PHARMACEUTICAL POLICIES AND ACCESS TO MEDICINES: A HOSPITAL-PHARMACY PERSPECTIVE FROM GHANA

Daniel Nii Amoo Ankrah

PHARMACEUTICAL POLICIES AND ACCESS TO MEDICINES: A HOSPITAL-PHARMACY PERSPECTIVE FROM GHANA

Medicatiebeleid en toegang tot geneesmiddelen:
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Daniel Nii Amoo Ankrah
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“IF I HAVE SEEN FURTHER,
IT IS BY STANDING ON THE SHOULDERS OF GIANTS”

Sir Isaac Newton (1676)

Chapter 1

INTRODUCTION

INTRODUCTION

Over the last sixty years (post-colonial era), access to medicines in Ghana has gone through a series of transitions. Just after independence, Ghanaians enjoyed a free health care system totally sponsored by the state. This was followed in the early seventies by a user fee system where a "token fee" was paid for limited services including drugs [1]. However, the most memorable period was in 1985 when, with the influence of the World Bank and the International Monetary Fund under the economic recovery program, a legislative instrument (LI) was enacted. Popularly referred to in Ghana as the LI 1313, it led to the introduction of "fee for service" [2] with a target of full cost recovery for health service in all public sector health institutions. In 1990 when the concept of "Cash and carry" under LI 1313 was fully enforced, this led to a sharp drop of about 25% in clinic attendance [2] in addition to perennial shortage of medicines in most government hospitals. The status-quo remained until in 2003 Ghana established a National Health Insurance Scheme (NHIS) under the umbrella of universal health coverage (UHC) [3] to improve access to health care. Under the NHIS all registered members with active registration received drugs covered by the Scheme for free. The NHIS does not allow any form of co-payment. This has increased access to and utilization of medicines by removing cost barriers, albeit a few existing challenges [3]. Ghana also has in place a National Drugs Policy (GNDP) with an aim to ensure access and equity to medicines [4]. The GNDP publishes and periodically updates the Essential Medicines List (EML) and the Standard Treatment Guidelines (STG). These are the main documents adopted and used by all health facilities in the country. Ghana was also among the seven countries chosen by the Medicines Transparency Alliance (MeTA), an initiative for access to medicines, transparency and good medicine governance [5]. Furthermore, Ghana has one of the most well established drug regulatory authorities in Africa, the Food and Drugs Authority (FDA) Ghana. The road looks good for Ghana to take a leading role in sub-Saharan Africa in the fight to ensure access to medicines. However, a few rough edges still linger on preventing a seamless operation in medicines access. As part of this, pharmaceutical policy analysis needs to be strengthened.

Among the eight Millennium Development Goals (MDG) which have now been succeeded by the Sustainable Development Goals (SDG), goals 4, 5 and 6 were clearly health related. Unfortunately, Ghana did not meet any of these three by the end of 2015. Although substantial progress was achieved in the case of MDG 6 (by stopping the rise in prevalence and on track to reverse the spread of HIV [6]), slow progress was made concerning MDGs 4 (under-five mortality rate of 60 deaths per 1000 was recorded instead of 40 deaths per 1000) and 5 (maternal mortality ratio of 385 deaths per 100,000 compared to the required mark of 190 deaths per 100,000) [6]. Limited access to medicines obviously played a role in these setbacks [7]. Ghana continues to experience shortages of antiretroviral drugs [8].There have been times when stocks of individual drugs of a particular combination of the highly active antiretroviral therapy (HAART) have run so low that treatment centres had to ration the dispensing of HAART [9,10]. On limited occasions (at our adherence counselling unit)

treatment regimen of some patients have been replaced briefly because one or more of the original HAART combination was out of stock. Such instances may lead to more frequent visits to treatment centres and may result in increased indirect medical costs in the form of transportation to patients.

IMPORTANCE OF PHARMACEUTICAL POLICY ANALYSIS

Pharmaceutical policy analysis (PPA) is that key ingredient that underpins any successful program on access and rational use of medicines. PPA serves as a benchmark tracking the activity of drug use in every society by way of evidence based continuous monitoring and periodic evaluation. From the WHO's "equitable access to essential medicines" framework [11], access to medicines is based on the following pillars:

- Rational selection
- Sustainable financing
- Affordable pricing and
- Reliable health and supply systems

Morrow [12] talked about the significant role played by pharmacists in medicine management, but yet did little when it came to medicines policy development. Pharmacists were charged to take leading roles in the development of medicines policy and to especially focus on patient utilization of medicines as well as on the decisions they make on patient treatment [12].

According to the WHO [6], "In most developed countries, research on medicines use is routine in health care facilities and numerous studies have demonstrated its effectiveness. However, most developing countries do not have data on this at the national level". These weaknesses, in addition to the lack of political will to invest in health research and a weaker human resource research capacity compared to developed countries [13] is a major stumbling block that needs to be circumvented to pave the way for cutting-edge research in sub-Saharan Africa in general and Ghana in particular.

Waning [14] noted in relation to pharmaceutical policies and access to medicines in developing countries that, "the research to date has focused largely on the effects of national pharmaceutical policies. The majority of those studies, however, have been small in scale and utilized simplistic pre and post measurement methodologies evaluating a single intervention through a few outcome measures; they do not reflect the reality of complex health system and policy environments". Studying access to medicines from the perspective of health systems, Bigdeli et al [15] after considering the existing main evidence [11, 16, 17], argued that the WHO framework on access to medicines could be more complex. Their framework has five main levels of health systems with each level having a series of different access to medicines (ATM) constraints. The five levels of health systems are:

1. Individuals, households and communities
2. Health service delivery
3. Health sector level
4. Public policies cutting across sectors, and
5. International and regional level

Level I involves perceived quality and health workers attitude. It also includes affordability of medicines and services. It embraces relationships between patients, households and communities and services providers at the point when the former is seeking health from facilities of the latter. Socio-cultural issues like stigma are also captured. Level II includes irregular availability and exorbitant medicine prices. Irrational prescribing and dispensing, medicines quality (including substandard, spurious, falsely labelled, falsified, and counterfeit medicines) also fall here as well as pharmaceutical services provided to mothers, newborns and children. The greatest opportunity of the hospital pharmacist in Ghana is the close interaction with patients, which enables them to enhance access to medicines at levels I and II. Level III works around registration of pharmaceuticals, selection, procurement, distribution, licensing of pharmaceutical establishment, inspection, control of promotion and control of clinical trials. Levels IV and V predominantly involve the health systems surrounding pharmaceutical. These include problems with public accountability, government bottlenecks, and the interface between public health and economic, trade and industry objectives.

The attitude of Ghanaian pharmacists, apart from those in academia, is just as described by Morrow [12]. Hospital pharmacists in Ghana stand a great chance if they collaborate with their counterparts in academia to leverage their competencies. This may serve as the watershed moment that may positively change the game plan for pharmaceutical policy analysis research.

Pharmaceutical policy is a dynamic discipline where policy makers may adopt and adapt interventions made in other countries or regions [18, 19]. It has been argued that the knowledge base of pharmaceutical policy analysis needs to be broad and the approaches are more varied than randomized controlled trials alone can provide [20]. The topic has been addressed from different angles by different researchers. For example, pharmaceutical policy and access to medicines was investigated using a market context of pharmaceutical supply, demand, and supply-demand intervals in low and medium-income countries (LMIC) [14]; Cameron [21] used information on medicine prices and availability to study the topic in LMIC; and the drivers and implications of private sector behaviour and how this influences pharmaceutical policy and access to medicines has also been explored [22]. While all these researchers looked at the role that systems play in shaping pharmaceutical policy and access to medicines, this thesis examines the situation from the role of the hospital pharmacist.

OBJECTIVES, THEMES AND SETTING OF THE THESIS

Objectives of the thesis

Hospital based pharmacy research by pharmacists in LMIC in general and in sub-Saharan Africa (SSA) in particular is quite scarce compared to the developed world [24]. However, hospital pharmacists in Ghana as well as in other SSA may play a significant role in ensuring and improving access to medicines. The present thesis aims to study different aspects of this role including access to paediatric formulations, provision of adequate information and services, adherence counselling and safety surveillance.

Research activity involving hospital pharmacists in Ghana is very low. The few that exists involve mostly descriptive studies. This is mostly due to non-availability of data and inadequate research skills among hospital pharmacists in Ghana. On the contrary, it has been observed that there is data available in developing countries but it is not being used [14], and there is the need for researchers, particularly those in academia, to take advantage and come out with innovative methods for research. In this thesis, various types of data will be used for research. Both qualitative and quantitative study designs will be involved. Quantitative methods include cross-sectional studies, case-control studies using data extracted from clinical and pharmacy records, cohort studies using data from electronic database, and descriptive studies.

Themes of the thesis

This thesis will concentrate on three themes which are all related to access to medicines in which hospital pharmacists in Ghana play a pivotal role. The three themes are:

1. Improving access to medicines: provision of information and services and suitable medicines.
2. The role of adherence in achieving optimal treatment outcomes in HIV treatment
3. Improving outcomes following immunization

Service delivery is one of the major pillars in the access to medicines cocktail, and provision of health information is an appendage of the former [15]. Improving access to services involves knowledge of what providers offer and education on how to best utilize practitioner-provided services [23]. Patients who were given the medicines information leaflet were found to be more knowledgeable, more satisfied and had better understanding of drug side effects compared to those without the information leaflet [24, 25]. Patients should be given all the necessary information on the medicines to enable informed decision making. Patient satisfaction has been reported to be associated with appointment keeping and improved medication use [26]. Sensitizing patients to improve medicine uptake would demand an intervention by the pharmacist to explain to patients what the benefits and risks of their medicines would be. For patients to accept and comply with such information, their perception of the pharmacist would most probably be an important factor.

Cameron [27] compared the availability of medicines used for chronic and acute diseases in LMIC and concluded that of the two types of medicines, the former were less available. Where medicines are less available, alternative formulations may be used to improve access. The use of specially formulated medicine is not limited to low and medium income countries like Ghana. In the United Kingdom these products are popularly called "specials" or "special order product" [28]. Most specials are unlicensed formulations of a licensed medicine [28].

Access to medicines involves improved availability of medicines to individuals, households and communities [15]. Improving medicine supply without considering adherence may result in low treatment outcomes. For sub-Saharan African countries, the case of HIV/AIDS still lingers. In the last 25 years, the one single disease that has plunged the whole of sub-Saharan Africa into an economic, social, and health abyss is Acquired Immunity Deficiency Syndrome (AIDS), caused by the Human Immune Virus (HIV). As of 1996, "every day over 6,500 adults were newly infected in Africa; 800 in Southeast Asia; and 270 in the industrialized world" [29]. Dubbed as the "Copernican revolution for AIDS" [29], the news of highly active antiretroviral therapy (HAART) at the 11th International AIDS Conference in 1996 was the watershed moment in the history of HIV/AIDS and a big relief for AIDS patients and advocates. In Ghana the spread of HIV has been halted [6] but the country is just about getting things right with reversing the spread of the disease and so narrowly missed the target for attaining MDG 6 [6].

This discovery notwithstanding, HAART does not kill the virus and patients have to be on treatment for the rest of their lives. With the most important hurdle cleared, the remaining challenges including adherence to lifelong therapy, has since been staring at the face of society. As of the end of 2010, 6.6 million people in LMIC were on ART [30]. Every teaching and regional hospital in Ghana has an HIV/AIDS clinic that provides antiretroviral therapy (ART). Monitoring of adherence is among the early warning indicators (EWI) [30] of the WHO with regards to ARTs, and this is sacrosanct at all ART centers in Ghana. Analysis from IMS Institute for Healthcare Informatics [31] shows that non-adherence to medicines is the single most influential factor to the worlds avoidable cost, contributing 57% of the total. It explains that a total of 4.6% (amounting to $269 billion) of global health expenditure can be saved if optimal adherence to medicines are maintained. According to the WHO framework [11], common examples of irrational (rational) use of medicines include prescribing too many medicines for the same patient (polypharmacy) and lack of adherence to prescribed medicine. Polypharmacy is reported to be associated with a reduced level of adherence [32-37]. Hence there is a positive correlation between rational use of medicines and adherence. Antiretroviral adherence will be considered in this thesis because of the improved availability, equity and distribution compared to other treatments.

Improved health outcomes is an important yardstick for measuring service delivery. The past 50 years saw interventions with efficacious vaccines that led to the control or eradication of some deadly diseases. However, the names Wakefield and Montgomery [43, 44], are very ubiquitous among public health practitioners, vaccinologists and vaccine regulatory

agencies because of their publication linking the measles, mumps and rubella (MMR) vaccine to pervasive developmental disorder (autism) and inflammatory bowel disease suggesting a causal relationship [43-45]. On the 31st August, 1998, the Food and Drugs Administration (FDA) of the USA registered Rotashield for the immunization of infants against rotavirus, only to be voluntarily withdrawn on the 15th October, 1999 by Wyeth-Lederle Vaccines, the Marketing Authorization Holder, because of an association with intussusception [46]. What society learnt from the aftermath of these debates was that monitoring of adverse events following immunization and disseminating information, whether in infants, children, adolescents or adults, is among the most useful parameters required for immunization programs to succeed. Although vaccines have played a remarkable role in societies by drastically reducing morbidity and mortality, their use is associated with undesirable iatrogenic diseases which need to be identified early and minimized [47]. Spontaneous reporting of adverse events is still one of the cornerstones of pharmacovigilance of vaccines and (hospital) pharmacists play an important role in this reporting system [48].

Setting

Most of the studies in this thesis will be conducted at the Korle-Bu Teaching Hospital (KBTH), the premier teaching hospital in Ghana. Established in 1923, the KBTH is now a 2000 bed referral hospital located in Accra, the capital of Ghana. In 1963, the KBTH assumed the status of teaching hospital as a result of the establishment of the University of Ghana Medical School for the training of medical doctors. The KBTH legally operates as a semi-autonomous organisation by virtue of the promulgation of Act 525 of 1996 of the Republic of Ghana [49]. Today, training of medical personnel has enlarged to the status of College of Health Sciences and students undertake their training and research in the Korle-Bu Teaching Hospital. There is a referral HIV/AIDS clinic under the department of Medicine. This comprises of an adult clinic, an adolescents clinic for children between 12 years and 19 years, and a children's clinic for those below 12 years. There is an HIV/AIDS adherence and drug dispensing clinic that is under the supervision of pharmacists. In 2014 alone, the total out-patient attendance was 369,798 with 62.2% (n=230,193) being female. On average, 9320 new patients reported every month to the hospital in 2014 [50]. The percentage bed occupancy in the same year was 62.5%. To stimulate research activities in the hospital that will inform policy and enhance practice, the KBTH setup a Protocol and Ethical Review Committee in September 2015 [51].

OUTLINE OF THE THESIS

An effective patient centered research by pharmacists, which is the scope of **Chapter 2**, will be accentuated by a continuous relationship between the patient and the pharmacist [52]. **Chapter 2.1** focuses on the patient (medication) information leaflet (PIL) and assesses the effect of advice given by pharmacists to patients to read the PIL in a cross-sectional study. **Chapter 2.2** is a cross-sectional study involving exit interviews of patients at an out-patient pharmacy to identify patient perception of the role of the pharmacist among other members of the health care team. Using a prospective cross-sectional method, **chapter 2.3** studies insufficient access to oral paediatric medicines that are not readily available on the Ghanaian market and are therefore prepared extemporaneously.

Chapter 3 describes the role of adherence in achieving optimal treatment outcomes in HIV/AIDS management. **Chapter 3.1** is a historical cohort study that examines highly active antiretroviral therapy (HAART) utilization over a 5-year period (2008-2012). This involves the use of a database to find out the trends in antiretroviral drug use and their possible causes during the study period. **Chapter 3.2** focuses on the association between adherence and treatment change. This was a matched case-control study nested in a cohort. Data for this study includes chart reviews of patient clinical records as well as pharmacy records. As a follow up on this paper, **chapter 3.3** identifies the risk factors of non-adherence to ART among patients on first-line treatment. **Chapter 3.4** looks at barriers to and facilitators of adherence to ART among adolescents aged between 12 to 19 years. This is achieved using semi-structured interviews in a qualitative study.

Chapter 4 contains two studies that look at monitoring of adverse events following immunization (AEFI). **Chapter 4.1** is a prospective active surveillance study of the H1N1 vaccination programme in Ghana. The study reports on AEFIs recorded after immunization of health care workers at the KBTH in Ghana. In **chapter 4.2** vaccine reports in the national regulatory database in Ghana collected in real time using active surveillance are used to detect signals using the proportional reporting rates approach for six commonly used vaccines.

Finally the results of this thesis are put in perspective in **chapter 5**. The main findings of the thesis are discussed looking at the bigger picture from the position of a typical resource limited country like Ghana. In addition, challenges in medicines access including capacity building and education, types of research methods and the possible study limitations, and the absence of big data in this and other similar settings are considered.

REFERENCES

1. Arhinful DK. The solidarity of self-interest. Ph D dissertation, research report 71/2003, African Studies Centre, Leiden University, the Netherlands.
2. Britwum RB. The cost of sustaining the Ghana's "Cash and Carry" system of health care financing at a rural health centre. *West Afr J Med* 1994 Apr-Jun;13(2):124-7.
3. Ashigbie PG, Devine Azameti A, Wirtz VJ. Challenges of medicines management in the public and private sector under Ghana's National Health Insurance Scheme – A qualitative study. *JPPP* 2016;9:6.
4. Ghana National Drugs Policy. MOH, Ghana, 2004.
5. Kohler JC, Ovtcharenko N. Good governance for medicines initiative: Exploring lessons learnt. Anti-corruption research centre. U4 Issue 3, 2013.
6. Ghana Millennium Development Goal 2015 Report. Ghana, UN. September 2015
7. 2010 Ghana Millennium Development Goals Report. Ghana, UNDP, July 2012
8. Operational Plan Report – Ghana. FY 2013. PEPFAR. 2014.
9. Ghana News Agency. NACP receives stock of ARV supply to PLHIV. 2012. http://ghananewsagency.org/health/nacp-receives-stock-of-arv-supply-to-plhiv-52072. Accessed 17/07/2016
10. Daily Graphic. AIDS Control Programme receives ARVs. http://www.graphic.com.gh/news/health/aids-control-programme-receives-arvs.html. Accessed 17/07/2017
11. The World Medicines Situation, WHO. WHO/EDM/PAR/2004.5. 2004
12. Morrow NC. Pharmaceutical polic Part 1 The challenge to pharmacists to engage in policy development. *JPPP.* 2015;8:4.
13. Mutume G. Africa aims for a scientific revolution. More funding needed for research institutes and universities. http://www.un.org/africarenewal/magazine/october-2007/africa-aims-scientific-revolution. Accessed 16/07/2016.
14. Waning B. Innovative Approaches for Pharmaceutical Policy Research in Developing Countries: The View Through a Market Lens. http://dspace.library.uu.nl/handle/1874/218112. Accessed: 01/06/2016
15. Bigdeli M, Jacobs B, Tomson G, Laing R, Ghaffar A, Dujardin B, et al. Access to medicines from a health systems perspective. *Health Policy Plan*. 2013;28:692-704.
16. Centre for Pharmaceutical Management. 2003. Defining and Measuring Access to Essential Drugs, Vaccines, and Health Commodities: Report of the WHO-MSH consultative meeting. Ferney-Voltaire, France, 11–13, 2000.
17. Frost LJ, Reich MR. 2010. How do good health technologies get to poor people in poor countries. Boston, MA: Harvard Center for Population and Development Studies.
18. Larsen JB. The pharmaceutical distribution in Denmark – viewed in the light of deregulation. Copenhagen: The Danish University of Pharmaceutical Sciences, Department of Social Pharmacy, 2004. 11
19. ECON Analyse. Evaluation of the pharmaceutical legislation and the index price system. ECON-report no. 2004-10. Oslo: ECON Analyse, 2004. ISBN 82-7645-686-3.
20. Almarsdo´ttir AB, Traulsen JM. Studying and evaluating pharmaceutical policy—becoming a part of the policy and consultative process. *Pharm World Sci* 2006;28:6–12.
21. Cameron A. Understanding access to medicines in low and middle-income countries through the lens of price and availability indicators. http://dspace.library.uu.nl/handle/1874/258534. Accessed: 17/07/2016
22. Stephens P. Access to medicines: Common problems common solutions? http://dspace.library.uu.nl/handle/1874/308520. Accessed: 17/07/2016
23. Ensor T, Cooper S. Overcoming barriers to health service access: influencing the demand side. *Health Policy Plan* 2004;19(**2**): 69–79.
24. Gibbs S, Waters WE, George CF. Communication information to patients about medicine. Prescription information leaflet: A national survey. *J R Soc Med* 1990;83:292-297
25. Gibbs S, Waters WE, George CF. Benefits of prescription information leaflet (2). *Br J Clin Pharmal* 1989;28:345-351.
26. Williams B. Patient satisfaction: A valid concept? *Soc Sci Med* 1994;38(4):509-516.
27. Cameron A, Roubos I, Ewen M, Mantel-Teeuwisse A, Leufkens H, Laing R. Differences in the availability of medicines for chronic and acute conditions in the public and private sectors of developing countries. *Bull World Health Org* 2011;89:412–21.
28. Chaplin S. How drug tariff specials have reduced prescribing costs. Prescriber 2014;25(5):27-29.
29. Piot P. No Time to Lose: A life in pursuit of deadly viruses 2012. W.W. Norton & Company, Inc. New York, NY.
30. Assessment of World Health Organization HIV Drug Resistance Early Warning Indicators. Report of the Early Warning Indicator Advisory Panel Meeting. WHO 2011.
31. Advancing the responsible use of medicines. IMS Institute for Healthcare Informatics. October 2012.
32. Turner BJ, Hollenbeak C, Weiner MG, et al. Barriers to adherence and hypertension control in a racially diverse representative sample of elderly primary care patients. *Pharmacepidemiol Drug Saf*. 2009; 18:672–81. 31.
33. Stoehr GP, Lu SY, Lavery L, et al. Factors associated with adherence to medication regimens in older primary care patients: the Steel Valley Seniors Survey. *Am J Geriatr Pharmacother.* 2008; 6:255–63.
34. van Bruggen R, Gorter K, Stolk RP, et al. Refill adherence and polypharmacy among patients with type 2 diabetes in general practice. *Pharmacoepidemiol Drug Saf.* 2009; 18:983–91.
35. Chapman RH, Petrilla AA, Benner JS, et al. Predictors of adherence to concomitant antihypertensive and lipid-lowering medications in older adults: a retrospective, cohort study. *Drugs Aging.* 2008; 25:885–92.
36. Gazmararian JA, Kripalani S, Miller MJ, et al. Factors associated with medication refill adherence in cardiovascular-related diseases: a focus on health literacy. *J Gen Intern Med.* 2006; 21:1215–21.
37. Choudhry NK, Fischer MA, Avorn J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. *Arch Intern Med.* 2011; 171:814–22.
38. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006; 15: 565–574
39. Hosmer DJ, Lemeshow S, Sturdivant RS. Assessing the Fit of the Model, In Applied Logistic Regression (3rd Edition) 2013. John Wiley & Sons Inc. Hoboken, New Jersey, USA.
40. Ickovics JR, Cameron A, Zackin R, Bassett R, Chestney M, *et al* (2002). Consequences and determinants to antiretroviral therapy medication: results from the Adult AIDS Clinical Trial Group Protocol 370. *Antivir Ther* 7(3):185-193.
41. Moles R, Chaar B, Penm J. The World Hospital Pharmacy Research Consortium – Monitoring Global Practice in Relation to the Basel Statements. *JCPH* 2014;67(5):331-332.
42. Osterberg L, Blaschke T. Adherence to medication. *N Eng J Med* 2005;353(5):487-97.
43. Wakefield AJ, Montgomery SM. Measles, mumps, rubella vaccine: Through a glass, darkly. *Advers Drug React Toxicol* 2000;19(4):265-283.
44. Fombonne E, Chakrabarti S. No evidence for a new variant of measles-mumps-rubella-induced autism. *Paediatrics* 2001;108(4).E58.
45. Tom Heller. Ethical debate. Vaccination against mumps, measles, and rubella: is there a case for deepening the debate? *BMJ* 2001;323:838-840.

46. Dilage G. Rotavirus vaccine withdrawal in the United States: The role of postmarketing surveillance. *Can J Infect Dis* 2000;11(1):10-12.

47. Autran , B, Asturias EJ, Evans S, Hartigan-Go K, Hussey G, et al. Global safety of vaccines: strengthening systems for monitoring, management and the role of GACVS. *Expert Rev. Vaccines* 2009;8(16):705-716.

48. Lee A, Bateman DN, Edwards C, Smith JM, Rawlins MD. Reporting of adverse drug reactions by hospital pharmacists: pilot scheme. *BMJ* 1997;315:519

49. Ghana Health Service and Teaching Hospitals Act, 1996, Act 525. Ghana.

50. 2014 Annual Report. Korle-Bu Teaching Hospital, Accra, Ghana.

51. Korle-Bu Bulettin. Korle-Bu Teaching Hospital 2016.

52. Kucukarslan SN, Nadkarni A. Evaluating medication-related services in a hospital setting using the disconfirmation of expectation model of satisfaction. *Res. Social Adm Pharm* 2008;4(1):12-22.

Chapter 2

IMPROVING ACCESS TO MEDICINES: THE ROLE OF THE HOSPITAL PHARMACIST

Chapter 2.1

EFFECT OF ADVICE TO READ THE MEDICINE/PATIENT INFORMATION LEAFLET AMONG PATIENTS IN GHANA: A CROSS-SECTIONAL STUDY

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JPHSR. 2010;1(2):91-96

ABSTRACT

Background

Medicines, especially those that are packaged for the patient, are by law required to include a set of information. This informs the patient or client on his/her medication. Our aim was to investigate the factors that are associated with reading the medicine/patient information leaflet among patients who are advised to read the leaflet compared to those who are not, and to find out whether there are any significant differences between these two groups.

Method

A total of 531 adult patients from the main teaching hospital in Accra, Ghana, were asked to fill in a questionnaire. Information was gathered with emphasis on those whose medication came with a leaflet. The effect of advice to read the leaflet and other associations between covariates were examined.

Results

Of the 531 patients, 421 (79.3%) had received a leaflet before and of these 93.8% had received some verbal information from the health worker (doctor/pharmacist/ nurse). Only 139/421 (33.0%) said they were ever told to read the leaflet by their health worker. Those who recalled being advised to read the leaflet were about six times (odds ratio = 5.77; 95% confidence interval (CI) 2.76–12.04; $P < 0.001$) as likely to report having read the leaflet than those who did not, and they were also more likely (59% compared with 36%; c2 = 12.21; $P < 0.001$) to discuss with the health worker the problems they had while using the medication. Age group was a weak effect modifier ($P = 0.04$).

Conclusion

Educational status was the most important risk factor among those measured. Other risk factors were employment and marital status. Public awareness should be stepped up to encourage reading of the leaflet by patients.

INTRODUCTION

Medicines, especially those that are packaged for the patient, are by law required to come with information as represented in the Summary of Product Characteristics [1]. This should include the name of the drug, its form, how and when it should be administered and the frequency of administration. It should also include its side-effect profile, contraindications and its storage, to mention but a few items. This serves as first-hand information to, in particular, the patient who is using the medication. In Ghana, the Food and Drugs Law 1992, 000000000000000.P.N.D.C.L. 305B, section 18, as amended by Act 523, 1996 [2] provides guidance for registration of allopathic drugs in the country. This guidance specifies that the packages for all products submitted for registration shall include package leaflets, or patient information leaflets. This is the main source of information readily available to users of these drugs, apart from information on medicine (drug) packages. It is required that such information shall be in English [2], the lingua franca in Ghana.

Studies have supported the fact that written information on medicines can help patients understand and comply with their doctors' advice [3, 4], and patients who receive a leaflet are more likely to know the name of their medication [3, 4]. In a systematic review there was consistent evidence that the way in which risk descriptor information is portrayed in a leaflet influences side-effect knowledge [5] among users. However, the benefits of a leaflet are underpinned primarily by the extent to which it is read [5], and secondly the degree of understandability among patients who read it [6]. Comparing the effect of written information on medicines to oral information, it was observed that a combination of the two is more helpful [7]. In a randomized controlled trial to investigate the impact of providing a simple leaflet on reduction of re-consultation rates among adult patients initially treated with antibiotics, it was found that 16% of those with leaflets compared to 23% of those without leaflets returned for re-consultation ($P = 0.02$) [8]. Although the average Ghanaian can read and write, reading the leaflet may be quite challenging and therefore an encouragement to read it might possibly help. This study investigated the factors that are associated with reading the medicine/patient information leaflet among patients who were to read compared to those who were not, and tried to find out any significant differences between these two groups.

METHODS

Study group

The study was conducted in the main teaching (referral) hospital in Accra, the capital of Ghana. All patients aged 18 years and above were eligible to participate. Parents or guardians of patients aged less than 18 years were not interviewed. Patients were interviewed after agreeing by informed oral consent.

Sample-size calculation

A sample size of 324 was arrived at based on the formula [9],

$$n = 15.4 \times P\,(1 - P)\,W^2$$

where n is the sample size, P is the best guess of the expected percentage/proportion who read the leaflet and W is the desired width of the 95% confidence interval, based on the primary outcome variable of our study; that is, reading/not reading the prescription/medication information leaflet. In a study in the University of Southampton in the UK, 97% [10] of patients read their leaflet. In another study in Tel Aviv University, Israel, 51.5% [6] of respondents read their leaflets. But these two countries have higher literacy rates than Ghana, a country with a literacy rate of 53.7% [11]. Also, using daily newspaper reading as a proxy for reading, it was found that 63.6% of Ghanaians would never read a newspaper [11]. Based on this information, we assumed that about 30% of respondents would read their leaflets and we used a desired width of ±5% for the 95% confidence interval. This was a cross-sectional survey and there was an equal chance of interviewing people who had had leaflets before and those who had not.

Also, those who had had a leaflet before may decide to read it this time, or not. Because in this study we were more interested in those who had ever previously read a leaflet in their medication among respondents who read the leaflet in this study, we decided to add about 200 more respondents, leading to a final sample size of 531.

Data collection

Trained interviewers, with a tertiary educational background, using a simple random sampling method, interviewed patients aged 18 years and above who were waiting to collect their medication or who had just collected their medication from the various pharmacies of the hospital, with the exception of the paediatric pharmacy. The questionnaire was first validated through a pilot study, after which some modifications were made. They were asked whether they had ever been told to read the leaflet, whether they read the leaflet, whether they understood the information on the leaflet, whether they discussed with their health worker any problems they encountered with their medication as a result of reading the leaflet, where they normally acquired the medicines from, and many other questions. Most responses to the questions were recorded in the form of a Likert scale. This was done to encourage a response and for ease of analysis. The importance of the leaflet was explained to them after the interview. Those who refused to consent to be interviewed, but who were willing to listen, were advised on the need to read their medicine information leaflets.

Analysis strategy

Data from the questionnaire were coded and entered in Epidata software version 3.1. This was then transferred to Stata Intercooled version 9.0 for analysis. Using Pearson chi square statistics the presence or absence of an association between variables of interest was established. Using classical Mantel–Haenszel methods, measures of effect (odds ratios, ORs) were calculated and adjustment was made for single confounding variables. The primary outcome was reading/ not reading the leaflet, a binary variable. Logistic regression was used for multivariate analysis. The following potential risk factors were adjusted for confounding: education, age group, marital status, employment, place of acquisition of medicines and sex. Using forward stepwise adjustment the effect of each significant risk factor was adjusted for by all other significant risk factors. A p value of 0.2 [12] was used as the threshold. In analysing the results it was assumed that those with no educational background had read the leaflet if they had given it to their friends and relatives to read and explain to them.

RESULTS

A total of 531 participants were involved in this cross-sectional study. Out of this number 421 (79.3%) received a medication leaflet with their medication (see Table 1). Among participants who received a medication leaflet with their medication, 395 (93.8%) also received verbal information on their medication (irrespective of whether they were told to read the medication leaflet). The number of participants advised to read their medication leaflet was only 139/421 (33.02%). Some variables had missing values but the highest percentage of missing values per variable was only about 2% for the total distribution and about 1% for those who had ever received a leaflet in their medication. We therefore excluded missing values from our analysis. Among those whose medication came with a leaflet, 321 (76.3%) read it or gave to their friends/relatives to read and explain to them. Some 197/315 (62.5%) agreed strongly that medicines should always be accompanied by a leaflet; 110/315 (34.9%) agreed and 8/315 (2.5%) disagreed.

In a subgroup comprising all those who read their leaflets, we found that 59% of those who received advice to read the leaflet discussed the problems they had while taking their medications with the health worker (compared with 36% who did not; = 12.21; $p < 0.001$). Among those who had ever had their medication come with a medication leaflet, 91% read it if they were advised to, whereas only 69% of those who were not given such advice read the leaflet (2 = 26.65; $p < 0.001$). There was no significant association between the frequency (always, often or seldom) with which patient medicines come with a leaflet and reading the leaflet (2= 0.34; $P = 0.84$).

Females were less likely to read the medication information leaflet, with an OR of 0.72 (95% confidence interval (CI) 0.45–1.14) but this was not significant ($p = 0.157$). Apart from the age group 18–25 and 36–45 years, which recorded an odds of reading of 1, there was a gradual decrease in the odds of reading with increasing age, from 0.87 (95% CI 0.44–1.69; $p = 0.683$) in age group 26–35 years to 0.35 (95% CI 0.17–0.72; $p = 0.003$) in those older than 55 years. Compared to those with no basic education, those with basic education had 8.57 (95% CI 3.04–24.14; $P < 0.001$) times the odds of reading the medication information leaflet, those with secondary education had 26.38 (95% CI 7.84–88.70; $p < 0.001$) times the odds and those with tertiary education had 57.78 (95% CI 9.34–357.42; $p < 0.001$) times the odds

Table 1. Characteristics of all study participants and those whose medicines had ever come with a leaflet.

Variable	Total distribution	Distribution with leaflet (%), n=421
Age group (years)		
18-25	146 (27.50)	107 (25.42)
26-35	145 (27.31)	116 (27.55)
36-45	96 (18.08)	73 (17.34)
46-55	66 (12.43)	54 (12.83)
56-65	38 (7.16)	34 (8.08)
>65	37 (6.97)	35 (8.31)
Missing	3 (0.56)	2 (0.48)
Sex		
Female	310 (58.62)	246 (58.43)
Level of education		
None	61 (11.49)	32 (7.60)
Primary	35 (6.59)	33 (7.84)
School Certificate	53 (9.98)	52 (12.35)
Junior High School	68 (12.81)	52 (12.35)
GCE[a] 'O'[b]	62 (11.68)	48 (11.40)
SHS[c]	119 (22.41)	85 (20.19)
GCE 'A'[d]	35 (6.59)	30 (7.13)
Graduate/postgraduate	93 (17.51)	85 (20.19)
Missing	5 (0.94)	4 (0.95)
Marital status		
Single	223 (42.00)	172 (40.86)
Married	257 (48.00)	209 (49.64)
Divorce	4 (0.75)	4 (0.95)
Widow/er	28 (5.27)	22 (5.23)
Separated	15 (2.82)	12 (2.85)
Missing	5 (0.94)	2 (0.48)
Employment		
Employed	322 (60.64)	259 (61.52)
Unemployed	52 (9.79)	43 (10.21)
Retired	40 (7.53)	37 (8.79)
Student	109 (20.53)	79)18.76)
Missing	8 (1.51)	3 (0.71)
Place of acquisition of medicine		
Hospital pharmacy	315 (59.32)	261 (62.00)
Community pharmacy	155 (29.19)	105 (24.94)
Chemical sellers	40 (7.53)	38 (9.03)
Private clinic	17 (3.2)	15 (3.56)
Missing	4 (0.75)	2 (0.48)

Table 1. (continued)

Variable	Total distribution	Distribution with leaflet (%), n=421
Received medicine information from health worker?		
No	32 (6.03)	24 (5.70)
Yes	497 (93.95)	395 (93.82)
Missing	2 (0.38)	2 (0.48)
Ever been advised to read leaflet?		
No	385 (72.50)	282 (66.98)
Yes	146 (27.50)	139 (33.02)

[a]General Certificate of Examination; [b]Ordinary Level; [c]Senior High School; [d]Advanced Level.

of reading the medication information leaflet compared to those with no basic education (see Table 2). A test for dose–response effect showed an association between education and reading the information leaflet but there was a departure (p = 0.0004) from a linear increase per unit level of education. Those who were single had about four times (OR = 4.21; 95% CI 1.96–9.18) the odds of reading the leaflet compared to those with an interrupted marriage (including widows and widowers, divorcees and those with separated marriages), and the odds of reading the leaflet if you were married was about three-fold more than those with an interrupted marriage. Students were the most likely group to read the leaflet with an OR about five times that of the unemployed. Being employed was associated with 2.03 (95% CI 1.03–4.02; p = 0.037) times the odds of reading the leaflet compared to the unemployed. Although retirement was associated with 1.55 (95% CI 0.60–3.97) times the odds of reading the leaflet compared to the unemployed, this was not significant: p = 0.362. There was no significant difference (2 = 0.12; p = 0.78) in leaflet-reading habits among people who acquired their medication from a hospital, community pharmacy, chemical sellers or private clinic. The percentage frequency of leaflet reading for the various groups can be found in Table 2. The crude OR between reading the leaflet and advice to read the leaflet was 4.86 (95% CI 2.50–9.44), and this was adjusted for the effects of the various possible confounding factors. Interaction tests were also done to look for any signs of effect modification. The results, shown in Table 3, indicate that even after adjusting for the effect of sex, reading the leaflet was associated with advice to read the leaflet with an OR of 4.81 (95% CI 2.47–9.36); adjusting for the effect of age group and place of acquisition of medication had minimal influence on the crude OR but age seems to be an effect modifier (p = 0.04) for reading the leaflet. After taking care of the effect of educational status the OR increased to 5.87 (95% CI 2.71–12.72). Marital status as well as employment status both shifted the crude OR towards the null; however, these effects were not very strong.

Apart from age group showing weak evidence (p = 0.04) of effect modification, results of all the other interaction tests performed were not different from the null hypothesis. This

Table 2. Crude OR for each potential confounder and outcome (reading the leaflet)

Variable	OR (CI)	P value	% Reading leaflet
Age group (years)			
18-25	1.00	-	81.48
26-35	0.87 (0.44, 1.69)	0.683	79.31
36-45	0.65 (0.31, 1.32)	0.229	73.97
46-55	1.00 (0.43, 2.32)	1.00	81.48
>55	0.35 (0.17, 0.72)	0.003	60.87
Sex			
Male	1.00	-	79.55
Female	0.72 (0.45, 1.14)	0.157	73.58
Level of education			
None	1.00	-	18.75
Basic	8.57 (3.04, 24.14)	<0.001	66.42
Secondary	26.38 (7.84, 88.70)	<0.001	85.89
Tertiary	57.78 (9.34, 357.42)	<0.001	93.02
Marital status			
Interrupted marriage[a]	1.00	-	50.00
Married	3.27 (1.57, 6.78)	0.008	76.56
Single	4.24 (1.96, 9.18)	<0.001	80.92
Employment			
Unemployed	1.00	-	60.47
Employed	1.55 (0.60, 3.97)	0.362	70.27
Retired	2.03 (1.03, 4.02)	0.037	75.68
Student	5.16 (1.93, 13.79)	<0.001	88.75
Place of acquisition of medicine			
Private clinic	1.00	-	66.67
Chemical sellers	1.40 (0.38, 5.19)	0.613	73.68
Community pharmacy	1.78 (0.55, 5.79)	0.330	78.10
Hospital pharmacy	1.58 (0.52, 4.81)	0.417	75.95

[a]Combination of Widow/er, Divorcees and those with separated marriages.

is shown in Table 3. We explored the effects of educational status, employment status and marital status as risk factors/potential confounders.

Controlling educational status changed the estimate of the OR for advice to read the leaflet from 4.56 to 5.74 (95% CI 2.76–11.91), indicating that education confounds the relationship between an advice to read the leaflet and reading the leaflet even after marital status had been taken care of. The likelihood ratio test (LRT) provided strong evidence (likelihood ratio statistic, LRS = 28.51; $p < 0.0001$) against the null hypothesis that after controlling education

Table 3. Results showing the effect of adjusted variables for confounding and interaction tests performed.

OR (95% CI)	Adjusted for	P-value for interaction
4.86 (2.50, 9.44)	Crude	-
4.94 (2.48, 9.82)	Age group	0.04
4.81 (2.48, 9.33)	Place of acquisition	0.39
4.68 (2.33, 9.04)	Employment status (∞)	0.43
4.56 (2.33, 8.90)	Marital status (α)	0.21
4.81 (2.47, 9.36)	Sex	0.76
5.87 (2.71, 12.72)	Educational status (¥)	0.63
4.51 (2.35, 8.67)	∞ + α	-
5.80 (2.74, 11.78)	α + ¥	-
5.68 (2.74, 11.78)	∞ + ¥	-
5.77 (2.76, 12.04)	∞ + α + ¥	-

and marital status there was no association between an advice to read the leaflet and reading the leaflet.

A similar test between education and employment status shifted the OR from 4.68 to 5.68 (95% CI 2.74–11.78) and the LRT provided strong evidence (LRS = 28.29; $p < 0.0001$) against the null hypothesis. This strong association remained (LRS 25.97; $p < 0.0001$) even after taking care of the effects of marital status and employment status. After taking into account all three risk factors (educational status, marital status and employment status) advice to read the leaflet was still strongly associated with actually doing so (LRS = 28.22; $P < 0.0001$) and the OR for advice to read the leaflet was 5.77 (95% CI 2.76–12.04). Stratum-specific Wald test *P* values for all other levels of education compared to no education (baseline) were all less than 0.001. However, for marital status, those who were married had a *p* value of 0.89 compared to those with interrupted marriage (baseline), and for single people compared with the baseline the stratum specific *P* value was 0.114. For employment status, retirees had a *p* value of 0.80 compared to baseline. The *p* value for the unemployed was 0.78. For students the stratum-specific *p* value was 0.08.

According to the results from the subgroup who received and read their leaflet, only 14.64% found it very easy reading the leaflet and 2.80% admitted that reading the leaflet was not easy at all (see Table 4). Some 71.34% of those who read the leaflet accepted that it was very important and 61.37% agreed that their medication should include a leaflet. Some 2.49% disagreed with the inclusion of a leaflet in their medication.

DISCUSSION

This study investigated the factors that are associated with reading the medicine/patient information leaflet among patients who are advised to read it compared to those who are not, and tried to find out whether there were any significant differences between these two

Table 4. Characteristics of the subgroup of participants who had ever received and read the leaflet.

Covariate (n=321)	Percentage distribution
Ease of understanding of leaflet content	
Very easy	14.64
Easy	56.07
Not easy	25.23
Not easy at all	2.80
Missing	1.25
Importance of leaflet	
Very important	71.34
Important	26.79
Not very important	-
Missing	1.87
Inclusion of leaflet with medication	
Strongly agree	61.37
Agree	34.27
Disagree	4.46
Strongly disagree	-
Missing	-

groups. A total of 421 (79.3%) of participants had ever received a leaflet and 93.8% of all such participants had been given verbal information on their medications before. Nader *et al* [13] in a questionnaire-based survey in Iran reported that 28% of respondents received no information from the pharmacist or physician. The rate of reading the leaflet was 76.3%. This was higher than that from the study in Israel [5] where only 51.5% read the leaflet.

However, it was lower than that in the study done at the University of Southampton in the UK [10] where 97% of participants read the leaflet. The high rate of reading in our study may be because it was conducted in a referral hospital where patients are more likely to be sicker and hence more likely to have health-seeking behaviour. However, it must be mentioned that respondents at the polyclinic (which provides primary care) of the hospital were also part of the survey. Koo *et al* [14] reported an association between the nature of the health problem and an interest by the patient in written materials. The urban location of the study may have also contributed due to higher literacy rates [15].

It was found that after controlling for the suspected risk factors, those who recalled being advised to read the leaflet were around six times (OR 5.77; 95% CI 2.76, 12.04; $p < 0.001$) as likely to report having read the leaflet. We did not find any comparative study on this and therefore more research work will be needed.

Educational status was a strong predictor (risk factor) for reading the leaflet. People with higher education [6, 12, 14] in our study, were more likely to read the leaflet, among those who were advised to do so. Table 3 shows that education was a negative confounder,

the absence of which may have attenuated [16] the effect of advice to read the leaflet among those who read it. Being single (marital status) and being a student (employment) were the other confounders. Age group was a weak ($p = 0.04$) effect modifier.

