles SIAs in these countries, with overall reported vaccination coverage of 91%. Thereafter, with the financial and technical support of the Measles Initiative, all African countries (except Algeria, Mauritius, Seychelles and Morocco) conducted at least one catch-up nationwide SIA between 2000 and 2010.[7, 56, 61-67] Most of the SIAs were high-quality and achieved administrative coverage of 95% or more. Apart from SIAs, countries are recommended to introduce a routine second dose of a measles-containing vaccine (MCV2). Eleven countries in the WHO African Region had introduced MCV2 by 2011, two more introduced in 2012, and at least 30 countries are expected to have introduced MCV2 by 2015.[53] The implementation of the measles mortality reduction strategies resulted in a dramatic reduction in measles deaths on the continent. As shown in Figure 4, measles deaths in sub-Saharan Africa reduced by 92% between 2000 and 2008 (from 371,000 to 28,000 deaths); mainly as a result of the high-quality SIAs.[61, 66]

Figure 4: Estimated reduction in measles mortality in sub-Saharan Africa, 2000-2008



Following the significant reduction in measles deaths, the WHO African Regional Measles Technical Advisory Group proposed the adoption of a measles pre-elimination goal to be met by 2012. The African Regional Task Force for Immunization endorsed the proposal in December 2008. In 2009 the 59th session of the WHO Regional Committee for Africa adopted a regional goal of measles elimination by 2020, with an interim goal of pre-elimination by 2012.[53]

The measles pre-elimination targets were stated as:

1. More than 98% reduction in measles mortality between 2000 and 2012;
2. Less than 5 cases per million inhabitants per year in all countries;
3. More than 90% of countries achieving MCV1 coverage of at least 90% at national level and at least 80% in all districts;
4. At least 95% SIA coverage in all districts; and
5. All countries having high-quality measles case-based surveillance.[53]

The progress in measles control in Africa, however, has been compromised by sub-optimal routine measles immunisation coverage at district level in many countries. In 2005, only 11(21%) African countries reported at least 80% routine first-dose measles-containing vaccine (MCV1) coverage in at least 80% of their districts. This proportion increased only slightly to 32% (17/53) in 2010.[24] With regards to national routine MCV1 coverage, 23(44%) countries reported less than 80% MCV1 coverage in 2010; with two countries (Chad and Somalia) having less than 50% MCV1 coverage at national level.[24] Due to the low MCV1 coverage and delayed or sub-optimal follow-up SIAs, 27 countries in Africa experienced widespread measles outbreaks between 2009 and 2011.[61, 65, 68-70]

2.6.3. Control of yellow fever

Thirty three African countries are considered to be at risk for yellow fever.[53] By 2000, 27% (9/33) of these countries had introduced yellow fever vaccination into their EPI schedules. And in 2010, 81% (27/33) reported yellow fever vaccination in their EPI schedules.[19, 24, 53] However, there have been more than 20 outbreaks of yellow fever since 2000. Most of these occurred in districts with rural settlements but a few urban outbreaks were also recorded.[19, 53] Since 2001, a global stockpile of yellow fever vaccines has been set up for access to vaccines for emergency response to yellow fever outbreaks. With GAVI support, this stockpile was increased to six million doses of yellow fever vaccine per year over a five-year period (2006-2010). In addition, around 46 million doses of yellow fever

vaccine were administered during preventive yellow fever SIAs conducted between 2006 and 2009 in nine selected GAVI-eligible countries in Africa.[53]

2.6.4. Elimination of neonatal tetanus

Neonatal tetanus remains a major public health problem in Africa.[24, 71] It was estimated that 18(67%) out of the 27 countries that accounted for 90% of all neonatal tetanus cases in the world in 1999 were in Africa.[71] In 2010, 94% (i.e. 50/53) of African countries reported tetanus toxoid vaccination for pregnant women in their schedules. The remaining three countries instead had Td (i.e. tetanus toxoid plus reduced strength diphtheria vaccine) for adolescents and women of child bearing age on their schedules. The latter include Algeria (which gives Td at 11-13 and 16-18 years of age), Egypt (Td at 6 and 10 years), and Tunisia (where Td is given at ages 1, 7, 12, 18 years, and women of childbearing age).[24] According to WHO and UNICEF estimates of immunisation coverage, 60% of African countries had achieved at least 80% national coverage with two or more doses of tetanus toxoid in pregnant women by 2010; a significant improvement from 17% in 2000.[24] In 2005, 20(38%) African countries reported validation of neonatal tetanus elimination (i.e. attained an incidence of less than 1 case of neonatal tetanus per 1000 live births in every district). By 2010, the number of countries with validated neonatal tetanus elimination had increased to 27 (51%) of the 53 countries on the Africa continent.[24]

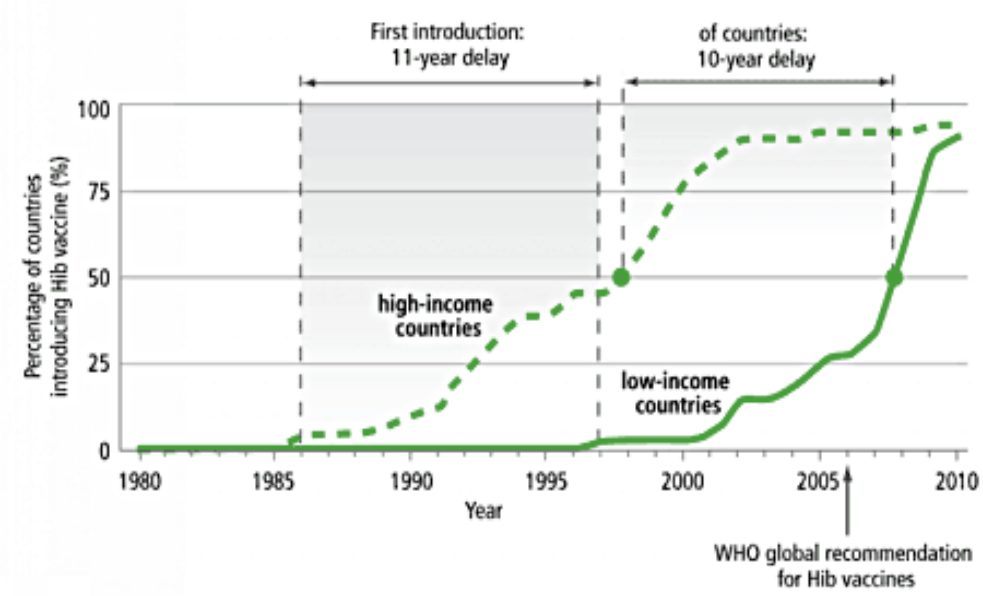
2.7. Introduction of new and under-utilised vaccines

The term “under-utilised vaccines” is used to refer to vaccines that have been available for decades in high-income countries but are not yet widely available in low and middle-income countries; such as Hepatitis B (HepB), *Haemophilus influenzae* type b (Hib), and yellow fever vaccines.[16-20] The “under-utilised vaccine” phenomenom is illustrated in Figure 5, using the Hib vaccine as an example. On the other hand, the term “new vaccines” refers to recently licensed vaccines; such as pneumococcal conjugate,

rotavirus, and meningococcal group A conjugate vaccines.[4, 5, 11-15] The last decade saw significant progress in the introduction of new and under-utilised vaccines into EPI programmes in Africa, mainly with support from GAVI.[26] Most African countries are eligible for various forms of support from GAVI, including support for the introduction of new and under-utilised vaccines.[26]

The HepB vaccine was first licensed in the United States of America (USA) in 1981. However in 2000, nearly 20 years later, only eight African countries had introduced the HepB vaccine into their EPI programmes. Conversely, by 2005, 70%(37/53) of African countries had introduced the HepB vaccine in their EPI schedules; mostly with GAVI support.[24] In addition, significant improvements (p=0.0004) were observed by 2010, with 96% (51/53) of countries having introduced the vaccine in their EPI schedules. Only two African countries (Equatorial Guinea and Somalia) did not report the HepB vaccine in their EPI schedule in 2010. [24]

Figure 5: Introduction of Hib vaccine in high and low-income countries



Source: GAVI (http://www.gavialliance.org/library/news/roi/2010/hib-initiative--a-gavi-success-story/)

The Hib vaccine was first licensed in the USA in 1985. Very few African countries had introduced the vaccine into the EPI schedule before the onset of GAVI in 2000. However

by 2005, 14(26%) African countries reported Hib vaccine inclusion in their EPI schedules. By 2010, the number had increased to 45(85%) African countries with Hib vaccine in national EPI schedules.[24] Figure 5 shows the delay between introduction of the Hib vaccine in high-income countries and low-income countries. The Gambia introduced the vaccine in 1997 (following a donation from the manufacturer), 11 years after the first high-income country (Canada) introduced the vaccine into routine immunisation. After The Gambia introduced the Hib vaccine, there was another long delay which was only broken when GAVI launched the multi-million dollar Hib Initiative in 2005; to catalyse Hib vaccine introduction in low-income countries. In most African countries HepB and Hib vaccines were introduced as the combined pentavalent vaccine, DTP-HepB-Hib.

Pneumonia and diarrhoea are the leading causes of death in children under five in Africa, and new vaccines against these major child killers have become available in the last five years. These vaccines are very costly and, without external support, are largely unaffordable by most African countries. Ten percent (5/53) of African countries had the pneumococcal conjugate vaccine in their EPI schedule by 2010, and an additional 16 countries plan to introduce this vaccine by 2013; mostly with GAVI support.[24, 26] Only two countries (South Africa and Morocco) had introduced the rotavirus vaccine into their EPI schedules by 2010. In 2011 Sudan became the first GAVI-eligible African country to introduce routine nationwide rotavirus vaccination, followed by Ghana in 2012; and nine other countries are planning to introduce the vaccine by 2013.[24]

Epidemic meningitis is a serious public health problem among the 25 countries in the "African Meningitis Belt", which extends from Senegal on the shores of the Atlantic Ocean to Eritrea along the Red Sea (Figure 6). About half a million people living in this region are at risk of epidemic meningitis each year. In 1996, there was a particularly devastating meningitis outbreak, which caused more than 250,000 cases and 25,000 deaths; mainly due to *Neisseria meningitides* group A (Men A). In 2001, a public-private partnership called the Meningitis Vaccine Project (MVP) was created with the goal of eliminating meningococcal epidemics in Africa.[14, 15] The key partners were the Program for Appropriate Technology in Health (PATH), WHO, and the Serum Institute of India Limited. The MVP is a modern vaccine success story, as within 10 years the partnership

developed an affordable Men A conjugate vaccine. Within two years of licensing the Men A vaccine, 10 countries (Benin, Burkina Faso, Cameroon, Chad, Ghana, Mali, Niger, Nigeria, Senegal, and Sudan) have already received GAVI support to introduce the vaccine.[14, 15, 26]

Figure 6: The African Meningitis Belt

Source: Meningitis Vaccine Project (http://www.meningvax.org/epidemics-africa.php)

2.8. Role of the private sector in provision of immunisation services

In African countries, there is paucity of data on the role of the private sector in the provision of immunisation services.[72-74] The little available information indicates that the private not for-profit health sector plays an important role in the provision of immunisation services in Africa, while for-profit healthcare providers play a relatively small role. The proportion of total national immunisation services given by private for-profit healthcare providers was 0.05-3% in Zimbabwe in 1998, 0.7% in Ethiopia in 2006, 5% in Morocco in 1998, and 10% in Mauritania in 2003; higher in urban than in rural areas.[72] Data on the proportion of total immunisation services provided by NGOs were only available for two African countries (Kenya and Ghana). The available data show the proportion of total immunisation services provided by private not-for-profit providers to be 40% in Ghana and 45-60% in some north and north-eastern districts of Kenya in 2006. It is suggested though undocumented that not-for-profit organisations are providing a significant share of traditional EPI immunisation services under different arrangements in 'fragile states' such

as the Democratic Republic of Congo, Sierra Leone, and Somalia. Data from facility surveys in five countries indicate that a majority of NGO health facilities offer immunisation services, while the proportion of private for-profit facilities offering immunisation varies widely, from 25% in Ghana to 81% in Kenya and Uganda.[72]

2.9. Implications of the findings of Chapter Two

The strength of this chapter lies in our adherence to the standardised guidelines on the conduct and reporting of systematic reviews. We conducted comprehensive searches of both peer-reviewed and grey literature, without limiting the searches to a specific language. We assessed study eligibility using pre-defined inclusion criteria and extracted data in duplicate, resolving differences by consensus. The major weakness of our review relates to inherent shortcomings in the primary data included. African countries belong to two independent WHO regions; with North African countries belonging to the WHO Eastern Mediterranean Region (EMRO) and sub-Saharan Africa to the WHO African Region (AFRO). At times the two regions have different epidemiological profiles for various diseases and thus have different disease control priorities; the consequence being that comparable data were not always available for countries of both regions. These reasons notwithstanding, we believe that this chapter provides a comprehensive picture of childhood immunisation programmes on the African continent.

It is estimated that 1.5 million children died globally in 2010 from vaccine-preventable diseases for which effective vaccines exist, including pneumonia and diarrhoea.[75] Approximately 20 million children did not receive the full series of three doses of the DTP vaccine worldwide in 2010, with more than one-third of these children living in Africa.[33] Even with the majority of African countries eligible for GAVI support, many are not on track with regards to meeting their GIVS and MDGs targets by 2015.[42, 75, 76] Although many countries have introduced HepB and Hib vaccines, the majority have not yet introduced pneumococcal conjugate and rotavirus vaccines, and may not do so by 2015.[24, 26] This continued failure to meet agreed targets suggests that general and country specific challenges with regards to immunisation programmes in Africa have not

been fully identified, understood and/or addressed effectively.[77] While Africa has made remarkable improvements in immunisation services, this agenda remains largely unfinished with large numbers of African children remaining unreached, unimmunised, and still dying from vaccine-preventable diseases.

We believe that in order for Africa to take advantage of the new decade of vaccines and extend the full benefits of immunisation to its citizens by 2020 and beyond, a critical assessment would be a basic step. The Decade of Vaccines Collaboration has just coordinated the development of yet another global immunisation strategy, the Global Vaccine Action Plan (GVAP), which is guided by six principles; country ownership, shared responsibility and partnership, equity, integration, sustainability, and innovation.[32] While these global initiatives offer generalised strategies for attaining outlined EPI goals, it is absolutely necessary for complementary evidence-informed African approaches.[21, 37, 38] Therefore, locally-relevant research is needed to ensure the effectiveness, efficiency, and equity of childhood immunisation policies in Africa. This PhD project has hopefully added to the valuable body of knowledge, which is needed by African countries to attain the outlined immunisation goals.

CHAPTER 3: Determinants of childhood immunisation research productivity in Africa

3.1. About this chapter

In this chapter we assess Africa's contribution to the global immunisation research output. In addition, we examine whether childhood immunisation research productivity is associated with childhood immunisation coverage in Africa. A descriptive analysis of study types, quality, and outcomes is beyond the scope of bibliometric analyses, including the present study; and we have not provided such data in this chapter.

3.2. Introduction

During the past four decades national EPI programmes in Africa have developed or adapted and implemented a broad range of strategies and activities aimed at bringing services closer to the targeted community, increasing demand for immunisation services, reaching previously unreached children, and improving immunisation data quality.[3, 7, 28, 30, 47] Through these efforts, the mean proportion of annual birth cohort that received a full series of three doses of the diphtheria, tetanus, and pertussis vaccine (DTP3) reached 77% in sub-Saharan Africa in 2010.[33, 76] Ideally, the development or adaptation and implementation of EPI improvement strategies should be informed by the best available local evidence.[78, 79] The increase in childhood immunisation coverage in Africa over the last four decades would therefore be expected to have been accompanied by a similar growth in published childhood immunisation research literature from the continent.

Research publications have an important role in the scientific process providing a key linkage between knowledge generation, uptake, and use.[37, 39, 80] For long, bibliometrics have been the method of choice for quantitative assessments of academic research at international, national, institutional, and individual levels.[81-84] Bibliometric analysis is also a feasible tool to comprehensively recognise the research advances in the past and future research trends in a specific field. In the context of the African continent, to date,

factors related to variation in immunisation research productivity have not been examined; although bibliometric studies with data on Africa exist in other disciplines.[82-96] Therefore, this study aims to fill some of the gaps in existing research by providing insights into the history and growth of childhood immunisation research in Africa. We hypothesised that research productivity influences immunisation coverage in Africa.

3.3. Methods

3.3.1. Data collection

We searched the PubMed database in November 2011 in order to obtain the childhood immunisation research volume of each African country from the inception of the EPI in 1974 to 31 December 2010. We used childhood immunisation articles indexed in PubMed as a surrogate for total childhood immunisation research productivity. Articles originating from each country, published between 1974 and 2010 were generated by selecting the advanced-search option and then selecting the "publication date" field. Next, the "affiliation" field was searched for each country. The names of the countries were imputed in their different possible forms; for example, Cameroon and Cameroun for Cameroon, and Côte d'Ivoire and Ivory Coast for Côte d'Ivoire. Some names of countries are also names of parts of other countries; for example, Benin and Niger are names of places in Nigeria. To avoid errors arising from this, appropriate commands were used [i.e. (Niger [AD] NOT Nigeria)]. We then combined this with childhood immunisation Medical Subject Headings (Mesh): ("Immunization"[Mesh] OR "Vaccination"[Mesh] OR "Immunization, Secondary"[Mesh] OR "Immunization Programs"[Mesh] OR "Immunization Schedule"[Mesh] OR "Immunization, Passive"[Mesh] OR "Mass Vaccination"[Mesh]) AND ("Infant, Newborn"[Mesh] OR "Infant"[Mesh] OR "Child, Preschool" [Mesh]).

The 2010 data on DTP3 coverage, adult literacy rate, gross domestic product (GDP), public expenditure on education (as a percentage of GDP), human development index, research and development expenditure (using purchasing power parity), physicians (per 100,000 population), total expenditure on health, and private expenditure on health (as a

percentage of GDP) were obtained from the reports published by the WHO[24] and World Bank.[97]

3.3.2. Statistical analyses

We calculated the ratios of the number of publications from countries to their population, GDP, and health expenditure in order to allow weighted comparisons. We used Pearson's correlation analysis to examine the association between DTP3 coverage, GDP, health expenditure, and research productivity. Factors associated with variation in childhood immunisation research productivity were explored using univariable and multivariable negative binomial regression models.

We used negative binomial regression, a variant of the Poisson-based regression model for count data, because of statistically significant variability in the number of indexed articles than might be expected (i.e. overdispersion). Negative binomial regression models have been shown to employ a more robust method to fit count data in the presence of overdispersion than the Poisson regression model itself. Appendix 1 provides details on the model fit statistics and model comparisons. Univariable negative binomial regression analyses were used to investigate the bivariate relationship between each country-level factor (listed above) and total research productivity. Multivariable negative binomial regression analyses were carried out to determine which country-level factors were independently associated with total research productivity. Only factors significant at the univariable level were included in the multivariable model. Results were presented as incidence rate ratios (IRR) with 95% confidence intervals (CIs) and percentage change. For correlation analysis and negative binomial regression, country-level indicators were log transformed to linearise these associations. All tests were two-sided and statistical significance was defined at the 5% alpha level. Data were processed and analysed with Stata 12 software (Stata Corp., College Station, TX, USA).

3.4. Results

A total of 1641 articles on childhood immunisation indexed by PubMed between 1974 and 2010 are described in this study. The summary statistics for all country-level factors included in this study are shown in Table 3. The percentage of children that received DTP3 based on WHO/UNICEF 2010 estimates[46] ranged from as low as 33% in Equatorial Guinea to 99% in Cape Verde, Eritrea, Morocco, Seychelles and Mauritius. The median adult literacy was 66% (range 26.2% to 93.0%). The median number of physicians per 100,000 population was 31 (range 2 to 243).

Table 3: Descriptive statistics of selected country-level variables

Variable	Median	Range
DTP3 coverage (%)	81.2	33.0 to 99.0
Gross domestic product (USD billions)	27.9	0.2 to 282.8
Adult literacy rate (%)	66.0	26.2 to 93.0
Physicians per 100,000 population	31.1	2.0 to 243.0
Total expenditure on health (% of GDP)	6.1	2.0 to 13.0
Private expenditure on health (% of GDP)	3.2	1.0 to 12.0
R&D expenditure (PPP, USD millions)	129.6	0.0 to 2494.0
Human development index	0.5	0.3 to 0.8

USD, United States Dollar; R&D, Research and development; PPP, purchasing power parity

The number of childhood immunisation articles indexed in PubMed from each country is shown in Table 4. Africa's publication output trends show that its contribution to global childhood immunisation publications has been low during the period 1974-2010. The percentage share of global childhood immunisation research output increased from 6.6% in 1974-1980 to 9.6% in 2001-2010. The median number of articles was 16 (range 1 to 346). Figure 7 shows the number of articles broken by quartiles. Three countries (South Africa, Nigeria and The Gambia) are in the highest quartile with more than 100 articles. Four countries belonged to the second quartile (i.e. 50 to 99 articles) and 27 to the third

quartile (i.e. 10 to 49 articles). Twenty countries with less than ten articles belong to the lowest quartile.

