Report on the first year of biomedical operational research of the AMC-CPCD within participating clinics in Nigeria in the Health Insurance Fund Nigeria project.

Center for Poverty-related Communicable Diseases
Academic Medical Center
University of Amsterdam
Amsterdam, the Netherlands

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Summary

Background & methods

The AMC Center for Poverty-related Communicable Diseases (AMC-CPCD) is contracted by the Health Insurance Fund (HIF) to conduct independent operational research within the HIF-program. The AMC-CPCD focuses on epidemiological and bio-medical operational research. The main objectives of the research of the AMC-CPCD are to quantify and qualify the impact of the HIF program intervention. Focus of the research is on the quality of the health care provided by the participating clinics and the benefits of the HIF program on the health of the participating populations. A secondary objective is to provide the HIF with independent feedback and recommendations on how to improve the HIF project with respect to both medical and organizational aspects.

The AMC-CPCD research consists of two main parts. The first is a series of household surveys that will be performed together with the Amsterdam Institute for International Development (AIID). These surveys contain a biomedical module, which will provide data on the health status of the (both insured and uninsured) population. The second is collection of detailed data during each individual clinic visit. The in-clinic research consists of a three phase approach. The first phase is the inventory phase, during which a data collection system was implemented in the participating clinics. Observational data generated from this system has been used to obtain a broad and comprehensive inventory of the health status and health care utilization of all the groups included in the HIF program. The AMC-CPCD focuses on the disease areas which are of greatest local medical and public health importance: infectious diseases, metabolic & cardiovascular diseases, and reproductive health. The second phase consists of more in-depth research focusing on indicator disease areas and the third phase consists of the introduction of new interventions related to preventable diseases.

Main findings of the inventory phase

Cumulative enrollment at the end of February 2008 was 36,579 in total. The mean number of enrolled family members is 4.3 in Kwara and 1.4 in Lagos. A total of 13,410 (laboratory) investigations, 45,818 clinical diagnoses, and 151,274 individual treatments were recorded. It is found that infectious diseases, metabolic diseases and antenatal care are the most frequent reasons for clinic visits. Other important observations include:

- Collection of quality (medical) data is still proving to be a challenge. Good-quality data are vital for the management and evaluation of the project.
- In Lagos it analysis has shown that adults are the most frequent users of the health care services. This is different from the conventional utilization distribution and could be a signal for adverse selection
- Patients presenting with fever of unknown origin are too often presumptively diagnosed with and treated for malaria / typhoid fever.
- The most frequent pediatric diagnoses are diarrhea and respiratory infections.
- Metabolic diseases are frequently diagnosed. Diabetes mellitus is relatively more frequent in Lagos compared to Kwara.
- Antenatal care is a frequent reason for clinic visits.

Recommendations

The findings of the AMC-CPCD in the first year of the HIF program in Nigeria lead to the following recommendations to the HIF:

For the organizational management the following recommendations are given:

- Improve the collection and management of data. Good-quality data are vital for the management and evaluation of the project.
    - Coding of investigations, diagnoses, and treatments
    - Cross-checks between enrollment and utilization datasets
    - Build-in checks in the data-entry system, e.g. dates, correct IDs, to minimize the risk of data entry errors
    - Better registration of lapsed contracts, terminations and renewals of insurances
- Investigate 'adverse selection' in Lagos. With the currently available data it can not be excluded that 'adverse selection' is taking place in Lagos with preferential enrollment of sick(er) individuals. This is evidenced by the remarkably low number of enrolled subjects per family and the considerably higher number of clinic visits per subject in Lagos compared to Kwara. This threatens the sustainability of the program in Lagos. This topic should receive considerable attention; the recruitment strategies in Lagos should be adjusted to avoid adverse selection as much as possible. The strategy should be to enroll whole groups of people at once, or at the least whole families.
- Investigate reasons for lapsed and terminated contracts. A large percentage of subjects both in Kwara and in Lagos do not renew their insurance in the first two months of the second year of the program.