Among those who had ever had a leaflet in their medication 91% read it if they were advised to, compared to 69% of those who were not advised (2 = 26.65; $P < 0.001$). Also among all those who read the leaflet, those who received advice were more likely (59% compared with 36%; 2 = 12.21; $p < 0.001$) to discuss with the health worker the problems they had while using the medication. George *et al* [3] found that patients who gained knowledge from their leaflets were more likely to recognise adverse effects, when they occurred, as being due to their medication. This is quite encouraging because one of the many problems facing health workers in Ghana is getting feedback on patient medication with regards to adverse events. If advice to read the leaflet can help then a policy should be implemented to ensure that this is done properly. Nathan *et al* [17] recommends that reading the leaflet should be advocated as a useful practice. However, they warned that this should not replace an obligation to provide verbal information. Furthermore, there was no association (2 = 0.34; $P = 0.84$) between the frequency (always, often or seldom) with which patient medication came with a leaflet and reading the leaflet. This implies that the presence of the leaflet alone may not be enough to promote reading. First verbal information, then telling patients that written information is important, is better than just giving a leaflet [18–20].

Where a patient normally received medications from had little effect (2 = 0.12; $P = 0.78$) on whether they recalled reading the leaflet. Hospital pharmacy, community pharmacy and clinics dispense restricted [21] drugs compared to chemical sellers where only class C [21] drugs are dispensed. Putting hospital pharmacy, community pharmacy and clinics into one group and comparing it with chemical sellers still did not yield any significant difference (2 = 0.12; $P = 0.73$). This is a bit worrying because dispensers of restricted drugs are professionally more qualified and therefore we expected to find some difference in the way the patients behaved towards the leaflets.

From Table 4, only 14.64% of respondents said it was very easy to understand the leaflet and a quarter claimed it was not easy. Nathan *et al* [17] reports that 56.2% reported that the leaflet was very easy to understand, and only 8.5% said it was somewhat difficult. In most developed countries (USA and those of the European Union) the patient information leaflet is designed to be as patient-friendly as possible and drug manufacturers are required by law [22] to adhere to this format. The Food and Drugs Board of Ghana may in future prescribe a package leaflet format for local pharmaceutical industries with the hope of improving readability for patients. That almost 98% of those who read the leaflet agreed that it was at least important and about 95% at least agreed that the leaflet should be included with their medication gives the assurance that if patients in Ghana are encouraged to do so they may read the leaflet and may benefit from it. This study is the first of its kind in Ghana and it is hoped that more work will be done in future to empower patients to take a more active role in their own management.

Limitations of the study

Being a typical cross-sectional study, the issue of response bias cannot be overlooked. This is because patients who are more conscious of their health were more likely to consent to the interview compared to those who are not. Selection bias may be the likely cause of variations in age distribution. This is because patients from the maternity pharmacy were part of those interviewed and they were more likely to be younger.

That a total of 421 (79.3%) recalled having ever received a leaflet – in other words, a fifth of respondents did not recall having received a leaflet – may result in information bias.

However, currently there is no policy in Ghana for mandatory inclusion of a leaflet with every dispensed medicine. Age as an effect modifier could have been due to chance because of the weak evidence ($p = 0.04$) against the null hypothesis.

Residual confounding could be a limiting factor. For example, we did not look at the effect of the nature of disease (whether chronic or acute) on reading the leaflet. Further research is required here.

CONCLUSIONS

The health worker, according to our study, is doing creditably with regards to providing verbal information to the patient. However, the health worker should make a conscientious effort to tell the patient to read the medicine information leaflet because this study has observed a significant association between a recommendation to read the leaflet and actually reading it. In this regard, more emphasis should be directed towards those who are less educated. Media advertisements on over-the-counter medicines may be designed to include advice to read the leaflet. The format of packaged leaflets (medicine/patient information leaflets) may be prescribed to include basic information [23] which may be presented as questions with appropriate answers to crave the indulgence of the patient. More research is needed in the design of such information leaflets.

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REFERENCES

1. Knapp P *et al*.Written information about medicines for consumers. *Cochrane Database Syst Rev* 2005;3:CD002104.
2. Food and Drugs Board Ghana. Guidelines for registration of allopathic drugs. www.fdbghana.gov.gh/pdf/drugs/ALLOPATHIC%20DRUGS%20REGISTRATION.pdf. (accessed 1October 2009).
3. George C *et al*. Prescription information leaflet: a pilot study in general practice. *BMJ* 1983;287:1193–1196.
4. Kenny T *et al*. A PIL for every ill? Patient information leaflets (PILs): a review of past, present and future use. *Fam Pract* 1998;15:471–479.
5. Raynor DK *et al*. A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines. *Health Technol Assess* 2007;11:iii,1–160.
6. Vinker S *et al*. The effect of drug information leaflets on patient behaviour. *Isr Med Assoc J* 2007;9:383–386.
7. Griffin JP, Griffin JR. Informing the patient. *J R Coll Phys* 1996;30:102–103.
8. Macfarlane J *et al*. Reducing consultation for acute lower respiratory tract illness with an information leaflet: a randomised control study in primary care. *Br J Gen Pract* 1997;47:719–722.
9. Thomas M *et al*. Prevalence of dysfunctional breathing in patients treated for asthma care: cross-sectional survey. *BMJ* 2001;322:1098–1100.
10. Gibbs S *et al*. The benefits of prescription information leaflets. *Br J Clin Pharmacol* 1989;27:723–739.
11. Ghana Statistical Service. *Ghana 2003 Core Welfare Indicators Questionnaire (CWIQ 11) Survey Report*. Ghana: Ghana Statistical Service, 2005.
12. Kirkwood B, Stern J. Regression modelling. In: *Essential Medical Statistics*, 2nd edn. Oxford: Blackwell Publishing 2003;315-342.
13. Nader F *et al*. Patient sources for drug information in Iran – a questionnaire based survey. *PharmWorld Sci* 2008;30:764–767.
14. Koo M *et al*. Enhancing patient education about medicines: factors influencing reading and seeking for written medicine information. *Health Expect* 2006;9:174–187.
15. Ghana Statistical Service. *Ghana Living Standards Survey (GLSS)*. Report of the fourth round. Ghana: Ghana Statistical Service, 2000.
16. Szklo M, Nieto F. Identifying non-causal associations: confounding. In: *Epidemiology Beyond the Basics*, 2nd edn. Sudbury, MA: Jones and Bartlett Publishers, 2007;151–182.
17. Nathan J *et al*. Patients use and perception of medication information leaflets. *Ann Pharmacother* 2007;41:777–782.
18. Doak C *et al*. *Teaching Children with Low Literacy Skills*. Philadelphia, PA: Lippincott Publishers, 1985.
19. Baker D *et al*. Evaluation of drug information for cardiology patients. *Br J Clin Pharmacol* 1991;31:525–531.
20. Gauld V. Written advice, compliance and recall. *J Roy Coll Gen Practitioners* 1981;31:525–531.
21. *Pharmacy Act 1994* (Act 489), Republic of Ghana.
22. Directive 2001/83/EEC, European Parliament and Council on the Community Code Relating to Medicinal Products for Human use.
23. Miselli M, Tognoni G. What information for the patient? Large scale pilot study on experimental package inserts giving information on prescribed and over the counter drugs. *BMJ* 1990;301:1261–1265.

Chapter 2.2

PATIENTS' PERCEPTION AND EXPECTATIONS OF SERVICES PROVIDED BY PHARMACISTS IN GHANAIAN HOSPITALS

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ABSTRACT

Background

A customer's perceived value of service has been identified as one of the most important drivers of satisfaction. Using a cross-sectional survey among out-patients with a chronic disease in Ghana, this study assessed their perception on the role of the hospital pharmacist, their expectation of services provided by the hospital pharmacist and the factors encouraging them to speak to the hospital pharmacist.

Methods

This was a cross-sectional survey of out-patients during visits to pharmacies at the Korle-Bu Teaching Hospital. Six pharmacies with a high patronage of patients with chronic diseases were purposively selected. A structured questionnaire was completed using a face-to-face approach and the results were presented in the form of descriptive and analytical (logistic regression) statistics.

Results

In all 331 respondents made up of 56.8% women and 43.2% men were interviewed. The mean age of respondents was 42 years. Of those who responded 87.3% (289/331) have had at least basic education and 63.7% of respondents were in some form of employment. In all 77.2% at least agreed that the pharmacist is a health professional just like doctors and nurses, and only 3.8% of respondents strongly disagreed that their awareness of the role of the pharmacist has improved over the last five years. It was found that those who reported little difficulty identifying the pharmacy staff were about three times as likely (OR 3.19, 95% CI 1.78- 5.80, $p<0.001$) to request to speak with the pharmacist compared to those who found this difficult.

Conclusion

Counselling services at the various pharmacies in the Korle-Bu Teaching Hospital need improvement. More work should to be done by pharmacists to educate patients on the role of the pharmacist in providing pharmaceutical care.

INTRODUCTION

The perception of a service is one of the most important drivers of customer satisfaction [1]. Daily interactions between pharmacists and patients generate various opinions and views which if tapped, could improve current trends in service delivery and/or open avenues for communication and expectations between the two parties [2]. Consideration of patients' perspectives of the influence of health care services on the needs and expectations can improve health care systems in various ways [3].

Pharmacy users, as societal consumers, assertively challenge specialized knowledge and play an increasing role in demanding convenient services [4]. As in other health care professions, pharmacists' true societal power, including professional development, lies in the relationship between the service and the users [5]. It is therefore important that any implementation of a change in pharmacy practice in Ghana should entail a prior, thorough understanding of who uses the pharmacy care resource, why and how it is used [6].

In a study in Singapore, Tam and Lim [7] were surprised that counseling on medicines which is a major responsibility of pharmacists was rated as the fourth most important service by respondents. If patients are aware that one of the most important functions of the pharmacist involves counseling on their medicines, then one will expect these patients to often request to speak to the pharmacist.

Hypertensive patients in a cross-sectional survey in Nigeria [8] reported that they were less likely to develop health related problems when they saw the pharmacist, however, the overall perception was that benefits received by such patients as a result of services received from the pharmacist was not substantial. As we monitor the quality of service delivery for gaps, patient evaluations may be valuable in unearthing their needs, perceptions, and other areas of service deficiency which may be valuable to health care providers [9].

Dispensing of medicines in Ghana is predominantly under the supervision of pharmacists and "chemical sellers". Pharmacists providing this service work in hospital/clinic pharmacies or in community pharmacies and "chemical sellers" work only in community chemical sellers' shops. Pharmacies need a superintendent pharmacist to supervise all activities because they work with all types of medicines (prescription only and over-the-counter). On the other hand, chemical sellers' shops only need a knowledgeable person to be in charge since they are restricted to over-the-counter medicines. In addition, the latter operate only in those areas deprived of services from pharmacies. A pharmacy technician may work in a pharmacy or a chemical sellers shop. In Ghana, patients decide on where to fill their prescriptions because they are not restricted to any drug dispensing facility.

According to Mead and Bower [10], the current emphasis on patient-centered approach to medicine has created the need for the patient's perspective of the services they receive to be monitored. Moreover, services of this nature can be used to evaluate and improve upon practice. Literature review to date shows no publication on patients' perception of the pharmacist's role or patients' expectation of services by the pharmacist using quantitative (or even qualitative) methods in Ghana. Using a cross-sectional survey among

out-patients with a chronic disease in Ghana, this study assessed their perception on the role of the hospital pharmacist, their expectation of services provided by the hospital pharmacist and the factors encouraging them to speak to the hospital pharmacist.

MATERIALS AND METHODS

Study design

This was a hospital-based study in which a sample of the out-patients visiting the pharmacies was surveyed over a five-day period in April 2013. A structured questionnaire was used in face-to-face communication by interviewers during patient's exit from the pharmacy. Every questionnaire was completed at the study site on the day of interview. A one day pilot study was conducted prior to the main study. The instrument was pre-tested during a pilot study. Two pharmacies were randomly selected by balloting and twenty people were interviewed at each site. The authors then held a meeting with the data collectors and issues raised were addressed.

Setting

This hospital-based survey was conducted in the Pharmacy department of the Korle-Bu Teaching Hospital (KBTH) in Ghana. The KBTH provides tertiary health care and the Pharmacy department has nine satellite pharmacies distributed in all the major clinical departments in the hospital to meet their specific needs. Six pharmacies with a high patronage by patients with chronic diseases were purposively chosen for questionnaire administration. These included the Paediatric pharmacy which caters for children less than 14 years old, the Surgical Pharmacy which provides treatment for all adult surgical cases excluding obstetrics and gynaecology patients, the Cardio-Thoracic pharmacy which supplies drugs to most patients suffering from cardio-vascular diseases, the Polyclinic pharmacy which serves all types of patients because the polyclinic is the gate-keeper of the hospital. Also included were the Korle-Bu pharmacy which serves all categories of patients of all ages and the Main pharmacy responsible for medical patients. In particular, dispensed medicines may differ among some of these pharmacies but general services rendered were not necessarily different. All of these facilities serve both in and out-patients. Patients were approached to participate during the morning shift (7.30 am – 3.00pm) at all six pharmacies. Each of the six pharmacies normally had between 2-5 pharmacists at post during the morning shift.

Study/Target population

The study population consisted of all out-patients who used the teaching hospital including its Polyclinic (a first port of call). The target population comprised of patients with chronic diseases visiting the various pharmacy units. In this study a "chronic" condition was defined as a condition with duration of at least 3 months as defined by the US National Centre for Health Statistics [11]. All those with a chronic disease who reported to the selected pharmacies at the KBTH for their medication were eligible to participate. Parents served as proxies for those aged 14 years or under. Clientele who were visiting any of the selected pharmacies for the first time, those with non-chronic diseases, pregnant women and babies under 3 months old were not included in the survey. By excluding first time visitors the results may not be adversely affected by a change in attitude of pharmacy staff during data collection (Hawthorne effect) because respondents had the opportunity to comment on their previous experience at the pharmacy.

2.2

Sample size

In calculating the sample size we considered the number of patients/clients who would request to speak to the pharmacist. According to the Ratiopharm Certified Financial Planner Report (Pharmacy Service) on consumers' perception of pharmacy in Canada, 43% of the time, interviewees talked to the pharmacist [12]. Because of the knowledge gap between Canada (a developed country) and Ghana (a country south of the Sahara) we assumed that requests to speak to the pharmacist would be made for only 30% of the time. Using a precision of 0.05, we obtained a sample size of 322. However, the total sample used for this study was 331.

Data Collection

The questionnaire was in four sections (predominantly closed ended questions). Section A was made up of questions concerning the demographic characteristics of respondents. Section B concerned the medical history of respondents. The third section (section C) measured respondents' expectations with regards to pharmaceutical services provided by pharmacists. Finally, the last section measured respondents' perception of pharmaceutical services provided by pharmacists. In this last section the perceived value of the role of pharmacists by respondents was ascertained using a Likert scale. The questionnaire was validated for content of information, representativeness of translations, ease of understanding and layout [13, 14]. This was done by an epidemiologist, a health systems researcher, two public health specialists and a psychologist (who are all members of the research team) and two patients with chronic disease. In all, three meetings were held. Trained data collectors, educated to at least tertiary level, were used for the study. Most of them were pharmacy interns. During the training sessions, the questionnaire was translated into Ga and Twi, the predominant local languages and back into English, to ensure that translation into the local language was uniform and did not alter the questions communicated to the respondents. Incorrect translation was resolved during the training sessions. During data collection two interviewers were assigned to each pharmacy and no identifiable clothes (laboratory coats) linked with the hospital or the pharmacy department was worn. Each interviewee was proficient in at least one of the two local languages. Data collectors introduced themselves as health workers carrying out research on patient perception. This was done to conceal the background of the researchers from respondents. Patients were approached as they walked out of the pharmacy without any structured preference or order. Eligibility was ascertained during

a brief friendly rapport. For those eligible, the study objectives and protocols were explained and they were given the opportunity to ask questions and seek clarification on the given information. Interested individuals were registered and interviewed after they had given oral informed consent. This study was approved by the Korle-Bu Teaching Hospital Management Committee.

Data processing and analysis

Data entry was done by two separate data entry clerks into Microsoft Excel version 2007 (Microsoft Corporation, Redmond, WA, USA). This was validated and transferred to STATA Intercooled Version 12 (StataCorp LP, College Station, TX, USA) for analysis. Descriptive data, including client demographic characteristics, details of pharmacy visits and customer services expected, were presented in percentages. Associations were determined using Chi squared tests (and Fisher's exact tests where appropriate) and multivariate analysis was done using logistic regression. A p-value less than 0.05 was used as the cut-off for significance.

RESULTS

Of the total of 331 respondents interviewed, 56.8% (188/331) were women. The mean age of participants was 42 (SD=11.2) years. The most used language of communication by respondents was Twi, followed by English and then Ga. Of those who responded 87.3% (289/331) have had a minimum of basic education and 63.7% of them were in some form of employment. There were some missing values but most of these were less than 10% of responses and may have had little effect on final outcomes. The distribution is as shown in Table 1 below.

There was an association ($p<0.0001$) between the place of service and provision of counselling by pharmacists. Those who said they were counselled after receiving their medication amounted to 63.2% from Main Pharmacy, 75.9% from Korle-Bu Pharmacy, 77.8% from surgical pharmacy, 88.9% from Child Health pharmacy, 95.9% from Polyclinic pharmacy and 97.0% from National Cardiothoracic Centre (NCTC) pharmacy. On average 79.7 respondents were counselled, see Fig. 1.

Among those who said they were counselled after receiving their medicines from the pharmacy, 42.0% said they had some information on drug interaction, 39.2% said they had some information on medicine side effects and 37.2% said they were given advice on healthy lifestyle. There was an association ($p=0.002$) between length of disease and whether one considers him/herself as a client, a customer or a patient. Only 33.3% of those with a disease history of at most one year considered themselves as "patients", while 57.2% of those with a disease history greater than one year considered themselves as patients. In particular, those with a disease history of at most one year were more likely to consider themselves as "clients" or "customers".

Those who participated in the survey were asked questions to identify their perception of the role of the pharmacist compared with other health service providers. For their

Table 1. Distribution of characteristics and responses from research participants

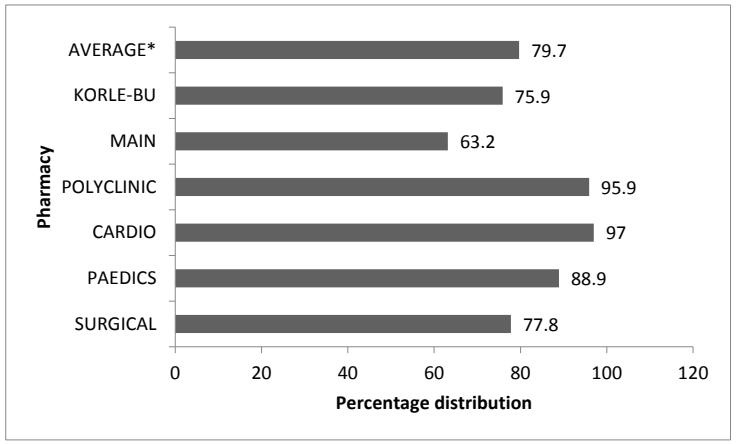
Variable	Distribution (N=331)	Percentage distribution (%)
Sex		
Male	134	40.5
Female	188	56.8
Missing	9	2.7
Age group (years)		
<25	45	13.6
25-34	60	18.1
35-44	50	15.1
45-54	77	23.3
55-64	56	16.9
≥65	27	8.2
Missing	16	4.8
Language of interview		
English	144	43.5
Twi	169	49.5
Ga	20	6.0
Ewe	0	0.0
Missing	2	0.6
Education		
None	38	11.5
Primary/Secondary	193	58.3
Tertiary	96	29
Missing	4	1.3
Marital status	100	30.2
Single	181	54.7
Married/Cohabiting	38	11.5
Divorced/Others	12	3.6
Missing		
Occupation		
Employed	211	63.7
Unemployed	77	23.3
Missing	43	13.1
Period on medication		
First time	75	22.7
About 1 month	31	9.4
About 3 months	26	7.9
Over 3 months	194	59.6
Missing	5	1.5

Table 1. (continued)

Variable	Distribution (N=331)	Percentage distribution (%)
Pharmacy visits in last 6 months		
Once	57	17.2
Twice	64	19.3
Monthly	154	46.5
Don't Know	34	10.3
Missing	22	6.7
Counselled after service		
Yes	238	71.9
No	63	19
Missing	30	9.1
Percentage of medicines dispensed*		
Yes	267	80.7
No	27	8.2
Missing	37	11.2
Type of chronic disease		
Hypertension	129	50.8
Diabetes	83	32.7
Arthritis	34	13.4
Asthma	8	3.2

*This is addressing the number of medicines dispensed as a percentage of the number prescribed.

Figure 1. Respondent's response on counselling services after dispensing.



*Represents the overall proportion of patients who reported to have been counselled.

responsibility for medications and minor ailments pharmacists scored 32.9% compared with 60.4% for doctors who nevertheless, were rated extremely highly compared to the former. The government, nurses, family members, and other health personnel were also not given high ratings with respect to the questions posed. Table 2 shows the percentage responses.

Using a Likert scale, we explored patients' expectations on services provided by the pharmacist. In all 60.2% of them at least agreed that over the last 5, years their understanding of the role of the pharmacist had improved. Only 3.8% strongly disagreed with this. 77.2% at least agreed that the pharmacist is a health professional just like doctors and nurses and 61.5% of respondents at least disagreed that pharmacist are just counting pills. Further results are shown in Table 3.

Further expectations of patients on additional pharmacy services that will enhance the quality of pharmacy practice were also investigated. The most recommended service among respondents was a queue-number system (40.3%). This was followed by provision of a public telephone booth (23.9%), pharmacy service at home (14.2%), screening of videos on health topics (11.2%), a system whereby prescriptions will be faxed to pharmacy and collected later (8.2%), and last but not least, provision of vaccination shots (2.2%).

Of those interviewed 41.3% said they would speak to the dispensing technician if the pharmacist is busy. Furthermore, 71.1% of respondents thought that the pharmacist and the dispensing technician are equally qualified to provide information on their medication.

Table 2. Patients' perception on role of pharmacists

Perception	Doctor	Pharm*	Govt.±	Nurse	Family	Other¶
Responsible for personal health and wellbeing	84.9%	3.4%	5.3%	0.6%	4.3%	1.5%
Responsible for information about health	93.6%	5.5%	0.3%	-	-	0.6%
Responsible for medications and minor ailments	60.4%	32.9%	0.3%	3.1%	2.4%	0.9%
Responsible for disease condition and information about minor ailments	92.0%	5.2%	-	2.8%	-	-

±Government; ¶Other health professionals; *Pharmacist.

Table 3. Expectations of patients on services provided by the pharmacist

Expectations	Strongly disagree	Disagree	Not sure	Agree	Strongly agree
Improved knowledge of pharmacist's role in the last 5 years	3.8%	11.6%	24.3%	39.0%	21.3%
Pharmacist are also health professionals	2.7%	8.2%	11.9%	57.1%	20.1%
Pharmacists give advice on health related issues	1.4%	8.7%	24.2%	52.6%	13.2%
Pharmacists just dispense medicines	19.6%	41.9%	19.2%	15.5%	3.8%
Pharmacists are just business people selling medicines	22.0%	35.8%	22.0%	17.6%	2.7%

We examined the relationship between knowing who was behind the counter in the pharmacy and a request by patients to speak to the pharmacist about their medication. The odds for a request to speak with the pharmacist increased with increasing educational level, however, only those with tertiary education were significantly associated with a request to speak to the pharmacist. Similar results were obtained for increasing number of visits per month. Those with at least three visits in the last six months were significantly associated (OR 2.60; 95% CI, 1.25- 5.43; p-value=0.008) with speaking to the pharmacist compared to those with only one visit. These are shown in table 4. In multivariate analysis we found

Table 4. Association between patient characteristic and request to speak to the pharmacist

Characteristic	Frequency (%)	Odds ratio (CI)*	p-value
Age group (years)			
<25	45 (14.3)	Reference	-
25-34	60 (19.1)	0.79 (0.32-1.92)	0.6000
35-44	50 (15.9)	0.78 (0.31-1.95)	0.590
45-54	77 (24.4)	1.24 (0.52-2.95)	0.636
55-64	56 (17.9)	1.50 (0.59-3.84)	0.395
≥65	27 (8.6)	2.18 (0.59-7.81)	0.237
Sex			
Male	134 (41.6)	Reference	-
Female	188 (58.4)	1.01 (0.60-1.70)	0.967
Education			
None	38 (11.6)	Reference	-
Up to secondary level	193 (59.0)	1.42 (0.81-2.50)	0.216
Tertiary	96 (29.4)	3.37 (1.15-9.88)	0.018
Occupation			
Unemployed	77 (26.7)	Reference	-
Employed	211 (73.3)	1.23 (0.67-2.23)	0.505
Pharmacy visits in last 6 months			
Once	57 (18.5)	Reference	-
Twice	64 (20.7)	1.44 (0.62-3.30)	0.393
≥ Three times	188 (60.8)	2.60 (1.25-5.43)	0.008
Type of chronic disease			
Hypertension	129 (50.8)	Reference	-
Diabetes	83 (32.7)	0.98 (0.52-1.84)	0.951
Asthma	8 (3.2)	0.61 (0.14-2.69)	0.513
Arthritis	34 (13.4)	0.89 (0.38-2.13)	0.800
Others	77 (23.3)	0.97 0.47-2.00)	0.926

*Unadjusted odds ratios.

that those who reported little difficulty identifying the pharmacy staff were independently associated with about three times the odds (OR 3.19, 95% CI 1.78-5.80, p<0.001) of speaking to the pharmacist on their medicines compared with those who had some difficulty. This was after adjusting for age, patients' education and number of visits in the last six months.

DISCUSSION

According to Hepler and Strand [15], pharmaceutical care is the responsible provision of medicine therapy with the purpose of achieving specific outcomes that improve a patient's quality of life. In determining improvement in the patient's quality of life his/her role is paramount. The main concern of this study was to determine patients' perception of the role of the hospital pharmacist and their expectations on services provided by the latter.

Between 63.2% and 97.0% of participants reported receiving counselling service from the pharmacist after collecting their medication from the pharmacies under investigation. This disparity is unlikely to be due to experience of the pharmacist because there is an even distribution of pharmacists to the various satellite pharmacies by the pharmacy administration to ensure good service delivery. It could be due to some pharmacists personally performing better than others. The type of chronic disease and medication received may have led to more or less counseling and this is reflected in the type of pharmacy visited. In a study among hospital pharmacists on their role in the health care system in Pakistan, at least 42.0% mentioned patient education about their medicines [16]. Studies [17-19] have shown that an increase in the frequency of counselling, in addition to monitoring and guidance may lead to higher satisfaction rating. But client perception is an important driver of satisfaction [1]. This calls for improvement in counselling services in all pharmacy outlets of the hospital with special emphasis on those areas with a lower score in this survey. The quality of information received is very likely to be limited to drug administration. This is because for information on "medication side effects" or "drug interaction" or "healthy lifestyles" less than 50.0% of respondents reported having received this service. This trend was reported by researchers from Nigeria [8], another West African country. In contrast, 76.0% of respondents in Australia [20] in a cardiovascular disease survey said that pharmacists are capable of providing advice on lifestyle changes. The low rates of special service (healthy life styles, contra-indications and drug interactions) provision reported in the present study could be due to high patient turnover during the morning shift leading to inadequate provision of drug information. Furthermore, if most of our clientele came for repeat prescriptions, it would be assumed that they had already been counselled on their first visit. Policy makers in the pharmacy directorate should take the opportunity to encourage the provision of adequate drug information in all pharmacies.

Concerning responsibility of their health care needs, doctors were highly rated compared to pharmacists, nurses, the government, family members or other health care workers by respondents. This sounds plausible because doctors are the leaders of the health care team thus making their role the most significant. However, in a study in Trinidad and Tobago,

nurses were rated higher than doctors or pharmacists [21]. This calls for further efforts by pharmacists to improve their status as members of the health care team.

Although 60.2% of those interviewed expressed an improvement of their knowledge of the role of the pharmacist over the last five years, it is clear that more than 1out of every 5 respondents were not sure if they understood the pharmacist's role in giving advice on health related issues. Furthermore, only about 20.0% of respondents strongly disagreed with the statement that pharmacists are just medicine dispensers. It would be desirable to improve patients' awareness of the values of pharmaceutical care in order to change their perception of the pharmacist.

If patients are aware that one of the main responsibilities of the pharmacist is to provide information on medicines they may request for consultation more often. This study identified that clients who said they found it difficult to identify professionals at the pharmacy were less likely to assess some services at the pharmacy when compared with those who did not. Most of the literature on patient perception of the pharmacist did not look at this issue using multivariate analysis.

Researching on asthma patients' perception of the pharmacist Ried et al [22] observed that the patient may not be in the best position to ascertain the technical quality of the care they receive but they still appreciate the social interaction with the pharmacist. This underscores the need for pharmacists in this setting to explore ways of convincing patients and clients to appreciate their contribution. It will also give patients the chance to access better health care from the pharmacist. An introduction of medicines use review, for example, may improve the relationship between the patients and the pharmacist. If wearing of staff identity badges could be encouraged, most patients (even on their first visit) would be better informed.

This study had its limitations. The study interviewed patients patronising pharmacies of different clinics. This may be responsible for the differences in levels of service provision. The advantage here is that being the first of its kind in Ghana, this study has revealed prevailing issues at the different pharmacies and future studies could be directed at resolving such challenges. The presence of missing values, although low in this study, may have had an effect on study validity. But these were minimal and their effects may not significantly alter the results. Response bias may have occurred due to more people with greater interest in their health consenting to participate in this study [23].

CONCLUSION

Reports from patients in this study showed that the quality of information provided at the various pharmacies in the hospital were different. Counselling services at the various pharmacies in the hospital need to be revamped with emphasis on side effects, drug interaction and healthy lifestyles. The role of the pharmacist in the hospital should be more clearly understood and appreciated by patients. It was also found that patients who had little difficulty in identifying the pharmacist were more likely to speak with him/her. More work should to be done by pharmacists to educate patients on the role of the pharmacist in the provision of pharmaceutical care.

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REFERENCES

1. McDougall GHG, Levesque T. Customer satisfaction with services: putting perceived value into the equation. *J Serv Mark*. 2002;14(5):392 – 410.
2. Kucukarslan SN, Nadkarni A. Evaluating medication-related services in a hospital setting using the disconfirmation of expectation model of satisfaction. *Res Social Adm Pharm*. 2008;4(1):12-22.
3. Curtiss FR, Fry RN, Avey SG. Framework for the pharmaceutical services quality improvement- A bridge to cross the quality chasm. Part I. The opportunity and the tool. *J Manag Care Pharm*. 2004;10:60-78.
4. Morgall JM, Almarsdottir AB. The new consumer – implications for the pharmacy. *Int J Pharm Pract*. 1997;7:198–200.
5. Abu-Omar SM, Weiss MC, Hassell K. Pharmacists and their customers: a personal or anonymous service? *Int J Pharm Pract.* 2000;8:135–43.
6. Hassell K, Rogers A, Noyce P. Community pharmacy as a primaryhealth and self-care resource: a framework for understanding pharmacy utilization. *Health Soc Care Community*. 2000;8(1):40–9.
7. Tam VHY, Lim MM. Patients perceptions and expectations of outpatient pharmacy services in a teaching hospital. *Int J Pharm Pract.* 1997;5:128-32.
8. Erah PO, Chuks-Eboka NA. Patients' Perception of the Benefits of Pharmaceutical Care Services in the Management of Hypertension in a Tertiary Health Care Facility in Benin City. *Trop J Pharm Res*. 2008;7(1):897-905.
9. Ford RC, Bach SA, Fottler MD. Methods of measuring patient satisfaction in health care organizations. *Health Care Manag (Frederick)*. 1997;22(2):74-89.
10. MeadN,BowerP.Patient-centredness:Aconceptual framework and review of the empirical literature. *Soc Sci Med.* 2000;51(7);1087-1110.
11. Larson JW. Patient satisfaction with delivery of products and information by an ambulatory care pharmacy. *Am J Health Syst Pharm*. 1998;55: 1025–9.
12. The Ratiopharm CFP Report on Pharmacy Services: Consumers' Perception of Pharmacy.
13. www.msp.mb.ca/ wp-content/ uploads/ 2014/ 03/ ratiopharm_ consumer_perception_.pdf/. Accessed 13/11/2014
14. Smith PG, Morrow RH (Editors),. Field trials of health interventions in developing countries: A toolbox. London: Macmillan Education. 1996
15. Kane RL, Radosevich DM. Conducting health outcomes research. Sudbury, Massachusetts: Jones & Bartlett Learning. 2011.
16. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm.* 1990;47(3):533-543.
17. Azhar S, Hassali MA, Ibrahim MMI. Perceptions of Hospital Pharmacist's Role in Pakistan's Healthcare System: A Cross-Sectional Survey. *TJPR*. 2011;10 (1):11-17
18. Liu MY, Jennings JP, Sammelson WM, Sullivan CA, Veltri JC. Asthma patients satisfaction with 'the frequency and content of pharmacist counseling. *J Am Pharm Assoc*. 1999;39(4):493-8.
19. Bultman DC, Svarstad BL. Effects of pharmacist monitoring on patient satisfaction with antidepressant medication therapy. *J Am Pharm Assoc*. 2002;42(1):36-43.
20. Singhal PK, Gupchup GV, Raisch DW, Schommer JC, Holdsworth MT. Impact of pharmacists' directive guidance behaviors on patient satisfaction. *J Am Pharm Assoc*. 2002;42(3):407-12.
21. Peterson GM, Lackson SL, Hughes JD, Fitzmaurice KD, Murphy LE. Public perception of the role of Australian pharmacists in cardiovascular disease. *Journal of Clinical Pharmacy and Therapeutics*. 2010;35:671-677.
22. Singh H, Haqq ED, Mustapha N. Patients' perception and satisfaction with health care professionals at primary care facilities in Trinidad and Tobago. *Bulletin of the World Health Organization*. 1999;77 (4):256-360
23. Ried LD, Wang F, Young H, Awiphan R. Patients' satisfaction and their perception of the pharmacist. *J Am Pharm Assoc (Wash)*. 1999;39(6):835-42.
24. Ankrah DNA, Ofei CN. The effect of advice to read the medicine/patient information leaflet among patients in Ghana: A cross-sectional study. *JPHSR*. 2010;1:91-96.

Chapter 2.3

INSUFFICIENT ACCESS TO ORAL PAEDIATRIC MEDICINES IN GHANA: A DESCRIPTIVE STUDY

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ABSTRACT

Background

Among the most vulnerable people in society are children and this is especially so in their access to health care Off-label prescription of paediatric medicines is known to be associated with safety outcomes some of which may be serious. This study identifies frequently prescribed children's medicines that are not readily available in Ghana and are prepared extemporaneously.

Method

All prescriptions for extemporaneous oral preparations for children presented to the local production unit of the Korle-Bu Teaching Hospital from November, 2013 were eligible for the study. Information from such prescriptions was recorded in a systematic format. Presence of the prescribed medicine on the World Health Organization Children's Medicine List was ascertained in addition to the anatomical and therapeutic classification code. The registration of the prescribed medicine for paediatric use by the Food and Drugs Authority, Ghana was also checked. Descriptive statistics of the data was presented.

Results

In all 622 prescriptions for 35 different paediatric formulations were served. Prescriptions from several health facilities including government hospitals (6.6%, N=622), private hospitals (2.4%, N=622) and the University of Ghana hospital (1.1%, N=622) were all honoured. Some of the prescribed medicines (Baclofen, Clonazepam, Hydroxyurea and Lamotrigine) were neither on the World Health Organization Children's Medicine list nor registered with the Food and Drugs Authority, Ghana. Most prescribed medicines (88.6%, N=35) were for non-communicable diseases.

Conclusion

Paediatric prescriptions including off-label medicines are prescribed and formulated extemporaneously in this setting. Steps should be taken to improve access and monitor benefit-risk profiles of paediatric medicines in order to improve treatment outcomes among children

INTRODUCTION

Children are among the most vulnerable people in society, and concerted efforts are being made to increase their access to health care [1]. In times of illness, children need the appropriate medicines at the right time. Such medicines should be safe, efficacious, affordable and cost-effective.

Most adult oral medicines exist as tablets, capsules or caplets while most paediatric formulations are available as solutions, syrups, suspensions or granules for suspension. Adult medicines that may be used by children are not always readily available as paediatric formulations. For such medicines the best option is an extemporaneous formulation. It is on record that off-label use of medicines in children is associated with adverse reactions [2].

Extemporaneous preparations are available only in limited hospital pharmacies in Ghana, although most hospital pharmacies are superintended by pharmacists capable of producing such formulations. No private independent facilities produce individualised extemporaneous preparations in the country to date. The resultant pressure on the few existing facilities producing such formulations is extreme. In the end, it is parents or guardians of affected children who endure the most of such inadequacies by searching for these limited pharmacies because there are no arrangements for medicine pick-ups. This may lead to late treatment initiation among new patients and non-persistence among those already on treatment.

In Ghana, there are no guidelines for paediatric extemporaneous preparations, in contrast to places like Australia [3], for instance. There is no particular mechanism on how the price of such products should be calculated. To make matters worse, such products are not represented on the national health insurance medicines list, and patients must pay for these medicines out-of-pocket.

Ghana has an essential medicines list, which was adapted for use from the WHO Essential Medicines list [4]. The Ministry of Health Ghana under the Ghana National Drugs Programme (GNDP) has accepted the WHO priority medicines list for children and maternal health as a working document [5]. Having these medicine lists is necessary but not sufficient to guarantee treatment. Policy makers must ensure that systems are in place to provide the required medicines in the medicines list. Although extemporaneous formularies are difficult to obtain, Pharminfotech (New Zealand) has a formulary that is electronically accessible and free of charge [6].

This study aimed to identify frequently prescribed children's medicines that are not readily available as manufactured preparations in Ghana and are thus prepared extemporaneously.

METHODS

Setting

The study was carried out at the local production unit (LPU) of the Korle-Bu Teaching Hospital (KBTH) in Accra, Ghana. KBTH is a referral hospital with a 2000-bed capacity.

The LPU is the arm of the Pharmacy Department of the hospital responsible for various extemporaneous formulations. Approximately 50 patients receive extemporaneous preparations from the LPU every week. These are predominantly in the form of oral suspensions and syrups. Preparations are formulated here with guidance from the Pharminfotech [6] online formulary.

Most of the prescriptions were from the hospital's Child Health Sub-Budget Management Centre (sub-BMC) and the children's unit of the National Cardio-Thoracic Centre (NCTC). The rest of the prescriptions were from other hospitals in the country.

Participants and data collection

All prescriptions for extemporaneous oral preparations for children presented to the LPU from November 2013 were eligible for the study. Information from such prescriptions was recorded in a systematic format. The date, treatment centre, patient's name and sex, age, name of preparation, and parent/caregiver-reported morbidity were captured prospectively**.** The data were anonymized for this study. Parent/caregiver reported morbidity was recorded because we did not use patient's health records. Data capture continued until no new prescriptions were received for 14 continuous days. Patients who came for the same medication with different prescriptions on different occasions were captured more than once. However, those who came for refills on the same prescription form were only captured once.

Analysis

The presence of the prescribed medicine on the WHO Children's Medicines List was ascertained. Registration of the prescribed medicine for paediatric use by the Food and Drugs Authority (FDA) Ghana was also determined. The anatomical and therapeutic chemical (ATC) classification by the WHO [7] was also identified. Descriptive statistics of the data are presented using Stata intercooled version 12 (Stata Corp LP, College Station, TX, USA).

RESULTS

There were 622 individual prescriptions for extemporaneous preparations that were submitted during the study period. The highest proportion of prescriptions (0.35, 217/622) was in the first month of the study. This amount decreased gradually with time. Prescriptions from the Child Health sub-BMC and the NCTC amounted to 87.1% of all requests for paediatric formulations, as would be expected given their association with the LPU. One prescription from Tamale Teaching Hospital, the most distant treatment site from the LPU (a distance of about 616 km from the study site) was dispensed. There were 7 (1.1%) prescriptions from the University of Ghana hospital (Table 1). Prescriptions dispensed involved those for neonates, infants and children below 9 years.

The most frequently reported morbidities were cardiovascular diseases, anaemia and seizures. Table 2 shows the list of drugs and their ATC classifications. Furosemide

Table 1. Characteristics at baseline

Characteristic	Frequency (N=622)	Percentage frequency	Average distance from dispensary (km)*
Period			
November 2013	217	35.0	Not applicable (N/A)
December 2013	182	29.2	N/A
January 2014	106	17.0	N/A
February 2014	117	18.8	N/A
Sex			
Male	272	43.7	N/A
Female	350	56.3	N/A
Hospitals			
Child Health Department	293	47.1	0
NCTC[τ]	249	40.0	0
Government Hospitals	41	6.6	72
37 Military Hospital	16	2.6	12
Private Hospitals/Clinics	15	2.4	15
Tamale Teaching Hospital	1	0.2	616
University of Ghana Hospital	7	1.1	18
Age groups			
≤ 1 month	37	6.0	N/A
>1 month – 12 months	167	26.8	N/A
> 12 months – 60 months	250	40.2	N/A
> 60 months	25	4.0	N/A
Missing	143	23.0	N/A

[τ] National Cardio-Thoracic Centre. *Average distance was used because of grouped data.

(31.2%, N=622), spironolactone (28.1%, N=622), folic acid (9.0%, N=622), propranolol (8.0%, N=622) and clonazepam (3.2%, N=622) suspensions were the top five most dispensed medicines. Some medicines were also dispensed, which were neither registered by the FDA Ghana nor present on the WHO Children Medicines List 2010 [1]. These included baclofen (1.9%, N=622), clonazepam (3.2%, N=622), hydroxyurea (2.6%, N=622) and lamotrigine (1.0%, N=622).

DISCUSSION

This study shows that a number of prescribed medicines for paediatric use are not readily available on the Ghanaian market, and are formulated extemporaneously using adult tablets. The formulations are prepared only at restricted facilities and care givers have to travel long distances for their medicines. Furthermore, the study reveals that some of the prescribed medicines are neither present on the WHO priority medicines list for children

Table 2. Prescribed medicines at baseline with ATC codes

Suspension/syrup	Number of prescriptions (%)	Prescription ever registered in Ghana	Prescription registered for oral paediatric use	Availability on children EML*	ATC code [7]
	(N=622)				
Baclofen	12 (1.9)	No	-[+]	No	M03BX01
Captopril	15 (2.4)	Yes	No	No	C09AA01
Clonazepam	20 (3.2)	No	-	No	N03AE01
Digoxin	2 (0.3)	Yes	No	Yes	C01AA05
Domperidone	2 (0.3)	Yes	Yes	No	A03FA03
Enalapril	2 (0.3)	Yes	No	Yes	C09AA02
Folic acid	56 (9.0)	Yes	Yes	Yes	B03BB01
Furosemide	194 (31.2)	Yes	No	Yes	C03CA01
Hydroxyurea	16 (2.6)	No	-	No	L01XX05
Levetiracetam	2 (0.3)	Yes	No	No	N03AX14
Lamotrigine	6 (1.0)	No	-	No	N03AX09
Lisinopril	3 (0.5)	Yes	No	No	C09AA04
Metoclopramide	2 (0.3)	Yes	Yes	Yes	A03FA01
Nalidixic acid	2 (0.3)	Yes	No	No	J01MB02
Nifedipine	4 (0.6)	Yes	No	No	C08GA02
Nitrofurantoin	3 (0.5)	Yes		Yes	J01XE01
Phenobarbitone	14 (2.3)	Yes	Yes	Yes	N03AA02
Prednisolone	2 (0.3)	Yes	Yes	Yes	H02AB06
Propranolol	50 (8.0)	Yes	Yes	Yes	C07BA05
Pyrimethamine	3 (0.5)	No	-	Yes	P01BD01
Ranitidine	2 (0.3)	Yes		Yes	A02BA02
Risperidone	7 (1.1)	Yes	No	No	N05AX10
Sildenafil citrate	13 (2.1)	Yes	No	No	G04BE03
Spironolactone	175 (28.1)	Yes	No	Yes	C03DA01
Sulfadiazine	3 (0.5)	No	-	Yes	J01EC02
Topiramate	3 (0.5)	Yes	-	No	N03AX12
Others	9 (1.4)	-	-	-	-

*WHO Model Formulary for Children 2010. [+]There was no information on product.