Table 4: Trends in African childhood immunisation articles per country as indexed by PubMed (1974 - 2010)

	Publications				
Country	**1974-1980**	**1981-1990**	**1991-2000**	**2001-2010**	**1974-2010**
South Africa	21	65	153	107	346
Nigeria	15	30	42	67	154
Gambia	1	20	43	40	104
Egypt	8	7	37	47	99
Kenya	11	16	24	36	87
Senegal	5	13	29	23	70
Ghana	11	4	13	26	54
Zimbabwe	1	14	22	9	46
Ethiopia	2	3	20	19	44
Uganda	6	7	10	17	40
Burkina Faso	0	5	11	24	40
Tanzania	1	8	9	21	39
Malawi	0	4	12	18	34
Sudan	1	11	11	10	33
Zambia	1	4	7	16	28
Democratic Republic of Congo	0	7	14	5	26
Cameroon	6	7	5	7	25
Mali	6	4	4	11	25
Cote d`Ivoire	2	6	8	9	25
Mozambique	0	8	3	13	24
Morocco	3	3	4	12	22
Chad	0	1	8	13	22
Guinea-Bissau	0	3	5	13	21
Tunisia	2	6	6	5	19
Guinea	0	0	10	9	19
Togo	2	3	6	7	18
Angola	0	0	10	6	16
Niger	1	0	6	8	15
Madagascar	1	1	6	7	15
Somalia	2	6	3	4	15
Congo-Brazzaville	0	4	5	6	15
Benin	0	1	4	8	13
Rwanda	0	1	6	5	12
Namibia	0	0	7	2	9
Central African Republic	1	0	5	1	7
Algeria	1	3	2	0	6
Gabon	0	1	3	2	6
Liberia	0	2	2	2	6

Continued in next page …

Country	1974-1980	1981-1990	1991-2000	2001-2010	1974-2010
Burundi	0	0	4	1	5
Sierra Leone	1	1	3	0	5
Djibouti	0	1	2	1	4
Botswana	0	0	4	0	4
Swaziland	0	0	3	1	4
Eritrea	0	0	1	3	4
Lesotho	0	0	3	0	3
Libya	0	2	1	0	3
Comoros	0	0	1	1	2
Cape Verde	0	1	0	1	2
Sao Tome and Principe	0	1	1	0	2
Seychelles	0	0	1	0	1
Mauritania	0	1	0	0	1
Mauritius	0	0	1	0	1
Equatorial Guinea	0	0	1	0	1
Total: Africa output	112	285	601	643	1641
Total: World output	1702	3485	5816	6679	18388
% world research output	6.6	8.2	10.3	9.6	8.9

Figure 7: Colour-coded map representing childhood immunisation research articles indexed in PubMed (1974 to 2010)

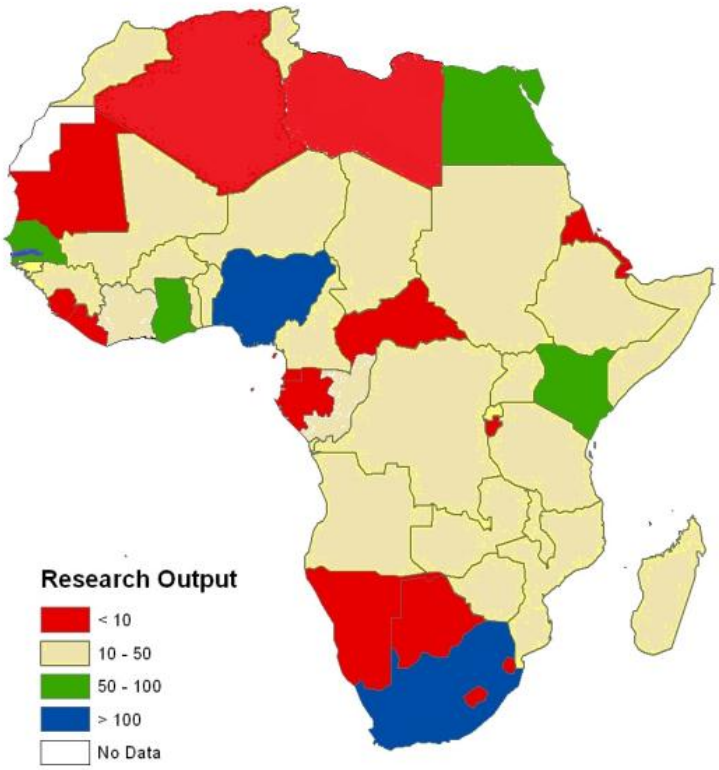


Table 5 shows the top-ranking countries in terms of relative contribution of each country to the total number of articles. In absolute terms authors from the top five countries combined produced almost half (48%) of the total indexed articles. Authors from South Africa produced the highest number of articles (n=346, 21%), followed by Nigeria (n=154, 9%) and The Gambia (n=104, 6%). As shown in Table 5, the Gambia, Guinea-Bissau, and Sao Tome and Principe had the highest number of publications after controlling for the country's population and GDP. When controlled for total expenditure on health, the top three countries were South Africa, Nigeria, and Kenya.

Table 5: Top 10 countries in terms of childhood immunisation research productivity 1974-2010, normalised by the indicated variable.

Rank	Country	Number (%)	Population	Gross domestic product	Total expenditure on health
1	South Africa	346 (21.1)	The Gambia	The Gambia	South Africa
2	Nigeria	154 (9.4)	Guinea-Bissau	Guinea-Bissau	Nigeria
3	The Gambia	104 (6.3)	Sao Tome & Principle	Sao Tome & Principle	Kenya
4	Egypt	99 (6.0)	Seychelles	Zimbabwe	Egypt
5	Kenya	87 (5.3)	South Africa	Malawi	The Gambia
6	Senegal	70 (4.3)	Senegal	Liberia	Senegal
7	Ghana	54 (3.3)	Djibouti	Togo	Ethiopia
8	Zimbabwe	46 (2.8)	Cape Verde	Senegal	Tanzania
9	Ethiopia	44 (2.7)	Gabon	Burkina Faso	Ghana
10	Burkina Faso & Uganda	40 (2.4)	Namibia	Guinea	Burkina Faso

The trend in total production of childhood immunisation articles in each geographical sub-region of Africa is displayed in Figure 8, which shows that West Africa was the most productive sub-region during the period studied. Apart from Central Africa and Southern Africa which experienced a drop between 2001 and 2010, there was a continuous increase in the production of research articles from all African sub-regions during the period 1974 to 2010. The total number of articles from West Africa, for example, increased from 44 in 1974-1980 to 248 in 2001-2010.

Figure 9 shows the correlation between total research production and country's GDP. There was a moderately positive and statistically significant correlation between the total number of published articles on childhood immunisation and the country's GDP (r = 0.548, p=0.000). Similarly, there was a moderately positive and statistically significant correlation between each country's research and development expenditure (r = 0.541, p=0.000) and the total number of articles from the country that were indexed between 1974 and 2010 (Figure 10). Country-level factors associated with total childhood immunisation research productivity are shown in Table 5. In the unadjusted model, GDP, total expenditure on health, private expenditure on health, and research and development expenditure were statistically significantly associated with increased childhood immunisation research productivity. In the univariable analyses, immunisation coverage, adult literacy rate, human development index, and physician density had no significant association with number of immunisation articles. Only private expenditure on health remained statistically significant in the adjusted multivariable model, when all factors were controlled for statistically. A unit increase in private expenditure on health increased the total research productivity by 182% (IRR 2.82; 95% CI 1.29 to 6.19).

Figure 8: Trends in Africa sub-regional childhood immunisation articles output indexed by PubMed (1974 - 2010)

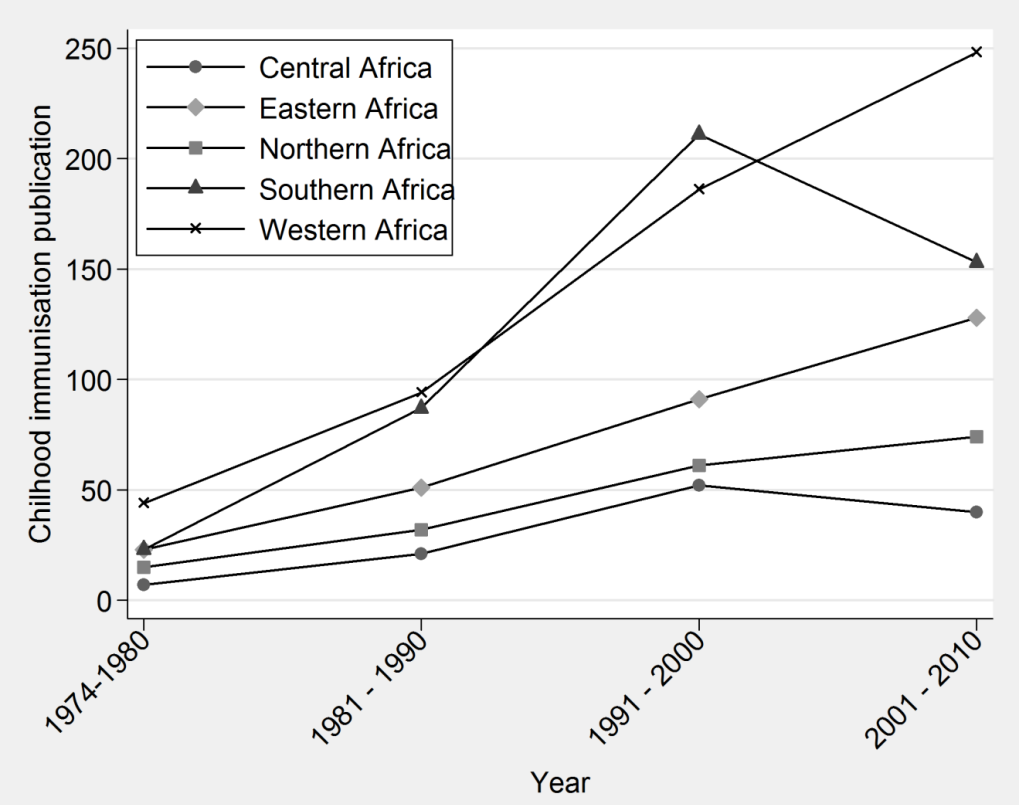
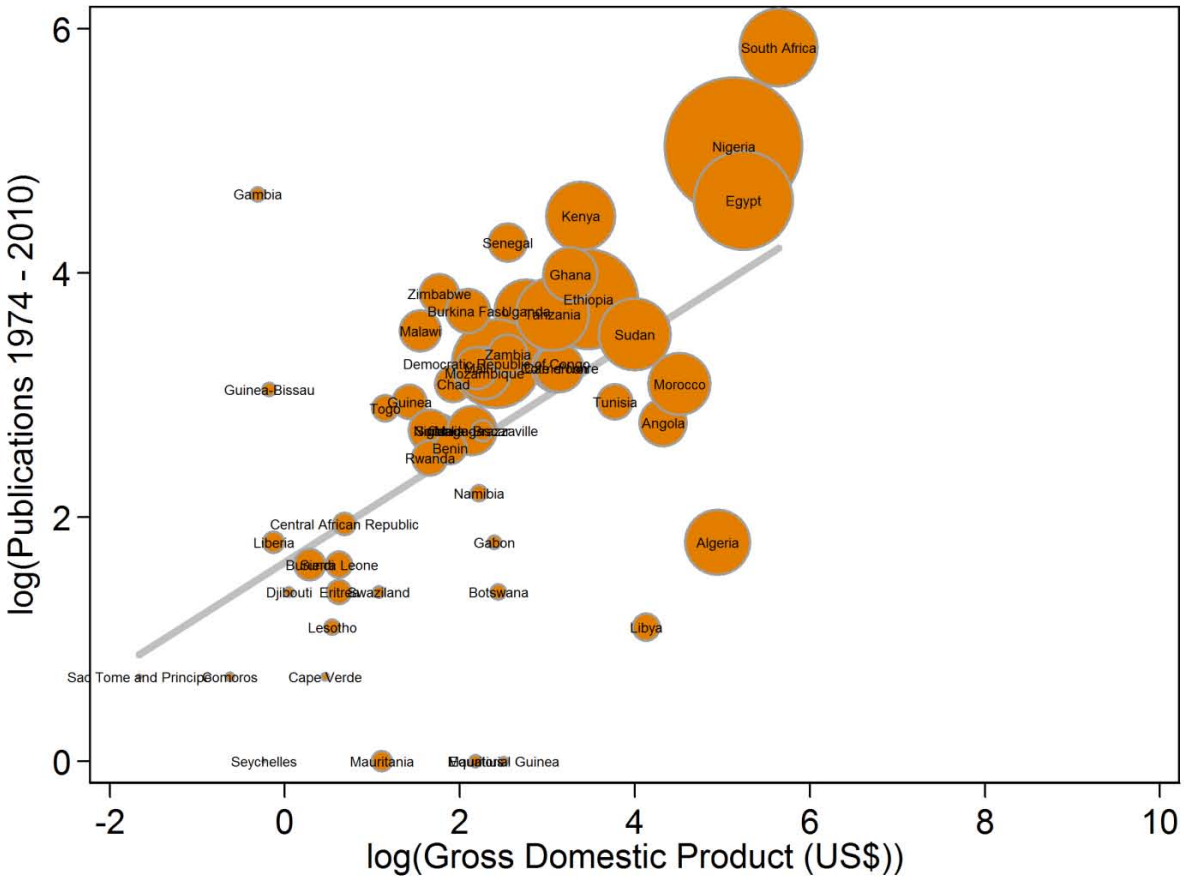
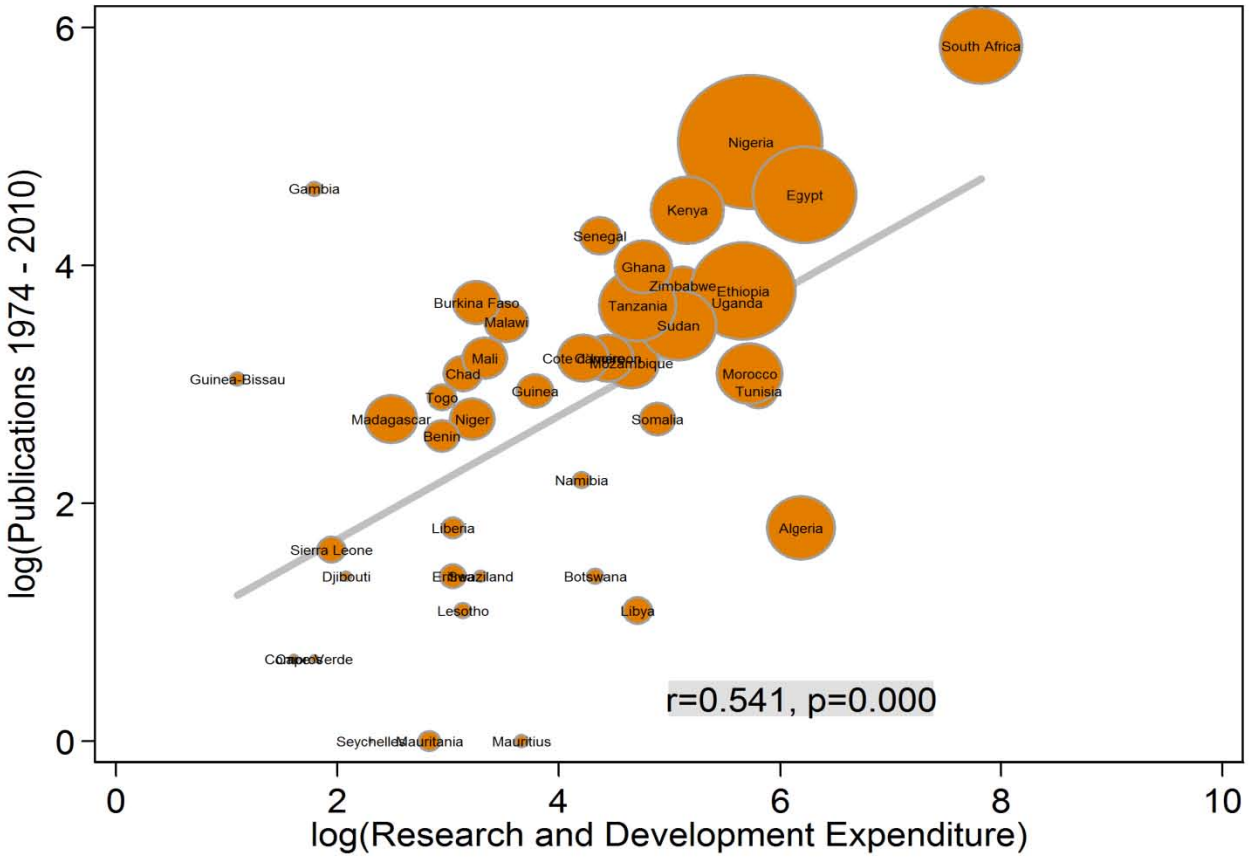


Figure 9: Scatter plot showing association between total publications and country's gross domestic product



Note: *Area of circle is proportional to the country's population*

Figure 10: Scatter plot showing association between total publications and country's research and development expenditure



Note: *Area of circle is proportional to the country's population*

Table 6: Factors associated with childhood immunisation research productivity identified by negative binomial regression models

	Univariable		*Multivariable*	
Variable	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
DTP3 coverage	0.40 (0.07, 2.36)	0.310	not included	
Gross domestic product (US dollar)	1.44 (1.24, 1.66)	0.000	1.27 (0.74, 2.18)	0.380
Adult literacy rate	1.16 (0.42, 3.18)	0.771	not included	
Physicians per 100,000 population	1.24 (0.96, 1.60)	0.096	not included	
Total expenditure on health	3.21 (1.09, 9.41)	0.034	0.66 (0.14, 3.11)	0.596
Private expenditure on health	2.77 (1.61, 4.79)	<0.0001	2.82 (1.29, 6.19)	0.010
Research and development expenditure	1.44 (1.22, 1.72)	<0.0001	1.09 (0.61, 1.94)	0.782
Human development index	2.37 (0.59, 9.51)	0.224	not included	

IRR – incidence rate ratio, CI confidence interval

3.5. Implication of the findings of Chapter Three

We found that childhood immunisation research productivity in Africa is highly skewed. South Africa, Nigeria, The Gambia, Egypt, and Kenya jointly account for almost half of the articles on childhood immunisation indexed in PubMed between 1974 and 2010. There was a significant increase in the number of publications from all African sub-regions between 1974 and 2010. However, Africa's contribution to global childhood immunisation publications has been minimal during the period studied. The Gambia, Guinea-Bissau, Sao Tome and Principe, Zimbabwe, and Malawi had better records when the total research productivity was adjusted for gross domestic product. When controlled for total expenditure on health, South Africa, Nigeria, Kenya, Egypt, and The Gambia were the most productive. Multiple medical schools and research institutions in South Africa, Nigeria, and Egypt may account for the large number of publications from these three countries. Similarly, the presence of the British Medical Research Council, the Kenyan Medical Research Institute, and a Danish research group (Bandim Health Project) may be the drivers of publications from The Gambia, Kenya, and Guinea-Bissau respectively. Even in many African countries without internationally supported institutions, most of the research projects are led by non-African research groups.

Although North-South collaboration is highly positive, it is legitimate to question the ownership of research in most of these countries mentioned.

The most significant predictor of research productivity in our study was found to be private health expenditure, which may be a proxy for the economic development status of a country. Rahman and Fukui studied factors related to worldwide variation in biomedical research productivity, and found that gross national product per capita and research and development expenditure were significant determinants of biomedical research productivity.[98, 99] We did not find these factors to be significant predictors of immunisation research productivity in Africa. However, if we consider private health expenditure to be a surrogate measure of the economic development of a country, then our results are consistent with those of Rahman and others that the better the economic ranking of a country the higher the quantity of its research productivity.[82, 96, 98-100] In addition, we confirm the findings of other authors that the contribution of authors from Africa to the global biomedical research literature is minimal.[85, 86, 89, 92, 96] This meagre biomedical research literature from the continent is dominated by non-communicable disease research.[90]

Locally-relevant health research is needed to ensure the effectiveness, efficiency, and equity of immunisation policies in Africa.[37, 54] In general, health research helps to answer questions, to generate the evidence required to guide policy, and to identify new tools. A descriptive analysis of study types, quality, and outcomes was beyond the scope of our bibliometric analysis.