For data collection and management the following recommendations are given:

- Register (causes of) deaths.
- Perform case note-investigations regularly (and randomly). This should be part of routine M & E (Monitoring & Evaluation) of the healthcare providers by PharmAccess (PAI). This allows for i) monitoring of progress in the improvement of documentation of provided healthcare, ii) monitoring of the quality of the data entered into the project database, and iii) it provides some degree of protection against fraud where non-existing provided care is claimed.

For clinical practice the following recommendations are given:

- Encourage the use of investigations to confirm diagnosis. This applies to routine laboratory investigations, but also to microbiology tests, serologic screening and physical diagnostics like X-rays. We acknowledge that indiscriminate testing should be avoided, but the current underutilization of the laboratory facilities can only result in misdiagnoses and therefore inadequate treatment of disease. The low utilization-rate of the diagnostic facilities also hinders the laboratory analysts from gaining adequate experience with testing methods, which contributes in a negative way to the vicious circle of basing clinical management on presumptive diagnoses. The very frequent presumptive diagnosis of "malaria / typhoid", which is often followed by empirical treatment for both diseases simultaneously, is the most prominent example of this practice.
- Emphasize protocollized treatment. Treatment for a specific disease differs greatly between healthcare providers, and even between patients for the same healthcare provider. However, it is unlikely that the patient population and/or disease organisms are much different. The healthcare providers should make much more use of protocols for the diagnosis and treatment of certain conditions. This is accepted good clinical practice and should be more vigorously enforced.

- Formularies of the pharmacies should be updated and standardized. Sometimes archaic and/or substandard treatments are used.
- Demand acceleration for HIV/AIDS treatment and care in upgraded primary/secondary clinics.

Planning for in-depth studies

The second phase of the AMC-CPCD will focus on the disease areas which are of greatest local medical and public health importance: infectious diseases, metabolic & cardiovascular diseases, and reproductive health.

Infectious diseases

- Malaria research will focus on making a proper laboratory-assisted diagnosis, this research will be performed in the larger setting of management of patients presenting with fever of unknown origin.
- Tuberculosis appears to be relatively rare, and is often managed in designated TB treatment centers. Therefore, in our in-depth studies we will only focus on screening / diagnosing TB and on the indiscriminate use of antibiotics with antituberculous activity for other diseases.
- For HIV-1 infection the same applies, it is relatively rarely diagnosed, and treatment is done outside the HIF Nigerian program in designated treatment centers. For HIV-1 the focus will be on improved screening of sentinel groups, like pregnant women presenting for antenatal care. There is a need to investigate further the quality of HIV/AIDS treatment and care given.
- Research into infant and childhood diarrhea will be extended with infant and childhood respiratory diseases as these infections also represent a heavy burden of disease in children. The research will focus on diagnostic and therapeutic practices.
- Vaccine-preventable diseases are rarely diagnosed in this cohort; the application of vaccine other than tetanus shots is also rarely captured in the database. From the current data it is unclear if this low number of cases is because of a true low incidence of disease, or because of problems with adequate diagnosing of these diseases and capture of vaccinations in the database. Initially we will integrate our research into vaccine preventable diseases in the research into antenatal care.

Metabolic diseases

- Metabolic diseases like diabetes mellitus and hypertension are frequently diagnosed. The in-depth research into metabolic diseases will go ahead as originally planned.

Maternal and pediatric issues

- Screening for and diagnosis of sexually transmitted diseases is rarely done. Apparently screening is only done as part of antenatal care for pregnant women, and not even in all pregnant women. The in-depth studies will therefore, just as for HIV-1, focus on appropriate screening methods in the setting of antenatal care.
- Family planning was originally short-listed as focus for further in-depth studies. Family planning is currently an integral part of the household survey of the AIID.
- As expected, pregnancy rates are high. The in-depth research into antenatal care for both women and neonates will go ahead as originally planned.
- The disease cluster “anemia, malnutrition, enteric parasites in children” will be added to the list of indicator diseases.