[1] nor registered with the Food and Drugs Authority in the country. The study also reveals that most of the formulated medicines are for management of non-communicable disease.

This article emphasizes the need to provide alternative and appropriate formulations for infants and children where manufactured formulations are not readily available. Our findings also suggest that pharmacists should learn the techniques involved in preparation of extemporaneous products to make life easier for patients and their caregivers without compromising safety.

There is an urgent need for immediate assessment and harmonization of the paediatric extemporaneous preparation situation in Ghana. Pharmacists should be trained in all regional hospitals and encouraged to train pharmacists in other practice settings throughout their regions. There should be proper evaluation of prescription patterns and provision of basic accoutrements for effective production and dispensing. Pharmacists involved with such formulations should be well motivated to deliver medication promptly and avoid excessive patient waiting times.

About 90% of formulated medicines are indicated in management of non-communicable diseases. According to the WHO, congenital anomalies and other non-communicable diseases contribute to 7% of all deaths among infants and children aged below 5 years [8]. This underscores the importance of these formulations or a search for appropriate pre-formulated alternatives. Policy makers need to make an immediate intervention to bring this situation under control.

Reports from UNICEF indicate that in 2012 about 44% of all deaths in children younger than 5 years occurred in neonates, but most of these deaths were preventable [9]. Although malnutrition has been cited as one of the underlying reasons for these deaths, unavailability of the appropriate prescribed medicine could also be a contributing factor [9].

The fact that teaching hospitals, university hospitals, government hospitals, private hospitals, and clinics are all prescribing these paediatric formulations indicates the extent to which they have become essential. The high number of prescriptions at the KBTH Child Health sub-BMC and the NCTC (both referral centres) in our study clearly shows that these medicines are mostly prescribed by specialists and/or consultants. This calls for re-evaluation of the national essential medicines list.

The use of unlicensed or off-label medicines among paediatric patients has been reported to be significantly associated with an increased risk of developing an adverse drug reaction [2]. Furthermore, among some hospitalised children, up to 90% of medicines are prescribed off-label [10-14]. For those medicines that are neither present on the Children's Medicines list nor registered with the FDA Ghana for paediatric use, measures should be taken to rectify the situation and encourage proper monitoring of benefit-risk profiles of such medicines among this subgroup.

The use of specially formulated medicines is not limited to low and medium income countries like Ghana. In the United Kingdom (UK) these products are popularly called "specials" or "special order product" [15]. Most specials are unlicensed formulations of a licensed medicine [15]. The difference is that such facilities are well established, accessible, and regulated. Special formulations are available in New Zealand [6] and Australia [3] where well established formularies are used.

Our study captured only those prescriptions that were filled. If prescriptions that were not dispensed had also been captured, this would have been more interesting. This would further emphasize the magnitude of the unmet need for paediatric formulations in Ghana. There were missing values for patient's age. This occurred because data were captured from prescription forms, some of which did not indicate the patient's age. This information would have allowed the most at-risk age group for these formulations to be identified.

CONCLUSION

In conclusion, the non-availability of pre-formulated paediatric medicines in Ghana has resulted in the extemporaneous formulation of such medicines using adult tablets. Only limited facilities provide this service. Ghana, and other countries facing this challenge could learn from the UK by encouraging the establishment of facilities for the preparation of specials at strategic positions throughout the country and regulate them. The current situation poses a challenge to care givers who have to travel long distance to procure these medicines. Some of these medicines are neither present on the WHO Children's Medicines list nor registered with the FDA Ghana, emphasizing the possibility of off-label use of medicines. Steps should be taken by policy makers to involve more facilities in the preparation of these medicines while the search for pre-formulated forms continue.

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REFERENCES

1. WHO Model Formulary for Children 2010. Based on the Second Model List for Essential Medicines for Children 2009. World Health Organization.
2. Neubert A, Dormann H, Weiss J, Egger T, Criegee-Rieck M, Rascher W, et al. The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. *Drug Saf*. 2004;27(13):1059-1067.
3. Department of Health, Pharmaceutical Benefits Scheme, Australia. Available: http://www.pbs.gov.au/ info/ healthpro/ explanatorynotes/ section1/ Section_1 _9 _Explanatory _Notes. Accesses: 25/10/2014.
4. Sinclair D, et al. Integrating Global and National Knowledge to Select Medicines for Children: The Ghana National Drugs Programme. *PLOS Medicine*. 2013;10(5):e1001449.
5. Priority medicines for mothers and children 2011. World Health Organization. Department of essential medicines and pharmaceutical policies. Available: http://www.who.int/medicines/publications/A4prioritymedicines.pdf. Accessed: 2/08/2014.
6. Pharminfotech. Available: www.pharminfotech.co.nz. Accessed 20 August, 2013.
7. ATC/DDD Index 2014. WHO Collaborating Centre for Drug Statistics Methodology. Norwegian Institute of Public Health. Available: http://www.whocc.no/atc_ddd_index/. Accessed 26/11/2014.
8. Committing to child survival: A promise renewed. Progress report 2013. Available: http://www.unicef.org/lac/Committing_to_Child_Survival_APR_9_Sept_2013.pdf Accessed: 01/12/2014.
9. Causes of death among children under five years 2013. Available: http://www.who.int/gho/child_health/mortality/causes/en/. Accessed 1 December, 2014.
10. McIntyre J, Conroy S, Avery A, et al. Unlicensed and off label prescribing of drugs in general practice. *Arch Dis Child* 2000; 83:498-501.
11. Pandolfini C, Impicciatore P, Provasi D, et al. Off-label use of drugs in Italy: a prospective, observational and multicentre study. *Acta Paediatr* 2002;91:339-347.
12. Conroy S, Choonara I, Impicciatore P, et al. Survey of unlicensed and offlabel drug use in paediatric wards in European countries. *BMJ* 2000;320:79-82.
13. Cuzzolin L, Zaccaron A, Fanos V. Unlicensed and off-label uses of drugs in paediatrics: a review of the literature. *Fundam Clin Pharmacol* 2003;17:125-131.
14. Stephenson T. Medicines for children - the last century and the next. *Arch Dis Child* 2001;85:177-179.
15. Chaplin S. How drug tariff specials have reduced prescribing costs. Prescriber 2014;25(5):27-29.

Chapter 3

THE ROLE OF ADHERENCE IN ACHIEVING OPTIMAL TREATMENT OUTCOMES IN HIV MANAGEMENT

Chapter 3.1

FIVE-YEAR TRENDS IN TREATMENT CHANGES IN AN ADULT COHORT OF HIV/AIDS PATIENTS IN GHANA

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Submitted

ABSTRACT

Background

There is limited information on patterns of treatment change among new initiators of highly active antiretroviral therapy (HAART) in the regions most affected by HIV/AIDS.

Objectives

To examine treatment change patterns over a five-year period among initiators of HAART.

Patients and Method

Data were obtained from the Fevers' Unit Database at the Korle-Bu Teaching Hospital. All adult treatment naive patients who started treatment with first line HAART between 1st January, 2008 and 31st December, 2012 were followed over a minimum period of three months. The main outcome was the rate of first treatment change, defined as the first substitution/switch in accordance with the standard treatment guidelines. Data were analyzed according to year of treatment initiation.

Results

A total of 3,933 patients were followed with almost equal numbers of initiators per year. The mean age (standard deviation) at treatment initiation was 39 (10.3) years. The most prescribed HAART combination was AZT/3TC/EFV, remaining relatively stable over the years. Utilization of stavudine containing HAART increased gradually until 2010 and by the end of 2012 had dropped to zero. There was an increase in the use of tenofovir (TDF), partly to compensate the reduced use of stavudine containing HAART combinations. Kaplan-Meier curves showed that treatment change was higher among those who started treatment later in the study period compared to those who started earlier.

Conclusion

A major treatment change in the utilization of antiretroviral medicines in Ghana occurred 2008-2012, mainly as a result of international policy changes to improve prognosis among HIV/AIDS patients.

INTRODUCTION

The most important intervention that delays the progression of HIV to AIDS, assuming optimum adherence, is treatment with highly active antiretroviral therapy (HAART) [1]. The first antiretroviral drug, zidovudine was mentioned in October 1985; currently there are at least seven categories of HAART in use, mostly in combinations of different antiviral products [2]. This has led to structured treatment strategies, virtually always under the guidance of national or institutional guidelines. Treatment of naïve patients starts with a first line HAART, but regimens may change depending on adverse effects or on inefficacy as a result of development of drug resistance (virological or immunological). Treatment guidelines are adjusted over time based on such insights and evidence. A typical case is the recommendation to phase out stavudine in the management of HIV/AIDS by the WHO from 2010, because of associated mitochondrial toxicities [3-5] manifested as lipodystrophy, lactic acidosis and peripheral neuropathy [6]. This underscores the importance of considering the content and revisions of treatment guidelines when studying time trends of HAART, but such studies are rare in the literature. Notwithstanding its toxicity profile, stavudine is not as expensive as other nucleoside (or nucleotide) transcriptase inhibitors [3].

In several countries, HIV/AIDS risk populations and treatment cohorts have been studied over the last decades. These include for example, the Amsterdam Cohort of homosexual men and drug users which started in 1984, the North-East London Cohort which has been the largest HIV-2 cohort in the United Kingdom, and the Swiss HIV Cohort which looked at uptake of antiretroviral therapy, survival and progression to AIDS [7-9]. Sub-Saharan Africa has several of such HIV/AIDS cohorts which is understandable because about more than three-quarter of the disease burden is from this region [10]. An example is the KwaZulu-Natal HIV/AIDS cohort nested within the Africa Centre Demographic Information System (ACDIS) cohort [11]. The existence of these cohorts notwithstanding, there is limited information on patterns and determinants of treatment change among new initiators of HAART in the regions most affected by HIV/AIDS.

In Ghana well organized government sponsored HIV/AIDS treatment began in the year 2003 following a period of dominance by private retailers who kept no structured records. As of December 2003, HAART for Ghana's HIV/AIDS population was being managed by only three treatment centers in the country, including the Korle-Bu Teaching Hospital (KBTH) treatment center in Accra. Treatment of HIV/AIDS has since been decentralized, increasing the number of treatment centers from just 3 in 2003 to 179 by December 2014 [12]. The situation has improved over the years but more work is on-going.

This study involves the HIV/AIDS cohort at the KBTH. It is a retrospective cohort study that examined HAART initiation and changes per individual inception year over a five-year period (2008-2012).

PATIENTS AND METHODS

Study site

The Fevers Unit of the KBTH was the study site. The Fevers Unit is one of many units of the Department of Medicine and Therapeutics. The Unit is responsible for the registration and management of all cases diagnosed as HIV/AIDS at the KBTH, as well as those referred from other health institutions in Ghana. Provision of antiretroviral therapy in the Unit started in December 2003. As of 2015, nearly 10,000 clients have been put on HAART at the treatment site. There are three major out-patient clinic days per week, each with an average clinic attendance of about 120 patients per day.

Subjects

All treatment naive patients who started treatment with first line HAART between 1st January, 2008 and 31st December, 2012 were eligible for this study if they were 15 years or older, enrolled at the Fevers Unit of KBTH and received HAART at the hospital's pharmacy. The date of exposure was the first date the patient received HAART and each patient was followed over a minimum period of three months. Patients were followed and analyzed per individual inception year, i.e. 2008, 2009, 2010, 2011, and 2012 respectively. All patients receiving treatment for prevention of maternal to child transmission (PMTCT) of HIV/AIDS were excluded from the study if they were not on full HAART. PMTCT patients who started on full HAART and those who resumed full HAART were enrolled on the date this occurred.

Data source

De-identified and anonymous data for this study were obtained from the Fevers Unit Database at the KBTH. In this database diagnostic and treatment records of all newly registered HIV/AIDS patients at the KBTH are captured. Variables in this study were electronically available, and included patient identity, age, sex, inception treatment type and date of inception, date of next treatment appointment and treatment change, and WHO disease stage at treatment initiation.

Study outcome

The main outcome was the first treatment change in the year of inception; each person had at least 3 months of follow-up in that year. First treatment change was defined as the first substitution with another first-line drug or a first switch to a second-line drug as recommended by the treatment guidelines for HAART in Ghana during the study period. Death was defined as any case captured as such in the database. A loss to follow-up was defined as any patient who missed a refill appointment and had no information in the database until 60 days after the next appointment date. For patients who did not change treatment, follow-up was censored at the death date (as captured in database), date of transfer to another treatment site, or end of study period, whichever occurred first.

Ethics

Anonymous data, with no identifiable information on participants were obtained from the data administrator. Permission to use data on HIV/AIDS patients in this facility was obtained from the Ethical and Protocol Review Committee of the University of Ghana Medical School in an earlier study by the same lead author.

Data analysis

Frequency distributions of baseline variables were calculated. Age was categorized into six bands and treatment initiation and changes were captured according to the HAART combination. Proportions of treatment initiation and change were calculated for type of initial HAART per inception year. Kaplan-Meier plots of year of treatment initiation and HAART combinations during follow-up from 2008 to 2012 were made and corresponding log-rank tests were done.

During the study period, HAART guidelines in Ghana were revised two times, the third edition in 2008 and the fourth in 2011 [13]. In the fourth edition, a major amendment was made replacing stavudine (d4T) with a nucleoside/nucleotide reverse transcriptase inhibitor (in our case tenofovir, TDF) due to stavudine induced side effects. The effects of this event on treatment change was captured in this study. SAS software version 9.3 (SAS Institute, Cary, NC, USA) was used for all analysis.

3.1

RESULTS

Over the 5-year period a total of 3,933 patients were followed with almost equal numbers of initiators per year. The mean age (and standard deviation) of females at treatment initiation was 37 (10.0) years and for males it was 42 (9.9) years, but overall the mean age at treatment initiation was 39 (10.3) years with most patients between ages 26 and 55 years (Table 1). Among those patients for whom WHO disease stage at baseline was known, WHO stage III was the most predominant group. The completeness of WHO stage recording improved over the years from about 40% in 2008 to virtually 100%, in 2012 respectively. The most prescribed HAART combination in this study was AZT/3TC/EFV, remaining relatively stable over the years. Stavudine containing HAART increased gradually until 2010 and dropped to zero in 2012 following WHO recommendations. There was an increase in the use of tenofovir (TDF), partly to compensate the reduced use of stavudine containing HAART combinations. Recorded deaths as a percentage of those who were initiated HAART from 2008 to 2012 were 3.8, 8.0, 6.5, 5.8, and 6.0 respectively.

Table 2 shows that for HAART type, stavudine combinations dominated treatment changes, reflected in two plausible patterns, i.e. before 2011 probably due to the surge of safety concerns, from 2011, onwards as a result of the WHO initiated guidelines revisions to ban stavudine. Stavudine combination therapy was deliberately replaced with other combinations from early 2011 and by the beginning of year 2012 most patients have been

moved to other HAART combination therapies. There was no trend among the different age groups and sex regarding treatment changes.

Table 1. Characteristics of five inception cohorts of HAART initiators (2008-2012)

Variable	2008 (%) N=836	2009 (%) N=810	2010 (%) N=804	2011 (%) N=753	2012 (%) N=730
WHO stage					
I	11 (1.3)	18 (2.2)	108 (13.5)	110 (14.6)	155 (21.2)
II	164 (19.6)	66 (8.2)	133 (16.6)	148 (19.7)	150 (20.6)
III	105 (12.7)	50 (7.4)	221 (27.5)	343 (45.5)	313 (42.9)
IV	71 (8.5)	52 (6.4)	123 (15.3)	143 (19.0)	102 (14.0)
Missing	485 (57.9)	614 (65.8)	218 (27.1)	9 (1.2)	10 (1.4)
Age group					
≤ 25 years	37 (4.4)	37 (4.6)	35 (4.4)	45 (6.0)	45 (6.2)
26 – 35	253 (30.3)	247 (30.5)	218 (27.1)	205 (27.2)	189 (25.9)
36 – 45	265 (31.7)	258 (31.8)	255 (31.8)	246 (32.7)	227 (31.1)
46 – 55	154 (18.4)	130 (16.0)	148 (18.4)	131 (17.4)	145 (19.9)
56 – 65	37 (4.4)	29 (3.6)	48 (6.0)	30 (4.0)	48 (6.6)
> 65	90 (10.8)	109 (13.5)	99 (12.3)	96 (12.8)	76 (10.4)
Gender					
Male	290 (34.7)	301 (37.2)	289 (36.0)	252 (33.5)	241 (33.0)
Female	546 (65.3)	509 (62.8)	515 (64.0)	501 (66.5)	489 (70.0)
Initial treatment					
AZT/3TC/EFV	331 (39.6)	263 (32.5)	271 (33.7)	286 (38.0)	317 (42.4)
AZT/ETC/NVP	238 (28.5)	193 (23.8)	166 (20.7)	147 (19.5)	154 (21.1)
d4T/3TC/EFV	154 (18.4)	208 (25.7)	239 (29.7)	117 (15.5)	0 (0)
d4T/3TC/NVP	101 (12.1)	137 (16.9)	103 (12.8)	58 (7.7)	0 (0)
TDF/3TC/EFV	3 (0.4)	2 (0.3)	7 (0.9)	100 (13.3)	202 (27.7)
TDF/3TC/NVP	0	1 (0.1)	3 (0.4)	26 (3.5)	41 (5.6)
Other	9 (1.1)	6 (0.7)	15 (1.9)	19 (2.5)	16 (2.2)
Recorded death	**32 (3.8)**	**65 (8.0)**	**52 (6.5)**	**44 (5.8)**	**44 (6.0)**
Number with treatment change	(N=234)	(N=240)	(N=280)	(N=171)	(N=35)
AZT/3TC/EFV	41 (17.5)	20 (8.3)	21 (7.5)	20 (11.7)	16 (45.7)
AZT/ETC/NVP	26 (11.1)	23 (9.5)	13 (4.6)	15 (8.8)	13 (37.1)
d4T/3TC/EFV	98 (41.9)	119 (49.2)	158 (56.6)	87 (50.9)	0
d4T/3TC/NVP	66 (28.2)	80 (33.1)	84 (29.9)	40 (23.4)	0
TDF/3TC/EFV	1 (0.4)	0	1 (0.4)	1 (0.6)	2 (5.7)
TDF/3TC/NVP	0	0	0	1 (0.6)	2 (5.7)
Other	2 (0.9)	0	3 (1.1)	7 (4.1)	2 (5.7)

Kaplan-Meier curves show that treatment change was higher among those who started treatment later in the study period compared to those who started earlier. This is shown on Figure 1. At the end of the study period (see figure 2), 91.1%, 97.7%, and 92.0% of those on a zidovudine combination therapy, tenofovir combination therapy, and those on "other" combination therapy respectively, were censored compared with only 34.6% of those on a stavudine combination therapy, (p<0.0001).

Table 2. Treatment changes stratified for HAART regimen and log-rank test by inception year.

Variable	2008	2009	2010	2011	2012
Initial treatment	**(N=234)**	**(N=240)**	**(N=280)**	**(N=171)**	**(N=35)**
AZT/3TC/EFV	41	19	21	20	16
AZT/ETC/NVP	26	23	13	15	13
d4T/3TC/EFV	98	118	158	87	0
d4T/3TC/NVP	66	80	84	40	0
TDF/3TC/EFV	1	0	1	1	2
TDF/3TC/NVP	0	0	0	1	2
Other	2	0	3	0	2
Log rank test p-value	<0.0001	<0.0001	<0.0001	<0.0001	0.012

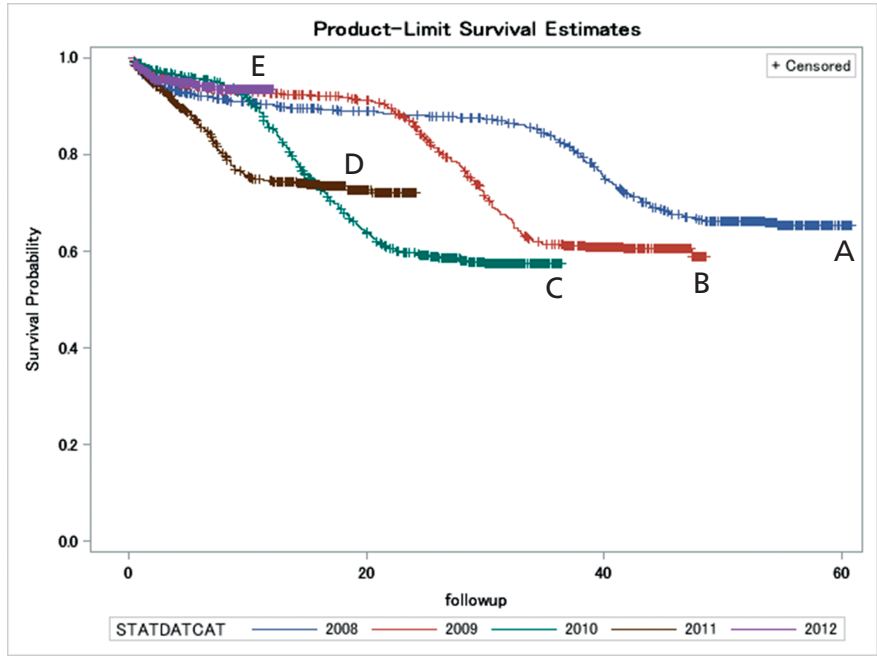

Figure 1. Kaplan-Meier (K-M) plots of treatment change patterns by year from 2008 to 2012. A - Year 2008, B - Year 2009, C – Year 2010, D – Year 2011, E – Year 2012.

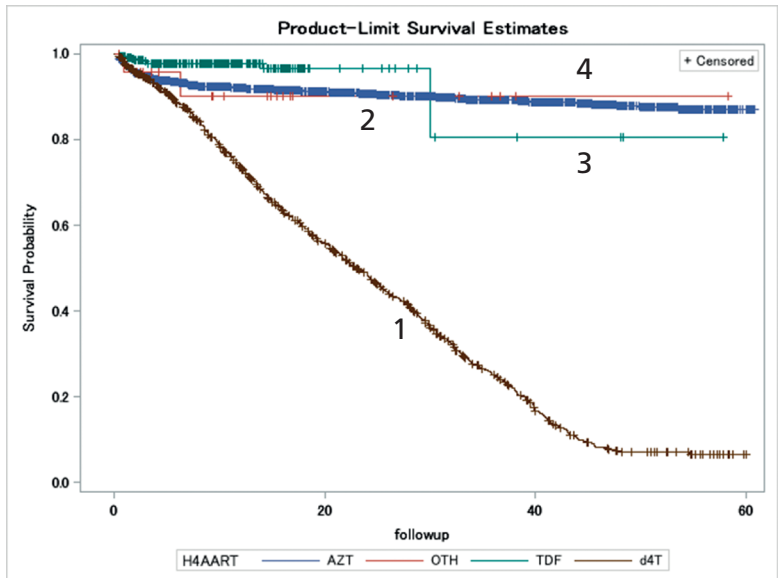

Figure 2. K-M plots of treatment change for the main HAART combinations during follow up. 1. Stavudine (d4T) base, , 2. Zidovudine (AZT) base 3. Tenofovir (TDF) base 4. Other (OTH) combinations.

DISCUSSION

This study showed that zidovudine based combination therapy was the most prescribed HAART over time in all the five inception cohorts. By the end of the study period, most patients on stavudine based combination therapy had their treatment replaced with a tenofovir or zidovudine based combination.

In the first three years during follow-up treatment change was initially gradual. This was followed by a period of steep treatment change and then it ended with another gradual phase. Those who started treatment from 2011 missed the initial gradual phase but experienced a steep phase followed by a gradual treatment changing phase. This implies that something may have triggered the treatment change after 2010. In particular, in the 2010 revision of the antiretroviral therapy for HIV infection for adults and adolescents [14], the WHO recommended a progressive replacement of stavudine in HIV/AIDS treatment centers, and gave directions on how less endowed health systems should roll out these changes in order to avoid wastage and contain cost. Patients at increased risk of toxicity were the first to be affected, and gradually, all those on stavudine had their treatment substituted. The need to change was as a result of empirical evidence of toxicity associated with the use of stavudine [3-6, 15, 16].

It was evident that most patients in this cohort, originally on stavudine, had a replacement with tenofovir over time. These changes were made based on well informed reasons. Stavudine-related dyslipidemia was reduced significantly after replacement with tenofovir [17]. This was due to improvement in total cholesterol, low density lipoprotein cholesterol and triglyceride levels [17]. In a randomized double blind study, Gallant et al [18] reported

that tenofovir was as efficacious as stavudine but the former had better lipid profiles and reduced lipodystrophy compared to the latter. This is a clear case of superior benefit-risk profile of tenofovir over stavudine. Changes from stavudine to zidovudine as observed in this study were moderate, in line with what we know about the about the differential profiles of these products [19]. All this adds to the commitment of HIV policy makers to ensure that HIV/AIDS patients attain optimum quality of life during treatment.

Our results underscore how effective the Ghanaian health system adhered to WHO's new treatment policy intervention, also in terms of adequate recording of patient data. This has been particularly reflective by the fact that in the 2008 cohort almost two-third of the cohort members had no recording about WHO disease stage, in the 2012 cohort recording was almost universal.

The observation of low frequencies of deaths in this study may be due to various reasons. Overall, the data show evidence for strong population treatment effects, even the study site was a national referral site with an increased probability of having the sickest HIV/AIDS patients from the country.

In conclusion, between 2008 and 2012, utilization of antiretroviral medicines in Ghana went through a major transition. In this period, stavudine was replaced predominantly with tenofovir. Stavidine has since been phased out of HIV/AIDS treatment among adults in Ghana. These changes were as a result of several factors, notably international policy changes firmly grounded on empirical evidence. Our findings mean that the policy was well accepted and implemented by the health sector in Ghana. Low and medium income countries need to hasten in the implementation of health interventions to safeguard public health and improve quality of life of patients.

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REFERENCES

1. Health Topics, HIV/AIDS. http://www.who.int/topics/hiv_aids/en/.
2. de Clercq E. Antiretroviral Drugs. *Curr Opin Pharmacol* 2010;10(5):507-515.
3. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach 2013. http://apps.who.int/ iris/ bitstream /10665 /85321/1/9789241505727_eng.pdf?ua=1.
4. Policy brief. AIDS medicines and diagnostic service: Transition to new HIV treatment regimens - Procurement and supply chain management issues. www.apps.who.int/iris/ bitstream/10665/104449/WHO_HIV_2014.4_ ENG.PDF?=1.
5. Gallant JE, Staszewski S, Anton L, Pozniak AL, DeJesus E, Suleiman JMAH et al. Efficacy and Safety of Tenofovir DF vs Stavudine in Combination Therapy in Antiretroviral-Naive Patients: A 3-Year Randomized Trial. *JAMA*. 2004;292:191-201
6. Boulle A, Orrell C, Kaplan R, Cutsem GV, McNally M, Hilderbrand K, *et al*. Substitutions due to antiretroviral toxicity or contraindications in the first three years of antiretroviral therapy in a large South African cohort. *Antivir Ther* 2007;12:753-760.
7. Coutinho RA. Amsterdam cohort studies on HIV and AIDS. *J Acquir Immune Defic Syndr* 1998;17(1):S4-S8
8. Elamin W, Bibby DF, Clark DA, Anderson J, Deayton JR. HIV-2 in the United Kingdom-the North East London Cohort. *HIV MEDICINE* 2013;14:53-53.
9. Staehelin C, Rickenbach M, Low N, Egger M, Ledergerber B, et al. Migrants from Sub-Saharan Africa in the Swiss HIV Cohort Study: access to antiretroviral therapy, disease progression and survival. *AIDS* 2003;17:2237–2244
10. UNAIDS. Global AIDS epidemic facts and figures, 2012: Geneva, Switzerland; UNAIDS; 2012.
11. Tanser F, Hosegood V, Barnighausen T, Herbst K, Nyirenda M, et al. Cohort Profile: Africa Centre Demographic Information System (ACDIS) and population-based HIV survey. *Int J Epidemiol* 2008;37:956–962
12. Country AIDS Response Progress Report, Ghana, January 2013 – December 2014. Ghana AIDS Commission, UNAIDS.
13. Guidelines for antiretroviral therapy in Ghana.Ministry of Health, Ghana Health Service. 2002, 2005, 2008 and 2011.
14. Antiretroviral therapy for HIV infection and adults and adolescents: recommendations for a public health approach. 2010 rev. WHO 2010.
15. Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N. Adverse effects of highly active antiretroviral therapy in developing countries. *Clin Infect Dis* 2007;45(8):1093-101.
16. McComsey G, Lonergan JT. Mitochondrial dysfunction: patient monitoring and toxicity management. *J Acquir Immune Defic Syndr* 2004;37 Suppl 1:S30-5.
17. Llibre JM, Domingo P, Palacios R, Santos J, Pe´rez-Eli´as MJ, la Rosa SR et al. Sustained improvement of dyslipidaemia in HAART treated patients replacing stavudine with tenofovir. *AIDS* 2006,20:1407–1414
18. Gallant JE, Staszewski S, Anton L, Pozniak AL, DeJesus E, Suleiman JMAH et al. Efficacy and Safety of Tenofovir DF vs Stavudine in Combination Therapy in Antiretroviral-Naive Patients: A 3-Year Randomized Trial. *JAMA*. 2004;292:191-201
19. Spaudling A, Rutherford GW, Siegfield N. Stavudine or zidovudine in three-drug combination therapy for initial treatment of HIV infection in antiretroviral naïve individuals. (Review) Copyright © 2011. The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.

Chapter 3.2

ADHERENCE AND TREATMENT CHANGE AMONG HIV/AIDS PATIENTS IN GHANA: A NESTED CASE-CONTROL STUDY

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ABSTRACT

Background

A level of 95% adherence to antiretroviral therapy (ART) has been found to benefit HIV/AIDS patients. Low adherence may lead to treatment failure, and may subsequently result in treatment change. The main objective of this study was to evaluate the effect of ART adherence on treatment change

Method

Data were extracted from available written clinical and pharmacy records, and the electronic database at the Korle-Bu Teaching Hospital. Cases comprised all those (≥15 years) who experienced a first treatment change after starting first-line ART between 1/1/2004 and 31/12/2009. Controls (who did not change treatment) were sampled from the same cohort of ART starters and matched to cases on date ART was started. Adherence was determined using the proportion of days covered (PDC) approach and poor adherence was defined as PDC levels below 95%. Measures of effect were calculated using conditional logistic regression.

Results

The 298 cases and 298 matched controls were similar in most baseline characteristics. Among cases 20.1% (60/298) switched to second-line therapy and the rest had treatment substitutions. Overall, 88.9% of controls compared with 79.9% of cases had adherence levels greater than or equal to 95% (p=0.003). After adjusting for possible confounders, an adherence level below 95% was associated with almost four times (ORadj=3.56 (95% CI 1.60 to 7.88)) the likelihood of having a treatment change.

Conclusion

This study showed that insufficient ART adherence was associated with about four times the likelihood of treatment change. Policy makers must partner researchers to engage patients more often, to unravel the causes of non-adherence, and make the necessary interventions for patients to achieve maximum benefits from dispensed medicines.

INTRODUCTION

Public access to antiretroviral medicines in Ghana began in mid-May 2003. By the end of December 2012, a total of 73,339 clients were receiving antiretroviral therapy (ART) [1] throughout the country. The availability of ART has led to improved quality of life and an increase in life expectancy among HIV/AIDS patients successfully treated [2]. This is primarily due to the achievement of low viral loads and improved CD4 cell counts [3] as a result of optimal adherence [4, 5].

For ART programs to succeed a policy document on treatment guidelines should be available. The first treatment guideline for ARTs in Ghana was published in 2002. By the end of 2009 there have been two revisions of the document, the first in 2005 and again in 2008 [6]) with each incorporating the most recent evidence. Presently, ART adopted for use in Ghana include only first and second line medicines. First line medicines include a combination of nucleoside reverse transcriptase inhibitors (NRTI) and a non-nucleoside reverse transcriptase inhibitor (NNRTI), and second line treatments comprise a combination of NRTI and a protease inhibitor. All patients (with the exception of those with HIV-2) begin treatment with a first line option.

Researchers have found that adherence plays a crucial role in viral suppression of HIV replication [7-9]. Other researchers have linked poor adherence to drug resistance [10, 11]. Paterson et al [12] and Low-Beer et al [13] have shown that among HIV/AIDS patients who administered at least 95% of their medication, 78%-84% showed undetectable viral load compared to 45%-64% among those who took between 90%-95% of their medication. In a sub-study of a multicentre, randomized, open-label, comparison-controlled trial, Ickovics et al [14] reported that HIV/AIDS patients whose degree of adherence was less than 95% were 3-5 times more likely to have treatment failure compared to those with adherence levels of 95% or higher. Furthermore, it has been found that low adherence is a major predictor of treatment failure [15] which may lead to changing from one group of medication to another. In resource limited settings adherence is determined most of the time from patient self-report or from pharmacy records [16] (where these exist and are up to date). In a study using pharmacy refill information it was shown that using adherence measurements to predict treatment failure were as accurate as CD4 cell counts [17].

If treatment outcomes are not as expected, a treatment change is the most possible alternative. In a study in West-Africa on reasons for treatment change to second line therapy, Landier *et al* [18] noted that ART modification could involve a replacement of one or more drugs in a combination or a change involving the introduction of a new drug class. Treatment modification could be as a result of a number of reasons. These include the possibility of an adverse drug reaction [19], a treatment failure, or due to ART policy changes as a result of new research findings. As ART is scaled up, chances are that more people will have their treatment changed to a second-line therapy. The cost of second line therapy is about six to ten times higher than first-line treatment [20]. Hence, there is the need to monitor those on first-line medications in order to prevent any unnecessary switches.

Some HIV studies [21, 22] so far have looked at treatment failure and discontinuation of ART from the perspective of temporal trends or taxonomy of possible determinants. The present study aims to elucidate a possible association between insufficient adherence to ART and treatment change among HIV/AIDS patients at the Korle-Bu Teaching Hospital in Ghana.

METHODS

Study setting

The Fevers Unit of the Department of Medicine and Therapeutics of the (KBTH) was the study site. The Unit is responsible for the registration and management of all patients diagnosed with HIV in the KBTH as well as those referred from other health institutions in Ghana. Provision of antiretroviral therapy in the Unit started in December 2003. As of December, 2009 about 4850 clients have been initiated antiretroviral treatment at the Fevers Unit with about 3,740 of them still on treatment. There are three major out-patient clinic days per week, each with an average clinic attendance of about 120 patients.

Study eligibility

Patients who started treatment between 1st January, 2004 and 31st December, 2009 were eligible for the study if they started treatment at least one month before the end of the study period. Only those 15 years or older, enrolled at the Fevers Unit of the KBTH, and received ART at the Pharmacy Department of the KBTH were included in the study. Patients were included in the study if they were on triple therapy. Patients were excluded from the study if their clinical records and/or pharmacy records were not available. Patients who were transferred to other centers to continue treatment were also excluded because such patients went along with their medical records.

Study design

This was a nested case-control study involving patients 15 years or older on antiretroviral therapy at the KBTH HIV treatment center. Cases were patients within the treatment cohort whose treatment were changed by an HIV clinician from the baseline (first-line) treatment to another first line treatment option (substitution) or from the baseline (first-line) treatment to a second-line treatment (switch). Changes in dose were not captured as treatment changes. The date of (first) change was the index date.

Controls were sampled from the same group of first-time ART users, at the time a case occurred, and matched on treatment initiation date plus or minus 15 days. The "Guidelines for Antiretroviral Therapy in Ghana"[6] was used as the reference for medicine classification as first or second line regimen.

Data collection and definitions

On every clinic visit day, patients are given a date for the next clinic appointment. At the pharmacy, medicines are dispensed to match the period until the next appointment

date. For treatment naïve patients the first two treatments cover a period of fifteen days each. The third treatment is for one month, and depending on the patient's adherence record and availability of medicines, subsequent treatment may be up to four months. In this study patients who experienced a change in therapy were traced backwards to at most the thirteenth month before the date of change in both clinical and pharmacy records to ascertain attendance information. For those whose backward history was less than twelve months the whole period of treatment was used to establish attendance information. This was also done for corresponding controls. The appointment dates and the actual reporting dates in clinical records during this period were compared. Because cases were matched to controls on treatment initiation date, every risk pair had similar period of observation. In the case of pharmacy records, the appointed dates for refill and the actual reporting dates were compared. Using pharmacy records the number of default days for each patient (proportion of days covered (PDC) [23]) was determined and this was used as a surrogate measure for adherence. Those with a PDC of less than 95% were classified as non-adherent and those with a PDC of 95% or higher were classified as adherent to ART. Additionally, those with 100% adherence were identified.

Using a data extraction questionnaire, socio-demographic and clinical information on selected patients was gathered from clinical records as well as pharmacy records. Socio-demographic variables included sex, education at baseline, marital status at baseline and occupation at baseline. For occupation the covariate "others" were predominantly people who were still in school. Other variables were religious affiliation at baseline and age at onset of treatment. Mean difference in BMI of cases and controls was defined as the mean of the difference between BMI at the start of treatment and BMI at treatment change/end of observation period for cases and controls respectively. Clinical data were made up of baseline variables including presence of HIV/AIDS symptoms, CD4 count, WHO staging, source of funding health care and treatment type. Physician reported adverse events during follow-up post-treatment were also captured. Socio-demographic and clinical variables were extracted from the clinical records. Information on type of ART used, date of treatment initiation, date of refill and date of treatment change were obtained from pharmacy records. Data extraction was carried out by only the lead author to maintain uniformity.

Ethical clearance

Ethical approval for this study was obtained from the Ethical and Protocol Review Committee (EPRC) of the University of Ghana Medical School.

Statistical analysis

Univariate analysis included descriptive statistics of socio-demographic, clinical and treatment data. Mean differences in continuous variables and normal distributions were determined using the t-test and scatter diagrams respectively. Classical Mantel-Haenszel method was used to calculate crude odds ratios and other exploratory statistics. For multivariate analysis conditional logistic regression was used. The effects of possible confounders including age,

sex, educational status, occupation, religion (i.e. socio-demographic variables) and baseline CD4 count, baseline WHO stage of disease, body mass index, source of funding, adverse drug event after treatment initiation (i.e. clinical variables) on the crude odds ratio were explored individually. Variables that shifted the crude odds ratio by at least 10% [24] higher or lower were kept in the final model and their combined effect on the relationship between adherence and treatment change was ascertained. Likelihood ratio tests were done to ascertain effect modification, suspecting that at least sex will modify the effect of the results.

RESULTS

There were 298 patients who had a treatment change (cases) and 298 matched patients who continued their initial ART medication (controls). The median age of cases was 42.7 years (inter-quartile range (IQR) 36-51 years), and for controls the median age was 42.7 (IQR 52-36). About 65% (195/298) of the cases were female. Among cases, 20.1% (60/298) changed treatment to a second line and the rest (79.9%) changed to another first line medicine.

Table 1 shows baseline socio-demographic variables for cases and controls, and the relationship between these variables and treatment change. It can be seen that most of the socio-demographic variables did not show any statistically significant difference between the two groups of patients.

Table 2 shows clinical or treatment parameters for both groups and data on possible determinants. At baseline the CD4 cell count ranged from 0 to 399 cells/mm^3 (mean=104.9 cells/mm^3) for cases and from 1 to 443 cells/mm^3 (mean=135.6 cells/mm3) for controls. At exit the CD4 cell counts ranged from 1 to 1020 cell/mm^3 and from 2 to 1024 cells/mm^3 for cases and controls respectively. The highest CD4 cell count recorded in this study was 1401 cells/mm^3. The mean difference in BMI among cases was 1.63 (SD=3.04) and for controls it was 1.92 (SD=2.66) which was not statistically significant between both groups. Using 95% adherence as the cut-off, 84.4% of all patients in this study adhered to treatment. A total of 88.9% of all patients who did not change treatment adhered to treatment compared with 79.9% (p=0.003) of those who changed treatment (Figure 1). When adherence was categorized into three bands (100%, between 99.99% and 95%, and below 95% only 48.8% of all patients in the study recorded 100% adherence with antiretroviral therapy (p<0.0001). Exploring adherence levels further among those who changed treatment, it was found that 79.4% adhered to treatment among those whose medication was changed from one first line treatment to another first line compared with 83.3% (p=0.01) of those who changed from one first line to a second line treatment.

Cases had a higher risk of clinical symptoms at treatment initiation (OR=1.67, 95% CI 1.19 to 2.34), developed a physician reported adverse reaction (OR=48.33, 95% CI 15.41 to 151.62), more frequently had CD4 counts less than150 cells/mm^3 (OR=2.08, 95% CI 1.10 to 4.15) and had a higher risk of being diagnosed with a WHO stage IV at baseline (OR=1.44, 95% CI 1.02 to 2.03) compared to controls. Furthermore, cases` seemed to use

Table 1. Socio-demographic characteristics of cases and controls

Variable	Cases (%)	Controls (%)	p-value
Sex	**(N=298)**	**(N=298)**	
Male	103 (34.6)	106 (35.6)	Reference
Female	195 (65.4)	192 (64.4)	0.802
Age (years)	**(N=298)**	**(N=298)**	
30-39	94 (31.5)	89 (29.9)	Reference
15-29	19 (6.4)	22 (7.4)	0.617
40-49	100 (33.6)	95 (31.9)	0.500
50-59	58 (19.4)	68 (22.8)	0.113
≥60	27 (9.1)	24 (8.0)	0.655
Marital status	**(N=293)**	**(N=296)**	
Single	63 (21.5)	55 (18.6)	Reference
Married/cohabiting	159 (54.3)	160 (54.1)	0.492
Divorced/separated	40 (13.7)	47 (15.9)	0.020
Widow/widower	31 (10.6)	34 (11.5)	0.617
Educational status	**(N=288)**	**(N=295)**	
Basic and Senior High	219 (76.0)	229 (78.6)	Reference
No education	42(14.6)	41 (13.9)	0.814
Higher education	27 (9.4)	25 (8.5)	0.758
Occupation	**(N=284)**	**(N=294)**	
Self-employed	196 (69.0)	221 (75.2)	Reference
Unemployed	32 (11.3)	27 (9.2)	0.343
Professionals	34 (12.0)	30 (10.1)	0.238
Others	22 (7.7)	16 (5.4)	0.564
Religious affiliation	**(N=287)**	**(N=297)**	
Christian	235 (81.9)	257 (86.6)	Reference
Other religions	52 (18.1)	40 (13.4)	0.123
Source of funding	**(N=289)**	**(N=293)**	
Out of pocket	180 (62.3)	203 (69.3)	Reference
Some form of funding	109 (37.7)	90 (30.7)	0.090

a stavudine based treatment more frequently (OR=1.36, 95% CI 0.96 to 1.91) but this was not statistically significant.