PubMed has been widely used for bibliometric analysis, but it is important to note that the database is dominated by English-language journals; therefore possibly contributing to selection bias due to language barriers. Therefore, we may have missed some publications from French- and Portuguese-speaking African countries. By using the author addresses listed in the by-lines of research articles, one can only identify countries and organisations where the authors were employed when the research was done or where the article was written, or both. These limitations notwithstanding, we

believe that this study is a good reflection of research productivity in the field of childhood immunisation in Africa.

In conclusion, this study examined almost three decades of childhood immunisation research production by authors from Africa. The results of the study showed that the five most productive countries, in terms of absolute number of publications indexed by PubMed from 1974 to 2010, are South Africa, Nigeria, The Gambia, Egypt, and Kenya. Based on the best possible estimate, the most significant determinant of immunisation research productivity in sub-Saharan Africa is private health expenditure, which may be a surrogate measure of the economic ranking of a country. The lack of association between research productivity and immunisation coverage may be an indication of lack of interactive communication between health decision-makers, programme managers, and researchers; to ensure that health decisions are always informed by the best available research evidence. However, the lack of association may also stem from lack of country ownership of research conducted by international groups in African countries.

CHAPTER 4: Determinants of low childhood immunisation coverage in Africa

4.1. About this chapter

In this chapter we describe the development, testing, and results of a model of childhood immunisation coverage that includes personal and family characteristics along with contextual characteristics defined at the community and country levels.

4.2. Introduction

As Africa continues to grapple with a range of programme and policy challenges related to childhood immunisation, we believe that one important element in improving the status quo is a comprehensive and relevant evidence base that would equip countries in the region to take informed actions. Without comprehensive information about the factors associated with failure to complete the full series of recommended vaccines, it is hard to plan substantial public health programmes that would improve childhood immunisation programmes in the continent.

Some studies have been conducted to examine factors associated with low childhood immunisation coverage in Africa.[101-109] Most of these studies have concentrated on individual-level factors [101-107] and only few have considered community-level factors. [101, 108, 109] To the best of our knowledge, there has been no multilevel study performed to date that examined the separate and independent contributions of individual, community, and country-level factors to the low uptake of immunisation services in Africa. We therefore conducted this study to fill this research gap and to draw attention to the largely unexplored contextual factors that may be associated with low childhood immunisation coverage on the continent. The objective of this sub-study was therefore to develop and test a model of childhood immunisation which includes individual-level characteristics along with contextual characteristics defined at the community and

country levels. We hypothesised that pre-specified community- and country-level factors are associated with childhood immunisation coverage in Africa.

4.3. Methods

4.3.1. Data collection

We based this study on an analysis of existing survey data collected by the Monitoring and Evaluation to Assess and Use Results Demographic and Health Surveys (MEASURE DHS) project (www.measuredhs.com). The Demographic and Health Survey (DHS) program was established by the United States Agency for International Development (USAID) in 1984. It was designed as a follow-up to the World Fertility Survey and the Contraceptive Prevalence Survey projects. The DHS project was first awarded in 1984 to Westinghouse Health Systems (which subsequently evolved into part of OCR Macro). The project has been implemented in overlapping five-year phases; DHS-I ran from 1984 to1990; DHS-II from 1988 to1993; and DHS-III from 1992 to1998. In 1997, DHS was folded into the new multi-project MEASURE program as MEASURE *DHS+*. Since 1984, the project has collected standardised nationally representative survey data in over 90 countries[110].

In November 2011 we selected the latest DHS from any country in sub-Saharan Africa that was conducted since the launch of MEASURE DHS project in 1997. We chose only sub-Saharan Africa (as opposed to all of Africa) for these analyses because, as shown in Chapter 2, immunisation coverage has been consistently above 90% in all North African countries. The factors related to immunisation coverage are therefore bound to be different in such settings, and it would not have made sense to lump the two geographical sub-regions together. The 24 surveys included in this study were conducted by the MEASURE DHS between 2003 and 2010. The surveys were approved by the Institutional Review Board of Macro International in Calverton in the United States of America and by the National Ethical Review Committees in Benin, Burkina Faso, Cameroon, Chad, Democratic Republic of Congo, Ethiopia, Ghana, Guinea, Kenya, Lesotho, Madagascar, Malawi, Mali, Namibia, Niger, Nigeria, Rwanda,

Sao Tome & Principle, Senegal, Sierra Leone, Swaziland, Uganda, Zambia, and Zimbabwe. All participants gave written informed consent before participation and all information was collected confidentially. We obtained the raw survey data and written consent of MEASURE DHS to use the data.

DHS surveys are implemented by respective national institutions and Macro International Inc., with financial support from the USAID. Selection of the countries in this study was determined by availability of comparable data on childhood immunisation. DHS data are nationally representative, cross-sectional, household sample surveys with large sample sizes, typically between 5,000 and 15,000 households. The sampling design typically involves selecting and interviewing separately nationally representative probability samples of women aged 15-49 years and men aged 15-59 years based on multi-stage cluster sampling, using strata for rural and urban areas and for different regions of the countries. A standardised questionnaire was administered by interviewers to participants in each country. The survey instruments (i.e. household questionnaire and women's questionnaire) were comparable across countries, yielding inter-country comparable data. We used the term community to describe clustering within the same geographical living environment. Communities were based on sharing a common primary sample unit within the DHS data. The sampling frame for identifying the primary sample unit in the DHS is usually the most recent census. Country-level data were collected from the reports published by the World Bank[97].

4.3.2. Variables

We used the WHO definition of an "unimmunised child" as the outcome variable. "Unimmunised child" was defined as a binary variable that takes the value of 1 if the child 12-23 months old has received DTP3 and 0, otherwise. We limited the analysis to one randomly selected child per woman in order to minimise over-representation of women with more than one child in the age category. The annual EPI cohort in each

country is the number of children aged 0-11 months. Therefore, the immunisation coverage among children aged 12-23 months during a survey year corresponds to the immunisation coverage in the EPI cohort of the previous year for that country. This explains why we focused on children aged 12-23 months during the survey year.

Our pre-specified determinant variables consisted of individual, community, and country-level factors. We included the following individual level factors: child's age (in months), child sex (male or female), high birth order (less than 24 months), number of under-five children, polygamous family, mother's age (15-24, 25-34, or 35 years or older), wealth index (poorest, poorer, middle, richer, richest), mother's and father's education (no education, primary, secondary, or higher), employment status (working or not working), media access (access to radio, television or newspaper), and maternal health seeking behaviours (prenatal visits, tetanus injection during pregnancy, medical assistance at delivery, knowledge of oral rehydration solution, and possession of a health card for the child).

We included the following community-level factors:

- *Neighbourhood poverty:* percentage of households below 20% of wealth index
- *Illiteracy rate*: percentage of women with no formal education in the community
- *Unemployment rate*: percentage of women not working in the community
- *Media access*: percentage of households with access to television, radio or newspaper
- *Average household size:* mean number of people in each community
- *Female-headed households*: percentage of households headed by women in an area.
- *Residential mobility:* proportion of households occupied by persons who had moved from another dwelling in the previous 5 years [111-113]

- *Place of residence:* urban or rural, as administratively defined by each country
- *Ethnic diversity* - an index of ethnic diversity was created using a formula that captures both the number of different groups in an area and the relative representation of each group [114] :

$$\text{Ethnic diversity index} = 1 - \sum_{i=1}^{n} \left[\frac{x_i}{y} \right]^2$$

where:

x_i =population of ethnic group *i* of the area,

y = total population of the area, and

n = number of ethnic groups in the area

Scores can range from 0 to approximately 1. For clarity of interpretation, each diversity index is multiplied by 100; the larger the index, the greater diversity there is in the area. If an area's entire population belongs to one ethnic group, then an area has zero diversity. An area's diversity index increases to 100 when the population is evenly divided into ethnic groups.

At country-level, we included fertility rate, gross domestic product (GDP), expenditure on health, and adult illiteracy rate. We categorised community- and country-level variables into two categories (low and high) to allow for nonlinear effects and provide results that were more readily interpretable in the policy arena. Median values served as the reference group for comparison.

We included the year the DHS was conducted as a partial control for a period trend to control for effects of unknown factors, which might have been introduced due to different timing of surveys across countries.

4.3.3. Statistical analyses

Multilevel logistic regression models were used to examine factors associated with childhood immunisation. We specified a 3-level model for the binary variable: an "unimmunised child" (level 1), living in a community (level 2), from a country (level 3). We constructed six models. The first model, an empty model, was without any determinant variables i.e. a simple component of variance analysis. The second model contained only the control variable (survey year). The third, fourth, and fifth models provided additional controls for individual-, community- and country-level factors respectively. The sixth model simultaneously controlled for survey year, individual-, community-, and country-level factors.

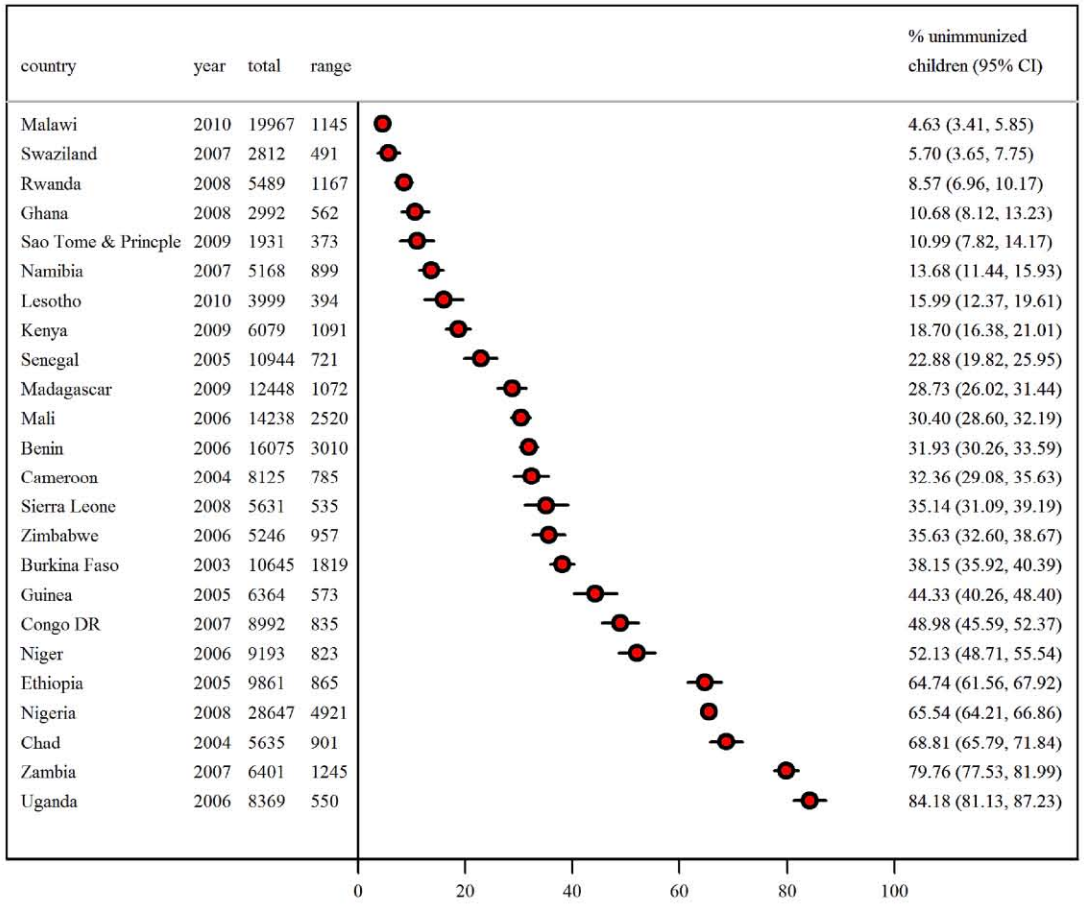
The measures of association (fixed-effects) were reported as odds ratios (ORs) with their 95% confidence intervals (CIs). The measures of variation (random-effects) included the variance, intra-cluster correlation (ICC), and median odds ratio (MOR). The ICC was calculated by the linear threshold according to the formula used by Snijders and Bosker. [115] The MOR is a measure of unexplained cluster heterogeneity and the method used for calculating the MOR has been described elsewhere. [116, 117] The multilevel models were fitted with MLwiN 2.24. [118] The statistical significance of covariates were calculated using the Wald test.[118] All significance tests were two-tailed and statistical significance was defined at the 5% alpha level.

4.4. Results

4.4.1. Sample characteristics

The survey characteristics are shown in Figure 11. The DHS were conducted between 2003 and 2010. The number of children included in the surveys ranged from 1,931 in Sao Tome and Principe to 28,647 in Nigeria. The age of children included in the analysis ranged from 12 to 23 months. The median number of children is 882 (range: 373 to 4921). The proportion of un-immunised children ranged from as low as 4.6% in Malawi to as much as 84.2% in Uganda.

Figure 11: Description of DHS data 2003-2010 in Africa by country



4.4.2. Measures of variation (random effects)

As shown in Table 6, Model 1 (the null model), there was a significant variation in the odds of being an "unimmunised child" across the countries (τ =1.031, p<.001) and across the communities (τ =0.554, p<.01). According to the intra-country and intra-community correlation coefficient implied by the estimated intercept component variance, 21% and 32% of the variance in the "unimmunised child" could be attributed to the country- and community-level factors respectively. The variations across communities and countries remained statistically significant, even after controlling for all factors in model 6.

Results from the MOR also confirmed evidence of community and country contextual phenomena shaping the odds of being an "unimmunised child". The high MOR (3.31) in Model 1 between children with a higher and lower propensity of being "unimmunised" in a community suggests that the community heterogeneity is substantial. When all factors were included in the model, the unexplained heterogeneity between communities remained substantial with an MOR of 2.29.

4.4.3. Measures of association (fixed effects)

The results of fitting the model including only the control variable (survey) is shown in Table 6 (model 2). There was no statistically significant association between the survey year and the odds of being unimmunised. The results of fitting the model including the control variable (survey) and individual-level factors is shown in Table 6 (model 3). For every one month increase in a child's age, the odds of being unimmunised decreased by 3% (odds ratio [OR] 0.97, 95% confidence interval [CI] 0.96 to 0.98). Compared with children of older mothers (i.e. 35 years or older), children of younger mothers were more likely to be unimmunised (OR 1.22, 95% CI 1.09 to 1.36). Similarly, children from the poorest households were more likely to be unimmunised than their counterparts from the richest households. Children born to mothers (OR 1.48, 95% CI 1.31 to 1.67) or fathers (OR 1.19, 95% CI 1.07 to 1.31)

with no formal education were more likely to be unimmunised than those born to parents with secondary or higher education respectively. Children whose mothers were unemployed were more likely to be unimmunised than those whose mothers were employed (OR 1.09, 95% CI 1.01 to 1.17). Maternal access to media reduced the odds of a child being unimmunised by 6% (OR 0.94, 95% CI 0.94 to 0.98). Mothers with health seeking behaviours were 46% less likely to have unimmunised children (OR 0.54, 95% CI 0.53 to 0.56).

The results of fitting the model including the control variable (survey) and community-level factors is shown in Table 6 (model 4). Children from urban areas were less likely to be unimmunised than those from rural areas (OR 0.84, 95% CI 0.77 to 0.92). Children from communities with high neighbourhood illiteracy (OR 1.62, 95% CI 1.50 to 1.74), poverty (OR 1.24, 95% CI 1.15 to 1.34), and unemployment (OR 1.14, 95% CI 1.07 to 1.22) rates were 62%, 24%, and 14% more likely to be unimmunised. Children from communities with high media access (OR 0.71, 95% CI 0.66 to 0.77) and female-headed households (OR 0.88, 95% CI 0.82 to 0.93) were 29% and 12% less likely to be unimmunised.

The results of fitting the model including the control variable (survey) and country-level factors is shown in Table 6 (model 5). Children from countries with higher fertility rates were more than four times more likely to be unimmunised.

The result of the full model including all co-variables is shown in Table 6 (model 6). With all factors controlled for statistically, the following factors remained significantly associated with the odds of being unimmunised: individual-level (child's age, polygamous family, mother's age, wealth index, mother's and father's education, media access, and maternal health seeking behaviours); community-level (place of residence and illiteracy rate); and country-level (fertility rate).

Table 7: Factors associated with unimmunised children in sub-Saharan Africa, identified by multilevel logistic regression

	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]	Model 6[f]
Factors	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Control variable						
Survey year						
2003		1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
2004		1.70 (0.21 - 13.89)	1.84 (0.26 - 12.80)	1.82 (0.20 - 16.58)	0.42 (0.04 - 4.74)	0.31 (0.03 - 2.98)
2005		1.26 (0.17 - 9.13)	1.11 (0.18 - 6.90)	1.25 (0.16 - 10.04)	1.47 (0.19 - 11.38)	0.98 (0.15 - 6.46)
2006		1.44 (0.22 - 9.39)	1.88 (0.33 - 10.67)	1.53 (0.21 - 11.05)	0.53 (0.07 - 4.15)	0.50 (0.08 - 3.10)
2007		0.96 (0.14 - 6.57)	1.73 (0.29 - 10.19)	0.98 (0.13 - 7.34)	0.59 (0.07 - 5.24)	0.54 (0.08 - 3.81)
2008		0.67 (0.10 - 4.54)	1.02 (0.16 - 6.33)	0.66 (0.09 - 4.99)	1.53 (0.15 - 15.87)	1.04 (0.13 - 8.38)
2009		0.39 (0.05 - 2.85)	0.61 (0.10 - 3.79)	0.39 (0.05 - 3.10)	0.22 (0.03 - 1.64)	0.24 (0.04 - 1.42)
2010		0.18 (0.02 - 1.48)	0.29 (0.04 - 2.05)	0.20 (0.02 - 1.81)	0.19 (0.02 - 1.92)	0.17 (0.02 - 1.36)
Child's age			0.97 (0.96 - 0.98)***			0.97 (0.96 - 0.98)***
Male (vs. female)			1.01 (0.95 - 1.08)			1.01 (0.95 - 1.07)
High birth order			1.05 (0.96 - 1.14)			1.05 (0.97 - 1.14)
Under-5 children			1.02 (0.99 - 1.05)			1.02 (0.99 - 1.05)
Polygamous family			1.08 (1.01 - 1.16)			1.08 (1.01 - 1.16)*
Mother's age						
15-24			1.22 (1.09 - 1.36)***			1.18 (1.06 - 1.32)**

	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]	Model 6[f]
Factors	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
25-34			1.07 (0.98 - 1.16)			1.05 (0.96 - 1.15)
35 or older			1 (reference)			1 (reference)
Wealth index						
Poorest			1.34 (1.17 - 1.52)***			1.36 (1.17 - 1.59)***
Poorer			1.25 (1.11 - 1.42)***			1.30 (1.13 - 1.51)***
Middle			1.14 (1.01 - 1.29)*			1.21 (1.06 - 1.39)**
Richer			1.09 (0.97 - 1.23)			1.15 (1.02 - 1.30)*
Richest			1 (reference)			1 (reference)
Mother's education						
No education			1.48 (1.31 - 1.67)***			1.35 (1.18 - 1.53)***
Primary			1.28 (1.15 - 1.43)***			1.26 (1.12 - 1.40)***
Secondary or higher			1 (reference)			1 (reference)
Father's education						
No education			1.19 (1.07 - 1.31)**			1.13 (1.02 - 1.26)*
Primary			0.99 (0.90 - 1.09)			1.00 (0.91 - 1.10)
Secondary or higher			1 (reference)			1 (reference)
Not working			1.09 (1.01 - 1.17)*			1.06 (0.98 - 1.14)
Media access			0.94 (0.90 - 0.98)**			0.94 (0.90 - 0.99)*
Health seeking beh.			0.54 (0.53 - 0.56)***			0.56 (0.54 - 0.58)***
COMMUNITY-LEVEL						
Urban (vs. rural)				0.84 (0.77 - 0.92)***		1.12 (1.01 - 1.23)*

	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]	Model 6[f]
Factors	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Ethnic diversity				1.05 (0.97 - 1.13)		1.08 (1.00 - 1.16)
Neigh. Poverty				1.24 (1.15 - 1.34)***		1.03 (0.94 - 1.13)
% female-headed				0.88 (0.82 - 0.93)***		0.95 (0.89 - 1.02)
Residential instability				0.98 (0.92 - 1.05)		1.02 (0.95 - 1.09)
Illiteracy rate				1.62 (1.50 - 1.74)***		1.13 (1.05 - 1.23)**
Unemployment rate				1.14 (1.07 - 1.22)***		1.03 (0.96 - 1.11)
% media access				0.71 (0.66 - 0.77)***		0.94 (0.86 - 1.02)
Av. Household size				1.07 (1.00 - 1.14)		1.02 (0.95 - 1.09)
COUNTRY-LEVEL						
Fertility rate					4.47 (1.19 - 16.74)*	4.43 (1.04 - 18.92)*
GDP (US$)					1.75 (0.48 - 6.31)	1.44 (0.33 - 6.37)
Health expenditure					0.37 (0.11 - 1.23)	0.62 (0.19 - 2.03)
Literacy rate					2.25 (0.71 - 7.07)	2.60 (0.90 - 7.50)
RANDOM PART						
Variance						
Country	1.031 (0.300)	0.761 (0.222)	0.648 (0.194)	0.842 (0.246)	0.631 (0.185)	0.492 (0.148)
Community	0.554 (0.029)	0.663 (0.032)	0.275 (0.029)	0.440 (0.028)	0.751 (0.035)	0.267 (0.028)
ICC (%)						
Country	21.1	16.1	15.4	18.4	13.5	12.1
Community	32.5	30.2	21.9	28.0	29.6	18.7

	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]	Model 6[f]
Factors	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
MOR						
Country	2.62	2.29	2.15	2.39	2.13	1.95
Community	3.31	3.11	2.49	2.93	3.06	2.89

* p<0.01, **p<0.001 ***p<0.0001; ICC – intra-cluster correlation; MOR – median odds ratio; OR- odds ratio; CI – confidence interval

[a]Model 1 is null model, baseline model without any determinant variable

[b]Model 2 is adjusted for control variable alone

[c]Model 3 is additionally adjusted for control variable and individual-level factors

[d]Model 4 is additionally adjusted for control variable and community-level factors

[e]Model 5 is additionally adjusted for control variable and country-level factors

[f]Model 6 is additionally adjusted for control variable and individual-, community-, and country-level factors

4.5. Implication of the findings of Chapter Four

We expanded upon previous literature by providing evidence of contextual factors, measured at community and country levels, associated with childhood immunisation coverage. In particular, the study provided evidence that unimmunised children were more likely to be from communities with high illiteracy rates and countries with high fertility rates. Contrary to our expectation, we found that children from urban areas were more likely to be unimmunised than those from rural areas. At individual level, children from poorest households, uneducated parents, mothers with no access to media, and mothers with low health seeking behaviours were more likely to be unimmunised. In addition, we found evidence of clustering effects of non-immunisation at both community and country levels, such that children from the same communities tended to have similar immunisation status. This suggests that children in the same neighbourhood are subject to common contextual influences;[119] thus, providing evidence of contextual phenomenon shaping children's risk of being unimmunised.