Background

The 'stichting Health Insurance Fund' (HIF) aims to improve access to comprehensive health care by making health insurance affordable to low and middle income groups in Africa. The HIF provides targeted subsidies to stimulate demand for prepaid health schemes and make it more accessible. Beneficiaries are always expected to pay part of the premium themselves. The overall objective of the HIF is to increase access to quality basic health care, including HIV/AIDS treatment and care, for people with a low and middle income in Sub-Saharan Africa through the provision of private health insurance and through this support MDGs 1 and 6: eradicate extreme poverty and hunger and combat HIV/AIDS, tuberculosis, malaria and other major diseases.

Through the HIF program, primary and limited basic secondary health care services, as well as a list of registered and approved medications, are provided. This includes primary and out-patient care, including consultation with a general medical practitioner; laboratory investigations; provision of prescribed drugs and diagnostic tests; preventive care including immunization; consultation with specialists; hospital care in a standard ward; eye-examination and -care; minor surgery; pre and post natal care and delivery; and voluntary counseling and testing for HIV. In Nigeria monitoring and provision of antiretroviral drugs is implemented through the public healthcare system.

AMC-CPCD will continuously monitor the quality of the provided health care. This is done by collecting and analyzing detailed clinical data for the indicator diseases regarding disease incidence & prevalence, diagnostic & therapeutic practices of the participating health care providers, treatment outcome, disease progression and complications. The main objectives of the operational research of the AMC-CPCD are i) to demonstrate that the HIF program indeed leads to improvements of the provided health care for the participants, and ii) to help HIF and partners to optimize the provided health care in the program. To this end AMC-CPCD will produce yearly reports with recommendations to improve the screening, diagnostic and treatment strategies for the indicator diseases.

The research started with an inventory phase, during which a data collection system has been implemented in the participating clinics. These data are vital for the HIF project as a whole as these data are necessary for administrative and accountability purposes. These observational data have been used in the current analyses to obtain a broad and comprehensive inventory of the health status and health care utilization of all the groups included in the HIF program. We estimated that this initial phase would take about a year.

AMC-CPCD will use these data as starting point for further in-depth research. The AMC-CPCD will focus on the disease areas which are of greatest local medical and public health importance: infectious diseases, metabolic & cardiovascular diseases, and reproductive health. The additional in-depth studies on these indicator disease areas will be conducted at selected clinics. Depending on the findings during the inventory phase of the project, the initial list of indicator disease areas may need to be adjusted. Eventually, during the later phases of the HIF program, the focus of the AMC-CPCD research will be extended to optimize the provided health care. This will be done in collaboration with the local providers by improving and modernizing existing prevention and treatment programs and/or by introducing new therapeutic and prevention interventions in the clinics.

Methods

Study objectives

In the inventory phase the AMC-CPCD has used the observational data to obtain a broad and comprehensive inventory of the health status and healthcare utilization of all the groups included in the HIF program in Nigeria. Furthermore, the diagnostic and therapeutic medical practices of the contracted health care providers have been evaluated by AMC-CPCD.

All medical data routinely collected at all participating health care providers has been utilized for this broad survey of the state of health of the insured population and of the medical (both diagnostic and therapeutic) practices of the health care providers. The following predefined topics have been investigated from the inventory phase onwards and continue throughout the total duration of the HIF program for all insured subjects from all participating clinics:

- What is the frequency and nature of the actual health care utilization?
- What are the incidence & prevalence of all diagnosed illnesses / conditions?
- Is the medical package composition appropriate and comprehensive?
- Which diagnostic strategies are employed by the health care providers?
- What are the instituted treatments?
- What is the rate and specific causes of deaths?
- Which subgroups (based on demographic characteristics) are at increased risk for health problems?