Univariate analysis showed that low adherence rates were associated with an increased risk of treatment change (OR=2.35 95% CI 1.33 to 4.15, see Table 3). Only the presence of an adverse drug reaction and occupational status shifted the crude odds ratio by a margin greater than 10% upwards or downwards. Only these two variables were therefore maintained in the final model for multivariate analysis. After adjusting for these two possible

Table 2. Clinical and treatment parameters of cases and controls and crude odds ratios of association

Variable	Case (%)	Control (%)	Odds ratio (CI)	p-value
Initial BMI (kg/m²)±	**(N=240)**	**(N=240)**		
20-24.99	91 (37.9)	98 (40.8)	Reference	
≥25	24 (10.0)	38 (15.8)	0.69 (0.30 to 1.62)	0.394
<20	125 (52.1)	104 (43.4)	1.18 (0.74 to 1.86)	0.486
Clinical symptoms[a]	**(N=294)**	**(N=298)**		
No	131 (44.6)	170 (57.0)	Reference	
Yes	163 (55.4)	128 (43.0)	1.67 (1.19 to 2.34)	0.003
Adverse drug reaction	**(N=289)**	**(N=287)**		
No	133 (45.6)	277 (95.8)	Reference	
Yes	159 (54.4)	12 (4.2)	48.33 (15.41 to 151.62)	<0.001
Initial CD4 cell count	**(N=293)**	**(N=295)**		
>250	20 (6.8)	36 (12.2)	Reference	
150-250	70 (23.9)	91 (30.8)	1.14 (0.41 to 3.15)	0.487
<150	203 (69.3)	168 (57.0)	2.08 (1.10 to 4.15)	0.019
Initial WHO staging	**(N=293)**	**(N=296)**		
I-III	229 (78.1)	251 (84.8)	Reference	
IV	64 (21.9)	45 (15.2)	1.44 (1.02 to 2.03)	0.038
Initial treatment	**(N=298)**	**(N=298)**		
AZT/3TC/EFV	85 (28.5)	70 (23.5)	Reference	
AZT/3TC/NVP	76 (25.5)	71 (23.8)	1.09 (0.70 to 1.71)	0.698
d4T/3TC/EFV	63 (21.1)	84 (28.2)	1.62 (1.03 to 2.55)	0.038
d4T/3TC/NVP	61 (20.5)	60 (20.1)	1.19 (0.73 to 1.94)	0.482
OTHERS	13 (4.4)	13 (4.4)	1.13 (0.51 to 2.79)	0.686
AZT or d4T combination	**(N=298)**	**(N=298)**		
AZT base	161 (54.0)	141 (47.4)	Reference	
d4T base	124 (41.6)	144 (48.3)	1.36 (0.96 to 1.91)	0.084
Other combinations	13 (4.4)	13 (4.4)	1.13 (0.50 to 2.53)	0.784

[a]Clinical symptoms at treatment initiation; ±Body mass index at baseline.

confounders (Table 3), the odds ratio between insufficient adherence and treatment change was 3.56 (95% CI 1.60 to 7.88). Stratification by type of treatment change yielded similar results; those who did not adhere to treatment among those who changed treatment from one 1st line ART to another 1st line were 2.40 (95% CI 1.31 to 4.38) times as likely to do so and for those who changed from a 1st treatment to a 2nd line treatment option, the OR was 2.00 (95% CI 0.37 to 10.92). Likelihood ratio tests performed did not show any significance of effect modification among the variables.

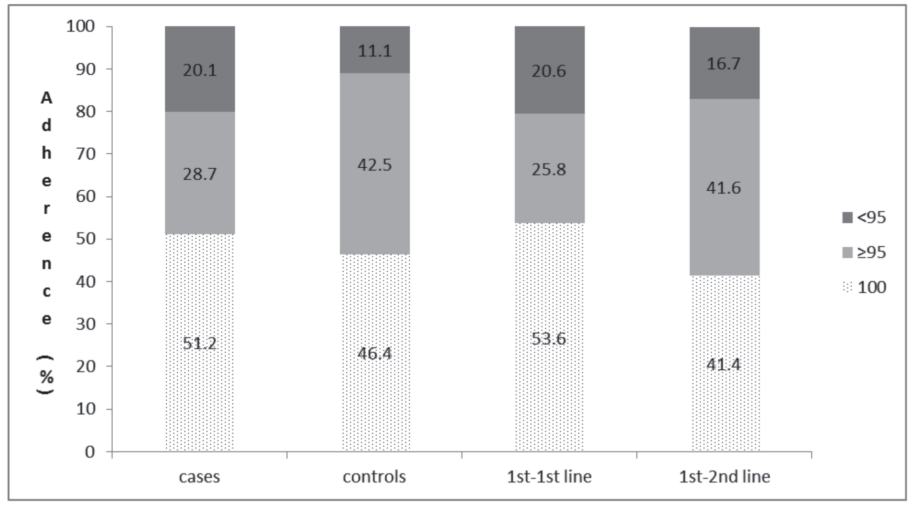

Figure 1. Adherence levels for cases and controls and for cases who changed treatment.

Table 3. Univariate and multivariate analysis of the relationship between adherence and treatment change

Adherence	Cases (%) (N=298)	Controls (%) (N=298)	Crude OR (95% CI)	Adjusted OR[1] (95% CI)	p-value
≥95%	238 (79.9)	265 (88.9)	Reference	Reference	
<95%	60 (20.1)	33 (11.1)	2.35 (1.33 to 4.15)	3.56 (1.60 to 7.88)	0.002
1st line to 1st line	**(N=238)**	**(N=238)**			
≥95%	189 (79.4)	213 (89.5)	Reference		
<95%	49 (20.6)	25 (10.5)	2.40 (1.31 to 4.15)		
1st line to 2nd line	**(N=60)**	**(N=60)**			
≥95%	50 (83.3)	51 (86.7)	Reference		
<95%	10 (16.7)	9 (13.3)	2.00 (0.37 to 10.92)		

[1]Adjusted for all variables that individually shifted the crude odds ratio by ≥ 10% higher or lower.

DISCUSSION

This study examined the association between adherence and treatment change using a matched case-control approach among adult patients who initiated ART in Ghana. Adherence was determined using the PDC method and 95% coverage or higher was taken as being sufficiently adherent. Controls in this study were more adherent to treatment compared with cases.

Multivariate analysis results showed that non adherence is independently associated with almost four times the odds of treatment change. Kwobah *et al* [21] identified that non adherence was associated with almost three times the odds of treatment failure and

Gonzalez-Serna [22] *et al* found that an adherence level greater than or equal to 95% independently reduced treatment discontinuation by 61%. Ickovics *et al* [14] have reported that HIV/AIDS patients whose degree of adherence was less than 95% were 3-5 times more likely to have treatment failure compared to those with adherence levels of 95% or higher and treatment failure is one of the most common reasons to switch therapy [25]. Interestingly, non-adherence was similarly associated with a change to another first line or to a second line therapy, although the latter was not statistically significant due to low numbers.

Demographic variables in this study were not associated with a change of therapy. The result is not very different from the multi-cohort study of 17 ART programmes [26]. Most clinical and treatment parameters, however, were associated with treatment change. With decreasing CD4 cell count at ART initiation there was an increasing tendency for a treatment change. A number of researchers [27-29] have made similar observations. These findings call for treatment initiation to begin during early diagnosis of HIV infection (when CD4 cell counts are most likely to be higher). Also counseling and testing services need to be stepped up to identify patients during early stages. The development of physician reported adverse drug reaction to ART in this study was linked to treatment change. Furthermore, patients with adverse drug events seemed to have developed low adherence levels. This link may be confirmed with the help of predictive studies beyond this paper but calls for patients to be more informed on the benefit-risk profiles of their medicines.

It was found that overall more patients adhered to treatment compared to the study in Cote d'Ivoire [30] in which 74.3% of participants adhered to treatment using a 95% cut-off for adherence calculated over a four day period. In the Royal Free Clinic cohort in London [27] 45% of participants adhered to treatment using the proportion of days covered approach. However, adherence in our study was lower (93.4% kept appointments regularly) than that reported by Baqi *et al* [31]. It is important to maintain the high adherence levels observed and continue to strive harder because of the consequences of low adherence [32,33]. At the Korle-Bu Teaching Hospital HIV patients undergo three sessions of adherence counseling before treatment initiation. This is to ensure that they have a good knowledge of the disease and the rational for better treatment outcomes during long periods of therapy. It is important therefore, to try and identify those factors that lead to poor adherence in this setting and carefully monitor and evaluate them (in addition to other known factors) so they do not fall below the levels recommended by the WHO [34].

There were limitations in this study. It was assumed that once an antiretroviral medicine is prescribed and dispensed, it will be administered but in reality it may be different. The best approach is to calculate actual doses administered, although this may be very difficult to achieve. But using the PDC [23] which is an objective measurement of adherence especially among chronic diseases [35], it is believed that errors will be minimal. Lack of a statistically significant association among the subgroup of those who switched to second line treatment could be as a result of reduced sample size leading to a wide confidence interval. In particular, odds ratios in matched case-control studies are dependent only on the discordant pairs. For a reduced sample size, the discordant pairs are reduced accordingly leading to a lowered statistical power [36] to predict an outcome even though one may exist. A more powered study is therefore recommended in future.

CONCLUSION

Among HIV/AIDS patients, the main guarantee for improved life expectancy is an intervention with antiretroviral therapy. However, successful treatment outcomes depends on optimum adherence levels. This study identified that adherence to ART is linked to treatment change, and non-adherent patients have increased tendency of being affected. This could pose a problem to most low and medium income countries because of higher costs of alternative antiretroviral medicines. Policy makers must partner researchers to engage patients more often to unravel the causes of non-adherence, and make the necessary interventions for patients to achieve maximum benefits from dispensed medicines.

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REFERENCES

1. HIV Sentinel Survey Report. National AIDS/ STI Control Programme, Ghana Health Service. Ministry of Health, Accra 2013.
2. May MT, Gompels M, Delpech V, Porter K, Orkin C, et al. Impact on life expectancy of HIV-1 positive individuals of $CD4^+$ cell count and viral load response to antiretroviral therapy. *AIDS* 2014;28:1193-1202.
3. Lampe FC, Smith CJ, Madge S, Kinloch-de LS, Tyrer M,*et al*. Success of clinical care for human immunodeficiency virus infection according to demographic group among sexually infected patients in a routine clinic population, 1999 to 2004. *Arch Intern Med* 2007;167:692–700.
4. Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clin Infect Dis* 2002;34:1115–1121.
5. Paterson DL, Swindell S, Mohr J, Brester M, Vergis EN, *et* al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000;133:21–30
6. Guidelines for antiretroviral therapy in Ghana. Ministry of Health, Ghana Health Service 2008.
7. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Ann Intern Med* 1999;131:81–87.
8. Nachega JB, Hislop M, Dowdy DW, Chalsson RE, Regensberg L, *et al*. Adherence to non-nucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. *Ann Intern Med* 2007;146:564–573.
9. Shuter J, Sarlo JA, Kanmaz TJ, Rode RA, Zingman BS. HIV-infected patients receiving lopinavir/ritonavir-based antiretroviral therapy achieve high rates of virologic suppression despite adherence rates less than 95%. *J Acquir Immune DeficSyndr* 2007;45:4–8**.**
10. Bangsberg DR, Acosta EP, Gupta R, Guzman D, Riley ED, *et al*. Adherence–resistance relationships for protease and nonnucleoside reverse transcriptase inhibitors explained by virological fitness. *AIDS* 2006;20:223–231.
11. Harrigan PR, Hogg RS, Dong WW, Yip B, Wynhoven B, *et al*. Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. *J Infect Dis* 2005;191:339–347.
12. Paterson DL, Swindell S, Mohr J, Brester M, Vergis EN, *et al*. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000;133:21–30
13. Low-Beer S, Yip B, O'Shaughnessy MV, Hogg RS, Montaner JS. Adherence to triple therapy and viral load response. *J Acquir Immune DeficSyndr* 2000;23:360–1.
14. Ickovics JR, Cameron A, Zackin R, Bassett R, Chestney M, *et al*. Consequences and determinants to antiretroviral therapy medication: results from the Adult AIDS Clinical Trial Group Protocol 370. *Antivir Ther* 2000;7(3):185-193.
15. Nachega JB, Hislop M, Dowdy DW, Lo M, Omer SB, *et al*. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. *J Acquir Immune DeficSyndr* 2006;43:78–84.
16. Chesney MA. The elusive gold standard. Future perspectives for HIV adherence assessment and intervention. *J Acquir Immune DeficSyndr* 2006;43(1):S149–S155.
17. Bisson GP, Gross R, Bellamy S, Chittams J, Hislop M, *et al*. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviraltherapy. *PLoS Med* 2008;5:e109.
18. Landier J, Akonde A, Pizzocolo C, Haidara I, Drabo M, *et al*. Switch to second-line ART in West African routine care: incidence and reasons for switching. *AIDS Care* 2011;23(1), 75-78
19. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *The Lancet* 2000;356:1423-1430
20. Lynen L, Van Griensven J, Elliott J. Monitoring for treatment failure in patients on first-line antiretroviral treatment in resource-constrained settings. *Curr Opin HIV AIDS* 2010;5:1–5.
21. Kwobah CM, Mwangi AW, Koech JK, Simiyu GN, Siika AM. Factors associated with first line antiretroviral therapy failure amongst HIV infected African patients: A case-control study. *World J AIDS* 2012;2:271-278.
22. Gonzalez-Serna A, Chan K, Yip B, Chau W, McGovern R, *et al* (2014). Temporal trends in the discontinuation of first line antiretroviral therapy. *J Antimicrob Chemother* 2014;69:2202-2209.
23. Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. http://www.ep.yimp.com/ty/cdn/epill/pdcmpr.pdf. Accessed: 01/02/2015.
24. Omland T, Persson A, Ng L, O'Brien R, Karlsson T, *et al* (2002).N-Terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation* 2002;106:2913-2918
25. World Health Organization (WHO). Antiretroviral therapy for HIV infection in adults and adolescents. Recommendation for a public health approach 2010 revision. Available from http://www.who.int/ hiv/ pub/ arv/ adult2010/ en/. Accessed 05/12/2014.
26. Keiser O, Tweya H, Boulle A, Braitstein P, Schechter M, *et al*. Switching to second-line antiretroviral therapy in resource-limited settings: comparison of programmes with and without viral load monitoring. *AIDS* 2009;23(14):1867-1874.
27. Cambiano V, Lampe FC, Rodger AJ, Smith CJ, Geretti AM, *et al*. Long-term trends in adherence to antiretroviral therapy from start of HAART. *AIDS* 2010;24:1153–1162.
28. Monforte A, Testa L, Adorni F, Chiesa E, Bini T, *et al*. Clinical outcomes and predictive factors of failure of highly active antiretroviral therapy in antiretroviral-experienced patients in advanced stages of HIV-1 infection. *AIDS* 1998;12:1631-1637.
29. Paredes R, Mocroft A, Kirk O, Lazzarin A, Barton SE, *et al* (2000). Predictors of virological success and ensuing failure in HIV-positive patients starting antiretroviral therapy in Europe. *Arch Intern Med* 2000;160:1123-1132.
30. Diabate S, Alary M, Koffia CK. Determinants of adherence to highly active antiretroviral therapy among HIV-1-infected patients in Cote d'Ivoire. *AIDS* 2007;21:1799–1803.
31. Baqi S, Abro AG, Salahuddin N, Ashraf MM, Qamar AS, *et al*. Four years of experience with antiretroviral therapy in adult patients in Karachi, Sindh, Pakistan. *Int Health* 2012;4(4):260-7.
32. Timmreck TC, Randolph JF. Smoking cessation: Clinical steps to improve compliance. *Geriatrics* 1993;48:63-66.
33. Farmae KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther* 1991;21:1074-1090.
34. Global HIV/AIDS response: epidemic update and health sector progress towards universal access. Progress report 2011. WHO, UNAIDS, UNICEF. Available from www.who.int/ hiv/ topics/ universalaccess/ en/ index.html. Accessed 25/05/2012
35. Branham A, Moose J, Ferreri S. Retrospective analysis of medication adherence and cost following medication therapy management. *Inov Pharm* 2010;1(12):1-8.
36. Steve S. Statistical Tools for Epidemiological Research. New York: Oxford University Press 2011.

Chapter 3.3

IDENTIFYING RISK FACTORS ASSOCIATED WITH NON-ADHERENCE TO ANTIRETROVIRAL THERAPY AMONG PATIENTS ON FIRST LINE TREATMENT IN GHANA

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ABSTRACT

Introduction

The correlation between adherence to therapy and patient outcomes in HIV/AIDS patients underscores the need to identify bottlenecks that can jeopardize the attainment of optimum adherence rates. This study aims to determine risk factors associated with non-adherence to first line antiretroviral therapy (ART).

Methods

We contrasted adherence to therapy, i.e. levels below 95% (cases) compared to 95% or more (controls), in adult HIV/AIDS patients. Patients were followed for a minimum of three months between January 2004 and December 2009. Adherence was calculated using the method of proportion of days covered. Logistic regression was used for analysis of patient and disease characteristics followed by a test for goodness-of-fit and calculation of the area under the receiver operating characteristic (ROC) curve.

Results

In all, there were 73 cases and 367 controls. The median age of cases was 41.0 years (interquartile range (IQR): 34.9-50.0), and 46 (63%) of them were female. For controls the median age was 43.0 years (IQR: 37-52.1), and 244 (66.5%) were female. The risk factors significantly associated with non-adherence to ART were WHO disease stage IV (age and gender adjusted OR (aOR) 3.03 [95% CI 1.70, 5.41]) which recorded a risk score of 11, presence of symptoms at baseline (aOR 1.70 [95% CI 1.00, 2.90] and risk score 5), and low CD4 cell count at treatment initiation (aOR 1.39 [95% CI 0.96, 2.01] and risk score 3). Pearson goodness-of-fit test produced a p-value of 0.663 and the area under ROC curve was 0.72 (95% CI 0.64, 0.85).

Conclusion

In this setting clinical baseline characteristics of HIV/AIDS patients influenced non-adherence to ART. Stepping up surveillance interventions for early identification and possibly early treatment of HIV/AIDS among Ghanaians by policy makers, health workers and HIV advocacy groups could be helpful since WHO disease status and low CD4 count were related to poor adherence.

INTRODUCTION

There is little doubt that the introduction of antiretroviral therapy (ART) among people living with HIV/AIDS (PLWHA) has been phenomenal in reducing related morbidity and mortality [1,2]. One of the most important factors to this success can be attributed to adherence to treatment. Adherence has been proved to be pivotal in increasing levels of CD4 cell counts [3,4], a marker for morbidity among PLWHA and thereby reducing the risk of deaths [5-7]. An adherence level of 95% or more compared to a level less than 95% has been found to strongly correlate with a CD4 cell count increase and viral load, as well as morbidity decrease [8]. This underscores the need for efforts to be made to identify at risk patients early enough and make necessary interventions to help in the attainment of optimum adherence rates..

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Several factors have been identified that have beneficial or adverse repercussions on adherence. Female sex [9], younger age [10-12], lack of social support [13,14] and lower education [15] have all been associated with reduced adherence. Adverse drug events have also been linked with a negative effect on adherence [16-18]. An advanced disease stage (opportunistic infection) has been identified to improve adherence [15]. Contrary to this, a qualitative study in Zambia by Grant et al [19] observed that looking and feeling better was a major factor that facilitated adherence to ART. So in different settings both feeling better and feeling worse have been linked to non-adherence. There have also been mixed reports about the effect of ethnicity on adherence. While some researchers showed that black race is associated with lower adherence [11,15], others [20,21] have reported contrasting results. This emphasizes that more research is needed among this population, e.g. in sub Saharan Africa.

Adherence to medicines is used to refer to a more active, voluntary and collaborative involvement of the patient in a mutually acceptable course of behaviour to produce therapeutic result [22]. There are contrasting reports concerning duration on treated and adherence levels. Some researchers [23, 24] have reported increases in adherence among patients on treatment for longer periods, while others [25-27] showed that adherence is better during the early phase of treatment. In a recent study, we showed that non-adherence is associated with treatment change which is potentially unwanted in case patients need to be switched to more expensive second line therapy [28]. Because of the low and decreasing prevalence rates (2.1% as of 2012) [29] of HIV in Ghana, coupled with the establishment of an organized state controlled distribution of ARTs, it is worth researching adherence to ARTs in this country. To optimize adherence, continuous monitoring and proactive interventions are needed for early identification of at risk patients. This study aimed to identify risk factors associated with non-adherence among adult patients living with HIV/AIDS who experienced treatment change at the Korle-Bu Teaching Hospital (KBTH) in Ghana.

METHODOLOGY

Setting

The Fevers Unit of the Korle-Bu Teaching Hospital was the study site. The Korle-Bu Teaching Hospital is a 2,000 bed referral hospital in Accra, Ghana. The hospital has 19 clinical departments including the Department of Medicine and Therapeutics. The Fevers Unit is one of the units of the Department of Medicine and Therapeutics. This Unit is responsible for the registration and management of all cases diagnosed as HIV in the KBTH as well as those referred from other health institutions in Ghana. Provision of antiretroviral therapy in the Unit started in December 2003.

Selection of study participants

This study involved patients on first line ART during the period January 2004 to December 2009. Patients who had a treatment change during the period were recruited at the point of change and adherence was calculated in the year prior to this date for as long as data were available. Among those who did not change therapy the same procedure was applied starting from the date of recruitment within the study period. Data were obtained from available and complete clinical and pharmacy records with the help of a structured record form. Adherence was calculated using the method of proportion of days covered (PDC) [30]. All those who scored below 95% adherence were classified as non-adherent (cases). Controls were those with a PDC of 95% or more. About 5 times as many controls as the number of cases were selected to improve the power of the study. Cases were compared with controls to examine risk factors for non-adherence to ART.

Characteristics of patients

Both demographic and clinical characteristics of patients were extracted from hand-written clinical records at baseline. For demographic characteristics sex, patient age, educational and marital status, distance from ART treatment site, occupation, religion, source of treatment funding, smoking status and alcohol drinking status were accessed at treatment initiation. For clinical characteristics WHO stage of disease, presence of symptoms (binary variable), CD4 cell count, body mass index and initial antiretroviral treatment were all captured at treatment initiation.. The presence of physician reported adverse drug event was captured during the course of antiretroviral treatment.

Statistical analysis

Exploratory and descriptive statistics were carried out using Stata intercooled version 12 (StataCorp LP, College Station, TX, USA) for analysis. Associations were studied using Chi squared tests, Fisher's exact tests where appropriate and logistic regression. A backward stepwise method was used allowing for a p-value threshold of 0.2 for statistical significance [31]. Goodness-of-fit of the final model was quantified using the Pearson test instead of the Hosmer-Lemeshow test because of group unevenness and the presence of small totals [32]. The receiver operating characteristic (ROC) curve was constructed and the area under the curve (AUC) was determined [33].

RESULTS

In all there were 73 (16.6%) patients who were below 95% adherent (cases) and 367 patients who were at least 95% adherent to ART (selected as controls). The median age of cases was 41.0 years (interquartile range (IQR): 34.9-50.0), and 46 (63%) of them were female. For controls the median age was 43.0 years (IQR: 37-52.1), and 244 (66.5%) of them were female. Table 1 shows the comparison of non-adherence between age, gender and baseline clinical variables captured in this study. WHO disease stage IV when compared with a combination of all other stages resulted in a significant association with non-adherence ($p<0.001$) to ART. Of those who were symptomatic compared to asymptomatic patients, 58.8% were non-adherent and 44.9% ($p=0.029$) were adherent to treatment. Among those on treatment who were non-adherent, 54.8% had a zidovudine base, and among those adherent to treatment 47.1% were zidovudine based; among those on treatment who were non-adherent, 41.1% were stavudine based and among those adherent to treatment 51.2% had a stavudine component; the rest were on different combinations. There was no significant association between treatment options and non-adherence ($p=0.116$).

Socio-economic variables in this study were not significantly associated with non-adherence to treatment as shown in Table 1. There was no significant difference in non-adherence between those on short term treatment compared with those on long term treatment. Of those with ≥ 95% adherence 65.4% of patient was on treatment for at least one year, while this percentage was 63.0 for patients with adherence levels < 95% ($p=0.697$). Subsequently both crude and age and sex adjusted odds ratios for non-adherence were calculated for the potential risk factors of non-adherence (Table 1). Compared with WHO disease stage I-III, a WHO disease stage IV was about three times as likely (aOR, 3.02 [95% CI 1.71-5.35]) to default adherence The other factor significantly associated with non-adherence was presence of symptoms at baseline (aOR, 1.65 [95% CI 1.00-2.81]).

Table 2 shows the association between risk factors and non-adherence after taking account of all other variables using the backward stepwise analysis method at a p-value of 0.2 and the associated risk scores. Only three variables were associated with non-adherence to ART in the final model. The variables were, WHO disease stage IV compared with stage I-III (OR, 3.03 [95% CI 1.70, 5.41]; p-value, <0.001), presence of symptoms compared with no symptoms (OR, 1.70 [95% CI 1.00, 2.90] p-value, 0.052), and CD4 cell count (OR, 1.39 [95% CI 0.96, 2.01]; p-value, 0.086). The Pearson goodness-of-fit test for the final model was not significant ($p=0.663$). The area under the curve (AUC) of the ROC was 0.72 (95% CI 0.64, 0.85). WHO disease stage IV compared with stage I-III recorded the highest risk score of 11 and CD4 cell count recorded the lowest risk score (3).

Table 1. Comparison of cases (adherence < 95%) and controls (adherence ≥ 95%), and crude and age and sex adjusted measures of effect between risk factors and non-adherence to ART.

Variable	Adherence <95% N(%)	Adherence ≥95% N(%)	p-value	cOR[#](95% CI^)	aOR[α](95% CI)
Sex[©]	**N=73**	**N=367**			
Male	27(37.0)	123(33.5)	0.568	Reference	Reference
Female	46(63.0)	244(66.5)		0.86(0.51-1.45)	0.77(0.45-1.34)
Age (years)[μ]	**N=73**	**N=367**			
<25	3(4.1)	8(2.2)	0.480	Reference	Reference
25-39	29(39.7)	103(33.5)		0.63(0.16-2.52)	0.61(0.15-2.45)
40-59	34(46.6)	203(55.3)		0.45(0.11-1.77)	0.41(0.10-1.65)
≥60	7(9.6)	33(9.0)		0.57(0.12-2.69)	0.50(0.10-2.44)
Education	**N=72**	**N=362**			
Nil	12(16.7)	46(12.7)	0.581	Reference	Reference
Basic-medium	55(76.4)	282(77.9)		0.75(0.37-1.50)	0.73(0.36-1.48)
Higher	5(6.9)	34(9.4)		0.56(0.18-1.75)	0.52(0.16-1.62)
Marital status	**N=73**	**N=362**			
Single	18(24.7)	66(18.2)	0.178	Reference	Reference
Married/cohabiting	42(57.5)	191(52.8)		0.81(0.43-1.50)	0.80(0.42-1.50)
Divorced	9(12.3)	59(16.3)		0.56(0.23-1.34)	0.59(0.24-1.43)
Widow/widower	4(5.5)	46(12.7)		0.32(0.10-1.00)	0.34(0.11-1.10)
Distance from ART site	**N=72**	**N=362**			
>10km	18(25.0)	124(34.3)	0.259	Reference	Reference
6-10km	22(30.6)	107(29.6)		1.68(0.90-3.15)	1.62(0.86-3.05)
0-5km	32(44.4)	131(36.2)		1.42(0.72-2.78)	1.37(0.67-2.71)
Occupation	**N=73**	**N=356**			
Unemployed	6(8.2)	36(10.1)	0.857	Reference	Reference
Low grade	55(75.3)	253(70.9)		1.30(0.52-3.23)	1.47(0.57-3.82)
High grade	7(9.6)	44(12.3)		0.95(0.29-3.09)	1.02(0.30-3.40)
Others (mostly students)	5(6.8)	24(6.7)		1.25(0.34-4.56)	1.05(0.27-4.03)
Source of funding	**N=72**	**N=359**			
Out-of-pocket	45(62.5)	241(67.1)	0.712	Reference	Reference
Health insurance	23(31.9)	99(27.6)		1.24(0.71-2.17)	1.25(0.70-2.25)
Other	4(5.6)	19(5.3)		1.13(0.37-3.47)	1.05(0.33-3.36)
Treatment duration	**N=73**	**N=367**			
< 1 year	27(37.0)	127(34.6)	0.697	Reference	Reference
≥ 1 year	46(63.0)	240(65.4)		0.90(0.54-1.52)	0.91(0.54-1.55)
Adverse drug event	**N=73**	**N=357**			
No	52(71.2)	258(72.3)	0.886	Reference	Reference
Yes	21(28.8)	99(27.7)		1.05(0.60-1.84)	1.12(0.63-1.98)
WHO stage (I-III vs IV)	**N=73**	**N=361**			
I-III	48(65.7)	309(85.6)	<0.001	Reference	Reference
IV	25(34.3)	52(14.4)		3.09(1.76-5.45)	3.02(1.71-5.35)
Presence of symptoms	**N=73**	**N=365**			
No	30(41.1)	201(55.1)	0.029	Reference	Reference
Yes	43(58.9)	164 (44.9)		1.76(1.06-2.92)	1.65(1.00-2.81)
CD4 cell count (cells/mm^3)	**N=73**	**N=361**			
>250	42(57.5)	228 (63.2)	0.485	Reference	Reference
150-250	21(28.1)	98 (27.1)		1.16(0.65-2.07)	1.11(0.60-2.03)
<150	10(13.7)	35 (9.7)		1.55(0.71-3.37)	1.42(0.66-3.12)
Body mass index (kg/m^2)	**N=60**	**N=305**			
<20	28(46.7)	151(49.5)	0.735	Reference	Reference
20-24.99	23(38.3)	118(38.7)		1.05(0.58-1.92)	1.09(0.72-2.07)
≥25	9(15.0)	36(11.8)		1.35(0.59-3.11)	1.41(0.76-3.39)
Treatment options	**N=73**	**N=367**			
Others	3(4.1)	6(1.6)	0.116	Reference	Reference
Zidovudine base	40(54.8)	173(47.1)		0.46(0.11-1.93	0.47(0.11-1.99)
Stavudine base	30(41.1)	188(51.2)		0.32(0.07-1,34)	0.34(0.08-1.44)

#crude odds ratio, ^onfidence interval, α odds ratio adjusted for age and sex, © adjusted for age, μadjusted for sex.

Table 2. Regression coefficient and score for each variable in the final model

Variable	Regression coefficient	Risk score*
CD4 cell count at treatment initiation	0.32	3
WHO disease stage (I-III versus IV)	1.14	11
Presence of symptoms (Yes versus No)	0.53	5
AUC of ROC (95% CI) = 0.72 (0.64, 0.85)		

*Obtained by multiplying the regression coefficient by 10 and rounding off the answer to the nearest integer.

DISCUSSION

In this study risk factors of non-adherence to antiretroviral therapy were examined using data extracted from clinical and pharmacy records of an HIV/AIDS cohort of patients in Ghana. The final model was made up of disease severity (using WHO staging), CD4 cell count and presence of symptoms, both at start of initial antiretroviral therapy.

Disease severity (identified after comparing WHO stage I-III with WHO stage IV) was identified as an important risk factor for non-adherence. Results from Singh et al [15] and Gao et al [34] were contrary to this finding, but in a systematic review and meta-analysis examining the relationship between disease severity and treatment adherence, DiMatteo et al [35], observed that the most severely ill patients who also have serious disease have the greatest propensity of non-adherence to treatment. Patients with worse conditions are very likely to be on multiple drug treatment, which is also a factor for poor adherence [36, 37]. Continuous treatment and improved adherence are very important among patients in this situation. These two components demand a shared responsibility between treatment providers on one side and HIV/AIDS patients (and their care givers) on the other side. Both parties need to play their roles optimally to meet the goals of therapy.

Looking and feeling better was a major factor that facilitated adherence to ART in a previous study by Grant *et al* [19]. Being symptomatic was an independent predictor of non-adherence in this study. HIV patients need to be assured always that if they adhere to treatment their chances of being asymptomatic and feeling better is high and that this may continue for as long as they remain adherent to treatment. There was no significant association between recorded adverse event and non-adherence to ART. Laing and Hodgkin [38] reported that side effects are rarely captured as predictors for sub-optimal adherence.

Adherence has been proved to be pivotal in increasing levels of CD4 cell counts [3,4], a marker for morbidity among PLWHA and thereby reducing the risk of deaths [5-7]. An adherence level of 95% or more compared to a level less than 95% has been found to strongly correlate with an increase in CD4 cell count [8]. In this setting, CD4 cell count is monitored every six months to ensure that patients attain the needed benefits for as long as they are on treatment. In our study, lower CD4 counts themselves were associated with non-adherence. Our findings strengthen the evidence of other researchers [3, 4] and call for more action against those clinical factors that predispose patients to non-adherence to ART. A recommended intervention will be to start antiretroviral treatment soon after diagnosis for all patients.

Period on treatment did not have any significant effect on non-adherence after separating participants into those on treatment below one year (short term) and after one year (long term). This was contrary to the finding of Carlucci et al [23], who reported that those on treatment for longer periods were more adherent to treatment after looking at a group on treatment for 30 days or more compared to those on treatment for less than 30 days. This difference may be due to the rather short period (just 30 days) of the short term treatment. However Cambiano et al [24] in a prospective study (13 years follow-up) at the Royal Free Hospital in London, UK, also recorded a significant increase in adherence with increasing time. The different situation in this study may be due to several factors including persistent counseling on the part of counselors or understanding of adherence information among patients, or patients' willingness to get better. Further work is needed to identify the real drivers. What is important is that attained viral suppresion may last longer and AIDS related deaths will be delayed if optimum adherence is maintained. One of the most recent interventions of the UNAIDS Programme Coordinating Board is the 90-90-90 initiative, "an ambitious treatment target to end the AIDS epidemic" by 2020 [39]. The aim is to work hand-in-hand with civil society, community health workers, and all stakeholders, for early identification of HIV sero-status, provision of adequate treatment with the intention to reduce viral loads [38]. Such intervention in this setting, would most probably be the watershed moment since it would address all the three risk factors, that is, there would be less severe disease, fewer people with lower CD4 cell count (by reducing viral loads) and less people with WHO disease stage IV.

3.3

CONCLUSION

This study shows that disease severity in HIV/AIDS at baseline is associated with non-adherence to ART during follow-up of treatment. This finding urges health care professionals, policy makers and patient and advocacy groups in HIV/AIDS to engage with patients as early as possible in their disease course in order to increase awareness and to assist in improving treatment adherence. Everything should be done to prevent a devastating spiral of high disease severity, low adherence to therapy, further deterioration and so on.

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REFERENCES

1. Hogg RS, Heath KV, Yip B, Craib KJ, O'Shaughnessy MV, Schechter MT, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA* 1998; 279:450–454.
2. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; 338:853–860.
3. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000; 133:21–30.
4. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. The impact of adherence on CD4 cell count responses among HIV-infected patients. *J Acquir Immune Defic Syndr* 2004; 35:261–268.
5. Hogg RS, Heath K, Bangsberg D, Yip B, Press N, O'Shaughnessy MV, et al. Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up. *AIDS* 2002; 16:1051–1058.
6. Garcia de OP, Knobel H, Carmona A, Guelar A, Lopez-Colomes JL, Cayla JA. Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. *J Acquir Immune Defic Syndr* 2002; 30:105–110.
7. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4R cell count is 0.200 to 0.350 T 10(9) cells/L. *Ann Intern Med* 2003; 139:810–816.
8. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000; 133:21–30.
9. Godin G, Cote J, Naccache H, Lambert LD, Trottier S. Prediction of adherence to antiretroviral therapy: a one-year longitudinal study. *AIDS Care* 2005; 17:493–504.
10. Carrieri P, Cailleton V, Le Moing V, Spire B, Dellamonica P, Bouvet E, et al. The dynamic of adherence to highly active antiretroviral therapy: results from the French National APROCO cohort. *J Acquir Immune Defic Syndr* 2001; 28:232– 239.
11. Halkitis P, Palamar J, Mukherjee P. Analysis of HIV medication adherence in relation to person and treatment characteristics using hierarchical linear modeling. *AIDS Patient Care STDS* 2008; 22:323–335.
12. Hinkin CH, Hardy DJ, Mason KI, Castellon SA, Durvasula RS, Lam MN, et al. Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *AIDS* 2004; 18 (Suppl 1):S19–S25.
13. Altice FL, Mostashari F, Friedland GH. Trust and the acceptance of and adherence to antiretroviral therapy. *J Acquir Immune Defic Syndr* 2001; 28:47–58.
14. Spire B, Duran S, Souville M, Leport C, Raffi F, Moatti JP. Adherence to highly active antiretroviral therapies (HAART) in HIV-infected patients: from a predictive to a dynamic approach. *Soc Sci Med* 2002; 54:1481–1496.
15. Singh N, Squier C, Sivek C, Wagener M, Nguyen MH, Yu VL. Determinants of compliance with antiretroviral therapy in patients with human immunodeficiency virus: prospective assessment with implications for enhancing compliance. *AIDS Care* 1996; 8:261–269.
16. Cooper JK, Love DW, Raffoul PR. International prescription nonadherence (compliance) in the elderly. *J Am Geriatr Soc* 1982;30:329-333.
17. Witteveen E, van Ameijden EJC. Drug users and HIV-combination therapy (HAART): Factors with impede or facilitate adherence. *Subst Use Misuse* 2002;14: 1905–1925.
18. Adam B, Maticka-Tyndale E, Cohen JJ. Adherence practices among people living with HIV. *AIDS Care* 2003;2: 263–274.
19. Grant E , Logie D , Masura M , Gorman D, Murray SA. Factors facilitating and challenging access and adherence to antiretroviral therapy in a township in the Zambian Copperbelt: a qualitative study. *AIDS Care* 2008;20(10):1155-1160.
20. Diabate S, Alary M, Koffi CK. Determinants of adherence to highly active antiretroviral therapy among HIV-1-infected patients in Cote d'Ivoire. *AIDS* 2007; 21:1799-1803.
21. Ware NC, Idoko J, Kaaya S, Biraro IA, Wyatt MA, et al. Explaining adherence success in sub-Saharan Africa: An ethnographic study. *PLoS Med* 2009, 6(1): e1000011. doi:10.1371/journal. pmed.1000011
22. Meichenbaum D, Turk DC (1987). Facilitating Treatment Adherence, A Practitioner's Guidebook. Plenum Press, New York, USA.
23. Carlucci JG, Kamanga A, Sheneberger R, Shepherd BE, Jenkins CA, et al. Predictors of Adherence to Antiretroviral Therapy in Rural Zambia. *J Acquir Immune Defic Syndr*. 2008; 47(5): 615–622.
24. Cambiano V, Lampe FC, Rodger AJ, Smith CJ, Geretti AM, et al. Long term trends in adherence to antiretroviral therapy from start of HAART. AIDS 2010; 24:1153–1162
25. Epstein LH, Cluss PA. A behavioral medicine perspective on adherence to long-term medical regimen on. *JCCP* 1982;50(6):950-971.
26. Ickovics JR, Cameron A, Zackin R, Bassett R, Chesney M, Johnson VA, Kuritzkes DR, for the ACTG 370 Protocol Team. Consequences and determinants of adherence to antiretroviral medication: results from Adult AIDS Clinical Trials Group protocol 370. *Antivir Ther* 2002; 7:185–193.
27. Howard AA, Arnsten JH, Lo Y, Vlahov D, Rich JD, Schuman P, et al. A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. *AIDS* 2002;16:2175–2182.
28. Ankrah DNA, Lartey M, Agyepong I, Luefkens HGM, Mantel-Teeuwisse AK. Adherence and treatment change among HIV/AIDS patients in Ghana-A nested case-control study. *J AIDS Clin Res* 2015;6:10
29. 2012 HIV Sentinel Survey Report. National AIDS/STI control programme, Ghana Health Service, Ministry of Health, Ghana, May 2013.
30. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. 2007 *JAMA* 297:177-86.
31. Kirkwood BR, Stern JAC. Regression Modeling, In Medical Statistics (2nd Edition) 2003. Blackwell Publishing Limited, Oxford, United Kingdom.
32. Hosmer DJ, Lemeshow S, Sturdivant RS. Assessing the Fit of the Model, In Applied Logistic Regression (3rd Edition) 2013. John Wiley & Sons Inc. Hoboken, New Jersey, USA.
33. Estat gof – Pearson or Hosmer-Lemeshow goodness-of-fit test. www.stata.com/manuals13/restatgof.pdf. Accessed 20/07/14
34. Gao X, Nau DP, Rosenbluth SA, Scott V, Woodward C. The relationship of disease severity, health beliefs and medication adherence among HIV patients. *AIDS Care* 2000; 12(4):387-398.
35. DiMatteo MR, Haskard KB, Williams SL. Health beliefs, disease severity, and patient adherence: A meta-analysis. *Med Care* 2007;45: 521–528)
36. Raboud J, Li M, Walmsley S, et al. Once daily dosing improves adherence to antiretroviral therapy. *AIDS Behav*. 2011;15(7):1397-1409.
37. Nachega JB, Parienti JJ, Uthman OA, et al. Lower Pill Burden and Once-daily Dosing Antiretroviral Treatment Regimens for HIV Infection: A Meta-Analysis of Randomized Controlled Trials. *Clin Infect Dis*. 2014;58(9):1297-307.
38. Laing R, Hodgkin C. Overview of antiretroviral therapy, adherence and drug-resistance. In, From access to adherence: the challenges of antiretroviral treatment. Studies from Botswana, Tanzania and Uganda. WHO, KTI and University of Amsterdam 2006.
39. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf. Accessed 04/02/16.

Chapter 3.4

FACILITATORS AND BARRIERS TO ANTIRETROVIRAL THERAPY ADHERENCE AMONG ADOLESCENTS IN GHANA

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ABSTRACT

Background

Adherence to antiretroviral therapy is known to be challenging among adolescents living with HIV/AIDS notwithstanding the life-saving importance of this therapy. Of the global total number of adolescents living with HIV in 2013, about 83% reside in sub-Saharan Africa. The aim of this study was to identify facilitators of and barriers to antiretroviral treatment adherence among adolescents in Ghana.

Method

A cross sectional qualitative study using semi-structured interviews for data collection was carried out among adolescents (aged 12-19 years) at the adolescents HIV clinic at the Korle-Bu Teaching Hospital in Ghana. Predominantly open-ended questions relating to antiretroviral therapy were used. Interviews were done until saturation. In total, 19 interviews were conducted. Analysis was done manually to maintain proximity with the text.

Findings

The main facilitators were support from health care providers, parental support, patient's knowledge of disease and self-motivation, patient's perceived positive outcomes, and dispensed formulation,. The identified barriers were patient's forgetfulness to take medicines, perceived stigmatization due to disclosure, financial barriers, and adverse effects of antiretroviral therapy. Support from health care workers was the most frequently mentioned facilitator, and patient's forgetfulness, and perceived stigmatization after disclosure were the most frequently mentioned barriers. Self-motivation (knowledge induced) to adhere to treatment was a specific facilitator among older adolescents.

Conclusion

Continuous information provision in addition to unflinching support from health care workers and parents or guardians may improve adherence among adolescents. Also, interventions to reduce patient forgetfulness may be beneficial. A multi-sectorial approach would be needed to address adolescent disclosure of HIV/AIDS status.

INTRODUCTION

As of 2013, of the total number of adolescents (people aged between 10-19 years [1]) living with HIV, 83% resided in sub-Saharan Africa [2]. Furthermore, between 2001 and 2013, while trends in global AIDS related deaths decreased among other age-groups, it increased among those aged 10-19 years [2]. Factors responsible for these observations may include a lack of knowledge of HIV, inequalities in health services, growing up without parents, early sexual activity and a generally risky behaviour [3], and non-adherence to antiretroviral therapy.

The advent of antiretroviral therapy (ART) was a major respite for people infected with HIV, but optimal adherence is need for best outcomes. Non-adherence to antiretroviral therapy adversely affects clinical [4, 5] immunological, and virological outcomes of patients.

In general, adherence among adolescents on chronic medication has been found to be lower compared with younger children or adults [6, 7] due mainly to the transition process of this subgroup [8]. Adherence enhancing interventions in this group have had poorly sustained interventions so far [9]. In addition, demographic factors like increasing age and female gender have been found to be associated with non-adherence among adolescents [10, 11].

Adherence levels are suboptimal averaging in up to 50% of the infected youth [12, 13]. Among young people living with HIV/AIDS numerous behavioral challenges such as peer pressure and concerns about body image, have been found that are associated with adherence behaviour [14]. Furthermore, psychological factors, threats to health status disclosure and interpersonal relations [15-17] have been reported that affect adherence to treatment. Also, stigma and discrimination by friends [18], a complex ART regime [19], and an adverse drug effect [20], have all been found to be associated with a decline in adherence.

According to Radclife et al [21], regular follow up of treatment improves adherence among young people. Adolescents who believed that quality of life was improved with medication were more likely to adhere to treatment [22]. In a systematic review, patient and caregiver education, self-monitoring, telephone follow-up and self-support [23] have been mentioned as key strategies to improve adherence among the youth. A schematic framework of adolescent adherence is shown as Appendix A.

Very few studies in sub-Saharan Africa (SSA) have targeted adherence among adolescents on ARTs resulting in an unmet need among this group. It is important to assess the perspective from adolescents themselves in what they see as main treatment barriers and facilitators helping them to achieve better treatment adherence. Using semi-structured interviews, this study aimed to explore barriers and facilitators to antiretroviral adherence among HIV infected adolescents on treatment in Ghana, a low and medium income country (LMIC) in SSA.