An evidence-informed approach to improving childhood immunisation programmes in Africa and, consequently, reducing child mortality in the continent demands first an understanding of why programmes have failed to reach their optimum potential. Secondly, appropriate strategies should be employed to address the identified short comings of immunisation programmes. Without such a systematic approach, significant proportions of scarce resources will continue to be squandered on ineffective interventions; and millions of children will continue to die from easily preventable causes [37, 39].

Our multilevel analysis revealed that low parental and community knowledge of immunisation and/or lack of access to information on childhood immunisation could be an important contributor to the high burden of unimmunised children in sub-Saharan Africa. This assertion is supported by the finding of significant reductions in the number of unimmunised children among parents and communities with access to mass media. In addition, unimmunised children were found to cluster in communities, increasing the risk of disease outbreaks. It is therefore important to identify effective interventions to enable parents and communities to understand the meaning and relevance of vaccination to their health and the health of their families and communities. However, at present, there is a paucity of synthesised research evidence on effective interventions for improving childhood immunisation programmes in low and middle-income settings such as sub-Saharan Africa.[74, 120-123] The few currently available systematic reviews relevant to childhood immunisation programmes in sub-Saharan Africa show that parent reminder and recall systems[124] and mass media interventions[125] have the potential to increase immunisation coverage. Verbal, video, or provider-delivered communication tools may also increase parents' understanding, especially if the tools are structured, tailored and interactive[126]. In addition, interventions to promote interaction between the community and health services may build trust and generate awareness and understanding of vaccination issues among parents.[121] Interventions of this nature embrace collective decision making and community involvement in planning, programme delivery, advocacy, and/or governance of immunisation programmes. The end result would be an increased demand for immunisation services[7].

Furthermore, the finding that women with health seeking behaviours are more likely to have their children immunised might be an indication that integration is an effective strategy in immunisation programmes.[3]

The main strengths of this chapter include having a pre-defined hypothesis and selection of determinant variables, conducting multi-level modeling, and having representative data across many countries. The only limitation was our reliance on cross-sectional dataset.

In conclusion, we found that individual and contextual factors were associated with childhood immunisation, suggesting that public health programmes designed to improve childhood immunisation coverage in sub-Saharan Africa should address people and the communities and societies in which they live. Synthesis of existing immunisation barriers and the evidence on effective interventions to address these barriers should be a systematic and integral component of childhood immunisation programmes in Africa, and elsewhere.

CHAPTER 5: Strategies for improving childhood immunisation coverage in Africa

5.1. About this chapter

In this chapter we summarised the current best evidence from systematic reviews and randomised controlled trials of interventions for improving childhood immunisation coverage. In addition, we discussed the relevance of the evidence to childhood immunisation programmes in Africa.

5.2. Introduction

The EPI faces a number of challenges in Africa.[70, 127-129] The vaccination coverage is low,[77, 130] epidemics of vaccine-preventable diseases are frequent,[10, 19, 60, 68, 70, 129, 131] healthcare infrastructure is weak, skilled human resources are scarce, and community knowledge of immunisation is low.[127] Making well-informed decisions about how best to achieve high and equitable immunisation coverage in Africa will depend partly on African policymakers accessing the best scientific evidence about what interventions work, and integrating this evidence into national health systems in the continent[37]. Interventions for improving immunisation coverage can be aimed at increasing demand for immunisation services by mothers and their children (demand-side strategies), or aimed at increasing the availability of immunisation services (i.e. supply-side strategies).[78] Demand-side (or patient-oriented or consumer-oriented) interventions address barriers to vaccination associated with parental knowledge and understanding, attitudes, beliefs and behaviour as well as socio-economic factors of households.[77] Supply-side (or provider-oriented) interventions refer to strategies such as the availability of effective vaccines, technologies to support their application, and healthcare workers to deliver services.[77] In order to ensure evidence-informed selection and implementation of effective healthcare interventions[37] that would overcome both demand and supply barriers[77] and reach most children in Africa with

life-saving vaccines, we conducted a comprehensive search of the peer-reviewed literature, identified, and synthesised systematic reviews and randomised controlled trials of strategies for improving childhood immunisation programmes.

We chose systematic reviews and randomised controlled trials because they occupy the two top spots in the hierarchy of evidence on the effects of interventions. A randomised controlled trial is the most rigorous way of determining whether a cause-effect relationship exists between an intervention and an outcome, and of assessing the cost-effectiveness of interventions. A systematic review of two or more randomised controlled trials provides even better evidence than a single randomised controlled trial. A systematic review is a summary of evidence in which bias and chance have been reduced by the systematic identification, appraisal, and synthesis of all relevant studies on a specific topic according to a transparent and predetermined method. Systematic reviews have an inherent ability to minimise systematic and random errors in the assessment of existing research as well as provide a means for researchers and policymakers to access all existing evidence on key questions in a thoughtful manner.[37]

5.3. Methods

5.3.1. Search and selection of systematic reviews

Between 20 and 30 March 2012 we searched PubMed, the Health Systems Evidence database, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effectiveness; using the search strategy shown in Appendix 2. We screened the search results, selected relevant systematic reviews, and assessed the quality of the selected reviews (using a revised version of the AMSTAR tool[132]). In particular, we assessed whether the review authors:

1. reported the study selection criteria;
2. conducted a literature search that was comprehensive enough to avoid publication, language and indexing biases;

3. undertook duplicate study selection and data extraction;
4. used reliable criteria to assess the risk of bias in included studies;
5. reported the characteristics of included studies appropriately; and
6. combined data from included studies using reliable methods.

Based on these criteria, we concluded whether the review was reliable or not.

5.3.2. Assessment of the quality of evidence from systematic reviews

The GRADE approach[133, 134] was used to assess the quality of the evidence for the effectiveness of the interventions reported in the reviews. This method results in an assessment of the quality of a body of evidence as high, moderate, low, or very low. High quality evidence implies that "further research is very unlikely to change our confidence in the estimate of effect". Moderate quality evidence means that "further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate". Evidence is considered of low quality if "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate", and very low quality if "we have very little confidence in the effect estimate". We began the rating of the quality of evidence with the study design; evidence from systematic reviews of randomised controlled trials as high-quality and that from systematic reviews of observational studies as low-quality. In addition, five reasons led us to downgrade the quality of evidence from systematic reviews of randomised controlled trials and three to upgrade the quality of evidence from systematic reviews of observational studies. For pooled data from randomised controlled trials, the factors that led to rating down the quality of evidence were risk of bias, heterogeneity, indirectness, imprecision, and publication bias. Regarding risk of bias, concerns that limited our confidence in the evidence include lack of allocation concealment, lack of blinding of outcome assessment, and a large loss to follow-up. Heterogeneity of effects across studies for which there were no compelling explanations also reduced our confidence in the evidence. Indirectness refers to differences between the population, intervention, comparison group and

outcome of interest to us, and those included in the relevant reviews. For imprecision, if we found that studies included relatively few participants and few events and thus had estimates of effects with wide confidence intervals, we rated down the quality of the evidence. Finally, we downgraded the quality of evidence if there was a high likelihood of publication bias.

5.3.3. Search and selection of randomised controlled trials

We complemented the search for systematic reviews with an exhaustive search for randomised controlled trials conducted in low and middle-income countries (Appendix 3), which have not yet been the subject of any systematic review of strategies for improving immunisation coverage. Between 27 March 2012 and 30 June 2012 we searched the electronic databases indicated below, selected eligible trials, and assessed the risk of bias in selected trials using standard Cochrane criteria i.e. random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting, and other sources of issues.[135] For each trial, we described what the trial authors reported that they did for each domain and made a decision relating to the risk of bias for that domain by assigning a judgement of 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias. The databases searched were the Cochrane Central register of Controlled Trials (CENTRAL), Cochrane Library, Issue 3, 2012; Medline In-Process and Ovid Medline, 1946 to present; Embase, 1980 to present; CINAHL (EBSCO), 1981 to present; LILACS (VHL); and Sociological Abstracts, 1952 to current (ProQuest).

5.4. Results

The search for systematic reviews yielded 1369 records as shown in Appendix 2. Detailed screening of titles and abstracts yielded 16 potentially eligible reviews.[54, 120-124, 136-145] Following screening of the full-text publications we included 11 systematic reviews in this study.[54, 120-124, 136-140] The five remaining systematic reviews were excluded either because a more recent or a more complete one on the same topic was included.[141-145] The characteristics of the systematic reviews are shown in Table 8.

The search for randomised controlled trials identified 542 records in CENTRAL; 2179 records in Medline; 879 records in Embase,; 66 records in Cinahl; 88 records in Lilacs; and 116 records in Sociological Abstracts. After removing duplicates, we were left with 3868 records. We then screened the titles and abstracts of the 3868 records and found 13 potentially eligible studies.[146-158] We retrieved the full text of the 18 articles, scrutinised them, and found five randomised controlled trials that met our eligibility criteria.[146-150]

The first review evaluated the effectiveness of home visiting programmes on the uptake of childhood immunisation (Table 8).[136] The authors (Denise Kendrick and colleagues) included 11 studies published by July 1996. Nine of the 11 studies reported comparable immunisation coverage data and their results were pooled in a meta-analysis. Fixed effect meta-analysis gave a pooled odds ratio (OR) of 1.40, 95% confidence intervals [CI] 1.16 to 1.68; with significant unexplained heterogeneity (heterogeneity P=0.005). The authors then conducted a random-effects meta-analysis, which did not show home visiting programmes to be effective in increasing the uptake of immunisation services (OR 1.17, 95%CI 0.33 to 4.17).[136]

Table 8: Characteristics of included systematic reviews

	Review ID*	Review objective	Data sources	Search outputs	Interventions	Settings	Data management	Quality of evidence**
1	Kendrick 2000.[136]	To assess the effects of home visiting programmes on the uptake of immunisation	Medline, Cinahl, Embase, Cochrane Library, the journal *Health Visitor*, reference lists	Last search: Sep 1996 Output: 1218 records Potentially eligible: 102 articles Included: 11 studies	9 RCTs and 3 non-RCTs 11 of home visiting programmes with at least one postnatal visit	USA (n=6) Canada (n=2) Ireland (n=1) UK (n=1) Turkey (n=1)	Conducted duplicate study selection, critical appraisal, and data extraction; and meta-analysis	Low: home visits
2	Maglione 2002.[137] .	To assess the effects of mass mailings on influenza immunisation coverage among Medicare beneficiaries in the USA	Health Care Quality Improvement Project database for controlled trials completed since 1993	Last search: 1999 (month not specified) Output: 6 records Potentially eligible: 6 Included: 6 studies	5 RCTs and 1 CCT of letters and post cards	USA (n=6)	Conducted duplicate study selection, critical appraisal, and data extraction; and narrative synthesis	Very low: mass mailing
3	Bordley 2000.[138]	To summarise the effectiveness of audit and feedback on immunisation delivery	Medline, reference lists, authors' personal files	Last search: 1998 (month not specified) Output: 60 records Potentially eligible: 44 Include: 15 studies	6 ITS, 5 RCTs, and 4 CBAs of audit and feedback interventions	USA (n=13) Uk (N=2)	Conducted duplicate study selection, critical appraisal, and data extraction; and narrative synthesis	Moderate: audit and feedback
4	Stone 2002.[139]	To assess the relative effectiveness of previously studied approaches for improving adherence to adult immunisation and cancer screening guidelines	Medline, EPOC register, Medicare Health Care Quality Improvement Project database, reference lists	Last search: Feb 1999. Output: 655 records. Potentially eligible: 137 Included: 108 studies	95 RCTs and 13 CCTs of reminder, feedback, education, financial incentive, organisational change, & mass media interventions	Not reported (but studies likely to be mainly from USA)	Conducted duplicate study selection, critical appraisal, and data extraction; and meta-analysis	Moderate: organisational change, parent reminders
5	Jacobson Vann 2005.[124]	To assess the effectiveness of patient reminder and recall systems in improving immunisation rates	Medline, Embase, Cinahl, PsychINFO, Sociological Abstracts, CAB Abstracts, EPOC register, reference lists, scientific meetings, authors' personal files	Last search: May 2007 Output: 398 records Potentially eligible: 122 Included: 47 studies	44 RCTs and 3 CBAs of letters, postcards, person-to-person phone calls, computer-to-person phone calls, & outreach	USA (n=36), Australia (n=2), Canada (n=5), Denmark (n=1), New Zealand (n=2), & UK (n=1)	Conducted duplicate study selection, critical appraisal, and data extraction; and meta-analysis	Moderate: parent reminders
6	Pegurri 2005.[122]	To describe the available literature about interventions designed to increase coverage; and to identify the interventions which can be reliably accepted as effective and cost-effective.	Medline, Popline, BIDS, CAB Abstracts, Web of Science, PubMed, EconLit, HEED, Cochrane Library, WHO regional databases.	Last search: Dec 2001. Output: 2621 records. Potentially eligible: 152 Included: 60 studies	3 RCTs and 57 ecological studies of various interventions	African (n=10), Asian / Pacific (n=6), and Central or South American (n=6) countries.	Conducted duplicate study selection, critical appraisal, and data extraction; and meta-analysis and narrative synthesis	Moderate: CHWs, channelling (i.e. door-to-door canvassing).
7	Batt 2004.[120]	To review the grey literature on the costs and effects of expanding immunisation services in low and middle-income countries.	WHO, UNICEF, PAHO, USAID, World Bank, UNICEF, BASICS II, PAHO, GAVI, DFID, National EPI programmes, SIGLE, Eldis, HTA Centre in York,	Last search: May 2003 Output: 1979 records. Potentially eligible: 88 Included: 34 studies	34 studies, none of them a controlled trial.	African (n=11), Central and South American (n=7), and Asian/Pacific (n=6) countries.	Conducted duplicate study selection, critical appraisal, and data extraction; and meta-analysis and narrative synthesis	Low: mass media, contracting out, integration.

	Review ID*	Review objective	Data sources	Search outputs	Interventions	Settings	Data management	Quality of evidence**
			Popline, CAB abstracts, regional WHO databases, Google, NGOs, consultancy firms, universities, BASICS II, PATH, Tearfund					
8	Ryman 2008.[123]	To determine strategies that may be used at the sub-national level to improve routine immunisation programmes	Medline, Embase, Cinahl, Sociological Abstracts, CENTRAL, ERIC, CDSR, DARE ACP Journal Club, CCTR, Web of Science, CAB Direct, Anthropology Plus, Access UN, and many other databases and websites/online resources.	Last search: 2005 (month not specified) Output: 11,500 records Potentially eligible: 264 Included: 25 studies	9 RCTs, 10 CBAs, and 6 observational studies of various types of interventions:	African (n=11) Central and South American (n=5) Asian/Pacific (n=9) countries. .	Conducted duplicate study selection, critical appraisal, and data extraction; and narrative synthesis	Moderate: CHWs, organisational change.
9	Oyo Ita 2011.[121]	To evaluate the effectiveness of intervention strategies to boost and sustain high childhood immunization coverage in LMICs	Medline, CENTRAL, Embase; Cinahl, EBSCO, LILACS, Sociological Abstracts, DARE, reference lists.	Last search: March 2011 Output: 3678 records Potentially eligible: 46 Included: 6 studies	6 RCTs of patient oriented, provider-oriented, and health system interventions; alone or in combination.	Africa (n=1), Asia/Pacific (n=3), European (n=1), and Central and South American (n=1) countries	Conducted duplicate study selection, critical appraisal, and data extraction; and meta-analysis and narrative synthesis.	Moderate: Home visits. Low: facility-based health education.
10	Glenton 2011.[140]	To assess the effects of LHW interventions on the uptake of childhood immunisation and to develop a typology of intervention models.	Medline, CENTRAL, Embase, Cinahl, British Nursing Index and Archive, AMED, POPLINE, WHOLIS, reference lists, contact experts/authors.	Last search: Feb 2009 Output: 3315 records. Potentially eligible: 55 Included: 12 studies	10 RCTs, 1 CBA, and 1 ITS studies in which the LHWs either promoted immunisations (n=10) or vaccinated children themselves (n=2).	USA (n=6), Ireland (n=1), Asia and the Pacific (n=2), Africa (n=1), Europe (n=1), Central and South America (n=1).	Conducted duplicate study selection, critical appraisal, and data extraction; and meta-analysis.	Moderate: CHWs
11	Wiysonge 2012.[54]	To assess the effectiveness of interventions proposed by EPI managers for improving programme performance	PubMed, Health Systems Evidence database, CDSR, DARE.	Last search: Nov 2011 Output: 2538 records Potentially eligible: 757 Included: 10 SRs	5 SRs of supply-side and 5 SRs of demand-side interventions.	Not reported, but studies included in the SRs were mostly conducted in high-income countries.	Conducted duplicate study selection, critical appraisal, and data extraction; and narrative synthesis.	High: education, supervision, audit and feedback. Moderate: mass media, incentives, communication.

* Surname of first author, year, and study reference; ** GRADE Quality of evidence categories are explained in the text; *** Only year of search given in the report, with no month specified.

BASICS II, Basic Support for Institutionalizing Child Survival - stage II; CBA, controlled before-and-after study; CENTRAL, Cochrane Central Register of Controlled Trials; CHW, community health workers; DARE, Database of Abstracts of Reviews of Effectiveness; DFID, UK Department for International Development; EPOC, Cochrane Effective Practice and Organisation of Care Group; GAVI, The Global Alliance for Vaccines; HTA, Health Technology Assessment; ITS, interrupted time series analyses; LHW, lay health workers; LMICs, low and middle-income countries; NGOs, Non-governmental organisations; PATH, Program for Appropriate Technologies in Health; PAHO, Pan American Health Organization; RCT, randomised controlled trial; SIGLE, System for Information on Grey Literature in Europe; SR, systematic review; UK, United Kingdom; USA, United States of America.