METHODOLOGY

Study setting and population

The study was conducted at the Fevers Unit of the Department of Medicine and Therapeutics of the Korle-Bu Teaching Hospital, Ghana. The Fevers Unit is a referral center responsible for

the registration and management of all cases of HIV in adults and adolescents older than 12 years. There are three out-patient clinic days per week, each with an average attendance of about 120 patients. In addition, there is a special clinic for HIV infected adolescents on Thursdays.

A qualitative cross sectional study was performed involving adolescents attending the adolescents HIV clinic aged between 12-19 years. The decision to choose 12 years as the lower limit instead of 10 years was because the adolescent clinic is attended by children aged 12 years and above. Adolescents, both school-going and non-school-going who had been on treatment for a minimum of six months at the study site were eligible for participation. There were no proxy interviews. Adolescents at the pharmacy waiting to refill antiretroviral prescriptions were approached and a request to participate in a study was made. Those who agreed signed a written informed consent. During selection an attempt was made to have a representative number of people in age groups 12-15 and 16-19. This was to ensure that the views of both younger and older adolescents were captured.

Ethics statement

Ethical approval was obtained from the Ethical and Protocol Review Committee of the University of Ghana Medical School, Accra, Ghana.

Data collection

Semi-structured interviews were administered to all participants using predominantly open-ended interview guide. There were follow-on questions depending on an interviewee's response to a previous question. Also, there were questions inviting participants to narrate a scenario, for example, *"tell me about how you started taking these antiretroviral medicines"*. All interviews were audio-recorded with the permission of interviewees and held in a secured cabinet (an office) at the pharmacy department. Interviews were in English or a local language preferred by the interviewee. Themes explored were on general medication use, adherence to treatment, influence of others and social activities (see Appendix). Interviews were conducted until no new information was emerging from the process (saturation). The interviews were conducted over a period of six weeks and were all done by the lead author. Each interview lasted between 20-40 minutes.

Data handling and analysis

Recorded interviews in English were transcribed verbatim. Interviews in the local language were translated and transcribed into English with back-translation checks. Data were coded by two researchers (the lead author and a social scientist with experience in qualitative research). Where discrepancies occurred, the two coders met, discussed and came to an agreement. All interviews were anonymized during this process.

Analysis

Analysis was done manually. Those who started ARTs from childhood as well as those who started later in life were identified. This gave an idea of those infected through vertical transmission and those from other forms of infection. Data analysis was done using framework analysis [24, 25]. The scripts were read again and again (between 4-6 times) to identify all key ideas and recurrent themes. With the aims and objectives of the study in focus, the data were indexed and labelled for further exploration. Emerging ideas were coded and assigned to various themes. A chart of the main themes and responses from corresponding interviewees was constructed. Information from the chart was continuously matched with coded information until all important facts providing explanation for the findings were identified. These facts were then structured as barriers and facilitators of adherence to ART.

FINDINGS

Sociodemographic characteristics

A total of 20 adolescents were approached for participation, but one declined because he was late for school. The mean age of interviewees was 16.3 years with a standard deviation of 1.9 years. The youngest person was 14 years and the oldest was 19 years. There were 3 boys and 5 girls in the 12-15 years age group and there were 4 boys and 7 girls in the older age group. Among those interviewed, 2 had completed senior high school, 4 were in senior high school, 12 were in junior high school and 1 dropped out of school at class 5. Of the 19 interviews, 17 were in English and two in the local language.

Only three of those interviewed knew the names of at least one of their antiretroviral medicines but most of them knew the name of the most used medicine for opportunistic infections (cotrimoxazole). Two patients (a boy and a girl) reported that their situation was not as a result of vertical transmission. The boy, a 14 year old, said he had the infection through the use of an infected needle and the other, a 19 year old girl, said she was infected by her former boyfriend.

There were unique themes that were classified as facilitators or barriers but occasionally there were specific ones that apart from encouraging adherence in some participants, made others default. A typical case was positive outcomes from antiretroviral treatment where one patient reported that it makes him think he is cured. The findings have been grouped under "facilitators" and "barriers" with the identified themes serving as sub sections.

Facilitators

Support from health care providers

All those interviewed said the contribution from clinical staff (doctors, nurses, laboratory technicians, registry staff) as well as pharmacy staff has helped them to be more conscientious in taking their medications. Consequently, this was the most frequently mentioned facilitator. This was how a 16 years old female reported it:

> The influence of the health workers has helped me a lot with my medicines. What they tell me at the clinic and at the adherence counselling unit encourages me to take my medicines regularly.

Some patients compared the care they had from other health workers with what is given them at the treatment site. This was what one of such patient (female, 17 years) said:

> It has helped me. If I were not being treated well I will stop coming here. I may even stop taking my medicine and this will surely affect my health. Unlike the doctors who treated me before…, those at the treatment centre are nice to me and they help me to take my medicine well.

Parental support

Although not all respondents said they were actively assisted by their parents, those who did, were happy with such support because it improved their medication taking habits. One respondent captured it as follows:

> At home my parents remind me to take my medicines when it is time. When I am taking it on my own I first show it to them. My parents have been supportive and this has helped a lot with the way I take my medicines.

Patient's knowledge of disease and self-motivation

Knowledge of the nature of HIV and knowing that HIV is only controlled by taking your medicines, facilitated the desire for some patients to remember to take their medicines. Almost all patients interviewed (n=16) mentioned that HIV is a killer disease found in blood. Some mentioned that being serious with your medication could avert such deaths. A 15 years old girl expressed knowledge of the disease as follows:

> It is a bad sickness that kills a lot. It is not good. When you take your medicines seriously you will not die but if you stop, you will die. It can be found in the blood. It is also in breast milk. If you use a blade and the same towel or sponge with an HIV infected person you can get HIV. If you have unprotected sex with someone who has the virus you can get the virus.

Self-motivation through acquired knowledge, though not the general view, was mentioned by older respondents as a motivator for taking medicines. An 18 years old post senior high school girl gave this account:

> First of all I was counselled on the benefits. Personally I read a lot about the medicines and learn a lot that way. At the moment I have assured myself that I am going to be on this medicine for the rest of my life and I do not think anything will hinder me.

Patient's perceived positive outcomes

Participants mentioned the physical changes they experience while on medication as a driver for adherence. One of the female patients was all praises for what the medicines had done for her,

> I think it is ok. At the moment I have gotten used to the medicines. I think it is very necessary; it is the reason I am alive today. It helps to boost my immune system and prevents further diseases from occurring. I believe it is by the grace of God these medicines were made.

Dispensed formulation

Some participants (n=5) in the study mentioned that tablets were more convenient compared with syrups. Because of their daily activities and the treatment times, adolescents needed to carry their medication from one place to the other. An 18 years old male said this about the tablets he takes now compared with the syrup he was previously using:

> My medicines have been changed before. I used to take syrup but when I moved to the Fevers Unit it was changed to tablets. I prefer the tablets to the syrup because it is more convenient to carry around.

Barriers

A number of reasons were mentioned as responsible for patients' inability to continue treatment as scheduled.

Patient's forgetfulness to take medicines

All respondents mentioned forgetfulness due to preoccupation with other life events as reason for non-adherence. These included activities such as attending church service, early start of school activities, socializing and helping parents/guardians with petty trading activities. For example, a boy of 14 indicated that he sometimes forgot to take his medicines because he goes out socializing with his peers:

> I take my medicine because I do not want to get ill like before. I want to feel healthy. I sometimes forget to take my medicines in the evening because I go out with my friends... Sometimes I do not come home early enough.

Perceived stigmatization due to disclosure

Fear of stigmatization by their mates in school and their friends or peers at home was mentioned by all those interviewed. While some interviewees would not even let their mates know that they are taking antiretroviral medicines, others admitted that their mates were aware but were not sure of what disease the drugs were for. Reasons like asthma and sickle cell anaemia were mentioned as some of the answers given when colleagues asked for the purpose of their medicines. One patient explained the situation in this form:

> At school I take my medicines normally. My friends see me and sometimes ask why I always take medicines. I just tell them it is because I have sickle cell anaemia,… if I tell them it is for HIV they will laugh at me. I will be ashamed and may not take my medicine. If I do not take my medicine I will die so I do not think it is right for me to tell them.

Financial barriers

Although ARVs are free, not all patients find it easy to pay the additional cost of frequent travels for their medication due to financial constraints on their parents/guardians. Such patients sometimes run out of ARVs and default in medication routine. A 15 years old girl living with her mother about 8 km from the treatment centre explained:

> I normally I come to the clinic with my mum but today I decided to come all by myself. I sometimes have a problem with transportation. Even today, my mum had to borrow money from a friend for my transportation to this place. She was complaining that she has not yet received her salary.

Adverse effects of ART

Adverse drug reactions associated with some of the medications particularly dizziness, was mentioned as one of the most worrying attributes that discouraged them from taking their medicines. This was how one 16 years old boy put it:

> Whenever I take the medicine I feel dizzy, I came to report and it was changed. I would have stopped taking it. If the side effects are severe I cannot take it.

Although most patients complained about the number of medicines taken they did not consider it as a direct cause for non-adherence. One boy explained it this way:

> I take haematinics and cotrimoxazole in addition to my medicines. I feel the medicines are a lot however, it does not affect the way I take them. In the morning I take the two medicines and the antiretroviral dose and I take only the antiretroviral in the evening.

DISCUSSION

Forgetfulness has been reported as a barrier to adherence among adolescent patients [26]. In a systematic review of qualitative studies on adherence to ART [27], forgetfulness was identified as a major contributor to non-adherence. Forgetfulness has also been reported as a major factor of non-compliance to medicines and clinic visits [28-30]. The effect of social activities according to this study had a strong effect on patients' ability to remember their treatment times. To overcome this, the use of reminders may be considered. The use of short message service (SMS) among the youth has been found to improve self-reported adherence [31], and Puccio et al [32] have reported the benefits of cell phone use among adolescents and young adults. Most adolescents in Ghana at the moment own mobile phones which come with reminder alarms. Care givers can take advantage of this and advise adolescents appropriately.

A factor that almost all interviewees reported as adversely affecting the way they take their medicine was perceived stigmatization as a result of disclosure to their friends and school mates. It was realized that for some children, their parents or guardians advised them not to discuss their sero-status or antiretroviral medication with their peers. While parents

and guardians want good health for their children, sometimes they may be over-protective. Parents need to encourage their wards to disclose their HIV status but would demand a lot of education on the part of the public on how to handle such information, otherwise it will be counter-productive. This is because of its profound effect on stigmatization and discrimination which has been found to be associated with adherence.[18] Perceived stigmatization and discrimination of HIV/AIDS patients (including those on treatment) cut across every facet of Ghanaian society and this will take a holistic approach to circumvent. A case worth mentioning involves the renowned 28 year old Ghanaian HIV/AIDS activists who, after testing positive in 2007, according to the Ghana National AIDS Commission [33], publicly disputed being an HIV patient [34] to avoid stigmatization. Parents and guardians, the health sector, the educational sector and HIV/AIDS advocacy groups should come together to discourse this agendum. Mburu *et al* have suggested a public health intervention to help adolescent patients and their parents or guardians [35]. Peer support [36], has been mentioned as a major facilitator of adherence among adolescents with a chronic disease, but this needs a lot of education on disease etiology among all those in this age group. The International Association of Providers of AIDS Care (IAPAC) in conjunction with the WHO and the Pan American Health Organization (PAHO) have just developed an appropriate training manual [37] for peer education of HIV positive adolescents and young adults. This may be helpful in improving the emotional and physical lives of adolescents.

Adverse drug effects also deterred adherence and most patients mentioned periodic dizziness as the cause. This calls for proper monitoring and early intervention to prevent non-adherence to treatment.

Respondents were unanimous about the benefits received from health care workers and its effect on medication administration. To improve or at least maintain such standards, lessons can be learned from the adolescents training curriculum developed by the Zambian Ministry of Health in collaboration with International Center for AIDS Care and Treatment Programs (ICAP) [38]. This is a youth-friendly HIV care manual for adolescents living with HIV and their caregivers.

Support from parents (both financial and social) was highly rated by interviewees. Studying adherence in general, practical support from parents for adolescents has been mentioned by Taddeo et al [39] as positive. They suggested the reinforcement of family closeness, cohesiveness and problem solving skills with adolescents.

Adolescents cannot always take their medicines at home because they may be involved with public activities that may overlap with their treatment times. They may want to keep their antiretroviral medicines away from their peers. For such patients tablets, rather than syrups, will be more convenient. On limited occasions liquid preparations have been dispensed to adult HIV patients in Ghana because there were shortages with tablets and treatment cannot be broken. Care must be taken to eliminate such situations.

Contrary to reports [19], a complex ART regimen was not problematic in this study. Claxton et al [40] have explained that treatment complexity is not the main issue but

the relationship between a patient's routine, expectations and preferences are crucial. Most respondents explained that taking the drugs was not very challenging because of the 12 hourly dose regimens.

This study has its limitations. Using a qualitative study provided opportunity to explore the issues of interests in depth in a way that would not be possible with quantitative studies. Although this may affect generalizability, qualitative studies tend to provide information as to what to investigate in a more statistically generalizable study. The research involved patients' own account of events which may be subjective. However, the degree of consistency in response is assuring, and a source of credibility to the study. This study did not assess the relationship between facilitators and barriers, and direct measurement of adherence.

CONCLUSION

The most recurrent barriers to ART adherence were forgetfulness and perceived stigmatization post-disclosure by patients. Adolescents were unwilling to reveal information on their HIV disease status to their peers, they mentioned other morbidities as responsible for their current situation. This observation needs to be addressed by all stakeholders of HIV/AIDS in order to move adolescent HIV treatment forward. The most frequently mentioned facilitators to ART adherence among adolescents in this study were the role of health care workers at the treatment site and parental support. The findings provide ideas as to interventions that can improve adherence among this subgroup, and provide the information to design, implement and evaluate their impact with a more statistically generalizable design.

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REFERENCES

1. WHO 10 facts on adolescent health. Available from: www.who.int/features/factfiles/adolescents_health/en/index.html. Accessed 19/03/2015.
2. ALL IN #EndAdolescentAIDS. 2015. Available from: www.unicef.org/ media/ files/ ALL_IN_brochure_En_v02(1).pdf. Accessed 26/07/2015.
3. Preventing HIV/AIDS in young people: a systematic review of the evidence from developing countries: UNAIDS interagency task team on HIV and young people. Editors: David Ross, Bruce Dick, Jane Ferguson 2006
4. Timmreck TC, Randolph JF. Smoking cessation: Clinical steps to improve compliance. *Geriatrics* 1993;48:63-66.
5. Farmae KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *ClinThera* 1999;21:1074-1090.
6. Wamboldt F, Bender B, Wamboldt M, et al. Psychosocial correlates of pediatric MDI adherence. *Am J Respir Care Med* 2000;161(13):A711.
7. Wamboldt F, Bender B, Ho , et al. Correlates of MDI adherence: A replication study. *Am J Respir Care Med* 2002;165(8):A197
8. Pai A L, Ostendorf H M. Treatment Adherence in Adolescents and Young Adults Affected by Chronic Illness During the Health Care Transition From Pediatric to Adult Health Care: A Literature Review. Childrens' Health Care 2011;40:16-33.
9. Bender B, Milgrom H, Apter A. Adherence intervention research: What have we learned and what do we do next? *J Allergy Clin Immunol* 2003;112(3):489-94.
10. Williams PL, Storm D, Montepiedra G, et al. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. *Pediatrics* 2006;118:e1745–e1757.
11. Chandwani S, Abramowitz S, Koenig LJ, Barnes W, D'Angelo A. A multimodal behavioral intervention to impact adherence and risk behavior among perinatally and behaviorally HIV infected youth: description, delivery, and receptivity of adolescent impact. *AIDS Educ P rev* 2011;23:222-235.
12. Murphy DA, Belzer M, Durako SJ, Sarr M, Wilson CM, Muenz LR. Longitudinal antiretroviral adherence among adolescents infected with human immunodeficiency virus. *Arch Pediatr Adolesc Med* 2005;159:764–770.
13. Becker SL, Dezii CM, Burtcel B, Kawabata H, Hodder S. Young HIV-infected adults are at greater risk for medication nonadherence. *MedGenMed* 2002;4:21.
14. More positive living. Strengthening the health sector response to young people living with HIV. Available from: http://whqlibdoc.who.int/publication/2008/9789241597098_eng.pdf. Accessed 19/09/2014.
15. Murphy DA, Wilson CM, Durako SJ, et al. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. *AIDS Care* 2001;13:27–40.
16. Hosek S, Harper G, Domanico R. Psychological and social difficulties of adolescents living with HIV: A qualitative analysis. *J Sex Educ Ther* 2000;25:269–276.
17. Murphy DA, Moscicki AB, Vermund SH, Muenz LR. Psychological distress among HIV(+) adolescents in the REACH study: effects of life stress, social support, and coping. The Adolescent Medicine HIV/AIDS Research Network. *J Adolesc Health* 2000;27:391–398.
18. Rao D, Kekwaletswe TC, Hosek S, Martinez J, Rodriguez F. Stigma and social barriers to medication adherence with urban youth living with HIV. *AIDS Care* 2007;19:28–33.
19. Murphy DA, Wilson CM, Durako SJ, Muenz LR, Belzer M. Adolescent Medicine HIV/AIDS Research Network. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. *AIDS Care* 2001;13:27–40.
20. Murphy DA, Sarr M, Durako SJ, Moscicki AB, Wilson CM, Muenz LR. Barriers to HAART adherence among human immunodeficiency virus-infected adolescents. *Arch Pediatr Adolesc Med* 2003;157:249–255.

21. Radcliffe J, Tanney M, Rudy B. Post-traumatic stress and adherence to medical treatment among youth with HIV. *J Adolesc Health* 2006;38:110–111.

22. Belzer ME, Fuchs DN, Luftman GS, Tucker DJ. Antiretroviral adherence issues among HIVpositive adolescents and young adults. *J Adolesc Health* 1999;25:316–319.

23. Reisner SL, Mimiaga MJ, Skeer M, et al. A review of HIV antiretroviral adherence and intervention studies among HIV-infected youth. *Top HIV Med* 2009;17(1):14-25.

24. Green J, Thorogood N. Qualitative Methods for Health Research (2nd Edition). London: SAGE Publications, 2009.

25. Pope C, Ziebland S, Mays N. Qualitative research in health care-Analysing qualitative data. *BMJ* 2000;320:114-6.

26. Murphy DVA. Barries to haart adherence among immunodeficiency vírus-infected adolescents. *Arch Pediatr Adolesc Med* 2003;157:249-55.

27. Vervoort SCJM, Borleffs JCC, Andy I.M. Hoepelman AIM, Grypdonck MHF. Adherence in antiretroviral therapy: a review of qualitative studies. *AIDS* 2007;27:271-281.

28. Hernandez-Ronquillo L, Tellez-Zenteno JF, Garduno-Espinosa J, Gonzalez-Acevez E. Factors associated with therapy noncompliance in type-2 diabetes patients. *Salud Publica Mex* 2003;45:191–7.

29. Ponnusankar S, Surulivelrajan M, Anandamoorthy N, Suresh B. Assessment of impact of medication counseling on patients' medication knowledge and compliance in an outpatient clinic in South India. *Patient Educ Couns* 2004;54:55–60.

30. Wai CT, Wong ML, Ng S, et al. Utility of the Health Belief Model in predicting compliance of screening in patients with chronic hepatitis B. *Aliment Pharmacol Ther* 2005;21:1255–62.

31. Dowshen N, Kuhns LM, Johnson A, Holoyds BJ, et al. Improving adherence to antiretroviral therapy for youth living with HIV/AIDS: A pilot study using personalized, interactive, daily text message reminders. *J Med Internet Res* 2012;14(2):e51.

32. Puccio JA, Belzer M, Olson J, et al. The use of cell phone reminder call for assisting HIV-infected adolescents and young adults adhere to highly active antiretroviral therapy: A pilot study. *AIDS Patient Care STDS* 2006;20(6):438-444.

33. Ghana AIDS Commission says Joyce Dzidzor tested positive for HIV. Available from: http://ameyawdebrah.com/Ghana-aids-commision-says-joyce-dzidzor-tested-positive-hiv/. Accessed: 03/07/2015.

34. IneverhadHIV–AGhanaianHIV/AIDSambassador confesses. Available from:http://graphic.com.gh/news/general=news/35460-i-never-had-hiv-in-ghanaian-hiv-aids-ambassador-confesses.html. Accessed 03/07/2015.

35. Mburu G, Hodgson I, Kalibala S, *et at*. Adolescent HIV disclosure in Zambia: barriers, facilitators and outcomes. *J Int AIDS Soc* 2014;17:18866.

36. Miller-Johnson S, Emery RE, Marvin SR, Clarke W, Lovinger R, Martin M. Parent–child relationships and management of insulin-dependent diabetes mellitus. J Consult *Clin Psychol* 1994;62:603–10.

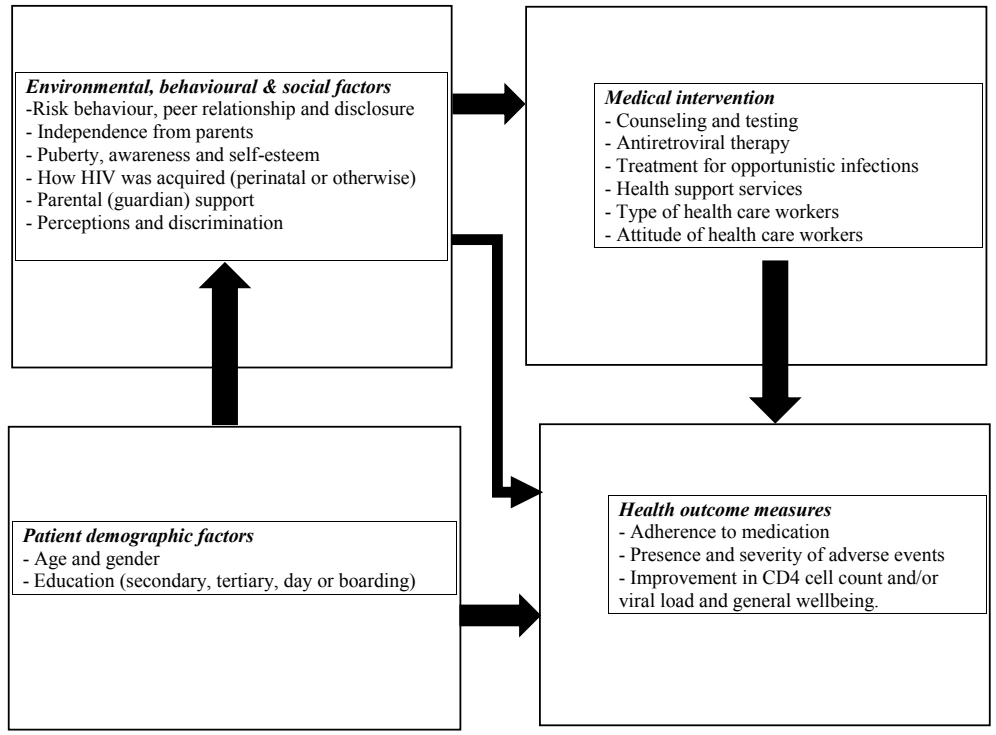
37. Peer Education Trainer's Manual – Increasing the Knowledge and Skills of HIV-Positive Adolescents and Young Adults to Live Emotionally, Physically, and Sexually Healthy Lives. The International Association of Providers of AIDS Care, December 2014.

38. Adolescent HIV Care and Treatment. Available from: files.icap.columbia.edu/files/uploads/1423_ZM_Participant_Manual.pdf. Accessed: 20/01//2015.

39. Taddeo D, Egedy M, Frappier J. Adherence to treatment in adolescence. *Paediatr Child Health* 2008;13(1):19-24.

40. Claxton A J, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;23(8):1296-1310.

APPENDIX A
SCHEMATIC FRAMEWORK OF ADOLESCENT ADHERENCE



APPENDIX B
THEMES EXPLORED DURING THE INTERVIEWS

Types of questions (English version)

Introduction (after consent form is signed/thumb printed)

Hello, you are welcome for this interview.
I will be asking you a few questions about your treatment for HIV and I will plead with you to answer to the best of your knowledge.
Please tell me what you know about the HIV/AIDS disease

General medication use

How many ARTs are you taking at the moment?
What is/are the name(s) of your medicine(s)?
Tell me something about when you started taking these medicines
Do you have other medicines in addition to these? How do you feel about the number of medicines you are taking so far?
How did you feel during the first two weeks after starting your medication?
Have you ever had a change of medication? What was the reason for this change?
What is your own perception of these medicines?

Adherence - medication intake behavior

How often do you taken your medicine?
Tell me what makes you take your medicines well.
Tell me what does not make you take your medicines well.
Please tell me on which days of the week you are most likely to forget to take your medicines.
Why in your opinion is this so?
Tell me about your experiences at home when taking your medicines.
Tell me about your experiences at school when taking your medicines.
Please describe your worst experience concerning your medicines.

Influence of others

What is your relationship with the health workers at the clinic?
What is your relationship with those who serve you medicines?
How has these influenced your attitude towards your medicines?
In your opinion how has living with (or without) your parents affected the administration of your ARTs?
Do you often discuss your condition (HIV status) with your peers?
If No to Q22, is there any reason(s) why?
If yes to Q22, how has that affected your drive to continue taking your ARTs?

Alcohol/drug use

Do you drink alcohol or smoke? Do you use other drugs like crack or cocaine?
If yes to Q25, do you get hangover from such practice? How does this affect your routine uptake of ARTs?

Conclusion

What else would you like to say about your medicines that we have not discussed today?

Thank you for your time and patience. You will hear from me soon.

Chapter 4

SAFETY SURVEILLANCE STUDIES IN GHANA

Chapter 4.1

INCIDENCE OF ADVERSE EVENTS AMONG HEALTH CARE WORKERS FOLLOWING H1N1 MASS IMMUNIZATION IN GHANA - A PROSPECTIVE STUDY

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ABSTRACT

Background

Cases of the A(H1N1) 2009 influenza were first recorded in Ghana in July, 2009. In June, 2010 when prioritized vaccination against the novel influenza A(H1N1) virus started in the country, health workers were among the selected groups. The main objective was to determine the distribution and types of adverse events reported following immunization of health care workers at the Korle-Bu Teaching Hospital (KBTH) from the day vaccination started until one week after the end of vaccination.

Method

Safety data collected during the AH1N1 influenza vaccination of health workers at the Korle-Bu Teaching Hospital (Accra, Ghana) was used for this study. All workers, 18 years and over were eligible for vaccination. For uniformity 0.5ml of Pandemrix® (equivalent to 3.75 micrograms of heamagglutinin antigen) was administered intramuscularly into the deltoid muscle of the left arm. Each vaccinee was issued with a card and was advised to report any adverse events following immunization to designated health workers for follow-up. Incidence rates of adverse events were estimated and compared to the Pandemrix® Summary of Product Characteristics (SPC)

Results

A total of 5870 people (64.9% females) with a mean age of 34.0 years were vaccinated. In all 140 vaccinees reported adverse events. The mean age among vaccinees reporting adverse events was 36.1 years. The overall incidence of vaccinees reporting adverse events and the overall incidence of adverse events was 232 (95% confidence interval {CI} 199 to 320) per 10,000 people and 930 (95% CI 820 to 1070) per 10,000 people respectively. In particular, we found no difference in the way males reported AEFI compared to females ($\chi 2 = 0.59$; $P > 0.2$) and we did not find any association between age as a categorical variable and vaccine adverse event reporting ($\chi 2 = 5.24$; $P > 0.1$). There were only three serious cases which led to hospitalization. All three cases occurred within 24 hours of receiving the vaccine. The incidence rates for the various reported events were all lower compared to those in the Pandemrix® SPC, but while injection site pain was the most frequent in the SPC and other foreign studies, we recorded headache as the most frequent. Even fatigue, muscle/joint aches and fever had higher incidence rates compared to injection site pain. Tachycardia (n=6), tinnitus (n=1) and decreased appetite (n=4) were reported although not included in the SPC.

Conclusion

The vaccine was safe among the population that was vaccinated. Although similar events were reported in other studies, the incidence was different and there were a few differences in the most frequently reported events. More of such studies should be encouraged in Low and Medium Income Countries to bridge the information gap with the developed world. In particular, health care workers could be used to obtain first-hand information.

INTRODUCTION

Safety reporting of marketed medicines has always been an issue of global importance. Especially in low and emerging economies it may be difficult to get information on medicine safety because of non- existent or weak monitoring structures. For most results obtained, this has been through the process of spontaneous reporting. However, in recent times, cohort event monitoring ((CEM) also called prescription event monitoring) is advocated as a tool in low and middle income countries because of its strengths in signal generation, and also because it is prospective [1, 2] leading to précised estimation of event rates.

So far, the CEM methodology has been proposed and used for malaria [1] and HIV [2] medications, but this or a similar tool may be applied to safety monitoring of vaccines such as the H1N1 vaccine. The use of health care workers as a special group for research has been very helpful in the past. Doll and Hill [3], investigated the effect of smoking on lung cancer among British doctors, the Nurses' Health Study cohort [4] and the Health Professional Study cohort [5] are important special group examples that can be cited. Logistically, using such defined groups is advantageous because problems with follow-up [6] are minimal.

In Ghana, when the Ministry of Health decided to vaccinate Ghanaians against the influenza, health care workers were among the first to be vaccinated after the first reports of A(H1N1) 2009 influenza in July 2009 [7]. For most developing countries including Ghana, vaccines were supplied by the World Health Organisation (WHO). Because of the nature of vaccine technology, it was evident that in the early stages of the pandemic, available vaccines would not be enough to cater for everyone [8]. To mitigate such anticipated shortfalls the Strategic Advisory Group of Experts on Immunization (SAGE) of the WHO identified three different objectives that countries could adopt as part of their pandemic vaccination strategy [9]. These were "(i) protecting the integrity of the health-care system and the country's critical infrastructure; (ii) reducing morbidity and mortality; and (iii) reducing transmission of the pandemic virus within communities". SAGE also recommended immunization strategies that should be used by countries depending on their epidemiological trends, resources and ease of access to vaccines [9].

The National Technical Coordinating Committee (NTTC) of the Ministry of Health, Ghana decided that vaccination should be prioritized [10] because Ghana received vaccines equivalent to just about 10% of the population. Health workers, national security personnel, pregnant women (after first trimester) and other high risk people (asthmatics, cardiovascular disease patients, diabetic patients, international travellers, etc) in that order, were scheduled to be vaccinated depending on availability of vaccines [10]. People below 18 years were not vaccinated. Vaccine deployment was under the auspices of the Vaccine Deployment Sub-committee of the NTCC and the disease surveillance departments; the National Program on Immunisation and the Food and Drugs Board of Ghana were responsible for safety surveillance.

Previous studies evaluated the safety of the H1N1 vaccine in daily practice. After using about 82 million doses of 2009 H1N1 influenza vaccines in the United States of America, safety reports from the Vaccine Adverse Event Reporting System (VAERS) showed that about

93% (9359/10085) of all such reports were not serious [11]. During monitoring of safety of vaccines and antivirals against the pandemic A(H1N1) 2009 influenza in France 3855 events were recorded after using 4.1 million doses of the Pandemrix® vaccine [12] (GlaxoSmithKline Biologicals s.a., rue de l'Institut 89, B-1330 Rixensart, Belgium). Only 5% of these were serious, the rest were non-serious and expected. The profile of adverse events reported during monitoring following mass immunization of various age groups in the Netherlands was comparable to that indicated in the summary of product characteristics (SPC [14].

However, Ghana is a sub-Saharan country located in the tropics where seasonal influenza is not endemic and nobody receives seasonal flu vaccination. According to reports [14], the last time an outbreak of this nature (the Spanish flu) occurred in Ghana (then Gold Coast) was in 1918 when the death toll was about 11,600. The population at the time was about 2 million [14] compared to the current population of about 24 million. Therefore, adverse events occurring after vaccination in the Ghanaian population may differ from other populations.

This article therefore reports on the distribution and types of adverse events following immunisation (AEFI) of healthcare workers in a health institution in a tropical country devoid of seasonal influenza, after receiving a single dose of the monovalent Pandemrix® A(H1N1) vaccine.

MATERIALS AND METHODS

Setting

The Korle-Bu Teaching Hospital is a tertiary health institution with 2000 beds. It shares the same premises with the University of Ghana Medical School and the School of Allied Health Sciences, the School of Nursing and the School of Pharmacy, and students of these education institutions use the hospital for their practical training. All healthcare workers of the Teaching Hospital age 18 years and older were eligible for vaccination. Those who had previously had the infection and had been treated were excluded. Each participant received one dose of 0.5ml of Pandemrix® (H1N1) vaccine with batch number A81CA656A. This was a monovalent, split virion, inactivated and adjuvanted vaccine propagated in eggs [15]. The seed virus was derived from A/California/07/2009 (H1N1) strain (where A is the virus type, followed by the geographical region, then the strain number, and then the year of isolation, and lastly, the strain type [16]). It is administered as a single dose of 0.5ml which is equivalent to 3.75 micrograms of heamagglutinin antigen.

For uniformity, the injection was administered intramuscularly into the deltoid muscle of the left arm. Trained Community Health nurses from the Ghana Health Service were used for the immunization program. At the Korle-Bu Teaching Hospital five immunization centres were set up at strategic locations to improve accessibility. Immunization was done from the 14th -18th June, 2010. All those who were vaccinated were issued with an immunization card.

Safety assessment

One week prior to initiation of immunization, letters were sent to all clinical departments to sensitize workers. Copies of the special adverse events reporting forms designed for the exercise (using the Vaccine Incident Report Form from the North Yorkshire Health Protection Unit and North Yorkshire and York NHS Primary Care Trust as a guide [17]) were attached to these letters so that they will be familiar with the form. All vaccinees at the vaccination centres were verbally informed of the risks associated with the vaccine and were advised to report suspected adverse events to designated members of the Public Health Unit (PHU) to complete the reporting form. The members of the PHU were made of two doctors and a pharmacist. Their role (among others) were to ensure that all those reporting had received the Pandemrix® vaccine previously. Those with serious [18] adverse events following immunization (AEFI) were referred to standby physicians at the Surgical/Medical Emergency Unit for monitoring. Adverse event data were collected from the first day of immunization until one week after the end of the immunization period. An AEFI in this study was defined as any untoward medical occurrence in a vaccine which follows immunization and which does not necessarily have a causal relationship with the administration of the vaccine [19]. Therefore, no causality assessment was carried out.

Data analysis

Data on collected adverse events were entered by two separate national service persons using Microsoft Excel version 2007. These were validated and transferred to Stata intercooled version 9 StataCorp LP, College Station, Texas, USA, for analysis. Collected AEFIs were recoded using medical dictionary for regulatory activities (MedDRA) system organ classification (SOC) codes version 11.1.

Those vaccinated were compared with the cases of adverse events collected using age (categorized in four bands) and sex. Using Pearson's chi squared test, we explored associations between adverse event reporting and age as well as sex. Incidence reporting rates were calculated per 10,000 patients/doses of the Pandemrix® vaccine administered and 95% confidence intervals were calculated. Incidences of specific AEFIs reported were compared to classification in the Summary of Product Characteristics [15] of Pandemrix®. There were four missing values on age which were excluded from the final analysis.

Ethical clearance

Ethical clearance to use the collected data for the study was given by the Ethical and Protocol Review Committee of the University of Ghana Medical School (UGMS), Accra, Ghana.

RESULTS

A total of 5870 people (64.9% females) were vaccinated (see Table 1). Nearly half of the healthcare workers vaccinated were less than 30 years old and mean age among

Table 1. Distribution of number of people vaccinated and vaccinees reporting adverse events following immunization by gender and age group.

	Age group				
	<30	**30-39**	**40-49**	**>=50**	**TOTAL**
Number of healthcare workers vaccinated (N=5870)					
Male (%)	849(29.8)	494(39.9)	407(50.1)	361(37.1)	2,111(35.1)
Female (%)	1,999(70.2)	743(60.1)	406(49.9)	611(62.1)	3,759(64.9)
Total (%)	2,849(100)	1,237(100)	813(100)	972(100)	5,870(100)
Vaccinees reporting adverse events following immunization (N=136[z])					
Male (r)	17(0.020)	10(0.020)	10(0.025)	6(0.017)	43(0.020)
Female (r)	39(0.020	20(0.027)	17(0.042)	17(0.028)	93(0.025)
Total (r)	56(0.020)	30(0.024)	27(0.033)	23(0.024)	136(0.023)

[z] There were 4 missing values (3 males and I female) for age which were excluded; r=age specific incidence rate.

vaccinees was 34.0 years. Vaccination of females outnumbered males in all age groups with the exception among those aged 40-49 who were almost equal in number.

A total of 140 vaccinees reported suspected adverse events, 94 (67.1%) of whom were women. The mean age of vaccinees reporting adverse events was 36.1 years. There were four missing values for age (3 males and a female) among those who reported. These were excluded from any age related analysis.

The total number of adverse events reported was 544, the reason being that most of the vaccinees reported multiple events. The mean number of adverse events reported was four. Figure 1 shows the distribution of adverse events reported, ranging from 1 to 8 events per reporting vaccinee.

The overall incidence of vaccinees reporting adverse events and the overall incidence of adverse events was 232 per 10,000 people (95% confidence interval (CI) 199 to 320) and 930 per 10,000 people (95% CI 820 to 1070) respectively. Table 1 shows the incidence distribution by gender and age group.

Apart from the incidence per 10,000 for females aged 40-49 years, all the other were rather similar (see Figure 2). In particular, we found no difference in the way males reported AEFI compared to females ($\chi 2 = 0.59$; $P>0.2$) and we did not find any association between age as a categorical variable and vaccine adverse event reporting ($\chi 2=5.24$; $P>0.1$).

There were only three serious cases which led to hospitalization. This amounted to a reporting rate of 5 (95% CI 2 to 9) per 10,000 people vaccinated. Each of them reported more than one event some of which were more severe (weakness, dizziness, breathing difficulty, fever, fast heartbeat, muscle and joint aches). All three cases occurred within 24 hours of receiving the Pandemrix® injection. Each case was detained overnight (for about 24 hours) and they all fully recovered.

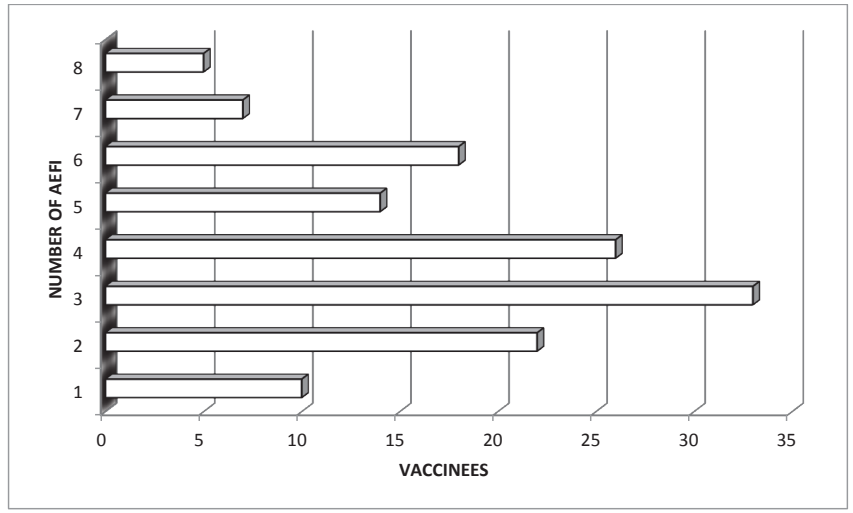

Figure 1. Distribution of multiple events among vaccinees who reported adverse events following immunization.

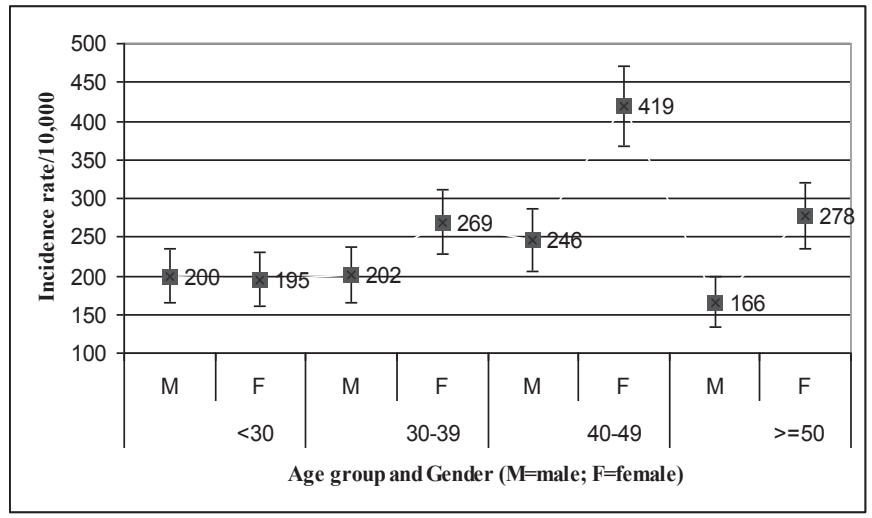

Figure 2. Incidence rates of adverse events reported per 10,000 people with 95% confidence interval.

Table 2 shows that adverse events classified as general disorders and administrative site conditions or nervous system disorders were the two most frequently occurring adverse events categories. The incidence rate per 10,000 doses for headache (a nervous system disorder) was 162 (95% CI 137 to 189). This was the most predominant adverse event that was reported. Other reported adverse events with high incidence rates in this study included

Table 2. Types and distribution of adverse events following immunization (AEFI) using MedDRA system organ class (SOC) codes.

Adverse event	MedDRA PT[a]	Frequency N=5870	IR[q]/10,000	IR[q]/10,0 00 (N ~5000)
Blood and lymphatic system disorders				
Lymphadenopathy	Lymphadenopathy	2	3	≥100 - <1000
Metabolism and nutritional disorders				
Loss of appetite	Decreased appetite	4	7	-
Psychiatric disorders				
Change in behaviour	Abnormal behaviour	10	17	≥10 - <100
Nervous system disorders				
Dizziness	Dizziness	48	82	≥10 - <100
Sleepiness	Somnolence	2	3	≥10 - <100
Headache	Headache	95	162	≥1000
Eye disorders				
Pain in eyes	Eye pain	1	2	≥100 - <1000
Ear and labyrinth disorders				
Ringing sound in the ear	Tinnitus	1	2	-
Cardiac disorders				
Fast heart beat	Tachycardia	6	10	-
Vascular disorders				
Paleness	Pallor	1	2	≥100 - <1000
Respiratory, thoracic and mediastinal disprders				
Hoarseness	Dysphonia	7	12	≥100 - <1000
Breathing difficulty	Dyspnoea	2	3	≥100 - <1000
Runny nose	Rhinnorhoea	1	2	≥100 - <1000
Sore throat	Pharyngolaryngeal pain	1	2	≥100 - <1000
Sneezing	Sneezing	1	2	≥100 - <1000
Gastrointestinal disorders				
Abdominal pain	Abdominal pain	1	2	≥10 - <100
Nausea	Nausea	29	49	≥10 - <100
Vomiting	Vomiting	4	7	≥10 - <100
Skin and subcutaneous tissue disorders				
Hives	Urticaria	3	5	≥10 - <100
Itching	Pruritis	3	5	≥10 - <100
Musculoskeletal and connective tissue disorders				
Pain in the neck	Neck pain	1	2	≥100 - <1000
Muscle and joint aches	Myalgia/arthralgia	80	136	≥1000

Table 2. (continued)

Adverse event	MedDRA PT[a]	Frequency N=5870	IR[q]/10,000	IR[q]/10,0 00 (N ~5000)
General disorders and administrative site conditions				
Weakness	Asthenia	89	152	≥1000
Chills	Chills	2	3	≥100 - <1000
High/low fever	Pyrexia	76	129	≥1000
Pain/redness at injection site	Injection site pain	61	104	≥1000

[a] Prefered Term; [α] Incidence rate per 10,000 in this study; [q] Incidence rate per 10,000 from Pandemrix® SPC[15].

4.1

body weakness (asthenia), muscles and joint aches (myalgia and arthralgia), fever, and pain/redness at the injection site. There were two reports of sleepiness (somnolence).

Most of the AEFIs reported were well established [15, 20]. However, events like tachycardia, tinnitus and decreased appetite were not recorded in the Summary of Product Characteristics (SPC) of the Pandemrix® A(H1N1) vaccine.

Further, Table 2 shows that all the events reported were either within or below the expected range when compared to information from the Pandemrix® SPC but the trends were not always the same. For example, the most predominantly reported adverse event in this study was headache but in the SPC, injection site pain was mentioned as the most frequently occurring adverse reaction.

DISCUSSION

This article presents the results of adverse events reported following immunization of healthcare workers in a Teaching Hospital in Ghana. Out of a total of 5870 people who were vaccinated, 140 reported adverse events. The overall incidence rate of reported cases was 239 per 10,000 people, and the highest number of adverse events reported per person was eight. Only 2.1% (3/140) of reported AEFI were serious.

The large number of vaccinees under 30 years is representative of the population pyramid of Ghana, 66% of who are below age 30 years [21], which enhances generalizability of our results. The proportion of patients reporting serious adverse events among those reporting any event was lower in this study (2.1%) than previously reported by Vellozi et al [11] who reported 7.2% (726/10,085) after administering 82.4 million doses using the Vaccine Adverse Event Reporting System (VAERS) and Liang et al [22], who reported 8.8% (711/8067) after using 89.6 million doses. However, this study involved a much smaller population size and used only the Pandemrix® vaccine but the other two studies used different vaccines. Kung et al [23], reported that 0.77% of the study subjects in a clinical trial reported any events that affected daily activities requiring medical attention. All findings from clinical practice, including our study results, imply that serious reactions may be associated with an influenza A(H1N1) 2009 vaccine. On the contrary, Greenberg et al [24], Vajo et al [25] and Plennevaux

et al [26], in separate randomised trials reported that no vaccine related serious adverse events were recorded.

We did not find any difference in adverse event reporting rates between the sexes and there was no association between vaccine adverse event reporting and the various age groups vaccinated. This is consistent with the review from Vellozzi et al [11].

Nervous system disorders, general disorders and administration site conditions, and musculoskeletal and connective tissue disorders accounted for most of the adverse events that occurred among cases. In particular, headache, pain at injection site, body weakness, pyrexia and myalgia/arthralgia occurred most frequently. This was also the situation with other studies [23-25, 27,28]. However, some reported adverse events such as tachycardia, tinnitus and decreased appetite were not yet included in the SPC.

For vaccines used in different populations comparability is essential for evidence-based understanding of safety concerns [29]. Case definitions may also differ depending on whether it was collected from clinical trials or passive post-marketing surveillance, or as a result of its origin i.e. from a developed or developing country [30-35]. The incidence rates for the various reported events were all lower compared to those in the Pandemrix® SPC [15] , but while injection site pain was the most frequent in the Pandemrix® SPC and other studies [24,28] we recorded headache as the most frequent. Even fatigue, muscle/joint aches and fever had higher incidence rates compared to injection site pain. Ghana is hyper-endemic for malaria [21] and infectious diseases are present. Headache, fever, muscle/joint aches and fatigue are characteristic symptoms of malaria. These high incidence rates could also be the result of background rates [36, 37] of such events being reported just because of their temporal association. Although temporality is essential, it is not sufficient to prove causality. It is well known that background rates could lead to over-ascertainment of an event and it is therefore necessary that these are accounted for during causality assessment of events. A selective increase in the number of reports following immunization could also have been possible due to notoriety bias [13].

Uncommon adverse events with relatively high incidence rates (dizziness, nausea and abnormal behaviour) per 10,000 doses may also be due to high background rates or as a result of co-medications. These would need to be further investigated in any future mass immunization activity. There were two reports of sleepiness (somnolence). Both cases were females and their ages were 36 years and 45 years. Nevertheless, there have been reports of possible association between Pandemrix® and narcolepsy [38-42] involving vaccination against H1N1 virus among children and adolescents. The Global Advisory Committee for Vaccine Safety (GACVS [43] after close monitoring of investigations indicated that the situation was not a general worldwide phenomenon and current available information was inadequate to prove association. That notwithstanding, GACVS agrees with the European Medicines Agency for Medicinal Products for Human use, that Pandemrix® should only be used by people twenty years and older [44]. Vajo et al [25] suggested the involvement of different ethnic groups in studies concerning the A(H1N) influenza vaccine. This is one such

study and it is hoped that it would serve as a comparator for similar studies, especially those in sub-Saharan Africa.

There were potential limitations which need to be mentioned. There is the propensity for under-reporting, a characteristic of most passive surveillance studies which may lead to biased estimates of events [45, 46]. However, the use of healthcare workers may have resulted in better reporting response than would have been the case compared to the general population. The short surveillance period (which was done to avoid the reporting of extraneous events) may have prevented the capturing of events of long latency. We hope to improve upon this subsequently. Background rates of adverse events were not calculated, and may lead to over-ascertainment of some events. Such a system of adverse event reporting may only be used for signal generation [47], it cannot prove causality.

4.1

Collection of data for this study was comparable to CEM in that it was observational and prospective [1, 2]. However, unlike CEM, there was no pre-treatment control period.

This article is concerned with vaccine adverse events collected after mass immunization of healthcare workers using Pandemrix® A(H1N1) vaccine. It has shown that monitoring of adverse events following immunization among healthcare workers can be a useful tool to study vaccine related adverse events. Efforts should be made to determine the actual vaccine adverse event incidence rates because this can impact positively on vaccine uptake in future.

Immunization is a public good and the higher the extent of coverage the better the effect on the general population. It has been observed that vaccine adverse event reports during vaccination campaigns can be used to inform the general public on the expected benefit-risks that may be associated with the vaccine and this may improve immunization levels in future programs [48]. Public health commitment to improve the knowledge on vaccines should be encouraged and should focus on both risks and benefits.

Using data from health care workers for this study was helpful for many reasons. First of all, these are knowledgeable people who are likely to report events they experienced. Further, should the need be for follow-up enquiries, this may not be difficult because of close proximity of reporters compared to the general population. For such programs to be successful prior notification of prospective vaccinees should be done well. Additionally, to forestall misguided publications, the press should be briefed. The estimated cost of operational activities of the program was $1,138,000.00 [10]**.** Irrespective of the limitations encountered in this study, the lesson learned for other countries, particularly those in low and medium income countries is that big studies are good if done well, but small studies, if carried out well, can also make a difference.

CONCLUSION

Among health workers at the Korle-Bu Teaching Hospital in Ghana, the Pandemrix® vaccine was relatively safe. The most prominent adverse events reported were headaches, dizziness, muscle and joint aches, weakness, fever and injection site pain. The types of AEFI reported

were similar to other studies but the frequency of occurrence did not follow the same pattern. While studies in the USA, Europe and China reported injection site pain as the most frequent AEFI, we recorded headache as the most frequent event. Even fatigue, muscle/joint aches and fever, were more frequent than injection site pain. The real benefits and risks of vaccines should be made known to the general public since this may improve uptake of immunization in future.

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REFERENCES

1. A practical handbook on the pharmacovigilance of malaria medicines. www.who.int/medicines/technical_briefings/tbs/handbook_antimalarialpharmacovigilance.pdf. Accessed 10/03/2012.
2. Pharmacovigilance of antiretrovirals in resource poor countries. WHO, HTP, MPS. www.who.int/medicines/ares/quality_safety/safety_efficacy/pharmacovigilance_for_antiretrovirals.pdf. Accessed: 10/03/2012
3. Doll R, Hill AB. Smoking and carcinoma of the lung, preliminary report. *Br Med J* 1950;(ii):739-48
4. Stampfer MJ, Willet WC, Colditz GA, et al. a prospective study of post-menopausal estrogen therapy and coronary heart disease. *N Engl J Med* 1985;313:1044-1049.
5. Ascherio A, Rim EB, Stampfer MJ, et al. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. *N Engl J Med* 1995;332:977-982.
6. Szklo M, Nieto FJ. Epidemiology beyond the basics. 2nd Edition. Jones and Bartlett Publishers, Sudbury, Massachusetts 2007.
7. Update on current situation: Pandemic influenza H1N1 in Ghana as at 12/08/2010; Ghana Health Service.
8. Nolan T, McVernon J, Skeljo M, Richmond P, Wadia U, Lambert S, et al. Immunogenicity of a monovalent 2009 influenza A (H1N1) vaccine in infants and children: a randomized trial. *JAMA* 2010;303:37-46
9. Weekly epidemiological record: Strategic Advisory Group of Experts on Immunization – report of the extraordinary meeting on the influenza A (H1N1) 2009 pandemic, 7 July 2009. www.who.int/wer/2009/wer8430.pdf. Accessed 21/11/2010.
10. Ministry of Health – Ghana. H1N1 Vaccine Deployment Plan. March 2010.
11. Vellozzi C, Broder K.R, Haber P, Guh a, Nguyen N, et al. Adverse events following influenza A(H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009-January 31, 2010. *Vaccine* 2010;28:7248-7255.
12. Jacquet A, Robine I, Durrieu G, Auriche P, Bidault I, Ouaret S, Millaret A, et al. Intensive pharmacovigilance monitoring for influenza vaccines and antiviral drugs used during the influenza A(H1N1)v pandemic: The French experience. *Drug Saf* 2010,33:10 (909-910).
13. van Puijenbroek E.P, Broos N, van Grootheest K. Monitoring adverse events of the vaccination campaign against influenza A(H1N1) in the Netherlands. *Drug Saf* 2010;33(12):1097-108
14. Ghana: population growth of the whole country. www.populstat.info/Africa/ghanac.htm. accessed 04/07/2011
15. Pandemrix® suspension and emulsion for emulsion for injection. Summary of Product Characteristics last updated on the eMC: 23/09/2010. www.medicines.org.uk/EMC/medicine/22352/SPC/Pandemrix +suspension +and +emulsion +for +emulsion+for+injection/. Accessed 21/11/10
16. Ho T, Wang S, Lui C, Historical review of pandemic influenza A in Taiwan, 2009, *Paediatric Neonatal* 2009;51(2),83-88.
17. Vaccine Incident Reporting Form. North Yorkshire Health Protection Unit and North Yorkshire and York NHS Primary Care Trust. www.nyypct.nhs.uk/ClinicalCommunity/docs/PGD_VI/Vaccine%20Incident%20Report%20Form%20v2.pdf. Accessed: 4/06/2010.
18. Mann R, Andrews E. (Editors) Legal Basis – United States. In: Pharmacovigilance. 2nd Edition. Chichester John Wiley & Sons. 2007, pp 25-34.
19. User Guide: Report of adverse events following immunization (AEFI). www.healthunit.org/professionals/Influenza/Resources/AEFI%20Form%20User%20Guide.pdf.
20. Pandemrix® Patient Information www.guysandstthomas.nhs.uk/resources/education_research/biomedical_research/hird-study/pandemrix-patient-info. Accessed 23/06/2010

21. Ghana Statistical Service (GSS), Ghana Health Service (GHS), and ICF Macro. Ghana demography and Health Health Survey 2008. Accra, Ghana:GSS, GHS, and ICF Macro, 2009.
22. Liang X, Li L, Lui D, Li K, Wu W, Zhu B, et al. Safety of influenza A(H1N1) vaccine in post-marketing surveillance in China. *N EnglJj Med* 2011;10.1056/NEJMoa1008553.
23. Kung H, Huang K, Kao T, Lee Y, Chang F, et al. A clinical study to assess the immunogenicity and safety of a monovalent 2009 influenza A (H1N1) vaccine in an area with low-level epidemics of pandemic influenza. *Vaccine* 2010;28:7337-7343.
24. Greenberg ME, Lai M.H, Hartel GF, Wichems CH, Gittleson C, et al. Response to a monovalent 2009 influenza A(H1N1) vaccine. *N Engl J Med* 2009;365(25):2405-2413.
25. Vajo Z, Tamas F, Sinka L, Jankovics I. Safety and immunogenicity of a 2009 pandemic influenza A H1N1 vaccine when administered alone or simultaneously with the seasonal influenza vaccine for the 2009-10 influenza season: a multicentre, randomized controlled trial. *Lancet* 2010;375:49-55.
26. Plennevaux E, Sheldon E, Blatter M, Reeves-Hoché MK, Denis M. Immune response after a single vaccine against 2009 influenza A H1N1 in USA: a preliminary report of two randomised controlled phase 2 trials. *Lancet* 2010;375:41-48.
27. Roman F, Vaman T, Kafeja F, Hanon E, Damme PV. ASO3A-adjuvanted influenza A(H1N1) 2009 vaccine for adults up to 85 years of age. *Clin Infect Dis* 2010;51(6):668-677.
28. Liang X, Wang H, Wang J, Fang H, Wu J, et al. Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: a multicentre, double blind, randomised, placebo-controlled trial. *Lancet* 2010;375:56-66.
29. Iskander JK, Gidudu J, Arboleda N, Huang W. Selected major issues in vaccine safety. *Ann Nestlé* [Engl] 2008;66:93-103
30. Kohl KS, Gidudu J, Bonhoeffer J, et al. The development of standardized case definitions for adverse events following immunization. *Vaccine* 2007;25:5671-5674.
31. Kohl KS, Bonhoeffer J, Braun MM, et al. The Brighton Collaboration: Creating a global standard for case definition (and guidelines) for adverse events following immunization; in AHRQ: Advances in patient safety concepts and methodology. Rockville, AHRQ, 2005;2:87-102.
32. Bonhoeffer J, Kohl KS, Chen RT, et al. The Brighton Collaboration-enhancing vaccine safety. *Vaccine* 2004;22:2046.
33. Bonhoeffer J, Heininger U, Kohl KS, et al. Standardized case definitions of adverse events following immunizations (AEFI). *Vaccine* 2004;22:547-550
34. Kohl KS, Bonhoeffer J, Chen RT, et al. The Brighton Collaboration: enhancing comparability of vaccine safety data. ISPE commentary. *Pharmacoepidemiol Drug Saf* 2003;12:335-340.
35. Bonhoeffer J, Kohl KS, Chen RT, et al. The Brighton Collaboration: addressing the need for standardized case definition of adverse events following immunization (AEFI). *Vaccine* 2002;21:298-302
36. Black S, Eskola J, Siegrist C, Halsey N, MacDonald N, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. *Lancet* 2009;374:2115-2122
37. Wang Y, Xiao Z, Wang W. Awareness of the background rates of sudden cardiac death during mass immunization with pandemic H1N1 influenza vaccines increases the intended vaccination rate. *Prev Med* 2010;51:445-446.
38. Dauvilliers Y, Montplaisir j, Cochen V, Desautels A, Einen M, et al. Post-H1N1 Narcolepsy-Cataplexy. *Sleep* 2010;33(11):1428-1430.
39. Caplan AL. Duty to Warn?—The Ethics of Disclosing Information about Possible Risks Associated with H1N1 Vaccination. *Sleep* 2010;33(11):1426-1427.
40. Zarocosters J. WHO backs further probes into possible link between H1N1 vaccine and narcolepsy in children**.** *Br Med J* 2011; 342:d909
41. Geoff W. New findings on H1N1 vaccine prompt revised prescribing advice (News). *Br Med J* 2011;342:d2524
42. Montastruc J-L, Durrieu G, Rascol O. Pandemrix®, (H1N1)v influenza and reported cases of narcolepsy (Letter to Editor). *Vaccine* 2010.12.092.
43. Statement on narcolepsy and Pandemrix. www.who.int/vaccine_safety/topic/influenza/pandemrix/h1n1_safety_assessing/narcolepsy_statement_Jul2011/en/. Accessed 10/03/2012
44. European Medicines Agency recommends restricting use of Pandemrix. www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109182.pdf. Accessed 10/03/2011
45. Varricchio F, Iskander J, DeStefano F, Ball R, Pless R, et al. Understanding vaccine safety information from the vaccine adverse reporting system. *Pediatr Infect Dis J* 2004;23(4):287-294.
46. Ellenberg SS, Chen RT. The complicated task of monitoring vaccine safety. *Public Health Rep* 1997;112(1):10-20.
47. C.D.C. Surveillance for safety after immunization: Vaccine adverse events reporting system (VAERS) – United States. 1991-2001. *MMWR Surveil Summ* 2003;52:1-24.
48. Broos N, van Puijenbroek EP, van Grootheest K. Fever following immunization with influenza A(H1N1) vaccine in children: a survey based study in the Netherlands. *Drug Saf* 2010;33(12):1109-15.

Chapter 4.2

REPORTING OF ADVERSE EVENTS FOLLOWING IMMUNIZATIONS IN GHANA - USING DISPROPORTIONALITY ANALYSIS REPORTING RATIOS

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ABSTRACT

Background

Timely reporting of safety information post vaccination is pivotal for the success of any vaccination program. Active surveillance, although costly, are more reliable for real time collection of adverse events following immunization (AEFI). In this study, AEFIs reports from the Food and Drugs Authority of Ghana using active surveillance were used to identify signals.

Method

De-identified data from active surveillance for AEFIs after H1N1, yellow fever, meningitis, measles-rubella, pneumococcal-rotavirus and human papilloma virus vaccinations were used. The vaccinations occurred between January 2010 and December 2013. The first ten most occurring events for each vaccination were captured. These were arranged using Medical Dictionary of Regulatory Agencies (MedDRA) Preferred Term (PT) and System Organ Classification (SOC) codes. Proportional reporting ratios (PRR, 95% CIs) were calculated.

Results

A total number of 5,141 reports were analysed ranging from 33 (human papilloma virus) to 1958 (measles-rubella). Only the first 10 most reported AEFIs per vaccine were used for the analysis. Between 22% and 55% of all AEFIs per vaccination were collected on the day of vaccination. For each vaccination, at least 87% of all reported AEFIs occurred in the first 7 days post-vaccination. Active surveillance lasted for 30 days for most vaccination programs. For H1N1 vaccination the signal with the highest PRR was dizziness (PRR 6.71 (95% CI 5.01, 8.18), Chi square 216.6); the signal with the highest PRR for human papilloma virus and measles-rubella was abdominal pain (PRR 8.15 (95% CI 3.46, 19.23), Chi square 30.2) and PRR 43.75 (95% CI 17.81, 107.45), Chi square 200.7) respectively; the signals with the highest PRR for yellow fever, meningitis and pneumococcal-rotavirus vaccinations were arthralgia, dizziness and injection site pain, in that order.

Conclusion

Almost all the signals generated were well-known and confirmed existing safety knowledge on the vaccines studied. But the results underscore the sensitivity of public health systems in sub-Saharan African countries (like Ghana) to pick up most frequently occurring and important vaccine related safety issues.

INTRODUCTION

An adverse event following immunization (AEFI) involves any event temporal to the administration of a vaccine. The WHO defines an AEFI as "any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease". Timely reporting of safety information post vaccination is pivotal for the success of any vaccination program [1]. This will not only help to ascertain the benefit-risk profile of vaccines, but may also encourage prospective vaccinees to avail themselves for vaccine uptake [1-3]. Because most vaccination programs involve large populations as against smaller sample sizes used in their pre-licensor stages, and because some of the events associated with vaccines are rare [4], have late-onset, are unexpected, or could be population specific [2], it is important to monitor vaccines post-licensor.

Public health surveillance is defined as the on-going, systematic collection, analysis, interpretation, and dissemination of data regarding a health related event for use in public health action to reduce morbidity and mortality and to improve health [5]. Surveillance systems in public health could be either passive (spontaneous) or active. Active surveillance is a useful tool to conduct near real-time search for potential vaccine adverse events. It helps in the detection of disease, irrespective of its severity in its early stages [6]. Spontaneous reporting systems sometimes may lead to incomplete information in the reports, involving exposures or outcomes, and this may restrict the value of data [7,8]. Active surveillance methods are therefore complimentary to passive surveillance because they offer more accurate AEFI reporting rates. However, active surveillance is expensive. It involves more time and resources [8], and is therefore not routinely done [6]. Active surveillance of AEFIs could lead to the detection of a signal defined as "a reported information of a possible causal relationship between an event and a drug (in this case a vaccine), the relationship being unknown or incompletely documented previously" [9]. The more a particular information is reported concerning a vaccine, the more likely it could be that they are associated or there is a causal relationship between them.

Signal detection is often used to establish safety signals for new medicines or vaccines and involves both quantitative and qualitative procedures. The most important quantitative signal detection methods involve both Frequentist and Bayesian statistical methods [10]. These include the proportional reporting ratios (PRR) [11] used by the European Medicines Agency (EMA) [12], the Bayesian Confidence Propagation Neural Networks (BCPNN) [13-15] used by the Uppsala Monitoring Center (UMC) which is also the WHO Collaborating Center for international drug monitoring, and the multi-item gamma Poisson shrinker (MGPS) [16], used by the US Food and Drugs Administration (FDA) [17]. Using the PRR and BCPNN in a paediatric pharmacovigilance study, Kajungu et al [18], reported that both data mining methods were equally satisfactory in generating suspected signals.

Quantitative signal detection using databases of AEFI results involving multiple vaccination programs is rare in sub-Saharan Africa. Apart from one multi-site multi-country clinical study using antimalarial drugs in children [18], there is no study using reports from multi-vaccine adverse events for signal detection. According to the Global Vaccine Safety Blueprint, of the 78 professionals from low and medium income countries (LMIC) who participated in the survey, only 15% reported conducting epidemiological studies using vaccine safety data [19].

The objectives of this study was to identify possible vaccine related safety issues using reports of AEFIs for 6 different vaccinations from the Food and Drugs Authority Ghana. PRRs for individually reported adverse events were determined in order to quantify identified signals.

METHODS

Setting and selection of data

National de-identified (anonymous) data on AEFIs were used for this study. In Ghana, national AEFI data are collected by the Expanded Programme on Immunisation (EPI) Ghana in collaboration with the Food and Drugs Authority (FDA) Ghana. To improve the quality of data collection, several training activities on monitoring and evaluation are held prior to any national immunization campaign. AEFIs on six different vaccinations were collected using active surveillance at different times between January 2010 and December 2013. These were:

- H1N1 2009 (swineflu) vaccination, 2010 – First time in Ghana
- Human papilloma virus (HPV) vaccination, 2013 – First time in Ghana
- Yellow Fever vaccination, 2012
- Meningitis (MenAfric) vaccination, 2012 – First time in Ghana
- Measles Rubella (MR) vaccination, 2013 – First time in Ghana
- Pneumococcal-rotavirus vaccination, 2013 – First time in Ghana

Vaccinations involved different age groups [A] depending on international agreements, groups at risk of exposure, and whether the disease is endemic in the region [B]. For example, for H1N1 2009, only adults, 18 years old and above were vaccinated [20]. For pneumococcal-rotavirus vaccination AEFIs were captured as though it was one vaccination because the two separate vaccines were administered concurrently. In Ghana, active surveillance is conducted for any vaccine on its maiden use. In the case of the yellow fever vaccination an active surveillance was conducted because prior to the vaccination there were a few yellow fever related deaths. In effect the data for all the six vaccines were from active surveillances.

Just after every vaccination, the vaccinated person was counselled by public health staff on the need to report any suspected events immediately. They were given mobile numbers to call and names of hospitals to visit immediately they observe any unusual changes.

The expected unusual changes were explained to them. Particular referral centres were selected to take care of patients who reported severe AEFIs. At the selected referral sites, physician specialists and consultants with knowledge in the management of the expected AEFIs were selected to be on stand-by in the event of any serious AEFI. A pharmacist with knowledge on AEFIs was selected to ensure that all medicines prescribed for patients who reported any severe AEFI are supplied. A laboratory personnel was also chosen to take care of any laboratory investigations that may be needed. All these personnel were trained before immunization started.

H1N1 vaccination was introduced in Ghana to combat the H1N1 2009 swine flu pandemic that affected many countries globally in 2009 [C]. Yellow fever vaccination was as a result of confirmed increase in yellow fever cases [D] and an increased risk of some districts having the disease as a result of risk assessments done. Because of this prior event, an active surveillance was also conducted for yellow fever although it was not being used for the first time. Besides, Ghana is located in a region endemic for yellow fever. Cerebrospinal meningitis is a seasonal outbreak that mostly affects Ghanaians living within the African Meningitis belt with case-fatality rate between 6-14% [21]. Measles, pneumonia and diarrhoeal diseases could be more serious among children under five years old.

Data analysis

The first ten most occurring AEFIs for each vaccination were captured. These were arranged using Medical Dictionary of Regulatory Agencies (MedDRA®) Preferred Term (PT) and System Organ Classification (SOC) codes version 11.1. Median age with corresponding interquartile range was calculated for each type of vaccination. Cumulative density frequencies of all the events were plotted for each vaccine type to identify the most critical period (best time to monitor AEFIs over an acceptable period) to do real-time monitoring. Proportional reporting rates (PRR) for the ten most occurring AEFIs per vaccination and corresponding 95% confidence intervals were calculated.

The PRR is a measure of association between the putative factor of interest (in this case the exposed vaccine) and a particular outcome (in this case the reported AEFI). The higher the PRR, the greater the strength of association between the exposure and the outcome [10, 11, 22, 23]. Mathematical formulae for calculating the PRR and its 95% confidence interval are shown on appendix I.

The sensitivity (total number of AEFIs combinations with association and a safety signal divided by the total number of AEFIs combinations with association, multiplied by 100) and specificity (total number of AEFIs combinations without association without a safety signal divided by the total number of AEFIs combinations without association, multiplied by 100) [E] of a safety signal were also calculated. In calculating these figures, the rule of thumb from the EMA guidelines [12] was used. According to EMA guidelines [12], a signal should be considered if the number of AEFIs reported for an event of interest is greater than or equal to 3, the Chi squared test result is greater than or equal to 4, and the PRR is greater

than or equal to 2. Microsoft Excel version 2007 (Microsoft Corporation, Redmond, WA, USA) followed by SAS software version 9.3 (SAS Institute, Cary, NC, USA) were used for the analysis.

RESULTS

A total of 5141 patients reported AEFIs for the six vaccinations. This comprised of 670 reports after H1N1 vaccination, 33 reports after HPV vaccination, and 1958 reports after M-R vaccination. The rest were 621 reports after meningitis vaccination, 1028 reports after pneumonia-rotavirus vaccination, and 831 reports after yellow fever vaccination. The total number of the first 10 AEFIs reported for all the 6 vaccines was 8089.

AEFI reports from females dominated that of males for all the vaccines under consideration (see Table 1). One person (female) and four people (three females and one male) respective died after receiving the H1N1 and meningitis vaccines. Furthermore, one female died after receiving the yellow fever vaccine. The number of vaccinees with unknown outcome was highest for H1N1 (45.2%). The time to reporting of AEFIs received for all six vaccines are shown in Fig 1.

AEFI reports for HIN1 vaccination were received over a period of 40 days; for MR, Prevnar13-Rotavirus, MenAfric, HPV and Yellow fever vaccinations, the AEFI reports were received over a period of 30 days or less. In particular, in the case of MenAfric vaccination, no reports were made after 15 days of surveillance. Between 22% and 58% of all AEFI reports were collected on the day of vaccination. For each vaccination, at least 87% of all reported AEFIs occurred in the first 7 days post-vaccination.

The most reported AEFI was fever, followed by urticaria. However, the single most reported AEFI by a vaccine was urticaria due to MR vaccination (768/1958). This was followed closely by fever, also after MR vaccination (710/1958). These and other reported AEFIs are shown on Table 2.

Table 1. Characteristics of those who reported AEFIs and type of vaccine used

	H1N1 (N=670)	HPV (N=33)	MR (N=1958)	Meningitis (N=621)	Pn-Rotavirus (N=1028)	Yellow fever (N=831)
Mean age (SD)					**(in weeks)**	
	33.9(10.9)	12(2.4)	5.5(4.0)	12.7(8.5)	8.1(4.6)	33.2(15.8)
Gender						
Female (%)	463(69.1)	33(100)	983(50.6)	330(53.4)	537(52.2)	517(63.8)
Outcome after event						
Recovered (%)	340(50.7)	33(100)	1931(97.7)	552(88.9)	942(91.6)	567(68.2)
Not recovered* (%)	26(3.9)	-	3(0.15)	38(6.1)	43(4.2)	135(16.3)
Death (%)	1(0.1)	-	-	4(0.66)	-	1(0.1)
Unknown (%)	303(45.2)	-	42(2.2)	27(4.35)	43(4.2)	128(15.4)
Vaccine ATC code	J07BB02	J07MB01	J07BD53	J07AH10	J07AL01/ J07BH01	J07BL01

*Condition of vaccinee at the time of reporting;.

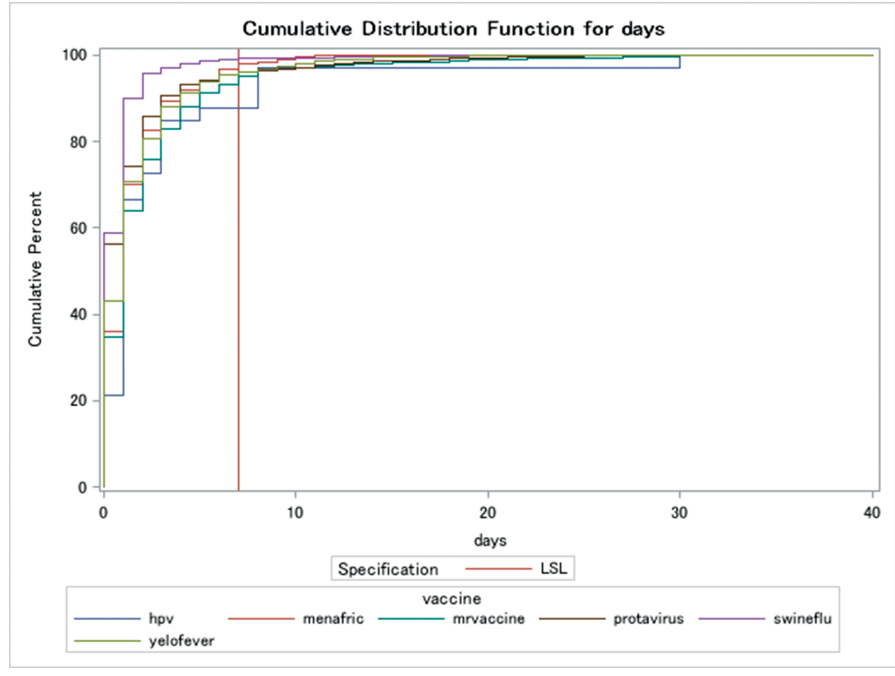

Figure 1. Plot of cumulative density function of AEFIs for all vaccines. The red vertical line on the graph signifies the 7th day after vaccination and intercepts with the number of AEFIs collected by the end of that period for each vaccination; hpv = human papilloma virus vaccine, manafric = meningitis vaccine, mrvaccine = measle-rubella vaccine, protavirus = neumonia/rotavirus vaccine, swineflu = H1N1 vaccine and yelofever = yellow fever vaccine.

The highest PRR for H1N1 vaccine was for dizziness (6.7 (95% CI 5.01, 8.18); χ^2=216.6), followed closely by asthenia (5.71(95% CI 4.52, 7.21); χ^2=268.7). The highest PRR for HPV was abdominal pain (8.15 (95% CI 3.46, 19.23); χ^2=30.2). Abdominal pain (43.75 (95% CI 17.81, 107.45); χ^2=200.7) recorded the highest PRR for the MR vaccine, and was immediately followed by urticaria (8.06 (95% CI 7.00, 9.29); χ^2=1223.3). Stomach ache (11.51 (95% CI 9.21, 14.40); χ^2=721.6) and dizziness (3.30 (95% CI 2.47, 4.43); χ^2=70.91) scored the highest PRR for the meningitis vaccine. For Pneumococcal-Rotavirus vaccination the highest PRRs was from injection site pain (9.21 (95% CI 7.55, 11.24); χ^2=701.11). Concurrent administration of Pneumococcal and Rotavirus vaccines (according to Table 2), led to reports of vomiting, but the PRR was not high enough to be captured as a signal. Watering eyes was a report made only among those vaccinated with Pneumococcal-Rotavirus vaccine. Pruritus (30.65 (95% CI 21.76, 48.45); χ^2=887.86) recorded the highest PRR for the Yellow Fever vaccine (see Table 3). Sensitivity and specificity results for PRRs were 63% and 97% respectively.

4.2

Table 2. Classification of top ten AEFIs associated with vaccination by MedDRA System organ classification (SOC) and Preferred Term (PT).

SOC & adverse event	MedDRA-PT	Type of vaccination (number of events)
General disorders and administrative site conditions		
Fever	Pyrexia	HPV[∞] (14) MR[α] (710) H1N1 (378), Meningitis (326), YF[^] (112), Pn-Rota* (580)
Injection site abscess	Injection site abscess	H1N1 (172), Pn-Rota (355), Meningitis (167)
Pain/ redness at site	Injection site pain	HPV (10), H1N1 (78), YF (40), Pn-Rota (310)
Weakness	Asthenia	H1N1 (151), Meningitis (36), Pn-Rota (84)
Nervous system disorders		
Headache	Headache	HPV (8), MR (91), H1N1 (249), Meningitis (219), YF (283)
Dizziness	Dizziness	HPV (2), H1N1 (108), Meningitis (71)
Lack of sleep	Insomnia	H1N1 (41)
Musculoskeletal and connective tissue disorders		
Joint pain	Arthralgia	H1N1 (142), YF (130)
Muscle (body) pain	Myalgia	H1N1 (147), YF (132), Meningitis (57)
Gastro-intestinal disorders		
Nausea/vomiting	Nausea/vomiting	HPV (3), MR (302), Pn-Rota, YF , H1N1 (35)
Abdominal pain	Abdominal pain	HPV (5), MR (93)
Diarrhoea	Diarrhoea	HPV (2), MR (48), Pn-Rota (63), YF (67)
Stomach ache	Abdominal pain upper	MR (54), Meningitis (234), YF (50)
Skin and subcutaneous tissue disorders		
Hives	Urticaria	HPV (7), MR (768), Meningitis (77), Pn-Rota (37), YF (103)
Itch	Pruritus	H1N1 (36), YF (184)
Respiratory, thoracic and mediastinal disorders		
Cough	Cough	HPV (2), MR (48), Meningitis (32), Pn-Rota (62)
Metabolism and nutrition disorders		
Loss of appetite	Decreased appetite	MR (192), Meningitis (103), Pn-Rota (45)
Eye disorders		
Excessive eye tearing	Watering eyes	Pn-Rota (51)

[∞]Human papilloma virus, [α]Measles rubella, [^]Yellow fever, *Pneumococcal-rotavirus.

DISCUSSION

We used proportional reporting ratios to detect signals on AEFIs collected during active surveillance involving six different vaccination programs in Ghana. Fever, injection site pain and injection site abscess, were seen for all the six vaccines studied. Headache, nausea/vomiting was recorded for five of them. Watering eyes was reported for only those vaccinated with the pneumonia-rotavirus vaccine administered concomitantly. Overall these results are in line with what we know on the safety of these vaccines. The public health system in Ghana was able to pick up these most frequently occurring vaccine related safety issues in an effective and efficient way.

Monitoring AEFIs from the day of vaccination is crucial [1] for attainment of results in real time. It is important not to miss any day, especially during the first seven days, because most

AEFIs occurred within this period. Field workers should be informed of this to improve the data collection process. Our findings suggest an association between H1N1 vaccination and headache, myalgia, arthralgia, dizziness, and asthenia. According to the summary of product characteristics (SPC) of Pandemrix [24], headache, myalgia and arthralgia are very common (affects more than 1 user in 10), dizziness is uncommon affecting 1 to 10 users per 1000. Asthenia is one of the symptoms of Guillian Barre syndrome (GBS), a rare disease temporally associated with H1N1 vaccination [25]. However, there are mixed reactions regarding the association between GBS and the H1N1 vaccine. Dieleman et al [26], did not find any temporally increased risk of GBS in a multinational case-control study. In a related but separate study [K] using a disaggregated data from this dataset, it was found that the frequency of occurrence of events in the SPC was higher when compared.

One of the most common AEFIs of HPV vaccine was injection site pain [27-29]. Gastro-enteritis was a severe AEFI that occurred in only about 0.1% of participants [27]. Our results on HPV vaccines and associated AEFIs was therefore consistent with current information.

Rotavirus is known to be associated with intussusception among children. However, because of low PRR in this database, vomiting was not captured as a probable signal (see Table 3). Watering eyes was a report made only among those vaccinated with Pneumonia-Rotavirus vaccine.

From the summary of product characteristics (SPC) of the yellow fever vaccine [30], headache is among the most frequently occurring advents events, and arthralgia and myalgia are commonly occurring. Pruritus, although uncommon in the SPC, occurred frequently in this dataset. This needs to be studied more carefully as subgroup, geographical as well as racial differences in AEFIs could occur. Signals generated in this study for measles-rubella vaccine were all consistent with the SPC of measles-rubella-mumps vaccine [31]. Urticaria was classified as a commonly occurring side effect but loss of appetite and gastro-intestinal effects were all captured as uncommonly occurring side effects. Results from meningitis vaccination, and pneumococcal-rotavirus vaccination did not yield any new signals. The concomitant administration of pneumococcal and rotavirus vaccines was the first time in Ghana. Similarly, the meningitis project (using MenAfric vaccine) [Q] in the meningitis belt of sub-Saharan Africa was the first time. Other countries in the meningitis belt who received the MenAfric vaccine before Ghana are Burkina Faso [32] and Niger [33]. AEFIs from these two countries [32, 33] were similar to those in Ghana. Of the ten most occurring AEFIs in Ghana, 8 were recorded in Burkina Faso [32] and 9 were recorded in Niger [33]. This study follows the Global vaccine safety blueprint's strategic goal of enhancing capacity for vaccine safety assessment in countries that introduce newly developed vaccines or introduce vaccines in settings with novel characteristics [19].

Table 3. First 10 most reported AEFIs per vaccine per vaccination type, showing PRR (95% confidence interval) and chi squared test results.

AEFI	H1N1 (SWINEFLU)	HPV	MR	Meningitis	Pneumonia-Rotavirus	Yellow fever
Fever	0.98 (0.89, 1.07), 0.2	1.00 (0.64, 1.57), 0.01	1.18 (1.09, 1.27), 16.9	0.93 (0.84, 1.02), 2.28	1.42 (1.32, 1.54), 72.11	0.34 (0.28, 0.40), 187.11
Headache	**1.88 (1.64, 2.15), 81.0**	1.44 (0.76, 2.74), 1.2	0.28 (0.23, 0.35), 166.0	1.78 (1.54, 2.05), 66.67	-	**2.99 (2.63, 3.40), 280.02**
Asthenia	**5.71(4.52, 7.21), 268.7**	-	-	0.78 (0.55, 1.11), 1.92	1.71 (1.33, 2.20), 17.62	-
Arthralgia	**4.96(3.93, 6.24), 221.7**	-	-	-	-	**5.49 (4.36, 6.91), 257.93**
ISA*	1.49 (1.27, 1.76), 23.2	-	-	1.62 (1.37, 1.91), 33.09	**3.98(3.47, 4.57), 423.75**	-
Dizziness	**6.71 (5.01, 8.18), 216.6**	2, 1.69 (0.43, 6.65), 0.6	-	**3.30 (2.47, 4.43), 70.91**	-	-
Myalgia	**3.53 (2.86, 4.34), 156.3**	-	-	1.05 (0.79, 1.38), 0.10	-	**3.88 (3.15, 4.79), 178.8**
ISP^	0.98 (0.77, 1.25), 0.02	**3.54 (2.01, 6.24), 18.9**	-	-	**9.21(7.55, 11.24), 701.11**	0.60 (0.44, 0.83), 10.06
Pruritus	0.89(0.62, 1.26), 0.4	-	-	-	-	**30.65 (21.76, 48.45), 887.86**
Urticaria	-	1.08 (0.54, 2.15), 0.04	**8.06 (7.00, 9.29), 1223.3**	0.43 (0.34, 0.54), 60.89	0.15 (0.11, 0.20), 200.30	0.69 (0.57, 0.84), 14.10
Abdominal pain	-	**8.15 (3.46, 19.23), 30.2**	**43.75 (17.81, 107.45), 200.7**	-	-	-
Nausea/ Vomit	0.37 (0.26, 0.51), 38.0	0.97 (0.32, 2.93), 0.01	**4.23 (3.52, 5.08), 282.5**	-	0.59 (0.45, 0.76), 16.6	1.00 (0.78, 1.28), 0.01
Diarrhoea	-	-	**2.53 (2.03, 3.16) 71.8**	-	**1.83 (1.44, 2.31), 25.4**	1.06 (0.78, 1.45), 0.2
Cough	-	2.14 (0.54, 8.70), 1.2	1.18 (0.83, 1.66), 0.9	1.46 (0.99, 2.16), 3.7	**2.88 (2.08, 3.98), 44.0**	-
Watering eyes	-	-	-	-	0.97 (0.96, 0.98), 195.2	-
DA+	-	-	**3.05 (2.48, 3.76), 120.3**	**2.22 (1.78, 2.78) 50.5**	0.58 (0.42, 0.79), 12.4	-
Stomach ache	-	-	54, 0.45 (0.34, 0.60), 32.3	**11.51 (9.21, 14.40) 721.6**	-	1.04 (0.78, 1.40), 0.1

*Injection site abscess; ^injection site pain; +Decreased appetite; **(suspected signals are highlighted and indented).**

For regular events sensitivity is expected to be higher [23] compared to rare events. The figure of 63% could be described as acceptable because most sensitivity estimates are lower [23]. High enough sensitivity is required to avoid missing true AEFIs. The specificity of 97% is very good. Specificity is normally higher than sensitivity with adverse events [23, 34] so our results conformed to existing practice. This implies that the PRR method has a high probability of correctly identifying non-signals (low false positive [34]) and has a good enough probability of correctly identifying signals (low false negative [34]).

This could serve as a quantitative method in addition to current methods of signal detection by regulatory agencies in low and middle income countries most of whom rely on introspection from experts. Notwithstanding, Puijenbroek et al [11] have cautioned that the use of sensitivity and specificity could be misleading and should be seen as relative measures.

The high number of unknown outcomes (condition of vaccinees after AEFI report) for some of the vaccinees could be a limitation that may cause ascertainment bias. It is very possible that such vaccinees fully recovered and decided not to report considering the level of media publication before, during and after the vaccination process.

CONCLUSION

Almost all the signals generated were well-known and confirmed existing safety knowledge on the vaccines studied. But the results underscore the sensitivity of public health systems in Ghana to pick up most frequently occurring and important vaccine related safety issues. The study also emphasizes the importance of vaccine surveillance studies in sub-Saharan African countries. Sustained investment in health databases as well as electronic medical records and stimulated reporting of adverse vaccine (drug) events will contribute to the critical success of vaccination campaigns.