We concluded that this review provided very low quality evidence that home visiting programmes could improve childhood immunisation coverage in Africa. Our main concerns were the unexplained heterogeneity in study results and the indirectness of the evidence; since there are marked differences in health systems between the Europe and North America (where the included studies were conducted) and African countries.[159, 160]

We did not find recent randomised controlled trials that assessed the effects of home visits on childhood immunisation coverage in low and middle-income countries. However, unlike in western countries, home visits in most of Africa would be conducted by community health workers; to identify un-immunised children and refer them for immunisation at the nearest health centre. As discussed later in this chapter, three systematic reviews which focused on studies from low and middle-income countries provide moderate quality evidence that the use of community health workers improves childhood immunisation coverage in Africa.[121-123]

The second review assessed the effects of mass mailings on influenza immunisation coverage among Medicare beneficiaries in the United States of America (USA) (Table 8).[137] Under Medicare in the USA, each state and territory is affiliated with a Peer Review Organization, which is required to conduct quality improvement projects and file reports of their results as part of the Health Care Quality Improvement Project. In early 1999, Margaret Maglione and collaborators searched the Health Care Quality Improvement Project database for controlled trials completed since 1993; the year coverage began for influenza vaccine. The authors identified six controlled trials of mass mailings. The first trial found a statistically significant, but modest improvement in influenza vaccination coverage among study participants who received a letter compared to those who did not, and was published in the Morbidity and Mortality Weekly Report. None of the five subsequent studies reported clinically meaningful results, and none of them was ever published. The mass mailings discussed in the review were not sent by the study participants' personal clinics or physicians, and are thus conceptually different from recall and reminders by one's clinic or personal physician. The review authors concluded that mass mailings

have had clinically trivial effects on increasing influenza vaccination among Medicare beneficiaries in the USA.[137]

We conclude that this review provides very low quality evidence that mass mailings could improve childhood immunisation coverage in Africa. The factors that lowered our confidence in the effectiveness of mass mailing to improve childhood immunisation coverage in Africa were the heterogeneity of effects and the indirectness of the evidence; since the review included only studies conducted among the adult population receiving preventive care from Medicare in the USA. These data may thus be of limited relevance to childhood immunisation programmes in Africa.[159] We found no new randomised controlled trial on mass mailing from a low or middle-income country. However, if mass mailing were found to be an effective strategy for improving immunisation coverage, it could easily be implemented in most African countries using mobile phone text messaging.

The third systematic review assessed the effects of audit and feedback on immunisation delivery by healthcare workers.[138] The review authors (Clayton Bordley and colleagues) defined audit and feedback as "any summary of clinical performance gathered over a defined period of time and presented to the healthcare provider after collection". They included 15 studies in the review, conducted in the USA (n=13) and United Kingdom (n=2); five of them randomised controlled trials (Table 8). Twelve studies found that audit and feedback was associated with improvements in immunisation coverage. The magnitude of effect varied from -17% to +49% change, but study design heterogeneity precluded a meta-analysis. Five of the fifteen included studies involved interventions aimed at increasing childhood immunisation coverage. Of these five, one was a randomised controlled trial, two were interrupted time series analyses, and two were before-and-after studies. The increase in childhood immunisation coverage in the five studies ranged from +3% to +25% percentage points.

Using the GRADE approach, we rated the quality of evidence from this review on the effectiveness of audit and feedback for improving childhood immunisation coverage in Africa as moderate. The main factor that led us to rate down the quality of the

evidence was indirectness (since the included studies were conducted in high-income countries and may not be directly relevant to national health systems in Africa).

We did not find a recent randomised controlled trial on the effects of audit and feedback for improving immunisation coverage in a low or middle-income country. However, a recent Cochrane review by Noah Ivers and colleagues provides high quality evidence that audit and feedback improves health worker behaviour.[161] The authors found the weighted median adjusted risk difference from 49 high-quality studies to be +4.3% (interquartile range +0.5% to +16%) absolute increase in healthcare professionals' compliance with desired practice. They also found the effect of audit and feedback to be larger when baseline performance was low, the source was a supervisor or senior colleague, delivered both verbally and written, provided more than once, and included both explicit targets and an action plan. We are confident that the findings of the Cochrane may be applicable to childhood immunisation programmes in Africa.

In the fourth included review, Erin Stone and colleagues assessed the effectiveness of interventions to increase the uptake of adult immunisation and cancer screening services.[139] The authors identified 108 controlled trials published by February 1999, which assessed the effectiveness of interventions to increase the use of immunisations for influenza and pneumococcal pneumonia as well as screening for colon, breast, and cervical cancer in adults; 95 randomised controlled trials and 13 non-randomised controlled trials (Table 8). Twenty nine studies focused on immunisation. Meta-regression revealed the adjusted odds ratios (OR) for increasing immunisation coverage to be 16.00 (95%CI 11.2 to 22.8) for organisational change; 3.80 (3.31 to 4.37) for provider reminders; 3.42 (2.89 to 4.06) for patient financial incentives; 3.21 (2.24 to 4.61) for provider education; 2.52 (2.24 to 2.82) for patient reminders; 1.29 (1.14 to 1.45) for patient education; 1.26 (0.83 to 1.90) for provider financial incentives; and 1.23 (0.96 to 1.58) for feedback. The organisational change studies in the meta-regression analysis could be classified into four general categories i.e. the establishment of a separate clinic devoted to screening and

prevention activities, use of a planned care visit for prevention, use of techniques similar to continuous quality improvement, and designation of specific prevention responsibilities to non-physician staff. Patient financial incentives included reducing or eliminating co-payments, which would not be applicable to childhood immunisation services in Africa that are provided at no cost to recipients in public health facilities. Client reminders consistently improved coverage, with personalised reminders or reminders signed by the patient's physician being more effective than generic reminders. The authors went on to do an exploratory analysis of features instrumental to the success of each organisational change intervention, using meta-regression. They found that explicitly designing an intervention that fosters collaboration or teamwork (OR 17.9, 95%CI 10.4 to 30.9), provides materials with high visual appeal (OR 3.25, 95%CI 2.09 to 5.06), or is based on needs or theory (OR 1.61, 95%CI 1.52 to 1.71), was associated with a statistically significant increase in immunisation coverage. In conclusion, this review suggests that the best strategies to increase immunisation coverage in an adult population in a high-income setting is implementation of organisational changes that involve collaboration and teamwork and are based on knowledge of needs, barriers, and theory; followed by patient reminders and patient financial incentives in that order.[139]

The included studies were conducted in high-income countries among adult populations. These factors limit our confidence in the transferability of these findings to childhood immunisation programmes in Africa, and we rated the quality of evidence as moderate for organisational change and parent reminders. Parent reminders can play a big role in EPI programmes in Africa especially with the widespread use of mobile phones in the continent; and are covered by the next review.[124]

We found a recent randomised controlled trial that assessed the effects of organisational change interventions on immunisation coverage in rural hard-to-reach populations in Bangladesh.[150] In this trial, Jasim Uddin and colleagues chose two sub-districts with the lowest immunisation coverage from each of two hard-to-reach districts. One sub-district in each district (Group A) was randomly chosen to receive

two interventions (modified EPI immunisation session schedule and community support groups), and one sub-district (Group B) was chosen to receive a different intervention (screening checklist). Modified EPI session schedules consisted of alternate session schedules intended to make EPI sessions more efficient, accessible, and convenient. In addition, community support groups (one for each EPI centre) were formed to involve the community with the EPI. The authors assessed the impact with post-intervention coverage surveys conducted in May 2010. The immunisation coverage increased significantly at endline compared to baseline in the study areas ($p < 0.001$). The findings also showed that the number of drop-outs and left-outs decreased significantly at endline compared to baseline in the study areas ($p < 0.001$). Drop-outs refer to children who start but do not complete the full series of vaccines on the schedule, while left-outs refer to children who have not yet taken any vaccines on the schedule.

In the fifth included review, Jacobson Vann and co-worker assessed the effectiveness of patient reminder and recall systems in improving immunisation coverage and compared the effects of various types of reminders in different settings or patient populations.[124] The authors found 47 trials published by 2007, twenty three of which are relevant to childhood immunisation. The rest involved influenza immunisations for patients 65 years or older, those with chronic illness, or both. Interventions included letters, postcards, person-to-person telephone calls, computer-to-person telephone calls, and home visits. Most of the studies were done in the USA; with none done in low or middle-income countries. The included studies were, however, done in diverse settings, some of which were aimed at low-income groups in high-income countries. The authors found that increases in immunisation coverage due to reminders were in the range of 1 to 20 percentage points. Reminders and recalls were effective for routine childhood vaccinations (OR 1.47, 95% CI 1.28 to 1.68) and childhood influenza vaccinations (OR 2.18, 95% CI 1.29 to 3.70). All types of reminders were effective, with the use of telephones being the most effective but most costly.[124]

We rated the quality of evidence on the use of parent reminder and recall systems for improving childhood immunisation coverage in Africa as moderate. Our main concern was indirectness of the evidence (because the review provided no direct evidence of how effective reminder and recall interventions are in low and middle-income countries). We did not find a recent randomised controlled trial on reminder and recall for improving childhood immunisation coverage in low and middle-income countries.

The sixth systematic review, conducted by Elisabetha Pegurri and colleagues, assessed the range of potential effects and costs of interventions to expand the coverage of immunisation programmes in low and middle-income countries (Table8).[122] The authors conducted a comprehensive search and identified 60 papers which they included in the review. Three of the publications were reports of randomised controlled trials and the rest were ecological studies. The studies assessed 49 distinct interventions, with 44 evaluated for effectiveness, 10 for costs, and three for cost-effectiveness. The interventions were most frequently reported from Africa (10 countries), Asia and the Pacific (n=6), and Central or South America (n=6). The authors found that supply-side interventions such as improvements in healthcare worker performance (through training, monitoring, and supportive supervision), bringing services closer to the people (through outreach teams or community health workers), and modification of immunisation schedules (to target children when more are likely to visit health centres by delivering the vaccines earlier and/or at shorter intervals) were effective in increasing immunisation coverage. Increasing demand among those already accessing health services was attempted by reorganising clinic procedures so as to shorten waiting times and by reducing missed opportunities (e.g. vaccinating all eligible children visiting health centres, even if ill). Reminders were used to target children that had accessed services in the past but had not returned. Children's records were sorted according to the time the next vaccination was expected in order to identify non-attendees and send reminders to their families, sometimes through school children. Channelling (or door-to-door canvassing) was also used in some studies to encourage non-returnees as well as those who have never attended vaccination clinics. Community health workers conducted home visits to identify and register children with incomplete vaccinations,

and referred them to health centres. Different strategies were used in various studies for increasing awareness among the children's parents including mass media interventions and provision of immunisation information to older children in schools. The authors found that all interventions increased vaccination coverage, with community health workers and channelling being the most effective and peer training and channelling the least costly.

We rated the quality of evidence as moderate for community health workers and channelling, and low to very low for the rest of the interventions. The main factors that reduced our confidence in the evidence are study limitations i.e. the low quality of the studies included in the review.[122]

The seventh included review was a review of the grey literature on the costs and effects of expanding immunisation services in low and middle-income countries, by Katherine Batt and colleagues.[120] The authors hand-searched documents at the headquarters of the WHO, UNICEF, Pan American Health Organization (PAHO), and USAID; and interviewed 28 international experts from The World Bank, UNICEF, Basic Support for Institutionalizing Child Survival – stage II (BASICS II), The United States National Institutes of Health, PAHO, WHO country offices, and national EPI programmes. In addition, they searched a wide range of grey literature databases (Table 8). The authors identified 34 relevant publications (of 24 interventions), which were available by May 2003. The interventions were evaluated in Africa (n=11 countries), Central and South America (n=7), and Asia and the Pacific (n=6). Supply-side interventions focused on endowing providers with increased responsibility and accountability by changing payments to performance-based systems and contracting with non-governmental organisations at varying levels of responsibility to provide immunisation services. Demand-side strategies were aimed at educating communities and health workers, improving awareness of missed opportunities, and reducing opportunity costs to families (e.g. by shortening waiting times).

This grey literature review provides low quality evidence that mass media, education for health workers, in-service training, community education, contracting out, integration of immunisation to existing health services, national plans of action, and

integrated supervisory checklists could improve childhood immunisation coverage in Africa. Although all studies were conducted in low and middle-income countries, our confidence in the effectiveness of these interventions for improving childhood immunisation programmes in Africa was reduced by the paucity of randomised controlled studies.[122]

In the eighth included review, Tove Ryman and colleagues conducted a comprehensive search of peer-reviewed and grey literature on strategies for improving childhood immunisation in low and middle-income countries.[123] They identified 25 papers that met their inclusion criteria i.e. a fairly rigorous study (not necessarily a controlled trial) conducted to improve routine immunisation programmes among humans in a low- or middle-income country. The authors grouped the papers into four strategic approaches: bringing immunisations closer to communities (n=11), using information dissemination to increase demand for vaccination (n=3), changing practices in fixed sites (n=4), and using innovative management practices (n=7).

The studies included in the category “bringing immunisations closer to communities” used community health workers to encourage people to seek immunisation services, or increased access to immunisation services by bringing services to communities, and additionally in some cases by increasing demand through educating communities. These studies were conducted in Africa (n=6), Asia and the Pacific (n=3), and Central and South America (n=1); and reported improvements in immunisation coverage of varying degrees. All six controlled clinical trials that reported data on fully vaccinated children recorded improvements in coverage ranging from 14% to 42%.

Three studies (one before-and-after and two observational) were conducted in Asia to assess the “use of information dissemination to increase demand for vaccination”. Information can be provided through numerous channels to either increase awareness of the benefits of immunisation or to promote participation. These strategies increase demand for vaccination without changing the service delivery. Mass communication campaigns have the potential to reach large numbers of

people, if access to the type of media selected is good. The controlled before-and-after study evaluated a mass media campaign focusing on measles vaccination delivered through routine services. An increase of 11% in the proportion of fully vaccinated children was observed with a year of starting the study. The two observational studies also led to increases in vaccination coverage.

Four studies assessed the effects of “changing fixed vaccination sites” to ensure that children who start vaccination complete the full series of vaccines (i.e. reducing drop-outs) and that children eligible for vaccination who come to the health facility are vaccinated (i.e. reducing missed opportunities). In a controlled trial in Ethiopia, the use of reminder stickers for parents resulted in decreasing dropout between the first and the third dose of the diphtheria-tetanus-pertussis vaccine from 13% to 7%. An observational study conducted in Sudan increased vaccination coverage by 32% by moving the immunisation location closer to the consultation room to provide immediate immunisations to children who had recently been seen in consultation, or having a physician write a prescription for immunisations during curative visits. A controlled before-and-after study in an urban setting in Nigeria increased the proportion of fully vaccinated children by 18% through reducing wait times by creating a quick immunisation line. In an observational study in a Mexican children's hospital missed opportunities were reduced by immunising all hospitalised children who were not up-to-date with their vaccines.

Two controlled before-and-after studies and four controlled trials in Asia and the Pacific (n=3), Central and South America (n=2) and Africa (n=1) assessed the effects of “using innovative management practices” (i.e. who should manage immunisation systems, and how systems might be improved to provide the highest quality services) on immunisation coverage and equity. These interventions (including contracting immunisation services to NGOs, use of data and community information for planning immunisation activities, peer-support) significantly improved immunisation coverage.

We rated the quality of evidence as moderate for strategies for bringing immunisations closer to communities (e.g. the use of community health workers) and innovative organisational changes (e.g. contracting out services), and low for the rest

of the interventions assessed by Tove Ryman and co-workers.[123] The main concern with the evidence is the paucity of scientifically rigorous studies.

Through an exhaustive search, we have identified new high-quality studies conducted in low and middle-income countries on interventions for improving childhood immunisation coverage.[146-150] We have reported the findings of these studies elsewhere in this chapter.

In the ninth included review, Oyo-Ita and colleagues assessed the effectiveness of strategies to boost and sustain high childhood immunisation coverage in low and middle-income countries.[121] The authors conducted a comprehensive search for randomised controlled trials, non-randomised controlled trials, and interrupted-time-series studies which were published by March 2011. They identified six studies; all of them randomised controlled trials. The studies were carried out in Asia and the Pacific (n=3), Europe (n=1), Central and South America (n=1), and Africa (n=1). The review provided low quality evidence that facility-based health education may improve immunisation coverage (RR 1.18, 95% CI 1.05 to 1.33), and that a combination of facility-based health education and redesigned immunisation cards may improve coverage (RR 1.36; 95% CI 1.22 to 1.51). They also found moderate quality evidence that evidence-based discussions during home visits improve immunisation coverage (RR 2.17, 95% CI 1.80 to 2.61). Our main concerns with the evidence from this review relates to study limitations; with four studies having a high risk of bias.

Our search identified a new randomised controlled trial by Hussain Usman and colleagues,[149] which assessed the effects a combination of facility-based health education and redesigned immunisation cards in a rural community in Pakistan. The study authors state that the EPI card currently used in Pakistan has two main shortcomings i.e. it is small (hence, information on child's identity, immunisation schedule, information for mothers and next immunisation visits is crowded), and immunisation appointment dates are hand-written, often in very small and irregular letters). To address these issues, the authors designed a new simpler immunisation card whose most important intended functions were to act as a constant reminder to

mothers of the next immunisation visit and to make it easy for them to locate and read the date of the next immunisation. Mother-child pairs were enrolled when they came for the first dose of the diphtheria-tetanus-pertussis vaccine and randomised to four study groups: redesigned card (n=378), facility-based education (n=376), combined redesigned card and facility-based education (n=374), and standard care (378). Children in the redesigned card (RR 1.7, 95% CI 1.5 to 2.0), facility-based education (RR 1.5, 95% CI 1.3 to 1.8) and combined intervention group (RR1.7, 95% CI 1.4 to 2.0) groups were significantly more likely to complete the full three series of the diphtheria-tetanus-pertussis vaccine than those in the routine care group. This trial strengthens the evidence that facility-based education to mothers and a combination of facility-based education and user-friendly immunisation cards probably improve childhood immunisation coverage in Africa.

In the tenth included review, Claire Glenton and colleagues assessed the effects of community health worker interventions on childhood immunisation coverage.[140] They conducted the last search in 2009 and identified twelve studies, ten of which were randomised controlled trials. Five of the studies were carried out in low and middle-income countries in Asia and the Pacific (n=2), Africa (n=1), Europe (n=1), and Central and South America (n=1). The studies from low and middle-income countries were conducted among poor populations or populations from areas where immunisation coverage was particularly low; in both urban and rural settings. The studies from high-income countries took place among economically disadvantaged urban populations. In ten studies, community health workers promoted childhood immunisation and in the remaining two studies, community health workers vaccinated children themselves. In most of the studies, the control group populations received standard care or no intervention. Most of the studies showed that community health workers increased immunisation coverage.

We rated the quality evidence on the effectiveness of community health workers to increase childhood immunisation coverage as moderate. Our concern with the evidence is the paucity of high-quality studies from low and middle-income countries included in the review.

In the eleventh included review, Charles Wiysonge and colleagues requested EPI programme managers in South Africa to identify key barriers to effective implementation of the EPI programme and to propose appropriate corrective interventions.[54] The authors collated the managers' responses and conducted a comprehensive search for systematic reviews on the effectiveness of the proposed corrective interventions. The authors conducted the last search in November 2010 and identified 10 systematic reviews that met their inclusion criteria. The latter were reviews which: (1) conducted a literature search that was comprehensive enough to avoid publication, language and indexing biases; (2) undertook duplicate study selection and data extraction; (3) used reliable criteria to assess the risk of bias in included studies; (4) reported the characteristics of included studies appropriately; and (5) combined data from included studies using reliable methods. The authors found high-quality evidence that interactive educational meetings, audit and feedback, and supportive supervision of healthcare workers are effective supply-side interventions for improving childhood immunisation coverage. Regarding demand-side interventions, the authors found moderate quality evidence that parent reminder and recall systems, use of community health workers, mass media interventions, conditional cash transfers, and structured interactive communication lead to improvements in childhood immunisation coverage. Conditional cash transfers refer to monetary transfers made to disadvantaged households on the condition that they comply with some pre-determined requirements in relation to health care, such as vaccinating their children.[162]

We found newly published randomised controlled trials which increased our confidence in the effectiveness of consumer incentives and community health workers for improving immunisation coverage,[146, 148] and in the integration of immunisation services to other primary health care services.[147]

Abhijit Banerjee and colleagues used a clustered randomised controlled study design to assess the efficacy of modest non-financial incentives on immunisation coverage, compared to the effect of only improving the reliability of the supply of services.[146] The authors randomised 134 villages to one of three groups: a once-monthly reliable

immunisation clinic (intervention A; 379 children from 30 villages); a once-monthly reliable immunisation clinic with small incentives (raw lentils and metal plates for completed immunisation; intervention B; 382 children from 30 villages); or control (no intervention, 860 children in 74 villages); in Rural Rajasthan, India, from June 2004 to February 2007. Among children aged 1-3 in the end point survey, rates of full immunisation were 39% (148/382) for intervention B villages (reliable immunisation with incentives), 18% (68/379) for intervention A villages (reliable immunisation without incentives), and 6% (50/860) for control villages. After 18 months, the risk ratio for complete immunisation was 6.7 (95%CI 4.5 to 8.8) for reliable immunisation with incentives compared to no intervention, and 2.2 (1.5 to 2.8) for reliable immunisation with incentives compared to reliable immunisation without incentives. The average cost per immunisation was 28.00USD for reliable immunisation without incentives and 56.00USD for reliable immunisation with incentives.