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REFERENCES

1. Bonhoeffer J, Bentsi-Enchill A, Chen RT, Fisher MC, Gold MS, Hartman K, et al. Guidelines for collection, analysis and presentation of vaccine safety data in surveillance systems. *Vaccine* 2009;27:2289-2297.
2. Ellenberg SS, Chen RT. The complicated task of monitoring vaccine safety. *Public Health Reports* 1997;112:10–19.
3. Chen RT, DeStefano F, Pless R, Mootrey G, Kramarz P, Hibbs B. Challenges and controversies in immunization safety. *Infect Dis Clin North Am* 2001;15:21–39.
4. Rennels MB. The Rotavirus vaccine story: a clinical investigators view. *Paediatrics* 2000;106:123-125.
5. Thacker SB, Berkelman RL. Public health surveillance in the United States. *Epidemiol Rev* 1988;10:164-190.
6. Razuri H, Romero C, Tinoco Y, Guezala MC, Ortiz E, Silva M, et al. Population based active surveillance cohort studies for influenza: lessons from Peru. *Bull World Health Organ* 2012;90:318-320.
7. Huang Y, Moon J, Segal J. A comparison of active adverse event surveillance systems worldwide. *Drug saf* 2014;37:581-596.
8. The use of epidemiological tools in conflict affected populations: open access educational resource for policy makers. www.conflict.lshtm.ac.uk/page_75.htm. Accessed: 11/01/2016.
9. A practical handbook on the pharmacovigilance of antimalarial medicines. WHO 2007.
10. Rani S. Pharmacovigilance: Statistical aspects. http://www.synchronresearch.com/pdf_files/PHARMA-STAT-ASPECTS.pdf. Accessed: 11/01/2016.
11. van Puijenbroek EP, Bate A, Leufkens HGM, Lindquist M, Orre R, Egberts ACG. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf* 2002;11:3-10.
12. European Medicines Agency Evaluation of Medicines for Human use. Doc. Ref. EMEA/106464/2006.
13. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol* 1998; 54: 315–321.
14. Lindquist M, Sta°hl M, Bate A, Edwards IR, Fucik H, Nunes AM. From association to alert—a revised approach to international signal analysis. *Pharmacoepidemiol Drug Saf* 1999; 8:S15–S25.
15. Lindquist M, Sta°hl M, Bate A, Edwards IR, Meyboom RH. A retrospective evaluation of a data mining approach to aid finding new adverse drug reaction signals in the WHO international database. *Drug Saf* 2000; 23: 533–542.
16. DuMouchel W. Bayesian Data Mining in Large Frequency Tables, with an application to the FDA Spontaneous Reporting System. *Am Stat.* 1999;53(3): 177.
17. Almenoff J, Tonning JM, Gould AL, Szarfman A, Hauben M, et al. Perspectives on the use of data mining in pharmaco-vigilance. *Drug Saf Int J Med Toxicol Drug Exp.* 2005;28(11): 981–1007.
18. Kajungu DK, Erhart A, Talisuna AO, Bassat Q, Karema C. Paediatric pharmacovigilance: Use of pharmacovigilance data mining algorithms for signal detection in a safety dataset of a paediatric clinical study conducted in seven African countries. *PLoS ONE* 2014;9(5): e96388.
19. World Health Organization. Global vaccine safety blueprint-the landscape analysis. *WHO IVB* 12.04:2012.
20. Moodley I, Tathiah N, Mubaiwa V, Denny L. High uptake of Gardasil vaccine among 9 - 12-year-old schoolgirls participating in an HPV vaccination demonstration project in KwaZulu-Natal, South Africa. S. Afr. med. j. 2013;103 n.5.
21. Guthmann JP, de La Rocque F, Boucherat M, van Cauteren D, Fonteneau L, Lécuyer A, et al. BCG vaccine coverage in private medical practice: First data in children below two years old, seven months after the end of compulsory vaccination in France. Archives de Pediatrie 2009;16(5):489-495.
22. Ministry of Health, Ghana. H1N1 vaccine deployment plan. Accra: Ministry of Health, 2010.
23. Centers for Disease Control and Prevention. 2009 H1N1 Flu. Situation update. http://www.cdc.gov/h1n1flu. Accessed: 30/08/2016.
24. Emergency preparedness, response. Yellow fever in Ghana. http://www.who.int/csr/don/2012_02_03b/en/. Accessed: 30/08/2016
25. Meningococcal disease: situation in the African meningitis belt.
26. http://www.who.int/csr/don/2012_03_23/en/. Accessed 14/04/2016
27. Ferreira G. Prescription-Event Monitoring: Developments in Signal Detection. *Drug Saf* 2007; 30 (7): 639-641.
28. Matsushita Y, Kuroda Y, Niwa S, Sonehara S, Hamada C, Yoshimura I. Criteria revision and performance comparison of three methods of signal detection applied to the spontaneous reporting database of a pharmaceutical manufacturer. *Drug Saf* 2007;30(8):715-726.
29. Li C, Xia J, Deng J, Jiang J. A comparison of measures of disproportionality for signal detection on adverse drug reaction spontaneous reporting database of Guangdong province in China. *Pharmacoepidemiol Drug Saf*, 2008;17:593–600.
30. Pandemrix suspension and emulsion for emulsion for injection. http://www.medicines.org.uk/EMC/medicine/22352/SPC/Pandemrix? suspension?and? emulsion?for?emulsion?for?injection/. Accessed 03/03/2016.
31. Prestel J, Volkers P, Mentzer D, Lehmann HC, Hartung H, et al. Risk of Guillain–Barré syndrome following pandemic influenza A (H1N1) 2009 vaccination in Germany. *Pharmacoepidemiol Drug Saf* 2014; 23: 1192–1204.
32. Dieleman J, Romio S, Johansen K, Weibel D, Bonhoeffer J, Sturkenboom M, et al. Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. *BMJ* 2011;343:d3908
33. Ankrah DNA, Mantel-Teeuwisse AK, De Bruin ML, Amoo PK, Ofei-Palm CN, Agyepong I, Leufkens HGM. Incidence of Adverse Events Among Healthcare Workers Following H1N1 Mass Immunization in Ghana: A Prospective Study. Drug Saf 2013;36(4):259-66.
34. Huang CM. Human Papillomavirus and vaccination. *Mayo Clin Proc*. 2008;83(6):701-707
35. Joura EA, Leodolter S, Hernandez-Avila M, Wheeler CM, Perez G, et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *The lancet* 2007;369(9574):1693–1702.
36. Slade BA, leidel L, Vellozzi C, Woo EJ, Wua W, Sutherland A, et al. Post-licensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine. *JAMA* 2009;302(7):750-757.
37. SPC, yellow fever (Stamaril) vaccine. www.medicines.org.uk/emc/medicine/9846. Accessed: 03/03/2016.
38. SPC, measles-rubella-mumps (Priorix) vaccine. www.medicines.org.uk/ emc/medicine/2054. Accessed: 03/03/2016.
39. The Meningitis Project. A public health breakthrough. WHO, PATH. http://www.meninvax.org. Accessed: 30/08/2016.
40. Ouandaogo C, Yaméogo TM, Diomandé FVK, Sawadogo C, Ouédraogo B, e al. Adverse events following immunization during mass vaccination campaigns at first introduction of a meningococcal A conjugate vaccine in Burkina Faso 2010. *Vaccine* 2012;30S: B46– B51.
41. Chaibou MS, Bakoa H, Salisoua L, Yaméogob TM, Samboc M, et al. Monitoring adverse events following immunization with a new conjugate vaccine against group A meningococcus in Niger. *Vaccine* 2012;30:5229– 5234.
42. Li C, Xia J, Deng J, Jiang J. A comparison of measures of disproportionality for measures of signal detection on adverse drug reaction spontaneous reporting database of Guangdong province in China. *Pharmacoepidemiol Drug Saf* 2008;17:593-600.

Chapter 5

GENERAL DISCUSSION

INTRODUCTION

From the second half of the 20th Century and throughout the 21st Century, access to health in general, and to medicines in particular, has been a major focus at both the United Nations (UN) and the World Health Organization (WHO) which is the arm of the UN representing the health sector.

The adoption of the International Covenant on Economic, Social and Cultural Rights (ICESCR) in 1966 by UN Member States and its enforcement in 1976 set in motion a legal dispensation that recognizes "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health" [1]. The right to access to medicines is implicit in this covenant. As part of their contribution to the World Medicines Situation in 2011, Hogerzeil and Mirza [2] made 5 recommendations to national governments. So far only the second recommendation which involves the provision of a national medicine policy with an implementation plan and an update national list of essential medicines, has been fully adopted in Ghana. Although the right to essential medicines has not been vigorously contested in Africa, this is a big issue in parts of Central and Latin America [3].

In recent times, the development of medicines for the treatment/elimination of neglected tropical diseases (NTD) [4], most of which are predominant in developing countries, has been on the table of a joint collaboration of private and public policy makers. The plan to eliminate 10 NTDs by the year 2020 with the help of improved technology including research and development (R & D) [4] is still on-going. Further development include the permission of intellectual property rights of innovator pharmaceutical companies to be used by others [5] in the manufacture of medicines.

Progress made so far signifies that Ghana is on the way to improve access to medicines among its citizenry. This progress includes among others, the availability of Universal Health Coverage (UHC); a National Drugs Program [6] that ensures the presence of an Essential Medicines List (EML) and a Standard Treatment Guideline (STG), as well as guarantees the periodic review and update of these policy documents; a generics prescribing policy. A functional drugs and therapeutic committee (DTC) [7] is in place in all teaching hospitals and all regional hospitals. Furthermore, Ghana has adopted the priority Medicines List released by the WHO in 2011 [6]. However, it is only when there is a seamless integration of the available systems and patient practices concerning medicine use that the real gains of access to medicines will be recognized and achieved.

In the 2002 assessment of the pharmaceutical sector in Ghana, the median percentage availability of selected key medicines in public health facilities was 78.6% and the percentage of prescribed medicines dispensed to patients was 89.2% [8]. During this period medicines were dispensed to patients by out-of-pocket payment. Universal health coverage started in 2004 in Ghana. Four years later, in 2008, assessment of the pharmaceutical sector showed an increase to 80.0% for selected key medicines available in public health facilities, and the percentage of prescribed medicines dispensed to patients appreciated to 94.2% [9].

Pharmacy practice in Gold Coast (now Ghana) began at the Korle-Bu Hospital (now Korle-Bu Teaching Hospital) in 1930 with a two year certificate course [10]. Currently, there

are two streams of pharmacy students (B Pharm and Pharm D) and the first cohort of Pharm D students will complete their degree in 2018. The way forward is to train only Pharm D pharmacists in Ghana from 2018. According to the 2012 release of the pharmaceutical country profile of Ghana, there were 2900 (1.22/10,000 inhabitants) registered pharmacists with only 372 (0.16/10,000 inhabitants) located in the public sector [11] including hospital pharmacists. The density of Medical doctor-pharmacist-midwife personnel ratio was recorded as 1.11:1.22:9.78 per 10,000 inhabitants [11].

Community pharmacy practice is where most newly qualified pharmacists find themselves. A few of them work as hospital pharmacists while others work with the regulatory agencies, join academia, or go into industrial pharmacy.

Pharmaceutical services in hospitals in general has expanded from just responsibility for the availability and supply of medicines, and now embraces patient-centred outcome oriented practice [12]. Hospital pharmacists specialize as clinical pharmacists, public health pharmacists or as pharmacists in management. The hospital pharmacist's duties encompasses the entire way in which medicines are selected, prescribed, dispensed, administered and reviewed to optimise the contribution that medicines make to producing informed and desired outcomes among patients. Work is done in partnership with other members of the health care team. Hospitals pharmacists are also responsible for compounding, dispensing and monitoring of internal and topical medicines for individual patients when these are not available on the open market. They also engage in forecasting pharmaceutical inventory to avoid needless shortages or wastage. Given all of these tasks, hospital pharmacists can and should play a key role in ensuring access to medicines for the patients they care for.

This thesis looks at pharmaceutical policies and access to medicines from the viewpoint of the hospital pharmacist using three approaches:

- Provision of information, services and suitable medicines
- The role of adherence in achieving optimal treatment outcomes in HIV treatment
- Improving outcomes following immunization

Contributions from these three thematic areas in improving access to medicines are explained followed by a discussion of challenges in pharmacy practice research in Ghana. Based on the research findings, policy recommendations for improvement of the role of hospital pharmacists' research and areas for further research on pharmaceutical policies and access to medicines are discussed

PROVISION OF INFORMATION, SERVICES AND SUITABLE MEDICINES

Most hospitals in both developed and developing countries have drug information centres that provide information on medicines to health care workers as well as patients. Hospital pharmacists provide information to both out and in-patients. The medicine/prescription

information leaflet may be a good source of information for patients but its usefulness depends on how well it is read and understood. The use of plain language and more intuitive patient formatting in medicines information leaflets have been lauded, however, there are requests to avoid the use of jargons or challenging words or phrases [13]. In this regard, the European Federation of Pharmaceutical Industries and Associations (EFPIA) [14] has made a number of interventions to address challenges facing medicine users, and improve the reading of medicine package inserts. Ghanaians stand to benefit from such interventions because most of the drugs used originated from Europe. In **Chapter 2.1** it was found that those who read the leaflet were more likely to discuss problems they had with the health care worker compared to those who did not. It presupposes that between these two types of patients, those reading the leaflet are more likely to access health in the event of any subsequent outcome, for example, if an adverse reaction occurs after treatment. Consequently, such patients are more likely to have access to treatment in the event of an adverse drug reaction. Higher education was strongly linked to reading the leaflet in this chapter and therefore having a better chance to have access to medicines. One may argue that it is plausible that a highly educated person is more likely to read compared to an uneducated person, but because of the social systems in Ghana, most people tend to live in groups and support each other, so an uneducated person who is asked to read the leaflet can always consult a family member for assistance (most people do this). Education is a sine qua non for health survival. Links to sustainable development goal (SDG) 3 targets indicates that "children of educated mothers-even mothers with only primary schooling-are more likely to survive than children of mothers with no education" [15]. Low literacy patients have suggested the use of shorter information leaflets with images [16]. According to them this would increase appeal, help ask questions, and may lead to better recall and improved confidence. The International Pharmaceutical Federation's (FIP) statement of policy medicines information for patients [17], and FIP's pictogram Project [18] developed to assist pharmacists having communication problems (unfamiliar language or illiteracy) comes in handy here. This software is well tested globally for easy understanding among users. Hospital pharmacists in Ghana can collaborate with hospital medical illustration staff to design large sized medicine information pictograms to enhance communication with educationally deprived patients.

The effectiveness of pharmaceutical care from the perspective of the patient was assessed in **Chapter 2.2**. In this chapter a survey was conducted among seven out-patient pharmacies in the hospital. It was identified from patient responses that counselling services on their medication was uneven among the various pharmacies surveyed, and information to patients on medication side effects or drug interaction was low. The trend was similar in another country in the sub region [19]. The final port of call of most patients is the pharmacy. Here they are served medicines with the assurance that if taken well, their condition will be alleviated. Patients should be given clear directions on when and how to take their medicines. They should be counselled on the possible side effects associated with their medicines and on any existing drug-drug or drug-food interactions. They should

also be advised to return left-over medicines for disposal. Periodic medicine use review (MUR) [20, 21] was suggested in this setting to bring patients closer to hospital pharmacists and improve rapport between the two parties. The following activities are captured by the MUR system: "… with the patient's agreement, to improve the patient's knowledge and use of drugs by in particular: (a) establishing the patient's actual use, understanding and experience of taking drugs; (b) identifying, discussing and assisting in the resolution of poor or ineffective use of drugs by the patient; (c) identifying side effects and drug interactions that may affect the patient's compliance with instructions given to them by a health care professional for the taking of drugs; and (d) improving clinical and cost effectiveness of drugs prescribed to patients, thereby reducing the wastage of such drugs" [21]. Notwithstanding the benefits of MURs, it has been observed that the system only works to benefit patients if there is collaboration between pharmacists and doctors [22]. Where this has been the case [23, 24], patients quality of life improved and days of sickness reduced. In a systematic review on MURs involving physicians, pharmacists, and other health care workers and their patients, a significant association was found between the delivery of MURs and emergency department contacts but there was no association with all-cause mortality [25]. The authors recommended a prior randomized control study to ascertain benefits before any full scale MUR is implemented. As hospital pharmacists in Ghana work closely with physicians and nurses, our patients may also benefit from such an intervention if the necessary steps are taken

Chapter 2.3 depicts an insufficient access to paediatric medicines in Ghana, especially, medicines for the management of non-communicable diseases (NCD) for children are not readily available in either public hospital pharmacies or in community pharmacies. About 90% of the medicines in this study were for the management of non-communicable diseases. The most prescribed medicine were for cardiovascular diseases followed closely by anti-convulsants. Parents or guardians travel long distances in search of paediatric medicines because these are not readily available nationwide. Such medicines are only prepared extemporaneously in a limited number health facilities. Privatization of facilities for the preparation of extemporaneous products is one option that can circumvent the current challenge. A "Public-private NGO mix" has been prescribed as important in supporting access to essential medicines for an effective healthcare system [26]. In this case a decentralized private delivery system could be put in place where orders will be made from institutions that prescribe the medicines but deliveries will be made to patients. This will reduce the burden on parents and guardians because instead of chasing the medicine, now the medicine will chase them. However, such facilities will have to be well regulated to ensure that products are of good quality and are affordable, otherwise the very reason for their establishment will be defeated. Another option will be to train qualified personnel in existing health facilities to fill the gaps. Public Private Partnership (PPP) is another option that can adequately address the issue at stake. Here governments, after establishing a need for the service can either provide low tax loans to qualified partners to set up, or governments

can put up well equipped structures for interested qualified personnel to use and pay over a fixed period.

Another observation in **Chapter 2.3** was the off-label prescription of paediatric medicines. In this study 2.6% (16/622) of prescriptions of hydroxyurea were written for paediatric patients. This medicine was neither registered in Ghana nor registered for oral paediatric use. Off-label prescription of medicines is normal and not illegal [27], has rates of up to 40% in adults [28-31] and up to 90% in paediatrics [32-36]. However, use should be based on evidence because of clinical, safety and ethical ramifications [26]. "Even when services are available, they can be of poor quality, endangering the safety of patients and comprising health outcomes" [15]. The role of the hospital drug information pharmacist in assessing and reporting on the benefits and risks of medicines intended for off-label purposes prior to their use is very important in this instance. Such evidence-based searching and recommendation can subsequently lead to addition of off-label medicines to the hospital's formulary. A case worth mentioning is the choice of bevacizumab (off-label) over ranibizumab (registered drug) by the WHO for the management of neovascular age-related macular degeneration (AMD) using scientific evidence [37-39].

THE ROLE OF ADHERENCE IN ACHIEVING OPTIMAL TREATMENT OUTCOME IN HIV TREATMENT

Chapters 3.1 to 3.4 all studied the HIV cohort (adults and adolescents) at the Korle-Bu Teaching Hospital to obtain a better understanding of how optimal adherence can be achieved. In **Chapter 3.1**, we examined treatment trends among HIV patients over a five year period. During this period new treatment information led to revisions in treatment guidelines [40, 41]. One of the outcomes of access to medicines investigated in this research was the "rational use of medicines by health professionals". This is among the three elements that any sound rational drug use programme in any country must have [42]. It was evident in this research that prescribers in this setting adhered to treatment guidelines by replacing stavudine with either tenofovir or zidovudine as a result of the latter drug's toxicity profiles. This was done in real time to commensurate with the introduction of the new guideline and so patients were not needlessly exposed to any treatment hardships.

As universal coverage of antiretroviral therapy (ART) improves, it is important to consider adherence to treatment because high adherence levels are essential for survival as well as to prevent drug resistance [43, 44]. Drug resistance can occur in a number of forms. First of all, a patient may be infected with a drug resistant strain [45]. Secondly, drug resistance may occur after infection when the organisms are in the multiplication phase. During this period, mutations may occur leading to resistant strains [45]. It is known that first line drugs like non-nucleotide reverse transcriptase inhibitors (NNRTI) have lower genetic resistance compared to second line protease inhibitors [46-48]. Drug resistance may also be due to re-infection among people on ART. This may be as a result of unprotected sex or exchange of needles

with people with blood resistant strains. When drug resistance occurs, it most probably, leads to treatment switch to a higher level treatment regimen. Antiretroviral therapy gets more and more expensive (in term of cost) as one switches upwards from first line treatment. Due to the high cost of treatment as one moves up the levels, less numbers would receive treatment with the same amount of money [43]. This will definitely have a negative impact on the treatment coverage. It may pose a threat to access to antiretroviral medicines, and calls for concern. **Chapter 3.2** explored the relationship between adherence among adult patients (on first line treatment) and treatment change, either to another first line drug (substitution) or to a second line drug (switch). It found that non-adherence to ART was associated with more than 3 times the odds (odds ratio=3.56, 95% CI 1.60, 7.88) of treatment change. Adherence plays an important role in the early warning indicators [49] of HIV/AIDS therapy, if researchers could identify all the factors responsible for non-adherence to therapy and address these challenges that would be a turning point in patient management. In another study among HIV/AIDS patients in the same setting, therapy change was found to be linked with adverse drug events [50]. **Chapter 3.3** considered factors associated with non-adherence to treatment. Clinical factors at baseline (WHO disease stage at treatment initiation, CD4 cell count at treatment initiation and presence of symptoms at treatment initiation) were found to be the most important variables that were independently associated with non-adherence to antiretroviral treatment among adult HIV patients in this setting. Chapters 3.1 to 3.3 are evident of the role of hospital pharmacists in Ghana with regards to access to medicines among HIV/AIDS patients. The data provides information on which patients have risks and which factors are linked to non-adherence. Hospital HIV adherence pharmacists can target such groups and provide consistent adherence service. Findings from IMS information explains that a total of 4.6% (amounting to $269 billion) of global health expenditure can be saved if optimal adherence to medicines are maintained [51]. A systematic review of randomized controlled trials on general adherence to medicines has observed that using pharmacy refill records to monitor adherence, ceteris paribus, leads to valid and reliable results because of reduced bias [52]. The authors cautioned that non-adherence can only be controlled by continuously engaging patients on self-administered medicines to adhere to treatment. This calls for persistent affirmative action from hospital pharmacists purposefully targeted at defaulting patients while maintaining close surveillance on all others to ensure the 90-90-90 [53] dream of ending the AIDS epidemic.

Global trends show that HIV/AIDS is the second highest cause of death among adolescents [54, 55] and the highest cause of death among adolescent females [54]. As of 2013, of the 2.1 million adolescents living with HIV, 83% resided in sub-Saharan Africa [56]. Adolescents are the generation that closely follow adults. Hence when the adolescent population of a society shrinks it will create a void in social and economic development in the near future and that will have a profound effect on progress. This is even more so in sub-Saharan Africa where life expectancy is lower compared to high income countries. In 2006 the UN reported that, "In the 31 countries at the bottom of the list, 28 of which are in sub-Saharan Africa, a person can hope to live on average only 46 years, or 32 years less than the average life expectancy in countries of advanced human development, with 20 years slashed off life

expectancy due to HIV/AIDS" [35]. Although this figure has improved to 59 by 2014 [57], there is still a deficit of 22 years when compared to high income countries. The situation puts adolescent health in this part of the world in serious jeopardy. **Chapter 3.4** looked at facilitators and barriers of adherence to ART among adolescent HIV patients in Ghana in a qualitative study. The main facilitators were support from health care providers, parental support, patient's knowledge of disease and self-motivation, patient's perceived positive outcomes, and dispensed formulation,. The identified barriers were patient's forgetfulness to take medicines, perceived stigmatization due to disclosure, financial barriers, and adverse effects of antiretroviral therapy. Outcomes in this study were similar to those of a mixed methods study [58] involving adolescents in the second largest referral hospital in Ghana located about 255km away. Looking at the time the two studies were submitted, accepted and published, they seemed to have been done concurrently but inadvertently. This confirms the reliability of the study information and the validity of our results. It assures us that our results could be generalizable at least, among adolescents in Ghana.

The way forward for HIV/AIDS adherence research should include the use of disaggregated data for the identification of most at risk groups. This will be beneficial in the management of the disease because more time will be devoted for such groups instead of treating everyone similarly. However, for this to be effective large and reliable datasets must be available. Disaggregated studies shrink the sample size and this may not be possible if data is parsimonious.

IMPROVING OUTCOMES FOLLOWING IMMUNIZATION

Access to medicines and access to vaccines are implicitly linked such that when one mentions the former, it is acknowledged that latter has also been mentioned. According to the UK NHS, "because of vaccinations, we no longer see smallpox, and polio has almost been eradicated. No wonder vaccination is considered a modern miracle.

Vaccination is one of the greatest breakthroughs in modern medicine. No other medical intervention has done more to save lives and improve quality of life" [59]. Vaccines prevent against related diseases including cancer (for example, human papilloma vaccine and cervical cancer) increase life expectancy, and societies have made substantial gains from their use [60]. Notwithstanding their monumental benefits, vaccines have safety concerns which when not handled properly could lead to reduction in vaccine uptake and re-emergence of disease [61]. This calls for continuous monitoring of vaccine effects using either passive and/or active surveillance for the identification and possible confirmation of signals. Monitoring of vaccine effects are for various purposes. These include:

- To detect unusual numbers of associated adverse events
- To identify events of infrequent occurrence attributable to the vaccine
- To make health workers aware of vaccine risks and win their confidence for future vaccination programs
- To identify areas or subgroups that require special investigation.

Chapters 4.1 and 4.2 investigated adverse events following immunization (AEFI). The 2009 A (H1N1) swine flu pandemic was the first influenza infection that affected all the WHO regions of the world in the 21st century [62-64]. This was followed by mass vaccination of most at risk persons with the hope of halting the spread of the disease. **Chapter 4.1** involves AEFI information collected among health care workers who were vaccinated with the H1N1 vaccine in real time using active surveillance. Hospital pharmacists played an important role in this vaccination program by educating prospective vaccinees on the benefit-risks of the vaccine before, during and after vaccination. The results were compared with the results in the summary of product characteristics (SPC) of the vaccine used for immunization (Pandemrix®). Incidence rates for all the reported events in this study were lower than those in the SPC but tachycardia, tinnitus and decreased appetite, although reported in our study, were not reported in the SPC. Further studies was recommended to investigate the discrepancy. **Chapter 4.2** was a disproportionality analysis involving AEFIs of six vaccinations from the Food and Drugs Authority (Ghana) database. Our aim was to assess the timely reporting of safety information to the Ghanaian Food and Drugs Authority and generate signals by comparing the safety profile of one vaccine with rest in the database. The findings in this study were consistent with the information in the literature underscoring the sensitivity of public health systems in sub-Saharan Africa (like Ghana) to pick up most frequently occurring and important vaccine related safety issues.

For most mass vaccination programmes in Ghana there is a corresponding active surveillance for the collection of AEFIs. However, due to the high cost of active surveillance studies, surveillance for routine vaccinations as well as for other medicines are done passively. All the data for chapter 4.2 were from active surveillance studies. While data are available for such mass vaccination programmes, the same cannot be said about other vaccines or medicines. According to a qualitative study in Australia among medical practitioners, local council immunization and general practice nurses, it was found that time constraints and unsatisfactory reporting processes were among common barriers to AEFI reporting [65]. Nurses were found to be more likely to have had formal training in reporting compared to medical practitioners [65]. This is very plausible because most immunization programs are under the care of community health nurses. Furthermore, a systematic review on the impact of educational intervention (EI) on adverse events reporting has shown that EI improves reporting [66]. These two studies are complementary. This calls for more action to encourage spontaneous reporting of events. Hospital pharmacists contribute the most spontaneous reports in Ghana, followed by medical doctors [67]. In 2015, the Ghanaian FDA launched the patient engagement in medicine safety reporting program [67]. This program encourages patients with suspected adverse events to contact the Ghanaian FDA using a mobile phone short code. Patients can also report using an internet access provided on the Ghanaian FDA website. Chapters 4.1 and 4.2 show that safety monitoring of vaccines (and medicines) can be done and to what extent it can be done in Ghana as a resource limited country. If only we could take advantage of the SDG goal 17 [15] to develop partnerships for development, then most resource poor countries would learn from Ghana. Over the years contributions from African countries to the Uppsala Monitoring Centre of the WHO keep on increasing. As of 1992 there were only 2 African countries in the Programme for International Drug Monitoring compared to 35 in 2015 [68]. The cumulative number of individual case series reports submitted to Vigibase also increased considerably albeit insignificant compared to the rest of the world [68]. This calls for more work from the African region. The WHO has always been at the forefront in empowering African nations in this regard. This is epitomised with the establishment of the Pharmacovigilance Sans Frontier (PVSF) in 2007 with an aim to improve pharmacovigilance on the African continent by developing advanced drug safety capacities [69] and the WHO Collaborating Center for Advocacy and Training in Pharmacovigilance [70]. For LMIC the need to invest in well-organized databases cannot be over-emphasized. Olsson et al [71] have advocated for logistics support to boost data collection in LMIC. It is important to empower researchers from this region with tools for data analysis. This has been emphasised by PVSF [69]. Many vaccine adverse event studies have focused on data from patient reports. It makes it rather difficult to find out why patients report or not report AEFIs. Future research should focus on more direct interaction with patients using qualitative interviews or mixed methods research to tease out information. This may unearth new and useful information that may improve vaccine uptake and AEFI reporting.

FINAL REFLECTIONS

As was stated in the general introduction of this thesis, patient centered research activities involving hospital pharmacists in Ghana is very low. This challenge is most probably as a result of non-availability of structured data and inadequate research skills among hospital pharmacists. According to the UN report on Sustainable Development Goals, "most low- and lower-middle-income countries lack civil registration and vital statistics (CRVS) systems, well-functioning health facilities and community information systems, disease surveillance systems, health workforces and health financing accounts" [15]. The use of primary data for research could be time consuming and such data are normally not very large. However, using secondary data, including claims databases and electronic medical records (EMR) short cuts the time spent in data acquisition. The size of the data in this case is normally larger and more likely to meet the demands of statistical power. Claims data are useful for decision making in health and disease management such as finding prevalent chronic conditions and gaps in quality of care [72], as well as drug utilization of a population. The Ghana National Health Insurance Agency (NHIA) has claims data that may be used for research [73]. A piloted E-Claims version began in 2013 [74] and nationwide electronic data submission started in 2014. However, not all facilities transmit data electronically. The Ghana Health Service in collaboration with the University of Oslo developed the District Health Information Management System (DHIMS) [75]. DHIMS is available in all the districts of the Ghana Health Service and data is collated at a central point. Using secondary observational data has its

limitations including selection bias, but this can be minimised using adequate research designs and analytical techniques such as multivariable regression methods [76].

It is difficult to secure funding opportunities for hospital pharmacy practice research in this region most probably due to the nature of the study design or inadequate sampling methods, but some hospitals support small scale operational research. Most hospital pharmacy practice research are funded by the researchers themselves. The only choice, most of the time, is a convenience sampling approach. This results in small samples with higher uncertainty in the results because the studies are underpowered. Despite these limitations, this thesis has shown that with smaller data, credible research on access to medicines can be done to impart positively on practice. What is needed is adequate training on how to use such data for useful research.

The Ministers Summit on "The benefits of responsible use of medicines" in 2012 [77] focused on the prescription and dispensing of the appropriate medicine, provision of the needed support to ensure maximum benefits from pharmacotherapy, and the use of data analytics for effective evaluation of interventions. These are all implicit in this thesis. In **Chapter 2.3,** we could have been more accurate in predicting the level of insufficiency in access to paediatric medicines if we had captured both prepared medicines as well as those that were not available. Future research could take this up and provide real estimates of stock-outs for planning purposes. The most challenging aspect of this thesis involved manual data extraction (chart reviews) from patient medical records and pharmacy records involving **Chapters 3.2 and 3.3**. It was time consuming and demanded expert involvement. Further, adequate training and direction given to data collectors before and during data collection, in addition to piloting of the study, is of utmost importance to ensure data validity in cases where data are not electronically available but collected from folders and files. The saying goes that science would be in turmoil if behaviour of clinician scientists regarding the keeping of their lab books had been the same way as they completed clinical records [78, 79]. Primary data collection could be time consuming and expensive [80]. This underscores the urgent need for well-structured electronic health records or databases in this setting and other similar settings. The use of secondary data saves time for researchers, especially quantitative researchers [80] but the downside of secondary data is that they are not collected with your research in focus. This may be restrictive, especially if they do not contain all the variables of your choice. This was our challenge in the case of **Chapter 3.1**.

It is over ten years now since the introduction of the 4 tier access to medicine concept by the WHO [81]. At that time the emphasis was on "access to medicines", however, in recent years we see statements like "access to quality medicines" and even "access to high quality medicines". Sustainable Development Goal 3, addresses good health and well-being, and goal 3.8, empowers us to "achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all" [15] by the year 2030. These changes have become necessary to address challenges occurring in time and place. There are calls for a modification of the WHO model [82] to account for such events. Apart from

the important research areas explored in this thesis other themes have been posited where hospital pharmacists in developing countries can serve as protagonists in the realization of access to medicines

The first, concerns the situation of substandard, spurious, falsely labelled, falsified, and counterfeit medicines (SSFFC). Substandard medicines are more prevalent in resource-poor countries [83, 84]. Half of all the medicines used for serious diseases in poor countries have little or no active ingredient [85]. This may have serious economic (because a lot of money is invested in the procurement of medicines) and health (because patients may take longer times to recover or may not respond to treatment at all depending on the levels of deviation from required standards) implications on the population in these settings.

In a systematic review of counterfeit and substandard medicines using mostly communicable disease data predominantly from Asia and Africa, Alghannam et al [86] observed that only 9% of research articles attempted all levels of quality analysis. The researchers [86] called for further research into SSFFC. One of the best places to identify substandard medicines is the hospital where patients are treated and monitored using both locally manufactured and imported medicines. In such cases, treatment outcomes are very likely to fall below expectation if SSFFC exits. It is important to record such episodes on local and national levels and collaborate with existing regulatory authorities for follow up investigation. Secondly, access to medicines requires that the right product is delivered to the right recipient at the right time (within a satisfactory time period). This is in accordance with Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme (PIC/S) guide to good distribution practice for medicinal products [87]. Although the PIC/S guide is not mandatory, it is useful and worth emulating. In most developed countries, drug supply is done by a limited number of very large distribution wholesalers. A UK survey by the Office of Fair Trading (OFT) in 2007 reported that there were only 10 full-line wholesalers for prescription medicines and just 3 of them supplied more than 85% of the total market volume [88]. Most of these wholesalers are computerised and drugs are supplied at least twice a day to pharmacies, resulting in an average stock-out period of only 12 hours. On the contrary, there are few large distribution wholesalers in Ghana. At the last tender for medicines for the Korle-Bu Teaching Hospital alone, there were over 40 prospective bidders. All teaching hospitals as well as regional hospitals procure medicines through a tender system. In a typical hospital, the time between the day an award letter for medicines is served to a wholesaler and the day the medicines arrive at the facility is unpredictable for most of the time. This could lead to stock-outs of essential medicines. Of 600 health facilities surveyed in Ghana, Kenya and Uganda between May to November in 2012, over 30% of expected essential medicines were not available during the period of study and patients had to go from one facility to the next in search of their medicines [89]. The authors having noted that this may have a profound effect on access to medicines and consequently may affect their health, called for pharmaceutical procurement strengthening and increased autonomy for stock management [89]. That there are issues with access to pharmaceuticals among sub-Saharan African countries cannot be overemphasized. Hospital

pharmacists are placed in a strategic position that should encourage them to venture into drug supply management and good distribution practices (GDP) research.

Thirdly, research on the burden of medicine-related harm and their preventability needs to be created in developing countries in addition to capacity building with analytical competencies to carry out independent benefit/risk assessments [61]. This calls for training [69] with quantitative pharmacoepidemiological and pharmacoeconomic skills.

CONCLUSION

The various roles played by hospital pharmacists in relation to pharmaceutical policies and access to medicines in low and medium-income countries should be countenanced and they should be empowered to always live up to expectation. This thesis has shown that even where big data is not available, using the right methodology can produce credible results that will be good enough for policy decision making. The thesis also emphasizes the need to promptly link health policies to patients (including patients' advocates), and maintain continuous engagement in order to attain and preserve optimal health benefits. As hospital pharmacists continue to provide improved and essential health service to patients, the pharmacist-patient relationship is bound to improve considerably and this may have a profound effect on care outcomes. Pharmaceutical policies and access to medicines remain very important in low and medium income countries. This could improve if attention is given to the gaps suggested in this thesis

REFERENCES

1. International Covenant on Economic, Social and Cultural Rights (ICESCR), 1966. Adopted and opened for signature, ratification and accession by General Assembly resolution 2200A (XXI) of 16 December 1966. Entered into force 3 January 1976 in accordance with article 27.
2. Hogerzeil HV, Mirza Z. The World Medicines Situation 2011. Access to essential medicines as part of the right to health. WHO, 2011.
3. Hogerzeil HV, Samson M, Casanovas JV, Rahmani-Ocora L. Access to essential medicines as part of the fulfilment of the right to health enforceable through the courts. *Lancet* 2006;368:305-311.
4. Private and Public Partners Unite to Combat 10 Neglected Tropical Diseases by 2020. Http://www.gatesfoundation.org/media-center/press-releases/2012/01/private-and-public-partners-unite-to-combat-10-neglected-tropical-diseases-by-2020. Accessed: 28/09/2016.
5. Stephens P, Leufkens HG. The World Medicines Situation 2011. Research and Development. WHO, 2011.
6. Laing RO, Hogerzeil HV, Ross-Degnan D. Ten recommendations to improve use of medicines in developing countries. *Health Policy Plann*.2001;16(1): 13–20
7. Sinclair D, Gyansa-Lutterodt M, Asare B, Koduah A, Andrews E, Garner P. Integrating Global and National Knowledge to Select Medicines for Children: The Ghana National Drugs Programme. *PLOS Med* 2013;10(5):e1001449.
8. Arhinful DK. An assessment of the pharmaceutical sector in Ghana. MOH. 2002.
9. Arhinful DK. WHO Pharmaceutical Situation Assessment Level II - Health Facilities Survey in Ghana. Ministry of Health, Ghana. 2009.
10. Faculty of Pharmacy and Pharmaceutical Service. KNUST. Ghana. www.pharmacy.knust.edu.gh/about. Accessed: 10/09/2016.
11. Ghana Pharmaceutical Country Profile. MOH, Ghana. WHO. 2012.
12. Standards for pharmaceutical care for public health facilities in Ghana. Ghana National Drugs Programme. MOH. GHS. 2002.
13. Bailey SC, Navaratnam P, Black H, Russell AL, Wolf MS. Advancing Best Practices for Prescription Drug Labeling. *Ann Pharmacother* 2015;49(11):1222–1236.
14. Position on shortcomings of the Summary of Product Characteristics and the Package Leaflet and proposals to resolve them. EFPIA, 2014.
15. Health in 2015: from MDGs Millennium Development Goals to SDGs Sustainable Development Goals. WHO 2015.
16. van Beusekom MM, Grootens-Wiegers P, Bos MJW, Guchelaar H, van den Broek JM. Low literacy and written drug information: information-seeking, leaflet evaluation and preferences, and roles for images. *Int J Clin Pharm* 2016. doi:10.1007/s11096-016-0376-4.
17. FIP statement of policy: medicines information for patients. FIP 2008.
18. Vailancourt R, Dawson J, Besancon L. Pictograms drawing solutions FIP, 2012.
19. Erah PO, Chuks-Eboka NA. Patients perception of the benefits of pharmaceutical care Services in the management of hypertension in a Tertiary Health care Facility in Benin City. *Trop J Pharm Res* 2008;7(1):897-905.
20. Manfrin A, Thomas T, Krska J. Randomised evaluation of the Italian medicines use review provided by community pharmacists using asthma as a model (RE I-MUR). *BMC Health Serv Res* 2015;15:171.
21. Briefing for GP practices: Achieving best value from the community pharmacy medicines use review service. London; NHS Employers, BMA, PSNC, 2009.
22. Latif A, Pollock K, Boardman HF. Medicines use reviews: a potential resource or lost opportunity for general practice? *BMC Family Practice* 2013, 14:57

23. Rigby D. Collaboration between doctors and pharmacists in the community. *Aust Prescr* 2010;33:191-3.
24. Haahtela H, Tuomisto LE, Pietinalho A, Klaukka T, Erhola M, Kaila M, et al. A 10 years asthma programme in Finland: major change for the better. *Thorax*. 2006;61:663–70.
25. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. *Cochrane Database Syst Rev* 2013,2:CD008986.
26. World Health Organization. Equitable access to essential medicines: a framework for collective action. WHO policy perspectives in medicine. Geneva 2004.
27. Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL, Campbell TJ. Off-label use of medicines: consensus recommendations for evaluating appropriateness. *Med J Aust* 2006; 185 (10): 544-548.
28. Rayburn W, Farmer K. Off-label prescribing during pregnancy. *Obstet Gynecol Clin North Am* 1997; 24: 471-479.
29. Laetz T, Silberman G. Reimbursement policies constrain the practice of oncology. *JAMA* 1991; 266: 2996-2999.
30. Brosgart C, Mitchell T, Charlebois E, et al. Off-label drug use in human immunodeficiency virus disease. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; 12: 56-62.
31. Douglas-Hall P, Fuller A, Gill-Banham S. An analysis of off-licence prescribing in psychiatric medicine. *Pharm J* 2001; 267: 890-891.
32. McIntyre J, Conroy S, Avery A, et al. Unlicensed and off label prescribing of drugs in general practice. *Arch Dis Child* 2000; 83: 498-501.
33. Pandolfini C, Impicciatore P, Provasi D, et al. Off-label use of drugs in Italy: a prospective, observational and multicentre study. *Acta Paediatr* 2002; 91: 339-347.
34. Conroy S, Choonara I, Impicciatore P, et al. Survey of unlicensed and offlabel drug use in paediatric wards in European countries. *BMJ* 2000; 320:79-82.
35. Cuzzolin L, Zaccaron A, Fanos V. Unlicensed and off-label uses of drugs in paediatrics: a review of the literature. *Fundam Clin Pharmacol* 2003; 17:125-131.
36. Stephenson T. Medicines for children — the last century and the next. *Arch Dis Child* 2001; 85: 177-179.
37. Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ; CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897-908.
38. Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, et al.; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119(7):1388-98.
39. Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, et al.; IVAN Study Investigators. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology*. 2012;119(7):1399-411.
40. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 rev. WHO 2010.
41. Guidelines for antiretroviral therapy in Ghana. Ministry of Health, Ghana Health Service. 2008 and 2011.
42. Essential Medicines and Health Products. Rational use of medicines: activities. http://www.who.int/medicines/areas/rational_use/rud_activities/en/. Accessed: 05/08/2016.
43. Hardon A, Davey S, Gerrits T, Hodgkin C, Irunde H, Kgatlwane J, et al. From access to adherence: the challenges of antiretroviral treatment. University of Amsterdam, WHO, KTI 2006.
44. Nachega JB, Hislop M, Dowdy DW, Lo M, Omer SB, et al. Adherence to antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. *J Acquir Immune Defic Syndr* 2006;43:78-84.
45. HIV treatment: Drugs resistance. AIDSinfo. https://aidsinfo.nih.gov/education-materials/fact-sheets/21/56/drug-resistance. Accessed: 17/09/2016.
46. Margot NA et al. Development of HIV-1 drug resistance through 144 weeks in antiretroviral-naive subjects on emtricitabine, tenofovir disoproxil fumarate and efavirenz compared with lamivudine/zidovudine and efavirenz in study GS-01-934. *J Acqui Immune Defici Syndr*, 2009, 52:209–221.
47. Maserati R et al. Emerging mutations at virological failure of HAART combinations containing tenofovir and lamivudine or emtricitabine. *AIDS*. 2010, 24:1013–1018. 13.
48. Svicher V et al. Different evolution of genotypic resistance profiles to emtricitabine versus lamivudine in tenofovir-containing regimens. *J Acqui Immune Defic Syndr*. 2010, 55:336–344.
49. Meeting report on assessment of World Health Organization HIV drug resistance early warning indicators: report of the Early Advisory Indicator Panel meeting, 11-12 August 2011, Geneva, Switzerland 2011.
50. Tetteh RA, Nartey ET, Lartey M, Mantel-Teeuwisse AK, Leufkens HG, Yankey BA, et al. Association Between the Occurrence of Adverse Drug Events and Modification of First-Line Highly Active Antiretroviral Therapy in Ghanaian HIV Patients. *Drug Saf*. 2016;39(11):1139-1149.
51. Advancing the responsible use of medicines. IMS Institute of Healthcare Informatics. 2012.
52. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2014;11:CD000011.
53. 90-90-90. An ambitious treatment target to help end the AIDS epidemic. UNAIDS 2014.
54. Global Health Estimates: Deaths, disability-adjusted life year (DALYs), years of life lost (YLL) and years lost due to disability (YLD) by cause, age and sex, 2000–2012. WHO.
55. Health for the world's adolescents: a second chance in the second decade. WHO; 2014.
56. ALL IN #EndAdolescentAIDS. 2015. www.unicef.org/media/files/ALL_IN_brochure_En_v02(1).pdf. Accessed: 26/07/2015.
57. Life expectancy is sub-Saharan Africa is lower now than 30 years ago – UN index. UN News Centre. http://www.un.org/apps/news/story.asp?NewsID=20548. Accessed: 10/08/2016.
58. Enimil A, Nugent N, Amoah C, Norman B, Antwi S, Ocran J, et al. Quality of Life among Ghanaian Adolescents Living with Perinatally Acquired HIV: A Mixed Methods Study. *AIDS Care*. 2016;28(4):460–464.
59. How vaccination saves lives. http://www.nhs.uk/conditions/vaccinations/pages/vaccination-saves-lives.aspx. Accessed: 10/08/2016
60. Andre FE, Booy R, Bock HL, Clemens J, Datta SK, John TJ, et al. Vaccination greatly reduces disease, disability, death and inequity worldwide. *Bull World Health Organ* 2008;86:140-146.
61. Atkinson P, Cullinan C, Jones J, Fraser G, Maguire H. Large outbreak of measles in London: reversal of health inequalities. *Arch Dis Child* 2005; 90: 424-5.
62. Scalera NM, Mossad SB. The first pandemic of the 21st century: a review of the 2009 pandemic variant influenza A (H1N1) virus. *Postgrad Med* 2009;121(5):43-7.
63. Shindo N, Briand S. Influenza at the beginning of the 21st century**.** *Bull World Health Organ* 2012;90:247-247A.
64. Al Hajjar S, McIntosh K. The first influenza pandemic of the 21st century**.** *Ann Saudi Med*. 2010; 30(1): 1–10.
65. Parrella1 A, Braunack-Mayer A, Gold M, Marshall H, Baghurst P. Healthcare providers' knowledge, experience and challenges of reporting adverse events following immunisation: a qualitative study. *BMC Health Serv Res* 2013, 13:313.

66. Pagotto C, Varallo F, Mastroianni P. Impact of educational interventions on adverse drug events reporting. *Int J Technol Assess Health Care*. 2013 Oct;29(4):410-7.

67. DrugLens, FDA Ghana Newsletter, Issue 3, March 2015.

68. Ampadu HH, Hoekman J, de Bruin ML, Pal SN, Sten Olsson S, Sartori D, et al. Adverse Drug Reaction Reporting in Africa and a Comparison of Individual Case Safety Report Characteristics Between Africa and the Rest of the World: Analyses of Spontaneous Reports in VigiBase. *Drug Saf* (2016) 39:335–345.

69. Uppsala Reports. Covering the world of pharmacovigilance. Issue 72. April 2016.

70. WHO Collaborating Center for Advocacy and Training in Pharmacovigilance. www.who-pvafrica.org. Accessed: 27/09/2016

71. Olsson S, Pal SN, Dodoo A. Pharmacovigilance in resource-limited countries. *Expert Rev Clin Pharmacol* 2015;8(4):449-460.

72. Solz H, Gilbert K. Health claims data as a strategy and tool in disease management. *J Ambul Care Manage*. 2001;24(2):69-85.

73. Antwi S, Zhao X. A logistic regression model for Ghana National Health Insurance Claims. *Int J Bus Soc Res*. 2012;2(7):139-147

74. National Health Insurance Authority. 2013 Annual Report.

75. District Health Information Management System. DHIMS II: The Data Challenge for Ghana Health Service. GHS. Ghana.

76. Beaty LA. Primer for understanding diagnostic-related groups and inpatient hospital reimbursement with nursing implications. *Crit Care Nurs Q*. 2005;28(4):360-369.

77. Ministers Summit. The benefits of responsible use of medicines. Setting policies for better and cost-effective healthcare. Amsterdam, The Netherlands 2012.

78. Weed LL. Medical records that guide and teach. *N Eng J Med* 1968a;278(11):593-600.

79. Weed LL. Medical records that guide and teach. *N Eng J Med* 1968b;278(12):652-657.

80. Hox JJ, Boeije HR, Data collection; primary vs secondary. *Encyclopaedia of Social Measurement* 2005;1:593-599.

81. The Pursuit of Responsible Use of Medicines: Sharing and Learning from Country Experiences. http://www.who.int/medicines/areas/rational_use/en/. Accessed: 10/8/2016

82. Bigdeli M, Jacobs B, Tomson G, Laing R, Ghaffar A, Dujardin B, et al. Access to medicines from a health systems perspective. *Health Policy Plann* 2013;28:692-704.

83. Caudron J-M, Ford N, Henkens M, Mace C, Kiddle-Monroe R & Pinel J (2008) Substandard medicines in resource-poor settings: a problem that can no longer be ignored. *Trop Med Int Health* 13, 1062–1072.

84. Newton PN, Green MD & Fernandez FM. Impact of poor-quality medicines in the 'developing' World. *Trends Pharmacol Sci* 2010;31, 99–101.

85. Newton PN, Green MD, Fernández FM, Day NP, White NJ. Counterfeit anti-infective drugs. *Lancet Infect Dis* 2006;6:602-13.

86. Alghannam AFA, Aslanpour Z, Evans S, Schifano F. A systematic review of counterfeit and substandard medicines in field quality surveys. *Integrated Pharmacy Research and Practice* 2014;3:71–88

87. PIC/S guide to good distribution practice for medicinal products. PIC/S June 2014.

88. Medicines distribution. An Office of Fair Trading Market Study. 2007.

89. Masters SH, Burstein R, DeCenso B, Moore K, Haakenstad A, et al. Pharmaceutical Availability across Levels of Care: Evidence from Facility Surveys in Ghana, Kenya, and Uganda. *PLoS ONE* 2014;9(12): e114762.

Chapter 6

SUMMARY AND SAMENVATTING

Chapter 6.1

SUMMARY

SUMMARY

Access to quality medicines is a universal human right that has featured prominently on the agenda of the WHO over the past decades. From the Alma Ata Declaration in 1978, through the Millennium Development Goals in 2000 until the current Sustainable Development Goals, the importance of medicines in improving health has always been emphasized. As one of the custodians of medicines, hospital pharmacists play a pivotal role in ensuring that treatment outcomes are optimal.

In **Chapter 1**, the introduction outlines the WHO's initial model of access to medicines and the suggestions for expansion of the model by various researchers. It discusses the importance of pharmaceutical policy analysis and the need for pharmacists to engage in research involving access to medicines. The hospital is an interface where many of the stakeholders (health workers, policy makers, academics) in the health sector meet as they attempt to find the best solutions for the patient, who unarguably is the most important stakeholder. Notwithstanding the role of other players, patients need to play an active part in their care issues. For instance, for best treatment outcomes, there should be optimum adherence on the part of patients. Hospital pharmacists in Ghana as well as in other Sub-Saharan African countries may play a significant role in ensuring and improving access to medicines. The present thesis aims to study different aspects of this role including provision of adequate information and services, access to paediatric formulations, adherence counselling for antiretroviral therapy and safety surveillance of vaccines.

Chapter 2 studies the provision of medicines' information, pharmaceutical services and suitable medicines to patients. **Chapter 2.1** discusses provision of medicines' information to the patient by way of the medicine information leaflet. In this cross-sectional study adult patients from the main teaching hospital in Accra, Ghana, were interviewed. Information was gathered with emphasis on those whose medication came with a leaflet. The effect of advice to read the leaflet and other associations between covariates were examined. Of the 531 patients, 421 (79.3%) had received a leaflet before and of these 93.8% had received some verbal information from the health worker (doctor/pharmacist/ nurse). Only 139 (33.0%) said they were ever told to read the leaflet by their health worker. Those who recalled being advised to read the leaflet were about six times (odds ratio (OR) = 5.77; 95% confidence interval (CI) 2.76–12.04; $P < 0.001$) as likely to report having read the leaflet than those who did not, and they were also more likely (59% compared with 36%; $P < 0.001$) to discuss with the health worker the problems they had while using the medication. Age group was a weak effect modifier ($P = 0.04$). It is important to step up public awareness on the importance of the leaflet and to encourage more people to read the medicine information leaflet.

Chapter 2.2 assesses the perception of out-patients on the role of the hospital pharmacist, their expectation of services provided by the hospital pharmacist and the factors encouraging them to speak to the hospital pharmacist. This was in the form of exit interviews at various out-patient pharmacies of the Korle-Bu Teaching Hospital. Six pharmacies with a high patronage of patients with chronic diseases were purposively selected. A structured

questionnaire was completed using a face-to-face approach and the results were presented in the form of descriptive and analytical (logistic regression) statistics. In all, 331 respondents made up of 56.8% women and 43.2% men were interviewed. The mean age of respondents was 42 years. In all 77.2% at least agreed that the pharmacist is a health professional just like doctors and nurses, and only 3.8% of respondents strongly disagreed that their awareness of the role of the pharmacist had improved over the last five years. It was found that those who reported little difficulty identifying the pharmacy staff were about three times as likely (OR 3.19, 95% CI 1.78- 5.80, p<0.001) to request to speak with the pharmacist compared to those who found this difficult. Pharmacists need to step up counselling services at the various pharmacies in hospitals and should invest more time for patient care.

The fact that frequently prescribed children's medicines are not readily available in Ghana is addressed in **chapter 2.3**. All prescriptions for extemporaneous oral preparations for children presented to the local production unit of the Korle-Bu Teaching Hospital from November, 2013 until February, 2014 were eligible for the study. Presence of the prescribed medicine on the World Health Organization Children's Medicine List was ascertained in addition to the anatomical and therapeutic classification code. The registration of the prescribed medicine for paediatric use by the Food and Drugs Authority, Ghana was also checked. Descriptive statistics of the data was presented. In all 622 prescriptions for 35 different paediatric formulations were served. Prescriptions from several health facilities including government hospitals (6.6%, N=622), private hospitals (2.4%, N=622) and the University of Ghana hospital (1.1%, N=622) were all honoured. Some of the prescribed medicines (baclofen, clonazepam, hydroxyurea and lamotrigine) were neither on the World Health Organization Children's Medicine list nor registered with the Food and Drugs Authority, Ghana. Most prescribed medicines (88.6%, N=35) were for non-communicable diseases. It was recommended that steps should be taken to improve access and monitor benefit-risk profiles of paediatric medicines in order to improve treatment outcomes among children.

Studies on the role of adherence in achieving optimal treatment outcomes in HIV/AIDS patients were included in chapter 3. Patterns of treatment change among new initiators of highly active antiretroviral therapy (HAART) were studied in **chapter 3.1**. Data were obtained from the Fevers' Unit Database at the Korle-Bu Teaching Hospital. All adult treatment naive patients who started treatment with first line HAART between 1st January, 2008 and 31st December, 2012 were followed over a minimum period of three months. The main outcome was the rate of first treatment change, defined as the first substitution/switch in accordance with the standard treatment guidelines. Data were analyzed according to year of treatment initiation. A total of 3,933 patients were followed with almost equal numbers of initiators per year. The mean age (standard deviation) at treatment initiation was 39 (10.3) years. The most prescribed HAART combination was AZT/3TC/EFV, remaining relatively stable over the years. Utilization of stavudine containing HAART increased gradually until 2010 and by the end of 2012 had dropped to zero. There was an increase in the use of tenofovir (TDF), partly to compensate the reduced use of stavudine containing HAART combinations. Kaplan-Meier curves showed that treatment change was higher among those who started treatment later in the study period compared to those who started earlier. The removal of stavudine from HIV treatment was an international policy decision taken to mitigate the associated risks. Trends showed that prescribers and dispensers complied with the policy intervention.

The success of any drug treatment is underpinned by a sound adherence to treatment regimen. The main objective in **chapter 3.2** was to evaluate the effect of ART adherence on treatment change in a nested case-control study. Data were extracted from available written clinical and pharmacy records, and the electronic database at the Korle-Bu Teaching Hospital. Cases comprised all those (≥15 years) who experienced a first treatment change after starting first-line ART between 1/1/2004 and 31/12/2009. Controls (who did not change treatment) were sampled from the same cohort of ART starters and matched to cases on date ART was started. Adherence was determined using the proportion of days covered (PDC) approach and poor adherence was defined as PDC levels below 95%. Measures of effect were calculated using conditional logistic regression. The cases and matched controls were similar in most baseline characteristics. Among cases 20.1% (60/298) switched to second-line therapy and the rest had treatment substitutions. Overall, 88.9% of controls compared with 79.9% of cases had adherence levels greater than or equal to 95% (p=0.003). After adjusting for possible confounders, an adherence level below 95% was associated with almost four times (ORadj=3.56 (95% CI 1.60 to 7.88)) the likelihood of having a treatment change. This study showed also that insufficient ART adherence may very likely lead to treatment change. Policy makers must partner researchers to engage patients more often, to unravel the causes of non-adherence, and make the necessary interventions for patients to achieve maximum benefits from dispensed medicines.

Chapter 3.3 aimed to determine risk factors associated with non-adherence to first line antiretroviral therapy (ART). This was a sequel to chapter 3.2 using the same dataset. Adherence to therapy was contrasted, i.e. levels below 95% (cases) were compared to 95% or more (controls).Logistic regression was used for analysis followed by a test for goodness-of-fit and calculation of the area under the receiver operating characteristic (ROC) curve. In all there were 73 cases and 367 controls. The median age of cases was 41.0 years (interquartile range (IQR): 34.9-50.0), and 46 (63%) of them were female. For controls the median age was 43.0 years (IQR: 37-52.1), and 244 (66.5%) were female. The risk factors significantly associated with non-adherence to ART were WHO disease stage IV (age and gender adjusted OR (aOR) 3.03 [95% CI 1.70, 5.41]) which recorded a risk score of 11, presence of symptoms at baseline (aOR 1.70 [95% CI 1.00, 2.90] and risk score 5), and lower CD4 cell count at treatment initiation (aOR 1.39 [95% CI 0.96, 2.01] and risk score 3). Pearson goodness-of-fit test produced a p-value of 0.663 and the area under ROC curve was 0.72 (95% CI 0.64, 0.85). In this setting clinical baseline characteristics of HIV/AIDS patients influenced non-adherence to ART. Stepping up surveillance interventions for early identification and possibly early treatment of HIV/AIDS among Ghanaians by policy makers, health workers and HIV advocacy groups could be helpful.

6.1

Of the global total number of adolescents living with HIV in 2013, about 83% resided in Sub-Saharan Africa. **Chapter 3.4** identified facilitators of and barriers to antiretroviral treatment adherence among adolescents in Ghana. We organized a cross sectional qualitative study using semi-structured interviews among adolescents (aged 12-19 years) at the adolescents HIV clinic at the Korle-Bu Teaching Hospital in Ghana. A total of 19 interviews were conducted. Analysis was done manually to maintain proximity with the text. The main facilitators were support from health care providers, parental support, patient's knowledge of disease and self-motivation, patient's perceived positive outcomes, and dispensed formulation,. The identified barriers were patient's forgetfulness to take medicines, perceived stigmatization due to disclosure, financial barriers, and adverse effects of antiretroviral therapy. Support from health care workers was the most frequently mentioned facilitator; patient's forgetfulness, and perceived stigmatization after disclosure were the most frequently mentioned barriers. Self-motivation (knowledge induced) to adhere to treatment was a specific facilitator among older adolescents. We suggested that continuous information and persistent support from health care workers and parents or guardians may improve adherence among adolescents. Also, interventions to reduce patient forgetfulness may be beneficial. A multi-sectorial approach is needed to address adolescent disclosure.

Vaccination is one of the greatest breakthroughs in modern medicine. Notwithstanding their monumental benefits, vaccines have safety concerns which when not handled properly could lead to reduction in vaccine uptake and re-emergence of disease. This calls for continuous monitoring of vaccine effects using either passive and/or active surveillance for the identification and possible confirmation of signals. Ghana lies in the meningitis belt of Sub-Saharan Africa. Furthermore, Ghana is in the yellow fever zone, and several infectious childhood diseases need to be prevented. For these reasons chapter 4 looks at the role of hospital pharmacists in safety surveillance during immunization programmes. **Chapter 4.1** reports on the distribution and types of adverse events reported following immunization of health care workers at the Korle-Bu Teaching Hospital (KBTH) against the AH1N1 influenza in 2009. Safety data collected during the AH1N1 influenza vaccination of these health workers was used for this study. All workers, 18 years and over were eligible for vaccination. For uniformity 0.5ml of Pandemrix® (equivalent to 3.75 micrograms of heamagglutinin antigen) was administered intramuscularly into the deltoid muscle of the left arm. Each vaccinee was issued with a card and was advised to report any adverse events following immunization to designated health workers for follow-up. Incidence rates of adverse events were estimated and compared to the Pandemrix® Summary of Product Characteristics (SPC). A total of 5870 people (64.9% females) with a mean age of 34.0 years were vaccinated. In all 140 vaccines reported adverse events. The mean age among vaccinees reporting adverse events was 36.1 years. The overall incidence of vaccinees reporting adverse events and the overall incidence of adverse events was 232 (95% CI 199 to 320) per 10,000 people and 930 (95% CI 820 to 1070) per 10,000 people, respectively. In particular, we found no difference in the way males reported AEFI compared to females ($\chi 2 = 0.59$; $P > 0.2$) and we did not find any association between age as a categorical variable and vaccine adverse event reporting ($\chi 2 = 5.24$; $P > 0.1$). There were only three serious cases which led to hospitalization. All three cases occurred within 24 hours of receiving the vaccine. The incidence rates for the various reported events were all lower compared to those in the Pandemrix® SPC, but while injection site pain was the most frequent in the SPC and other foreign studies, we recorded headache as the most frequent. Even fatigue, muscle/joint aches and fever had higher incidence rates compared to injection site pain. Tachycardia, tinnitus and decreased appetite were reported although not included in the SPC. More of such studies should be encouraged in low and medium income countries to bridge the information gap with the developed world.

AEFIs reported using active surveillance from the Ghanaian Food and Drugs Authority's database was used to identify signals in **chapter 4.2**. De-identified data from active surveillance for AEFIs after H1N1, yellow fever, meningitis, measles-rubella, pneumococcal-rotavirus and human papilloma virus vaccinations were used. The vaccinations occurred between January 2010 and December 2013. The first ten most occurring events for each vaccination were captured. These were arranged using Medical Dictionary of Regulatory Agencies (MedDRA) Preferred Term (PT) and System Organ Classification (SOC) codes. Proportional reporting ratios (PRR, 95% CIs) were calculated. A total number of 5,141 reports were analysed ranging from 33 (human papilloma virus) to 1958 (measles-rubella). Between 22% and 55% of all AEFIs per vaccination were collected on the day of vaccination. For each vaccination, at least 87% of all reported AEFIs occurred in the first 7 days post-vaccination. Active surveillance lasted for 30 days for most vaccination programs. For H1N1 vaccination the signal with the highest PRR was dizziness (PRR 6.71 (95% CI 5.01, 8.18), Chi square 216.6); the signal with the highest PRR for human papilloma virus and measles-rubella was abdominal pain (PRR 8.15 (95% CI 3.46, 19.23), $\chi 2$ 30.2) and PRR 43.75 (95% CI 17.81, 107.45), $\chi 2$ 200.7) respectively; the signals with the highest PRR for yellow fever, meningitis and pneumococcal-rotavirus vaccinations were arthralgia, dizziness and injection site pain, in that order. Almost all the signals generated in this study were well-known and confirmed existing safety knowledge on the vaccines studied. The results underscore the sensitivity of public health systems in Sub-Saharan African countries (like Ghana) to pick up most frequently occurring and important vaccine related safety issues.

This thesis closes with a discussion in **chapter 5** which emphasizes the role of the hospital pharmacist in Ghana in access to medicines and pharmaceutical policies, especially related to antiretroviral therapy and vaccines. The chapter highlights the importance of medicines information, service provision by hospital pharmacists and provision of essential medicines to paediatric patients, adherence with reference to antiretroviral therapy, and the monitoring of adverse events following immunization and the detection of signals. Research gaps that will complement this work and eventually improve access to medicines in Ghana and other similar settings are identified. These include work on good distribution practices (GDP); research on substandard, spurious, falsely labelled, falsified and counterfeit medicines

(SSFFC); and lastly research and capacity building on benefit-risk analysis of medicines. We have shown that where big data is not available, using the right methodology can produce credible results that will allow for learned policy decision making. The thesis also emphasizes the need to align health policies to patients (including patients' advocates), and maintain continuous engagement in order to attain and preserve optimal health benefits. As hospital pharmacists continue to provide improved and essential health service to patients, the pharmacist-patient relationship is bound to improve considerably and this may have a profound effect on care outcomes. Pharmaceutical policies and access to medicines remain very important in low and medium income countries. This could improve if attention is given to the gaps suggested in this thesis.

6.1

Chapter 6.2

SAMENVATTING

SAMENVATTING

Toegang tot kwalitatief goede geneesmiddelen is een van de universele rechten van de mens. Dit recht heeft in de afgelopen decennia een prominente plek ingenomen op de agenda van de Wereldgezondheidsorganisatie (WHO). Van de Alma Ata Declaratie in 1978 tot aan de *Millenium Development Goals* in 2000 en de huidige *Sustainable Development Goals* is het belang van geneesmiddelen bij het verbeteren van de volksgezondheid benadrukt. Ziekenhuisapothekers spelen als een van de bewakers van geneesmiddelen een belangrijke rol bij het borgen dat uitkomsten van de behandeling met geneesmiddelen zo optimaal mogelijk zijn.

In de introductie in **hoofdstuk 1** worden het oorspronkelijke WHO model voor toegang tot geneesmiddelen en suggesties van verschillende onderzoekers om dit model verder uit te breiden beschreven. Het belang van farmaceutische beleidsonderzoek en de noodzaak om apothekers te betrekken bij het onderzoek naar toegang tot geneesmiddelen worden bediscussieerd. Het ziekenhuis is de plaats waar veel belanghebbenden in de gezondheidszorg (medewerkers in de gezondheidszorg, beleidsmakers en academici) elkaar ontmoeten om te komen tot de beste behandeling van de patiënt, die uiteindelijk de belangrijkste belanghebbende is. Patiënten moeten een actieve rol spelen in de vraagstukken die rondom hun behandeling opkomen. Om de beste uitkomst van een behandeling te kunnen bereiken is optimale therapietrouw bijvoorbeeld van groot belang. Ziekenhuisapothekers in Ghana en in andere delen van Sub-Sahara Afrika kunnen een prominente rol spelen in het verbeteren van toegang tot geneesmiddelen. In dit proefschrift worden verschillende aspecten van deze rol bestudeerd, zoals het geven van algemene voorlichting en diensten, bewaken van toegang tot geneesmiddelen voor kinderen, voorlichting rondom therapietrouw met antiretrovirale middelen en bewaken van veiligheidsaspecten van vaccins.

In hoofdstuk 2 is het verstrekken van geneesmiddelinformatie, farmaceutische dienstverlening en geschikte geneesmiddelen bestudeerd. **Hoofdstuk 2.1** richt zich op het verstrekken van informatie aan patiënten door middel van de bijsluiter. In een cross-sectionele studie werden volwassen patiënten die het Korle-Bu ziekenhuis in Accra, Ghana bezochten geïnterviewd om het advies om de bijsluiter te lezen te evalueren en determinanten van het lezen van de bijsluiter te kunnen bepalen. Van de 531 geïnterviewde patiënten hadden 421 (79.3%) een bijsluiter gekregen en 93.8% van deze patiënten had daarnaast enige mondelinge informatie van een medewerker (arts, apotheker of verpleegkundige) ontvangen. Slechts 139 (33.0%) patiënten gaven aan dat hun verteld was dat zij de bijsluiter zelf moesten lezen. Deze patiënten lazen de bijsluiter uiteindelijk bijna zes keer vaker dan patiënten die deze instructie niet kregen (odds ratio (OR) 5.77, 95% betrouwbaarheidsinterval (BI) 2.76-12.04, $p<0.001$) en tevens bespraken zij vaker problemen die zij bij het gebruik van geneesmiddelen tegenkwamen met hun behandelaar (59% vs. 36%, $p<0.001$). Leeftijd was daarbij een zwakke effectmodificator ($p=0.04$). Het is van belang om meer aandacht te besteden aan het belang van het lezen van de bijsluiter en patiënten hiertoe te stimuleren.

In **hoofdstuk 2.2** is de perceptie van poliklinische patiënten ten aanzien van de rol van de ziekenhuisapotheker in Ghana bestudeerd. Ook is gekeken naar hun verwachtingen ten aanzien van dienstverlening door ziekenhuisapothekers en factoren die samenhangen met het opnemen van contact met een ziekenhuisapotheker. Hiertoe werd een enquête gehouden onder patiënten die een van de zes geselecteerde uitgiftepunten van geneesmiddelen voor chronische ziekten van het Korle-Bu ziekenhuis hadden bezocht. De enquête werd mondeling afgenomen en de gegevens werden zowel descriptief als analytisch (logistische regressie) beschreven. In totaal waren er 331 respondenten, waarvan 56.8% vrouw was en de gemiddelde leeftijd 42 jaar. De ziekenhuisapotheker werd door 77.2% als een behandelaar beschouwd en slechts 3.8% gaf aan dat hun beeld van de rol van de ziekenhuisapotheker in de afgelopen vijf jaar niet veranderd was. Patiënten die bekend waren met ziekenhuisapothekers vroegen drie keer vaker een gesprek aan (OR 3.19, 95% BI 1.78-5.80, p<0.001) dan zij die dat niet waren. Ziekenhuisapothekers in Ghana moeten meer aan farmaceutische dienstverlening gaan doen en meer tijd besteden aan farmaceutische patiëntenzorg.

Hoofdstuk 2.3 gaat in op de beschikbaarheid van veel gebruikte geneesmiddelen voor kinderen in Ghana. In dit onderzoek werden alle voorschriften voor orale geneesmiddelen voor kinderen meegenomen, die in de periode november 2013 - februari 2014 werden aangeboden bij de lokale productieafdeling van het Korle-Bu ziekenhuis. Er werd gekeken of het betreffende geneesmiddel was opgenomen in de WHO Children's Medicines List, tot welke WHO ATC klasse het geneesmiddel behoort en of het geneesmiddel door de Ghanese Food and Drugs Authority (FDA) was geregistreerd voor het gebruik bij kinderen. In totaal werden 622 voorschriften voor 35 verschillende kinderformuleringen aangeboden. Deze waren afkomstig van verschillende instellingen waaronder publieke ziekenhuizen (6.6%), private ziekenhuizen (2.4%) en het ziekenhuis van de Universiteit van Ghana (1.1%) en werden allemaal gehonoreerd. Sommige van de geneesmiddelen (baclofen, clonazepam, hydroxycarbamide en lamotrigine) stonden niet op de WHO lijst en waren tevens niet door de FDA goedgekeurd voor gebruik bij kinderen. De meeste geneesmiddelen (n=33, 89%) waren voor chronische aandoeningen. Om de uitkomsten van de behandeling van kinderen verder te verbeteren is het van belang toegang te verbeteren en de balans tussen werkzaamheid en veiligheid te monitoren.

Onderzoek naar de rol van therapietrouw bij het bereiken van de beste uitkomsten van de behandeling van patiënten met HIV/AIDS is opgenomen in hoofdstuk 3. In **hoofdstuk 3.1** is gekeken naar patronen van veranderingen in de behandeling van patiënten die startten met zogenaamde *highly active antiretroviral therapy* (HAART, combinaties van verschillende antiretrovirale geneesmiddelen). De gegevens waren afkomstig van de database van de Fevers' Unit van het Korle-Bu ziekenhuis. Alle volwassen patiënten die in de periode 1 januari 2008 tot en met 31 december 2012 voor het eerst met eerstelijns HAART begonnen werden gevolgd voor een periode van minimaal 3 maanden. Het primaire eindpunt van het onderzoek was de eerste verandering in deze therapie, gedefinieerd als een vervanging van een geneesmiddel in lijn met de vigerende richtlijnen. De gegevens werden geanalyseerd naar jaar van start van de behandeling. Het cohort bestond uit 3933 patiënten, die gemiddeld 39 (standaarddeviatie (SD) 10.3) jaar oud waren bij de start van HAART. Elk jaar beginnen ongeveer evenveel patiënten met hun behandeling. De meest voorgeschreven combinatie door alle jaren heen was AZT/3TC/EFV. Het gebruik van combinaties met stavudine steeg licht tot 2010, maar daalde daarna tot nul aan het eind van 2012. Het gebruik van tenofovir (TDF) steeg in de onderzoeksperiode, ten dele om de daling in het gebruik van stavudine te compenseren. Kaplan-Meier analyses lieten zien dat veranderingen in de therapie meer voorkwamen bij patiënten in de latere jaren van het onderzoek dan bij patiënten die in de eerste fase startten. Het verwijderen van stavudine uit behandelrichtlijnen voor HIV was een internationale beleidsbeslissing om de risico's van dit middel te beperken. Het huidige onderzoek laat zien dat behandelaren in overeenstemming met dit beleid hebben gehandeld.

Therapietrouw is van groot belang voor het succes van elke behandeling met geneesmiddelen. Het doel van **hoofdstuk 3.2** was om de effecten van therapietrouw met antiretrovirale therapie op veranderingen in de behandeling te evalueren. Gegevens voor dit geneste patiënt-controle onderzoek waren afkomstig uit de medische dossiers en apotheekdatabase van het Korle-Bu ziekenhuis. Cases waren patiënten van 15 jaar en ouder die een eerste verandering in hun behandeling ondergingen in de periode 1 januari 2004 tot en met 31 december 2009. Controles hadden geen verandering in hun therapie en werden gematcht op datum van start antiretrovirale therapie. Therapietrouw werd bepaald aan de hand van het aantal dagen waarop het geneesmiddel werd gebruikt (*proportion of days covered*, PDC) en slechte therapietrouw werd gedefinieerd als een PDC lager dan 95%. Conditionele logistische regressie werd gebruikt om het effect te bepalen. De karakteristieken van cases en controles kwamen in grote lijnen overeen. Van de cases switchte 20.1% (60/298) naar een tweedelijns middel, terwijl bij de overige patiënten een of meer van de eerstelijnsmiddelen werden vervangen door een ander eerstelijns middel. Slechte therapietrouw kwam voor bij 79.9% van de cases en 88.9% van de controles (p=0.003). Na correctie voor mogelijke confounders bleek slechte therapietrouw geassocieerd te zijn met een bijna 4 keer (gecorrigeerde OR 3.56; 95% BI 1.60-7.88) verhoogd risico op een verandering in de behandeling. Beleidsmakers en klinische onderzoekers moeten gezamenlijk werken aan het vergroten van de betrokkenheid van patiënten bij hun behandeling, de oorzaken van therapietrouw verder in kaart brengen en noodzakelijke interventies ontwikkelen om patiënten te ondersteunen bij het bereiken van het grootst mogelijke voordeel van de behandeling.

In **hoofdstuk 3.3** had tot doel risicofactoren voor therapieontrouw met antiretrovirale middelen te bepalen. Dit onderzoek was een vervolg van het onderzoek in hoofdstuk 3.2 en maakte gebruik van dezelfde gegevens. In dit onderzoek werd de verschillende mate van therapietrouw tegen elkaar afgezet, namelijk therapietrouw van minder dan 95% (cases) tegen therapietrouw van 95% of meer (controles). Hiertoe werd gebruik gemaakt

6.2

van logistische regressie, gevolgd door een *goodness-of-fit* test en het berekenen van de oppervlakte onder de grafiek van de *receiver operating characteristic* (ROC-)curve. De gemiddelde leeftijd van de 73 cases was 41.0 jaar (interkwartielafstand (IQR) 34.9-50.0 jaar) en 46 patiënten (63%) waren vrouwen. De 367 controles waren gemiddeld 43.0 jaar (IQR 37.0-52.1 jaar) en 244 (66.5%) waren vrouw. The factoren die statistisch significant waren geassocieerd met therapieontrouw waren WHO ziektestadium IV (voor leeftijd en geslacht gecorrigeerde OR (aOR) 3.03; 95% BI 1.70-5.41), resulterend in een risicoscore van 11, de aanwezigheid van symptomen bij de start van de behandeling (aOR 1.70; 95% BI 1.00-2.90, risicoscore 5) en een laag aantal CD4 cellen bij de start van de behandeling (aOR 1.39; 95% BI 0.96-2.01, risicoscore 3). De p-waarde van de Pearson *goodness-of-fit* test bedroeg 0.663 en de oppervlakte onder de ROC-curve was 0.72 (95% BI 0.64-0.85). In deze setting bleken klinische karakteristieken bij aanvang van de therapie samen te hangen met therapieontrouw. Het opvoeren van interventies door beleidsmakers, medewerkers in de gezondheidszorg en HIV belangengroeperingen in Ghana om HIV/AIDS eerder te ontdekken en een vroege behandeling te kunnen starten, zouden in dit kader ook behulpzaam kunnen zijn.

Wereldwijd leefde in 2013 circa 83% van de adolescenten met HIV in Sub-Sahara Afrika. In **hoofdstuk 3.4** werden ondersteunende factoren en barrières voor therapietrouw met antiretrovirale middelen onder adolescenten in Ghana bestudeerd. In dit cross-sectionele, kwalitatieve onderzoek werden interviews gehouden met adolescenten (12-19 jaar) die de HIV-kliniek van het Korle-Bu ziekenhuis in Ghana bezochten. In totaal werden 19 interviews afgenomen. De gegevens werden handmatig geanalyseerd. De belangrijkste geïdentificeerde ondersteunende factoren betroffen steun door medewerkers in de gezondheidszorg, steun door ouders, eigen kennis van het ziektebeeld, zelfmotivatie, ondervonden positieve effecten van de behandeling en de formulering van het geneesmiddel. De geïdentificeerde barrières waren het moeite hebben met het niet vergeten van geneesmiddelen, ondervonden stigmatisering, financiële obstakels en bijwerkingen van de antiretrovirale therapie. De ondersteuning van medewerkers in de gezondheidszorg was de meest genoemde ondersteunende factor, de meest genoemde barrières waren vergeten van medicatie en stigmatisering. Zelfmotivatie die voortkwam uit het hebben van kennis over de ziekte kwam met name voor bij oudere adolescenten. De conclusie van dit onderzoek is dat het geven van voldoende informatie over de ziekte en ondersteuning door zowel professionals in de zorg als ouders kunnen bijdragen aan verbeterde therapietrouw onder adolescenten. Ook interventies die helpen om de inname van geneesmiddelen niet te vergeten kunnen een bijdrage leveren. Om daadwerkelijk verbetering van therapietrouw onder adolescenten te kunnen bewerkstelligen is een veelomvattende aanpak nodig.

Vaccinaties zijn een van de grootste doorbraken van de moderne geneeskunde. Ondanks hun grote voordelen zijn ook vaccins geassocieerd met veiligheidsrisico's, die van invloed kunnen zijn op de vaccinatiegraad en de hernieuwde opkomst van ziektes als zij niet met zorg worden afgehandeld. De veiligheid moet daarom continu worden bewaakt door middel van actieve of passieve bewakingsprogramma's en signalen van mogelijke bijwerkingen moeten door middel van nader onderzoek worden bevestigd. Ghana ligt in de zogenaamde 'meningitisgordel' van Afrika, ligt in het gebied waar gele koorts endemisch is en moet het optreden van infectieziekten onder kinderen voorkomen. In hoofdstuk 4 wordt daarom de rol van de ziekenhuisapotheker bij het bewaken van de veiligheid van vaccins in vaccinatieprogramma's nader belicht. In **hoofdstuk 4.1** is de distributie en het type bijwerkingen na vaccinatie van medewerkers van het Korle-Bu ziekenhuis met het AH1N1 griepvaccin in 2009 geanalyseerd. Alle medewerkers van 18 jaar en ouder kwamen in aanmerking voor vaccinatie. Zij kregen 0.5 ml Pandemrix® (overeenkomstig met 37.5 mcg hemagglutinine antigeen) intramusculair in de deltaspier van de linkerarm toegediend. Iedere gevaccineerde ontving een informatiekaart en werd geadviseerd bijwerkingen van de vaccinatie te melden aan specifieke medewerkers. De incidentie van bijwerkingen werd in dit onderzoek geschat en deze werden vergeleken met de bijwerkingen zoals gemeld in de officiële productkenmerken (*Summary of Product Characteristics*, SPC) van Pandemrix®. In totaal werden 5870 mensen (64.9% vrouwen) met een gemiddelde leeftijd van 34.0 jaar gevaccineerd. Zij rapporteerden 140 bijwerkingen. De incidentie van medewerkers die een bijwerking meldde bedroeg in dit onderzoek 232 (95% BI 199-320) per 10.000 mensen, terwijl de overall incidentie van bijwerkingen 930 (95% BI 820-1070) per 10.000 mensen was. Er werden daarbij geen verschillen in incidentie tussen mannen en vrouwen gevonden (χ^2=0.59; p>0.2). Ook vonden we geen associatie tussen verschillende leeftijdscategorieen en het rapporteren van bijwerkingen ten gevolge van de vaccinatie (χ^2=5.24; p>0.1). Drie ernstige bijwerkingen, die binnen 24 uur na vaccinatie ontstonden, leidden tot ziekenhuisopname. De incidenties voor de verschillende bijwerkingen waren allemaal lager dan vermeld in de SPC van Pandemrix®. Hoewel pijn op de injectieplaats de meest frequent genoemde bijwerking was in de SPC en in ander internationaal onderzoek, werd in deze studie hoofdpijn het meest gemeld. Ook de incidenties van het optreden van vermoeidheid, spier- en gewrichtspijn en koorts waren hoger dan die van pijn op de injectieplaats. Tachycardie, tinnitus en verminderde eetlust staan niet in de SPC, maar werden wel gerapporteerd. Om tegemoet te komen aan het verschil in beschikbare informatie over bijwerkingen tussen hoge inkomenslanden en lage en midden inkomenslanden, zou meer van dit soort onderzoek moeten worden uitgevoerd.

De meldingen van bijwerkingen die binnen actieve bewakingsprogramma's voor vaccins bij de Ghanese FDA werden gerapporteerd werden gebruikt voor signaaldetectie in hoofdstuk 4.2. Anonieme gegevens over bijwerkingen na vaccinatie voor H1N1, gele koorts, meningitis, mazelen-rode hond, pneumokokken-rotavirus en humaan papilloma virus (HPV) werden geanalyseerd. De vaccinaties vonden plaats tussen januari 2010 en december 2013. Van elk vaccin werden de meldingen voor de tien meest voorkomende bijwerkingen meegenomen. Classificatie van bijwerkingen vond plaats op basis van de Medical Dictionary of Regulatory Agencies (MedDRA) Preferred terms (PT) en System Organ Classification (SOC). *Proportinal reporting ratios* (PRR) en de bijbehorende 95% betrouwbaarheidsintervallen

werden berekend. Een totaal aantal van 5141 meldingen werd geanalyseerd, variërend van 33 voor HPV vaccinatie tot 1958 voor het vaccin tegen mazelen en rode hond. Tussen 22% en 55% van alle meldingen voor een vaccin werd verzameld op de dag van de vaccinatie. Voor elke vaccinatie werd tenminste 87% gemeld binnen de eerste 7 dagen. Active bewaking duurde bij de meeste vaccinatieprogramma's tenminste 30 dagen. Voor het H1N1 vaccin was het signaal met de hoogste PRR voor duizeligheid (PRR=6.71; 95% BI 5.01-8.18, χ^2=216.6). Voor zowel het HPV vaccin als het mazelen-rode hond vaccin werd de hoogste PRR gevonden voor buikpijn (respectievelijk PRR=8.15; 95% BI 3.46-19.23, χ^2=30.2 en PRR=43.75; 95% BI 17.81-107.45, χ^2=200.7). De signalen met de hoogste PRR waren gewrichtspijn voor het gele koortsvaccin, duizeligheid voor het meningitisvaccin en pijn op de injectieplaats voor het pneumokokken-rotavirusvaccin. Vrijwel alle gevonden signalen waren bekend en bevestigden de bestaande kennis over veiligheid van vaccins. De resultaten laten zien dat de gezondheidszorgsystemen in landen in Sub-Sahara Afrika gevoelig genoeg zijn om de meest frequent voorkomende signalen ten aanzien van de veiligheid van vaccins op te pikken.

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Dit proefschrift wordt afgesloten met een algemene discussie in hoofdstuk 5. Hierin wordt de rol van de ziekenhuisapotheker in Ghana ten aanzien van toegang tot geneesmiddelen en farmaceutisch beleidsonderzoek benadrukt, met name in de context van antiretrovirale geneesmiddelen en vaccins. Dit hoofdstuk vestigt de aandacht op het belang van verstrekken van informatie, farmaceutische dienstverlening door ziekenhuisapothekers, verstrekken van essentiële geneesmiddelen aan kinderen, therapietrouw bij de behandeling met antiretrovirale therapie en het bewaken van bijwerkingen die worden gerapporteerd na vaccinatie en de bijbehorende signaaldetectie. In dit hoofdstuk worden toekomstige onderzoeksvragen die het werk in dit proefschrift kunnen aanvullen en uiteindelijk leiden tot een betere toegang tot geneesmiddelen in Ghana geïdentificeerd. Hiertoe behoren vraagstellingen op het gebied van *Good Distribution Practices* (GDP), onderzoek naar verschillende vormen van kwalitatief onvoldoende of vervalste geneesmiddelen (*substandard, spurious, falsely labelled, falsified and counterfeit* (SSFFC) geneesmiddelen) en op het gebied van de analyse van baten en risico's van geneesmiddelen. Dit proefschrift laat zien dat in omstandigheden waar geautomatiseerde gegevensbestanden afwezig zijn, onderzoek met de juiste methodologie tot zinvolle resultaten kan leiden. Dergelijke resultaten kunnen worden gebruikt voor het onderbouwen van beleidsbeslissingen. De resultaten in dit proefschrift benadrukken daarnaast de noodzaak om farmaceutisch beleid af te stemmen op patiënten en hun vertegenwoordigers en deze te blijven betrekken bij het behalen en behouden van optimale gezondheidswinst. Als ziekenhuisapothekers verbeterde en essentiële farmaceutische dienstverlening blijven verstrekken aan patiënten, zal dit een positief effect hebben op de relatie tussen de ziekenhuisapotheker en de patiënt en dit zou de uitkomsten van de behandeling diepgaand kunnen beïnvloeden. Ondanks de in dit proefschrift gesignaleerde sterke punten en mogelijkheden, moeten de hiaten die zijn beschreven zo spoedig mogelijk zorgvuldig worden bestudeerd en aangepakt.

Chapter 7

ADDENDUM

Chapter 7.1

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LIST OF PUBLICATIONS

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Scientific publications related to this thesis

Ankrah D, Koster ES, Mantel-Teeuwisse AK, Arhinful DK, Agyepong IA, Lartey M. Facilitators and barriers to antiretroviral therapy adherence among adolescents in Ghana. *Patient Prefer Adherence* 2016;15(10):329-37.

Ankrah D, Turkson JT, Boateng EB, Amegavie FTT, Bruce E. Insufficient access to oral paediatric medicines in Ghana: A descriptive study. *BMC Health Serv Res* 2016,16:198.

Ankrah D**,** Lartey M, Agyepong IA, Leufkens HGM, Mantel-Teeuwisse AK. Adherence and treatment change among HIV/AIDS patients in Ghana – A nested case-control study. *J AIDS Clin Res* 2015;6: 510.

Ankrah D**,** Ofei-Palm CN, Nordor M, Nelson F, Ocansey D, Bruce E. Patients' perception of pharmacists' role in the provision of pharmaceutical services at the Korle-Bu Teaching Hospital in Ghana. *AJPP* 2014;8(46):1164-1172.

Ankrah D, Mantel-Teeuwisse AK, De Bruin ML, Amoo PK, Ofei-Palm CN, Agyepong IA, Leufkens HGM, Incidence of adverse events among healthcare workers following H1N1 Mass immunization in Ghana: a prospective study. *Drug Safety.* 2013;36(4):259-66.

Ankrah, D and Ofei-Palm, CN, The effect of advice to read the medicine/patient information leaflet among patients in Ghana: a cross-sectional study. *JPHSR 2010;*1:91–96.

Ankrah D**,** Lartey M, Mantel-Teeuwisse AK Leufkens HGM. Five-year trends in treatment changes in an adult cohort of HIV/AIDS patients in Ghana. Submitted.

Ankrah D, Darko DM, Sarblah G, Mantel-Teeuwisse A, Leufkens HGM. Reporting of adverse events following immunization in Ghana - a disproportionality analysis. Submitted.

Ankrah D, Lartey M, Agyepong IA, Heerdink ER, Leufkens HGM, Mantel-Teeuwisse AK. Identifying risk factors associated with non-adherence to antiretroviral therapy among patients on first line treatment in Ghana. Submitted.

Scientific publications not related to this thesis

Ankrah D, Turkson JT. Biologics and Pharmacy Schools' curricula in Ghana – Views of pharmacy interns. *Ghana Pharm J* 2016; 11(1):4-8.

Nelson F, Ankrah D, Ofei-Palm CN, Turkson JT, Bruce E. Pharmacy waiting time and rational medicine use at the Korle-Bu Teaching Hospital in Ghana. *Ghana Pharm J* 2015;10(1):13-18.

Agyepong IA, Aryeetey GC, Nonvignon J, Asenso-Boadi F, Dzikunu H, Antwi E**,** Ankrah D, Acquah CA, Esena R, Aikins M, Arhinful DK. Advancing the application of systems thinking in health: provider payment and service supply behaviour and incentives in the Ghana National Health Insurance Scheme – a systems approach. *Health Res Policy Syst* 2014 12:35.

Arhinful DK, Kusi A, Ankrah D, Sackey W. Identification of priority policy research questions in the area of access to and use of medicines in Ghana. Noguchi Memorial Institute 2011. http://www.who.int/alliance-hpsr/projects/noguchighana_medicines/en/index.html.

Chapter 7.4

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