In another trial, Aatekah Owais and colleagues conducted a randomised controlled trial to assess the impact of a low-literacy immunisation promotion educational intervention for mothers living in low-income communities in Pakistan on completion of the immunisation schedule.[148] Three hundred and sixty-six mother-infant pairs, with infants aged six weeks or less, were enrolled and randomised into either the intervention or control arm between August and November 2008. To address the needs of low literacy populations, easy-to-understand pictorial cards, using very simple language, to convey three key messages as part of the educational intervention were designed. The first key message highlighted how vaccines save children's lives. The second message provided logistic information about the address and location of the local vaccination centres. The third key message emphasised the significance of retaining immunisation cards, and the role they could play at the time of the child's school admissions. A copy of these pictorial messages was left with the mother. The intervention was delivered by trained community health workers during home visits, and it lasted about five minutes. The control group received general health promotion messages (hand-washing, breast-feeding, clean water, benefits of using oral rehydration solutions during diarrhoea, bringing the infant to nearby health centre when there are symptoms of acute respiratory illnesses, importance of

antenatal check-ups for mothers, and general information on vaccines) verbally. The control group intervention was delivered by trained community health workers and lasted approximately 10-15 minutes. At the four month assessment, among 179 mother-infant pairs in the intervention group, 129 (72.1%) had received DTP3, compared to 92/178 (51.7%) in the control group. Multivariable analysis revealed a significant and clinically important increase of 39% (adjusted RR 1.39; 95% CI 1.06 to1.81) in DTP3 coverage in the intervention group. The cost of the intervention per community health worker was estimated to be one USD; including the cost of laminated coloured pictorial cards used by the community health workers to educate the mothers in the intervention group, as well as pamphlets of the pictorial messages left at each participant's house.[148]

In another recent study, an open cluster-randomised trial, Alassane Dicko and colleagues assessed the efficacy of Intermittent Preventive Treatment in infants (IPTi) with Sulfadoxine-Pyrimethamine (SP) implementation on the coverage of EPI vaccines; in Kolokani district in Mali.[147] . The 22 sub-districts were randomised in a 1:1 ratio with 11 intervention and 11 control sub-districts. The study began in December 2006 and ended in December 2007In December 2006, the proportion of completely vaccinated children aged 9-23 months was 37% (95% CI 25% to 48%). A year later, the figure had risen to 53.8% in the non-intervention zone and 69.5% in the intervention zone (P <0.001).

5.5. Implication of the findings of Chapter Five

African governments have the responsibility to provide basic services, including immunisation services, to their citizens. However, the public sector is not often sufficiently well-equipped and financed to provide high quality health services that are accessible to all in African countries. Therefore, health policymakers in Africa need to use considerable judgement about how best to use the limited resources they have allocated for improving childhood immunisation programmes in order to maximise public health benefits. This thesis has revealed moderate to high quality evidence

that the use of interactive educational meetings and workshops, audit and feedback, supportive supervision, organisational changes (that involve collaboration and team work and are based on knowledge of needs, barriers, and theory), community health workers, (evidence-based discussions during) home visits, parent reminder and recall systems, targeted financial (and non-financial) incentives, mass media interventions, and interactive communication tools could be effective in improving EPI performance in Africa.

The settings and designs of the studies included in the systematic reviews that assessed the effects of supply-side interventions such as interactive educational meetings, audit and feedback, educational outreach visits, and organisational changes varied widely; but the studies consistently showed that these strategies can improve healthcare worker performance.[54, 139, 163-165] The consistency of effects across different study designs and healthcare settings and conditions suggests that these findings would be applicable to childhood immunisation programmes in Africa.

Social mobilisation for immunisation may include active community participation, contextualisation of information and involvement of a broad range of stakeholders and the mass media. The moderate quality of the evidence on parent reminder and recall systems,[124, 139] community health workers,[122, 123, 140, 141] interactive communication tools, targeted consumer-directed incentives[139, 146, 162], and mass media interventions[122, 123, 125] is an indication that these strategies could have significant effects in mobilising communities and increasing demand for routine childhood immunisation services in Africa.

Reminder and recall interventions rely crucially on a stable health system with ongoing immunisation programmes that can identify and follow potential recipients of vaccination. Other factors that need to be considered to assess whether the intervention effects are likely to be transferable to other settings include the availability of the technology or physical infrastructure to provide reminders (e.g. telephones, computers, a functioning postal system) and literacy of parents (e.g. for post cards); resources to provide the additional clinical and administrative infrastructure to implement reminder and recall programmes; and adequate quantities

of vaccines in health facilities. Low literacy levels may mean that the uptake of immunisations is not simply a matter of reminding parents.[77] EPI programmes may need to provide educational interventions to explain the benefits of immunisation.[148] Although the issues we have raised above regarding the structural differences between countries where most of the reminder and recall studies were conducted and African countries are real issues, it is reassuring to note that other technologies and avenues exist for adapting reminders to the African context. Children's immunisation records in health facilities should be sorted according to the time the next vaccination is due, and their parents contacted through school children, community health workers, or mobile phone text messaging to remind them of upcoming immunisations or ones that are overdue.[158, 166, 167]

Growing financial pressure to improve the efficiency of health systems amidst a chronic shortage of qualified health workers in the public health sector, is also leading to an increased interest in broadening the scope of practice of community health workers in Africa.[168] Vaccination of children by community health workers is highly relevant to such discussions. Four reviews included in our overview show promising benefits of community health workers on child immunisation coverage.[121-123, 140] They identified a number of intervention models for community health workers. However, these models are not exhaustive and more high-quality studies are needed, particularly from Africa; for example, we have little knowledge about the effect of using community health workers as part of a larger team as only two studies used this approach.[140] In addition, the costs and cost-effectiveness of using community health workers in immunisation programmes has not been fully evaluated. [140, 169]

A substantial proportion of the population in African countries seeks curative services in the private sector.[72, 73, 170] However, relatively few data are available on the role of the private sector in the provision of immunisation services in the continent. [72] Ann Levin and co-worker suggest that the private sector plays different roles and functions in different countries, according to economic development levels and the governance structure.[72] In low-income countries, the private for-profit sector contributes to immunisation service delivery and helps to improve access to EPI

vaccines.[72, 74] In middle-income countries, the private for-profit sector often acts to facilitate early adoption of new vaccines and vaccination technologies before their introduction in the public health sector.[72] The not-for-profit health sector plays an important role in extending access to traditional EPI vaccines, especially in low-income countries. Not-for-profit facilities are more likely to be coordinated with public services than the private for-profit sector. Although numerous studies NGO's suggest that the extent of NGO provision of immunisation services in low- and middle-income countries is substantial, the contribution of this sector is poorly documented. Studies on quality of immunisation service provision at private health facilities suggest that it is sometimes inadequate and needs to be monitored. Although some articles on public–private collaboration exist, the authors found little on the extent to which governments are effectively interacting with and regulating the private sector. They revealed many geographical and thematic gaps in the literature on the role and regulation of the private sector in the delivery of immunisation services in low and middle-income countries.[72, 73] If Africa is to achieve its immunisation goals, public-private partnerships need to be fully utilised to the best advantage in childhood immunisation programmes. Models for subcontracting immunisation services to the private sector should be tried, evaluated, and considered for scale-up if successful.[170]

The strength of this chapter lies in our adherence to standard guidelines on the conduct and reporting of systematic reviews as well as grading of the quality of evidence. We conducted comprehensive searches, assessed study eligibility using pre-defined inclusion criteria, and extracted data in duplicate; resolving differences by consensus. The major weakness of the chapter relates to inherent shortcomings in the primary data of the included reviews. Most of the studies included in the reviews were conducted in high-income countries, especially North America. However, we used novel methods to assess the quality of the evidence and its applicability to childhood immunisation programmes in Africa.

CHAPTER 6: Overall discussion and conclusion

The following are novel contributions of this thesis to the field of vaccinology:

1. Applying methods of evidence-based practice to childhood immunisation programmes in Africa;
2. Conducting the first bibliometric analysis of childhood immunisation research productivity from Africa;
3. Using advanced statistical techniques to determine the cross-continental factors that influence childhood immunisation coverage and research productivity in Africa; and
4. Employing novel techniques such as GRADE in assessing the applicability of global evidence to the African immunisation context.

This thesis employed evidence-based practice (EBP) techniques[34, 35] to evaluate the performance of EPI in Africa, the reasons for poor EPI performance in Africa, and the current best evidence on effective interventions for improving the performance of EPI on the continent; focusing on immunisation coverage. The proportion of the annual birth cohort which receives the full series of three doses of the diphtheria-tetanus-pertussis combined vaccine (DTP3) is an internationally accepted standard measure of immunisation coverage; and is generally accepted to reflect the overall performance of EPI programmes.[8, 40, 41] EBP applies systematic and transparent processes when accessing and appraising research evidence, in order to ensure that decision making is well-informed by the best available research evidence.[35] The EBP techniques employed in this thesis include systematic reviews (Chapter 2 and 5), the GRADE approach for assessing how much confidence to place in a given body of research evidence (chapter 5),[134, 159] and an assessment of the applicability of global evidence to an African context (Chapter 5).[160] In addition, we used generalised linear statistical models to assess factors associated with childhood immunisation coverage (Chapter 4) and research productivity (Chapter 3) in Africa.

The first sub-study of the thesis was a systematic review, which found significant improvements in EPI performance in Africa since the inception of the programme in 1974 (Chapter 2). A range of under-utilised vaccines, newly available vaccines, and new vaccination technologies are increasingly being introduced into national EPI programmes across the African continent.[24, 26] Furthermore, basic immunisation coverage has increased significantly. Continental DTP3 coverage increased from less than 5% in 1974 to 77% in 2010.[24, 33] However, the performance of EPI programmes varies widely between and within African countries, [24, 33, 47-49, 50] with many countries failing to meet the Global Immunisation Vision and Strategy (GIVS) targets.[28, 29] In 2010, only 22(42%) countries achieved national DTP3 coverage of 90% or more and only 16 (30%) achieved 80% DTP3 coverage in a least 80% of their districts. Besides, the quality of immunisation data in many African countries is poor, [47-49] and vaccines are administered well after the recommended ages; leaving children exposed to deadly vaccine-preventable diseases for long periods. [50]

This continued failure to meet agreed targets suggests that general and country-specific challenges with regards to immunisation programmes in Africa have not been fully identified, understood, and/or addressed effectively.[77] With the 2015 deadline for the MDGs fast approaching, it is necessary for Africa to stop, critically assess its position, take ownership of the regional and country specific problems, and strategise exactly how it plans to overcome the challenges identified. The progress in immunisation coverage in most African countries (between 1980 and 1990, and since 2000) has largely been due to the availability of international funding supplemented by government funding. Even with continued support from international donors, political will as well as financial planning and commitment from African governments are key factors for successful introduction and sustainability of new vaccines in EPI schedules on the continent. Regarding political commitment, The Republic of South Africa is to be commended for introducing several new vaccines in 2009 (i.e. the pneumococcal conjugate, rotavirus, and pentavalent vaccines) without external donor funding.[54, 171] Vaccine procurement and pricing strategies, as well as vaccine adaptation to suit low and middle-income countries remain essential components of helping to strengthen immunisation systems across Africa.[172] We believe that in order

for Africa to take advantage of the new decade of vaccines and extend the full benefits of immunisation to its citizens by 2020 and beyond, a critical assessment is a fundamental step. The DoV recently coordinated the development of the Global Vaccine Action Plan (GVAP) which is guided by six principles; country ownership, shared responsibility and partnership, equity, integration, sustainability, and innovation.[32] While such global initiatives offer generalised strategies for attaining outlined goals, it is absolutely necessary for complementary tailor-made African approaches. Evidence-informed African initiatives to improve immunisation coverage, strengthen immunisation systems, and hold African leaders accountable for honouring commitments made are urgently needed.

In the second sub-study, we conducted the first ever bibliometric analysis of childhood immunisation research productivity from Africa (Chapter 3). We used negative binomial regression models to explore the factors associated with research output on the continent. Between 1974 and 2010 authors from Africa produced only 8.9% of the global immunisation research output. Immunisation research productivity on the continent is highly skewed, with private health expenditure (which may reflect the economic development of a country) being the only independent predictor of research output. There was no significant association between research productivity and the country's immunisation coverage or other country-level factors. The lack of association between research productivity and immunisation coverage may be an indication of a lack of interactive communication between health decision-makers, programme managers, and researchers.

We recommended that during the new decade of vaccines, African countries should prioritise research capacity development in vaccinology in particular and in infectious diseases in general. Health research in general helps to answer questions, to generate the evidence required to guide policy, and to identify new tools. Therefore, contextualised research is needed to ensure the effectiveness, efficiency, and equity of immunisation policies in Africa. An evidence-informed approach to improving childhood immunisation programmes in Africa and, consequently, reducing child mortality on the continent demands first an understanding of why programmes have

failed to reach their optimum potential. And secondly, appropriate strategies should be employed to address the identified shortcomings of immunisation programmes. [36-39]

This was the rationale for the third sub-study, in which we developed and tested a model of childhood immunisation coverage that includes individual, community, and country level factors (Chapter 4). We used multilevel logistic regression models to analyse Demographic and Health Survey data for 27,094 children aged 12 to 23 months, nested within 8,546 communities from 24 countries in Africa. The model provides evidence of contextual factors, measured at community and country levels, associated with childhood immunisation coverage. At individual level, children from poorest households, uneducated parents, mothers with no access to media, and mothers with low health seeking behaviours were more likely to be unimmunised. In addition, we found evidence of clustering at both community and country levels, such that children from the same communities tended to have similar immunisation status. This suggests that children in the same neighbourhood are subjected to common contextual influences; thus, providing evidence of contextual phenomenon shaping children's risk of being unimmunised. Furthermore, the analysis reveals that low parental and community knowledge of immunisation and/or lack of access to information on childhood immunisation could be an important contributor to the high burden of unimmunised children in Africa. This assertion is supported by our finding of significant reductions in the number of unimmunised children among parents and communities with access to mass media. In addition, unimmunised children were found to cluster in communities, increasing the risk of disease outbreaks. It is therefore important to identify effective interventions to enable parents and communities to understand the meaning and relevance of vaccination to their health and the health of their families and communities. The finding that individual and contextual factors are associated with childhood immunisation, suggests that public health programmes designed to improve childhood immunisation programmes in Africa should address people and the communities and societies in which they live. Synthesis of existing immunisation barriers and the evidence on effective

interventions to address these barriers should be a systematic and integral component of childhood immunisation programmes in Africa, and elsewhere.

In the last sub-study, we conducted a comprehensive search of the peer-reviewed literature, identified, and synthesised randomised controlled trials and systematic reviews of effective interventions for improving childhood immunisation programmes (Chapter 5). Health policymakers in Africa need to use considerable judgement about how best to use the limited resources they have allocated for improving childhood immunisation programmes in order to maximise population benefits.

This thesis has revealed moderate to high quality evidence that the use of interactive educational meetings and workshops, audit and feedback, supportive supervision, organisational changes (that involve collaboration and team work and are based on knowledge of needs, barriers, and theory), community health workers, (evidence-based discussions during) home visits, parent reminder and recall systems, targeted financial (and non-financial) incentives, mass media interventions, and interactive communication tools could be effective in improving EPI performance in Africa. Decision makers need to consider population characteristics, available resources, and competing priorities when selecting a combination of these interventions to use for each community and at any given time point.

A successful immunisation programme depends upon effective vaccine supply and logistics, but it is just as important that the community has confidence in, and supports and demands, safe and effective immunisation services.[173] The moderate quality of the evidence on parent reminder and recall systems,[124, 139] community health workers,[122, 123, 140, 141] interactive communication tools,[126] targeted consumer-directed incentives[139, 146, 162], and mass media interventions[122, 123, 125] is an indication that these strategies could have significant effects in mobilising communities and increasing demand for routine childhood immunisation services in Africa. Immunisation services must meet the needs of communities and work with them to ensure their involvement and participation. To achieve this, both EPI managers and healthcare workers need to form a close partnership with communities, and use effective communication skills and tools.[126] Managers at all levels should keep

communities informed about services, and should seek the participation of local politicians, religious leaders, community group leaders, and parents in scheduling the days and hours for immunisation sessions, organising outreach activities, promoting immunisation, and monitoring performance. Advocacy is needed to promote the benefits and value of immunisation and to present the rationale for the community's involvement. It is particularly important to increase immunisation demand at community level in countries with large numbers of un-immunised children. Wireless telecommunications networks have spread rapidly throughout Africa, and sending text-messages on wireless mobile telephones has become an extremely popular means of communication among people in all sectors of society. Therefore mobile phone text-messaging offer an appropriate channel for reminding parents of upcoming immunisations or immunisations that are overdue. [158, 166, 167]

Most of the evidence on the effectiveness of interventions for improving immunisation coverage comes from studies conducted in high-income countries, and applicability to African countries may be limited. Thus, the implementation of these interventions in childhood immunisation programmes in Africa should be pilot-tested and their impacts and costs rigorously monitored and evaluated.[37] The range of interventions that we identified certainly does not exhaust the possibilities for increasing immunisation coverage. We propose the following areas for additional research, namely, use of school-based vaccination,[174] innovative strategies for integration of additional services with immunisation delivery, public sector collaboration with and regulation of the private sector, best approaches to new vaccine introduction, and innovative ways of handling vaccine hesitancy and building or maintaining public trust in immunisation programmes.[173] Accordingly, we suggest that more studies should be conducted in African countries. Such studies should be rigorously designed and executed; with long follow-ups, consideration of confounding factors, analyses of costs alongside effectiveness, and inclusion of broader outcomes regarding the quality and timeliness of vaccine delivery. These changes would improve the quality of study results, and African decision-makers could be more fully informed about the most desirable intervention or combination of interventions to improve immunisation programmes in their various settings. A substantial proportion of the population in

African countries seeks curative services in the private sector.[72, 73, 170] However, relatively few data are available on the role of the private sector in the provision of immunisation services on the continent. [72] If Africa is to achieve its immunisation goals, public-private partnerships need to be fully utilised to the best advantage in childhood immunisation programmes. Models for subcontracting immunisation services to the private sector should be evaluated, and considered for scale-up if successful.[170]

In summary, this thesis has highlighted the importance of applying an EBP approach to immunisation policies in Africa. EBP is indispensable in health sciences; it helps to ensure that patients and the public benefit from health research, and that research and healthcare resources are used efficiently.[175] Applying EBP principles to EPI in Africa will ensure that our children's right to health, development and survival is respected, protected and promoted; in line with the Millennium Development Goals. The EBP approach emphasises the need for collaboration among health policy makers, programme managers, and researchers in order to ensure the effectiveness, efficiency, and equity of immunisation policies in Africa.[54] This collaboration needs to be continuous, as challenges to childhood immunisation may vary from time to time; and policies would need to be adapted to the changing immunisation landscape. Such an approach would develop a comprehensive and relevant evidence base to equip countries on the continent with the arsenal for evidence-informed actions.[36-39]

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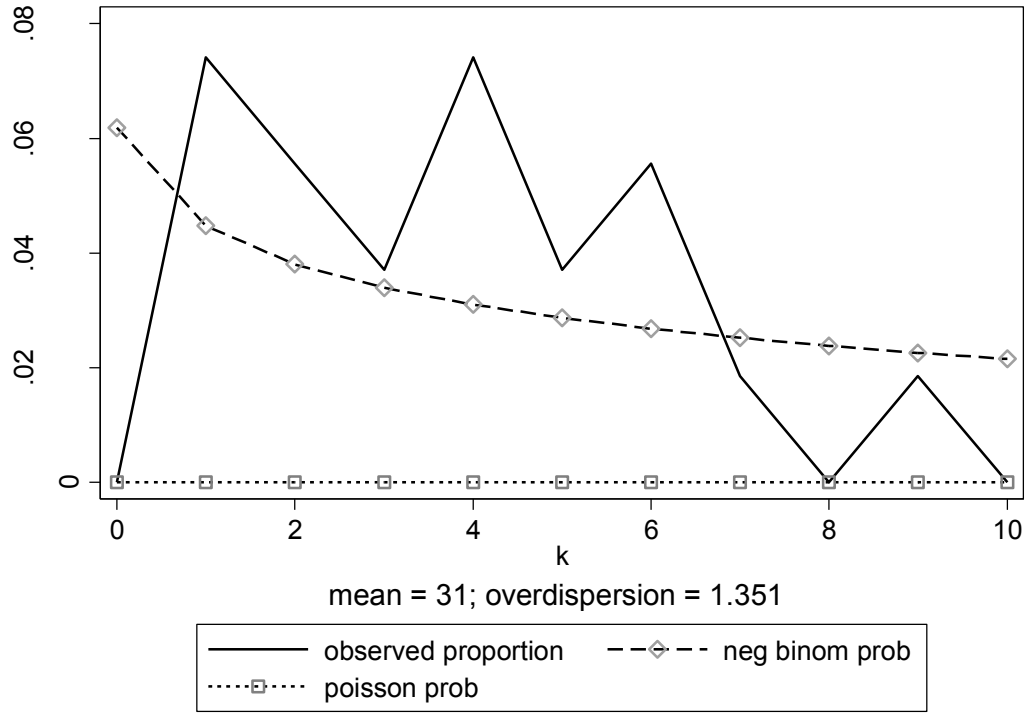
Appendices

Appendix 1: Comparisons of Poisson and negative binomial regression models for the bibliometric analysis (Chapter 3)

Test 1: The probability distributions which underpin the two models were examined to see how they fit the observed data

Result: As shown in Figure 1, the Poisson model was a poor fit, whereas the predicted values of the negative binomial were close to the observed. The negative binomial model produced the best fit for the entire range of publication values

Figure 1: Predicted proportions from intercept-only Poisson and negative binomial models compared with observed publication proportion



Test 2: Likelihood ratio test was used to test for overdispersion in Poisson regression model

Result: As shown below, the likelihood test for overdispersion comparing negative binomial to Poisson, which test Ho, alpha=0, yielded statistics of 764.72. The estimate of alpha was 0.85 (SE =0.18), which is significantly different from 0, therefore negative binomial model is favoured over the Poisson.

```
Poisson regression                              Number of obs   =         41
                                                LR chi2(5)      =    1334.48
                                                Prob > chi2     =     0.0000
Log likelihood = -555.46355                     Pseudo R2       =     0.5457

------------------------------------------------------------------------------
         pub |        IRR   Std. Err.      z    P>|z|     [95% Conf.
Interval]
-------------+----------------------------------------------------------------
     log_gdp |   1.369986   .0681946     6.32   0.000      1.24264
1.510382
     log_phy |   .8296561   .0235366    -6.58   0.000     .7847843
.8770937
  log_heaexp |   .8495908    .113514    -1.22   0.222     .6538538
1.103924
 log_heapriv |   1.954061    .138539     9.45   0.000     1.700551
2.245363
    log_rand |   1.370433   .0637301     6.78   0.000     1.251048
1.501211
       _cons |   3.645866   .6887461     6.85   0.000     2.517671
5.279618
------------------------------------------------------------------------------


Negative binomial regression                    Number of obs   =         41
                                                LR chi2(5)      =      26.21
Dispersion     = mean                           Prob > chi2     =     0.0001
Log likelihood = -173.10396                     Pseudo R2       =     0.0704

------------------------------------------------------------------------------
         pub |        IRR   Std. Err.      z    P>|z|  [95% Conf. Interval]
-------------+----------------------------------------------------------------
     log_gdp |   1.408463   .3888345     1.24   0.215     .8198875
2.419562
     log_phy |    .812031   .1090316    -1.55   0.121     .6241393
1.056486
  log_heaexp |    .637382   .4984073    -0.58   0.565     .1376557
2.951247
 log_heapriv |   3.086501   1.238905     2.81   0.005     1.405396
6.778509
```

```
    log_rand |   1.032388   .3032249     0.11   0.914     .5805431
1.835909
       _cons |   13.22316   15.65567     2.18   0.029     1.298818
134.6239
-------------+----------------------------------------------------------------
---
    /lnalpha |  -.1598321   .2153452                     -.5819009
.2622367
-------------+----------------------------------------------------------------
---
       alpha |   .8522869   .1835359                      .5588351
1.299834
------------------------------------------------------------------------------
---
Likelihood-ratio test of alpha=0: chibar2(01)= 764.72 Prob>=chibar2 = 0.000
```

Test 3: Bayesian Information Criterion (BIC), based on log likelihood was used as a measure of how well our different models fitted the data. A lower value on BIC indicates a better fit of the model

Result: As shown below, BIC was significant to reveal that the negative binomial regression provided a good fit to the data than Poisson model, as indicated by lower BIC.

Tests and Fit Statistics

	Current	Saved	Difference
Model:	nbreg	poisson	
N:	41	41	0
Log-Lik Intercept Only	-186.209	-1222.706	1036.497
Log-Lik Full Model	-173.104	-555.464	382.360
LR	26.210(5)	1334.485(5)	
1308.274(0)			
Prob > LR	0.000	0.000	.
BIC	219.946	980.952	-761.006
BIC used by Stata	372.203	1133.209	-761.006

PRM	BIC=	980.952	AIC=	27.388	Prefer	Over	Evidence
vs NBRM	BIC=	219.946	dif=	761.006	NBRM	PRM	Very strong
	AIC=	8.786	dif=	18.603	NBRM	PRM	
	LRX2=	764.719	prob=	0.000	NBRM	PRM	p=0.000
NBRM	BIC=	219.946	AIC=	8.786	Prefer	Over	Evidence

Appendix 2: Search strategy for identification of eligible reviews (Chapter 5)

Health Systems Evidence:	
Priority health system topics	Governance arrangement OR Financial arrangement OR Delivery arrangement OR Implementation strategy
Open search	immunization (search title and abstract fields) OR immunisation (search title and abstract fields) OR vaccination (search title and abstract fields)
Type of documents	Systematic review OR policy brief OR systematic review protocol
Limits	None
Search output	27 records
Cochrane Database of Systematic Reviews:	
Search all text	("Immunization"[Mesh] OR "Vaccination"[Mesh] OR "Immunization Programs"[Mesh])
Limits	None
Search output	338 records
Database of Abstracts of Reviews of Effectiveness:	
Search all text	(“Immunization”[Mesh] OR “Vaccination”[Mesh] OR “Immunization Programs”[Mesh])
Search output	160 records
Limits	None
PubMed:	
Search terms	("Immunization"[Mesh] OR "Vaccination"[Mesh] OR "Immunization Programs"[Mesh])
Publication date	01 January 2000 to 31 March 2012
Article type	Systematic reviews
Search output	844 records

Appendix 3: Search strategy for randomised controlled trials (Chapter 5)

MEDLINE (Ovid)

1. Immunization/
2. Immunization Schedule/
3. Immunization, Secondary/
4. Immunotherapy, Active/
5. Mass Immunization/
6. Immunization Programs/
7. Vaccination/
8. (vaccinat$ or revaccinat$ or immunization or immunisation or immunotherapy).tw.
9. or/1-8
10. Tetanus Toxoid/
11. Diphtheria Toxoid/
12. Diphtheria-Tetanus-Acellular Pertussis Vaccines/
13. Diphtheria-Tetanus-Pertussis Vaccine/
14. Diphtheria-Tetanus Vaccine/
15. Pertussis Vaccine/
16. Measles-Mumps-Rubella Vaccine/
17. Measles Vaccine/
18. Mumps Vaccine/
19. Rubella Vaccine/
20. Poliovirus Vaccines/
21. Poliovirus Vaccine, Inactivated/
22. Poliovirus Vaccine, Oral/
23. Tuberculosis Vaccines/
24. BCG Vaccine/
25. Viral Hepatitis Vaccines/
26. Hepatitis B Vaccines/
27. Haemophilus Vaccines/
28. ((tetanus or diphtheria) adj toxoid).tw.
29. ((tetanus or diphtheria? or pertussis or whooping cough or measles or mumps or rubella? or rubeola or mmr or polio$ or tuberculosis or tuberculoses or bcg or calmette$ or hepatitis b or haemophilus or triple) adj vaccine?).tw.
30. or/10-29
31. Tetanus/
32. Diphtheria/
33. Measles/
34. Mumps/
35. Rubella/
36. Whooping Cough/
37. Poliomyelitis/
38. Poliomyelitis, Bulbar/
39. Tuberculosis/
40. Tuberculosis, Pulmonary/

41. Mycobacterium Tuberculosis/
42. Hepatitis B/
43. Hepatitis B, Chronic/
44. Haemophilus Influenzae/
45. Haemophilus Influenzae Type B/
46. (tetanus or diphtheria? or measles or rubella? or rubeola or mumps or epidemic parotit$ or pertussis or whooping cough or polio$ or infantile paralysis or tuberculosis or tuberculoses or hepatitis b or haemophilus influenza?).tw.
47. or/31-46
48. exp Child/
49. exp Infant/
50. exp Child Care/
51. (child$ or infant? or newborn? or neonat$ or baby or babies or kid? or toddler?).tw.
52. or/48-51
53. 9 and (Tetanus/ or tetanus.tw.)
54. Tetanus Toxoid/ or (tetanus toxoid or tetanus vaccine? or tetanus prophylaxis).tw.
55. 53 or 54
56. Mothers/
57. Women/
58. Pregnant Women/
59. Female/
60. (woman or women or mother? or female?).tw.
61. or/56-60
62. 55 and 61
63. Developing Countries.sh,kf.
64. (Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America).hw,kf,ti,ab,cp.
65. (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brazil or Brasil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or

Kirghiz or Kirgizstan or Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia).hw,kf,ti,ab,cp.
66. ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti,ab.
67. ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti,ab.
68. (low* adj (gdp or gnp or gross domestic or gross national)).ti,ab.
69. (low adj3 middle adj3 countr*).ti,ab.
70. (lmic or lmics or third world or lami countr*).ti,ab.
71. transitional countr*.ti,ab.
72. or/63-71
73. randomized controlled trial.pt.
74. controlled clinical trial.pt.
75. multicenter study.pt.
76. (randomis* or randomiz* or randomly allocat* or random allocat*).ti,ab.
77. groups.ab.
78. (trial or multicenter or multi center or multicentre or multi centre).ti.
79. (intervention* or controlled or control group or compare or compared or (before adj5 after) or (pre adj5 post) or pretest or pre test or posttest or post test or quasiexperiment* or quasi experiment* or evaluat* or effect or impact or time series or time point? or repeated measur*).ti,ab.
80. or/73-79
81. exp Animals/
82. Humans/
83. 81 not (81 and 82)

84. review.pt.
85. meta analysis.pt.
86. news.pt.
87. comment.pt.
88. editorial.pt.
89. cochrane database of systematic reviews.jn.
90. comment on.cm.
91. (systematic review or literature review).ti.
92. or/83-91
93. 80 not 92
94. 9 and 47 and 52 and 72 and 93
95. 30 and 52 and 72 and 93
96. 62 and 72 and 93
97. 94 or 95 or 96

EMBASE (Ovid)
1. Immunization/
2. Active Immunization/
3. Mass Immunization/
4. Vaccination/
5. Revaccination/
6. (vaccinat$ or revaccinat$ or immunization or immunisation or immunotherapy).tw.
7. or/1-6
8. Tetanus Prophylaxis/
9. BCG Vaccination/
10. Measles Vaccination/
11. or/8-10
12. Tetanus Toxoid/
13. Diphtheria Toxoid/
14. Diphtheria Toxoid crm197/
15. Diphtheria Tetanus Toxoid/
16. BCG Vaccine/
17. Diphtheria Pertussis Poliomyelitis Tetanus Haemophilus Influenzae Type B Hepatitis B Vaccine/
18. Diphtheria Pertussis Poliomyelitis Tetanus Vaccine/
19. Diphtheria Pertussis Tetanus Haemophilus Influenzae Type B Hepatitis B Vaccine/
20. Diphtheria Pertussis Tetanus Haemophilus Influenzae Type B Vaccine/
21. Diphtheria Pertussis Tetanus Vaccine/
22. Diphtheria Poliomyelitis Tetanus Vaccine/
23. Diphtheria Tetanus Vaccine/
24. Diphtheria Vaccine/
25. Haemophilus Influenzae Type B Hepatitis B Vaccine/
26. Haemophilus Influenzae Type B Vaccine/
27. Haemophilus Influenzae Vaccine/

28. Haemophilus Vaccine/
29. Pertussis Vaccine/
30. Triple Vaccine/
31. Hepatitis a Hepatitis B Vaccine/
32. Hepatitis B Vaccine/
33. Hepatitis Vaccine/
34. Recombinant Hepatitis B Vaccine/
35. Measles Mumps Rubella Vaccine/
36. Measles Mumps Vaccine/
37. Measles Rubella Vaccine/
38. Measles Vaccine/
39. Mumps Vaccine/
40. Rubella Vaccine/
41. Chickenpox Measles Mumps Rubella Vaccine/
42. Poliomyelitis Vaccine/
43. Oral Poliomyelitis Vaccine/
44. ((tetanus or diphtheria) adj toxoid).tw.
45. ((tetanus or diphtheria? or pertussis or whooping cough or measles or mumps or rubella? or rubeola or mmr or polio$ or tuberculosis or tuberculoses or bcg or calmette$ or hepatitis b or haemophilus or triple) adj vaccine?).tw.
46. or/12-45
47. Tetanus/
48. Diphtheria/
49. Measles/
50. Mumps/
51. Rubella/
52. Pertussis/
53. Poliomyelitis/
54. Tuberculosis/
55. Lung Tuberculosis/
56. Mycobacterium Tuberculosis/
57. Hepatitis B/
58. Chronic Hepatitis/
59. Haemophilus Influenzae/
60. Haemophilus Influenzae Type B/
61. (tetanus or diphtheria? or measles or rubella? or rubeola or mumps or epidemic parotit$ or pertussis or whooping cough or polio$ or infantile paralysis or tuberculosis or tuberculoses or hepatitis b or haemophilus influenza?).tw.
62. or/47-61
63. exp Child/
64. exp Newborn/
65. Child Care/
66. (child$ or infant? or newborn? or neonat$ or baby or babies or kid? or toddler?).tw.
67. or/63-66
68. 7 and (Tetanus/ or tetanus.tw.)

69. Tetanus Toxoid/ or Tetanus Prophylaxis/ or (tetanus toxoid or tetanus vaccin$ or tetanus prophylaxis).tw.
70. or/68-69
71. exp Mother/
72. Female/
73. (woman or women or mother? or female?).tw.
74. or/71-73
75. 70 and 74
76. Developing Country.sh.
77. (Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America).hw,ti,ab,cp.
78. (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brazil or Brasil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese

Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia).hw,ti,ab,cp.
79. ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti,ab.
80. ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti,ab.
81. (low* adj (gdp or gnp or gross domestic or gross national)).ti,ab.
82. (low adj3 middle adj3 countr*).ti,ab.
83. (lmic or lmics or third world or lami countr*).ti,ab.
84. transitional countr*.ti,ab.
85. or/76-84
86. Randomized Controlled Trial/
87. Controlled Clinical Trial/
88. Quasi Experimental Study/
89. Pretest Posttest Control Group Design/
90. Time Series Analysis/
91. Experimental Design/
92. Multicenter Study/
93. (randomis* or randomiz* or randomly or random allocat*).ti,ab.
94. groups.ab.
95. (trial or multicentre or multicenter or multi centre or multi center).ti.
96. (intervention* or controlled or control group or compare or compared or (before adj5 after) or (pre adj5 post) or pretest or pre test or posttest or post test or quasiexperiment* or quasi experiment* or evaluat* or effect or impact or time series or time point? or repeated measur*).ti,ab.
97. or/86-96
98. (systematic review or literature review).ti.
99. "cochrane database of systematic reviews".jn.
100. Nonhuman/
101. or/98-100
102. 97 not 101
103. 7 and 62 and 67 and 85 and 102
104. 11 and 67 and 85 and 102
105. 46 and 67 and 85 and 102
106. 103 or 104 or 105

CENTRAL

#1 MeSH descriptor Immunization, this term only

#2 MeSH descriptor Immunization Schedule, this term only

#3 MeSH descriptor Immunization, Secondary, this term only

#4 MeSH descriptor Immunotherapy, Active, this term only

#5 MeSH descriptor Mass Immunization, this term only

#6 MeSH descriptor Immunization Programs, this term only

#7 MeSH descriptor Vaccination, this term only

#8 (vaccinat* or revaccinat* or immunization or immunisation or immunotherapy):ti,ab

#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)

#10 MeSH descriptor Tetanus Toxoid, this term only

#11 MeSH descriptor Diphtheria Toxoid, this term only

#12 MeSH descriptor Diphtheria-Tetanus-acellular Pertussis Vaccines, this term only

#13 MeSH descriptor Diphtheria-Tetanus-Pertussis Vaccine, this term only

#14 MeSH descriptor Diphtheria-Tetanus Vaccine, this term only

#15 MeSH descriptor Pertussis Vaccine, this term only

#16 MeSH descriptor Measles-Mumps-Rubella Vaccine, this term only

#17 MeSH descriptor Measles Vaccine, this term only

#18 MeSH descriptor Mumps Vaccine, this term only

#19 MeSH descriptor Rubella Vaccine, this term only

#20 MeSH descriptor Poliovirus Vaccines, this term only

#21 MeSH descriptor Poliovirus Vaccine, Inactivated, this term only

#22 MeSH descriptor Poliovirus Vaccine, Oral, this term only

#23 MeSH descriptor Tuberculosis Vaccines, this term only

#24 MeSH descriptor BCG Vaccine, this term only

#25 MeSH descriptor Viral Hepatitis Vaccines, this term only

#26 MeSH descriptor Hepatitis B Vaccines, this term only

#27 MeSH descriptor Haemophilus Vaccines, this term only

#28 (tetanus NEXT toxoid or diphtheria NEXT toxoid):ti,ab

#29 (tetanus NEXT vaccine* or diphtheria* NEXT vaccine* or pertussis NEXT vaccine* or whooping NEXT cough NEXT vaccine* or measles NEXT vaccine* or mumps NEXT vaccine* or rubella* NEXT vaccine* or rubeola NEXT vaccine* or mmr NEXT vaccine* or polio* NEXT vaccine* or tuberculosis

NEXT vaccine* or tuberculoses NEXT vaccine* or bcg NEXT vaccine* or calmette* NEXT vaccine* or hepatitis NEXT b NEXT vaccine* or haemophilus NEXT vaccine* or triple NEXT vaccine*):ti,ab

#30 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)

#31 MeSH descriptor Tetanus, this term only

#32 MeSH descriptor Diphtheria, this term only

#33 MeSH descriptor Measles, this term only

#34 MeSH descriptor Mumps, this term only

#35 MeSH descriptor Rubella, this term only

#36 MeSH descriptor Whooping Cough, this term only

#37 MeSH descriptor Poliomyelitis, this term only

#38 MeSH descriptor Poliomyelitis, Bulbar, this term only

#39 MeSH descriptor Tuberculosis, this term only

#40 MeSH descriptor Tuberculosis, Pulmonary, this term only

#41 MeSH descriptor Mycobacterium tuberculosis, this term only

#42 MeSH descriptor Hepatitis B, this term only

#43 MeSH descriptor Hepatitis B, Chronic, this term only

#44 MeSH descriptor Haemophilus influenzae, this term only

#45 MeSH descriptor Haemophilus influenzae type b, this term only

#46 (tetanus or diphtheria* or measles or rubella* or rubeola or mumps or epidemic NEXT parotit* or pertussis or whooping NEXT cough or polio* or infantile NEXT paralysis or tuberculosis or tuberculoses or hepatitis NEXT b or haemophilus NEXT influenza*):ti,ab

#47 (#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46)

#48 MeSH descriptor Child explode all trees

#49 MeSH descriptor Infant explode all trees

#50 MeSH descriptor Child Care explode all trees

#51 (child* or infant* or newborn* or neonat* or baby or babies or kid or kids or toddler*):ti,ab

#52 (#48 OR #49 OR #50 OR #51)

#53 MeSH descriptor Tetanus, this term only

#54 tetanus:ti,ab

#55 MeSH descriptor Tetanus Toxoid, this term only

#56 (tetanus NEXT toxoid or tetanus NEXT vaccine* or tetanus NEXT prophylaxis):ti,ab

#57 (#9 AND (#53 OR #54))

#58 (#55 OR #56)

#59 (#57 OR #58)

#60 MeSH descriptor Mothers, this term only

#61 MeSH descriptor Women, this term only

#62 MeSH descriptor Pregnant Women, this term only

#63 (woman or women or mother or mothers or female*):ti,ab

#64 (#60 OR #61 OR #62 OR #63)

#65 (#59 AND #64)

#66 (Africa or Asia or Caribbean or "West Indies" or "South America" or "Latin America" or "Central America"):ti,ab,kw

#67 (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brazil or Brasil or Bulgaria or "Burkina Faso" or "Burkina Fasso" or "Upper Volta" or Burundi or Urundi or Cambodia or "Khmer Republic" or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or "Cape Verde" or "Central African Republic" or Chad or Chile or China or Colombia or Comoros or "Comoro Islands" or Comores or Mayotte or Congo or Zaire or "Costa Rica" or "Cote d'Ivoire" or "Ivory Coast" or Croatia or Cuba or Cyprus or Czechoslovakia or "Czech Republic" or Slovakia or "Slovak Republic"):ti,ab,kw

#68 (Djibouti or "French Somaliland" or Dominica or "Dominican Republic" or "East Timor" or "East Timur" or "Timor Leste" or Ecuador or Egypt or "United Arab Republic" or "El Salvador" or Eritrea or Estonia or Ethiopia or Fiji or Gabon or "Gabonese Republic" or Gambia or Gaza or Georgia or Georgian or Ghana or "Gold Coast" or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or "Isle of Man" or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or "Kyrgyz Republic" or Kirghiz or Kirgizstan or "Lao PDR" or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania):ti,ab,kw

#69 (Macedonia or Madagascar or "Malagasy Republic" or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or "Marshall Islands" or Mauritania or Mauritius or "Agalega Islands" or Mexico or Micronesia or "Middle East" or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or "Netherlands Antilles" or "New Caledonia" or Nicaragua or Niger or Nigeria or "Northern Mariana Islands" or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or "Puerto Rico"):ti,ab,kw

#70 (Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or "Saint Kitts" or "St Kitts" or Nevis or "Saint Lucia" or "St Lucia" or "Saint Vincent" or "St Vincent" or Grenadines or Samoa or "Samoan Islands" or "Navigator Island" or "Navigator Islands" or "Sao Tome" or "Saudi Arabia" or Senegal or Serbia or Montenegro or Seychelles or "Sierra Leone" or Slovenia or "Sri Lanka" or Ceylon or "Solomon Islands" or Somalia or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or "Togolese Republic" or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or "Soviet Union" or "Union of Soviet Socialist Republics" or Uzbekistan or Uzbek or Vanuatu or

"New Hebrides" or Venezuela or Vietnam or "Viet Nam" or "West Bank" or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia):ti,ab,kw

#71 (developing or less* NEXT developed or "under developed" or underdeveloped or "middle income" or low* NEXT income or underserved or "under served" or deprived or poor*) NEXT (countr* or nation* or population* or world):ti,ab,kw

#72 (developing or less* NEXT developed or "under developed" or underdeveloped or "middle income" or low* NEXT income) NEXT (economy or economies):ti,ab,kw

#73 low* NEXT (gdp or gnp or "gross domestic" or "gross national"):ti,ab,kw

#74 (low NEAR/3 middle NEAR/3 countr*):ti,ab,kw

#75 (lmic or lmics or "third world" or "lami country" or "lami countries"):ti,ab,kw

#76 ("transitional country" or "transitional countries"):ti,ab,kw

#77 (#66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76)

#78 (#9 AND #47 AND #52 AND #77)

#79 (#30 AND #52 AND #77)

#80 (#65 AND #77)

#81 (#78 OR #79 OR #80)

CINAHL

#	Query
S95	S91 or S93 Exclude MEDLINE records
S94	S91 or S93
S93	S58 and S76 and S90
S92	S24 and S43 and S76 and S90
S91	S6 and S39 and S43 and S76 and S90
S90	S77 or S78 or S79 or S80 or S81 or S82 or S83 or S84 or S85 or S86 or S87 or S88 or S89

S89	TI ((intervention* or controlled or control W0 group* or compare or compared or before N5 after or pre N5 post or pretest or "pre test" or posttest or "post test" or quasiexperiment* or quasi W0 experiment* or evaluat* or effect or impact or "time series" or time W0 point* or repeated W0 measur*)) OR AB ((intervention* or controlled or control W0 group* or compare or compared or before N5 after or pre N5 post or pretest or "pre test" or posttest or "post test" or quasiexperiment* or quasi W0 experiment* or evaluat* or effect or impact or "time series" or time W0 point* or repeated W0 measur*))
S88	TI (randomis* or randomiz* or random* W0 allocat*) OR AB (randomis* or randomiz* or random* W0 allocat*)
S87	(MH "Health Services Research")
S86	(MH "Multicenter Studies")
S85	(MH "Quasi-Experimental Studies+")
S84	(MH "Pretest-Posttest Design+")
S83	(MH "Experimental Studies")
S82	(MH "Nonrandomized Trials")
S81	(MH "Intervention Trials")
S80	(MH "Clinical Trials")
S79	(MH "Randomized Controlled Trials")
S78	PT research
S77	PT clinical trial
S76	S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74 or S75
S75	TI transitional W0 countr* OR AB transitional W0 countr*
S74	TI (lmic or lmics or third W0 world or lami W0 countr*) OR AB (lmic or lmics or third W0 world or lami W0 countr*)

S73	TI low N3 middle N3 countr* OR AB low N3 middle N3 countr*
S72	TI (low* W0 (gdp or gnp or gross W0 domestic or gross W0 national)) OR AB (low* W0 (gdp or gnp or gross W0 domestic or gross W0 national))
S71	TI ((developing or less* W0 developed or under W0 developed or underdeveloped or middle W0 income or low* W0 income) W0 (economy or economies)) OR AB ((developing or less* W0 developed or under W0 developed or underdeveloped or middle W0 income or low* W0 income) W0 (economy or economies))
S70	TI ((developing or less* W0 developed or under W0 developed or underdeveloped or middle W0 income or low* W0 income or underserved or under W0 served or deprived or poor*) W0 (countr* or nation or nations or population* or world or area or areas)) OR AB ((developing or less* W0 developed or under W0 developed or underdeveloped or middle W0 income or low* W0 income or underserved or under W0 served or deprived or poor*) W0 (countr* or nation or nations or population* or world or area or areas))
S69	MW (Afghanistan or Bangladesh or Benin or "Burkina Faso" or Burundi or Cambodia or "Central African Republic" or Chad or Comoros or Congo or "Cote d'Ivoire" or Eritrea or Ethiopia or Gambia or Ghana or Guinea or Haiti or India or Kenya or Korea or Kyrgyz or Kyrgyzstan or Lao or Laos or Liberia or Madagascar or Malawi or Mali or Mauritania or Melanesia or Mongolia or Mozambique or Burma or Myanmar or Nepal or Niger or Nigeria or Pakistan or Rwanda or "Salomon Islands" or "Sao Tome" or Senegal or "Sierra Leone" or Somalia or Sudan or Tajikistan or Tanzania or Timor or Togo or Uganda or Uzbekistan or Vietnam or "Viet Nam" or Yemen or Zambia or Zimbabwe) or TI (Afghanistan or Bangladesh or Benin or "Burkina Faso" or Burundi or Cambodia or "Central African Republic" or Chad or Comoros or Congo or "Cote d'Ivoire" or Eritrea or Ethiopia or Gambia or Ghana or Guinea or Haiti or India or Kenya or Korea or Kyrgyz or Kyrgyzstan or Lao or Laos or Liberia or Madagascar or Malawi or Mali or Mauritania or Melanesia or Mongolia or Mozambique or

	Burma or Myanmar or Nepal or Niger or Nigeria or Pakistan or Rwanda or "Salomon Islands" or "Sao Tome" or Senegal or "Sierra Leone" or Somalia or Sudan or Tajikistan or Tanzania or Timor or Togo or Uganda or Uzbekistan or Vietnam or "Viet Nam" or Yemen or Zambia or Zimbabwe) or AB (Afghanistan or Bangladesh or Benin or "Burkina Faso" or Burundi or Cambodia or "Central African Republic" or Chad or Comoros or Congo or "Cote d'Ivoire" or Eritrea or Ethiopia or Gambia or Ghana or Guinea or Haiti or India or Kenya or Korea or Kyrgyz or Kyrgyzstan or Lao or Laos or Liberia or Madagascar or Malawi or Mali or Mauritania or Melanesia or Mongolia or Mozambique or Burma or Myanmar or Nepal or Niger or Nigeria or Pakistan or Rwanda or "Salomon Islands" or "Sao Tome" or Senegal or "Sierra Leone" or Somalia or Sudan or Tajikistan or Tanzania or Timor or Togo or Uganda or Uzbekistan or Vietnam or "Viet Nam" or Yemen or Zambia or Zimbabwe)
S68	MW (Albania or Algeria or Angola or Armenia or Azerbaijan or Belarus or Bhutan or Bolivia or Bosnia or Herzegovina or "Cape Verde" or Cameroon or China or Colombia or Congo or Cuba or Djibouti or "Dominican Republic" or Ecuador or Egypt or "El Salvador" or Fiji or Gaza or Georgia or Guam or Guatemala or Guyana or Honduras or "Indian Ocean Islands" or Indonesia or Iran or Iraq or Jamaica or Jordan or Kiribati or Lesotho or Macedonia or Maldives or "Marshall Islands" or Micronesia or "Middle East" or Moldova or Morocco or Namibia or Nicaragua or Palestin* or Paraguay or Peru or Philippines or Samoa or "Sri Lanka" or Suriname or Swaziland or Syria or "Syrian Arab Republic" or Thailand or Tonga or Tunisia or Turkmenistan or Ukraine or Vanuatu or "West Bank") or TI (Albania or Algeria or Angola or Armenia or Azerbaijan or Belarus or Bhutan or Bolivia or Bosnia or Herzegovina or "Cape Verde" or Cameroon or China or Colombia or Congo or Cuba or Djibouti or "Dominican Republic" or Ecuador or Egypt or "El Salvador" or Fiji or Gaza or Georgia or Guam or Guatemala or Guyana or Honduras or "Indian Ocean Islands" or Indonesia or Iran or Iraq or Jamaica or Jordan or Kiribati or Lesotho or Macedonia or Maldives or "Marshall Islands" or Micronesia or

	"Middle East" or Moldova or Morocco or Namibia or Nicaragua or Palestin* or Paraguay or Peru or Philippines or Samoa or "Sri Lanka" or Suriname or Swaziland or Syria or "Syrian Arab Republic" or Thailand or Tonga or Tunisia or Turkmenistan or Ukraine or Vanuatu or "West Bank") or AB (Albania or Algeria or Angola or Armenia or Azerbaijan or Belarus or Bhutan or Bolivia or Bosnia or Herzegovina or "Cape Verde" or Cameroon or China or Colombia or Congo or Cuba or Djibouti or "Dominican Republic" or Ecuador or Egypt or "El Salvador" or Fiji or Gaza or Georgia or Guam or Guatemala or Guyana or Honduras or "Indian Ocean Islands" or Indonesia or Iran or Iraq or Jamaica or Jordan or Kiribati or Lesotho or Macedonia or Maldives or "Marshall Islands" or Micronesia or "Middle East" or Moldova or Morocco or Namibia or Nicaragua or Palestin* or Paraguay or Peru or Philippines or Samoa or "Sri Lanka" or Suriname or Swaziland or Syria or "Syrian Arab Republic" or Thailand or Tonga or Tunisia or Turkmenistan or Ukraine or Vanuatu or "West Bank")
S67	MW ("American Samoa" or Argentina or Belize or Botswana or Brazil or Brasil or Bulgaria or Chile or Comoros or "Costa Rica" or Croatia or Dominica or Guinea or Gabon or Grenada or Grenadines or Hungary or Kazakhstan or Latvia or Lebanon or Libia or libyan or Libya or Lithuania or Malaysia or Mauritius or Mayotte or Mexico or Micronesia or Montenegro or Nevis or "Northern Mariana Islands" or Oman or Palau or Panama or Poland or Romania or Russia or "Russian Federation" or Samoa or "Saint Lucia" or "St Lucia" or "Saint Kitts" or "St Kitts" or "Saint Vincent" or "St Vincent" or Serbia or Seychelles or Slovakia or "Slovak Republic" or "South Africa" or Turkey or Uruguay or Venezuela or Yugoslavia) or TI ("American Samoa" or Argentina or Belize or Botswana or Brazil or Bulgaria or Chile or Comoros or "Costa Rica" or Croatia or Dominica or Guinea or Gabon or Grenada or Grenadines or Hungary or Kazakhstan or Latvia or Lebanon or Libia or libyan or Libya or Lithuania or Malaysia or Mauritius or Mayotte or Mexico or Micronesia or Montenegro or Nevis or "Northern Mariana Islands" or Oman or Palau or Panama or Poland or Romania or Russia or "Russian Federation" or Samoa or "Saint Lucia" or "St

	Lucia" or "Saint Kitts" or "St Kitts" or "Saint Vincent" or "St Vincent" or Serbia or Seychelles or Slovakia or "Slovak Republic" or "South Africa" or Turkey or Uruguay or Venezuela or Yugoslavia) or AB ("American Samoa" or Argentina or Belize or Botswana or Brazil or Bulgaria or Chile or Comoros or "Costa Rica" or Croatia or Dominica or Guinea or Gabon or Grenada or Grenadines or Hungary or Kazakhstan or Latvia or Lebanon or Libia or libyan or Libya or Lithuania or Malaysia or Mauritius or Mayotte or Mexico or Micronesia or Montenegro or Nevis or "Northern Mariana Islands" or Oman or Palau or Panama or Poland or Romania or Russia or "Russian Federation" or Samoa or "Saint Lucia" or "St Lucia" or "Saint Kitts" or "St Kitts" or "Saint Vincent" or "St Vincent" or Serbia or Seychelles or Slovakia or "Slovak Republic" or "South Africa" or Turkey or Uruguay or Venezuela or Yugoslavia)
S66	TI (Africa or Asia or "South America" or "Latin America" or "Central America") or AB (Africa or Asia or "South America" or "Latin America" or "Central America")
S65	(MH "Asia+")
S64	(MH "West Indies+")
S63	(MH "South America+")
S62	(MH "Latin America")
S61	(MH "Central America+")
S60	(MH "Africa+")
S59	(MH "Developing Countries")
S58	S51 and S57
S57	S52 or S53 or S54 or S55 or S56
S56	TI (woman or women or mother* or female*) or AB (woman or women or mother* or female*)
S55	(MH "Female")

S54	(MH "Expectant Mothers")
S53	(MH "Women")
S52	(MH "Mothers")
S51	S47 or S50
S50	S48 or S49
S49	TI ("tetanus toxoid" or "tetanus vaccine" or "tetanus vaccines" or "tetanus prophylaxis") or AB ("tetanus toxoid" or "tetanus vaccine" or "tetanus vaccines" or "tetanus prophylaxis")
S48	(MH "Tetanus Toxoid")
S47	S6 and S46
S46	S44 or S45
S45	TI tetanus or AB tetanus
S44	(MH "Tetanus")
S43	S40 or S41 or S42
S42	TI (child* or infant* or newborn* or neonat* or baby or babies or kid or kids or toddler*) or AB (child* or infant* or newborn* or neonat* or baby or babies or kid or kids or toddler*)
S41	(MH "Child Care+")
S40	(MH "Child+")
S39	S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38
S38	TI (tetanus or diphtheria* or measles or rubella* or rubeola or mumps or epidemic W1 parotid* or pertussis or "whooping cough" or polio* or "infantile paralysis" or tuberculosis or tuberculoses or "hepatitis b" or "haemophilus influenza" or "haemophilus influenzae" or "haemophilus flue") or AB (tetanus or diphtheria* or measles or rubella* or rubeola or mumps or epidemic W1 parotid*

	or pertussis or "whooping cough" or polio* or "infantile paralysis" or tuberculosis or tuberculoses or "hepatitis b" or "haemophilus influenza" or "haemophilus influenzae" or "haemophilus flue")
S37	(MH "Haemophilus Influenzae")
S36	(MH "Hepatitis B, Chronic")
S35	(MH "Hepatitis B")
S34	(MH "Mycobacterium Tuberculosis")
S33	(MH "Tuberculosis, Pulmonary")
S32	(MH "Tuberculosis")
S31	(MH "Poliomyelitis")
S30	(MH "Whooping Cough")
S29	(MH "Rubella")
S28	(MH "Mumps")
S27	(MH "Measles")
S26	(MH "Diphtheria")
S25	(MH "Tetanus")
S24	S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23
S23	TI (tetanus W1 vaccine* or diphtheria* W1 vaccine* or pertussis W1 vaccine* or "whooping cough" W1 vaccine* or measles W1 vaccine* or mumps W1 vaccine* or rubella* W1 vaccine* or rubeola W1 vaccine* or mmr W1 vaccine* or polio* W1 vaccine* or tuberculosis W1 vaccine* or tuberculoses W1 vaccine* or bcg W1 vaccine* or calmette* W1 vaccine* or "hepatitis b" W1 vaccine* or haemophilus W1 vaccine* or hib W1 vaccine* or triple W1 vaccine*) or AB (tetanus W1 vaccine* or diphtheria* W1 vaccine* or pertussis W1 vaccine* or "whooping cough" W1 vaccine* or measles W1 vaccine* or mumps W1 vaccine*

	or rubella* W1 vaccine* or rubeola W1 vaccine* or mmr W1 vaccine* or polio* W1 vaccine* or tuberculosis W1 vaccine* or tuberculoses W1 vaccine* or bcg W1 vaccine* or calmette* W1 vaccine* or "hepatitis b" W1 vaccine* or haemophilus W1 vaccine* or hib W1 vaccine* or triple W1 vaccine*)
S22	TI ("tetanus toxoid" or "diphtheria toxoid") or AB ("tetanus toxoid" or "diphtheria toxoid")
S21	(MH "HIB Vaccine")
S20	(MH "Hepatitis B Vaccines")
S19	(MH "Viral Hepatitis Vaccines")
S18	(MH "BCG Vaccine")
S17	(MH "Poliovirus Vaccine")
S16	(MH "Rubella Vaccine")
S15	(MH "Mumps Vaccine")
S14	(MH "Measles Vaccine")
S13	(MH "Measles-Mumps-Rubella Vaccine")
S12	(MH "Pertussis Vaccine")
S11	(MH "Diphtheria-Tetanus Vaccine")
S10	(MH "Diphtheria-Tetanus-Pertussis Vaccine")
S9	(MH "Diphtheria-Tetanus-acellular Pertussis Vaccines")
S8	(MH "Diphtheria Toxoid")
S7	(MH "Tetanus Toxoid")
S6	S1 or S2 or S3 or S4 or S5
S5	TI ((vaccinat* or revaccinate* or immunization or immunisation or immunotherapy)) or AB ((vaccinat* or revaccinate* or immunization or immunisation or immunotherapy))

S4	(MH "Immunization Programs")
S3	(MH "Immunotherapy")
S2	(MH "Immunization Schedule")
S1	(MH "Immunization")

Sociological Abstracts (ProQuest)

ALL(vaccination or vaccine or vaccines or immunization)

AND

ALL(child* or infant* or newborn or neonat* or baby or babies or kid or kids or toddler* or mother* or woman or women or female)

LILACS (VHL)

(immunization or inmunizacion or imunizacao or vaccination or vacunacion or vacinacao or vaccine or vaccines or vacuna or vacunas or vacina or vacinas) AND (tetanus or tetanico or diphtheria or difterico or pertussis or "whooping cough" or tosferina or "tos ferina" or "tos convulsa" or "tosse convulsa" or coqueluche or measles or sarampion or sarampo or mumps or paperas or caxumba or rubella or rubeola or mmr or polio* or tubercul* or "mycobacterium bovis" or bcg or calmette* or hepatitis or hepatite or haemophilus) AND (child or children or infant or infants or newborn or neonat* or baby or babies or kid or kids or toddler* or nino or ninos or crianca or criancas or lactante* or lactente* or "recien nacido" or "recien nacidos" or "recem nascido" or "recem nascidos") AND (randomi* or randomly or azar or acaso or control* or intervention* or evaluat* or effect* or impact or impacts or intervencion* or intervencao* or evaluar or evaluacion or avaliacao or efecto or efectos or efeito or efeitos or impacto or impactos or "serie de tiempo" or "series de tiempo" or "serie de tempo" or "series de tempo" or "serie temporal" or "series temporal" or "serie temporales" or "series temporales" or "serie temporais" or "series temporais" or "puntos de tiempo" or "pontos de tiempo" or "puntos de tempo" or "puntos de tempo" or "puntos temporales" or "pontos temporales" or "punto temporais" or "ponto temporais" or "medida repetida" or "medida repetidas" or "medidas repetida" or

"medidas repetidas" or "medicion repetida" or "medicion repetidas" or "mediciones repetida" or "mediciones repetidas")