In preparation for the second phase more in-depth analyses were performed for the set of anticipated indicator disease areas. Based on the site surveys performed and on the discussions with the health care providers in Nigeria, the initial list of indicator disease areas consists of the following:

- Infectious diseases
    - Malaria
    - Tuberculosis
    - HIV-1 infection
    - Infant and childhood diarrhea
    - Vaccine-preventable (childhood and adult) diseases
- Metabolic & cardiovascular
    - Hypertension
    - Diabetes mellitus
- Reproductive health
    - Sexually transmitted diseases (both males and females)
    - Family planning: use of contraceptives, unwanted pregnancies
    - Maternal health: complications during pregnancy, during and after delivery
    - Neonatal health: neonatal morbidity and mortality

For these indicator disease areas the following research questions were addressed:

- What are the incidence / prevalence of these indicator diseases in the target population?
- How are these diagnoses established?
- What is the disease stage / severity at the time of diagnosis?
- What are the predictors / risk factors for being diagnosed with these diseases?
- How are these diseases managed clinically?
- What is the outcome of the treatment?

- Which (sub)groups are at increased risk for disease progression / unfavorable treatment outcomes?

The in-depth studies on the indicator disease areas will be conducted at selected clinics. Currently, there are 19 clinics (6 in Kwara State, 13 in Lagos) involved in the Nigerian HIF project. Two to four large clinics, from both the urban and rural setting, will be selected based on local capacity, willingness to participate, the present standard of delivered health care, and the number of reported cases in the first year of the program.

Data collection & statistics

The HIF program provides for the collection of detailed information to reduce the possibilities for fraud, to enhance administrative control, and to improve the quality of medical data capturing. PharmAccess, in collaboration with Hygeia, is responsible for managing this database. The database contains information on the recruitment of subjects into the health insurance scheme, and information on the frequency and reasons for visits to the local healthcare providers. Collection of data on clinical status and disease outcomes is currently not (yet) provided for in the HIF program.

The CPCD is using this database to obtain a broad and comprehensive inventory of the health status of the participants in the insurance scheme, and on the diagnostic and treatment practices of the local healthcare providers. Currently, the clinical data in the HIF Nigerian database are not yet ICD-10 coded (the process of ICD-10 coding is ongoing, but not yet complete). Therefore, we implemented our own coding scheme to classify the 13,410 (laboratory) investigations, 45,818 clinical diagnoses, and 151,274 individual treatments.

Descriptive statistics are calculated and tabulated for enrollment numbers, family composition, demographic characteristics of the enrollees, overall rates of healthcare consumption, specific reasons (diagnoses) for contacts with healthcare providers. Separated tabulations will be performed for the designated ‘indicator diseases’. Risk factors for high rates of healthcare consumption, or specific clinical conditions, will be investigated using univariate and, when applicable, multivariate regression analyses. Diagnostic and therapeutic practices will be described and compared between healthcare providers. All analyses will be done separately for each separate geographic location: Kwara versus Lagos. When appropriate the analyses will be further stratified for gender, age, or other demographic characteristics.

Results

Database

At the time of analysis the HIF Nigerian database contained data on 36,579 individuals, who had had 43,547 contacts with the local health care providers, who performed 13,410 (laboratory) investigations, made 45,818 clinical diagnoses, and prescribed 151,274 individual treatments. There were 23,354 person years of follow-up, 19,738 pyr in Kwara, 3,615 pyr in Lagos.

Enrollment

The period from January 2007 has been analyzed, when the HIF Nigerian program started enrollment, until February 2008. A total of 36,579 individuals had been enrolled in that period (Figure "Enrollment-1", left panel).

Cumulative enrollment at the end of February 2008 was 30,052 subjects in Kwara and 6,521 subjects in Lagos. As six enrolled individuals were assigned HCHP-numbers that did not contain an 'area code', these figures do not add up to 36,579.

Enrollment in Kwara was encouraging.. A large and well-coordinated effort at the start of the program resulted in a recruitment of close to 11,000 subjects in the first 2 months alone. In March 2007 no new enrollments took place because there was no campaign in Kwara that month. In all following months there was a near-linear increase of the cumulative number of new enrollments in Kwara.

Enrollment in Lagos lagged much behind enrollment in Kwara. In mid-2007 the recruitment effort of Hygeia in Lagos was stepped up, which resulted in slightly higher monthly recruitment rates. However, with 6,521 subjects enrolled at the end of February, 2008 was still below the originally projected figures for Lagos.

Figure "Enrollment-1": Cumulative & current enrollment, lapsed contracts

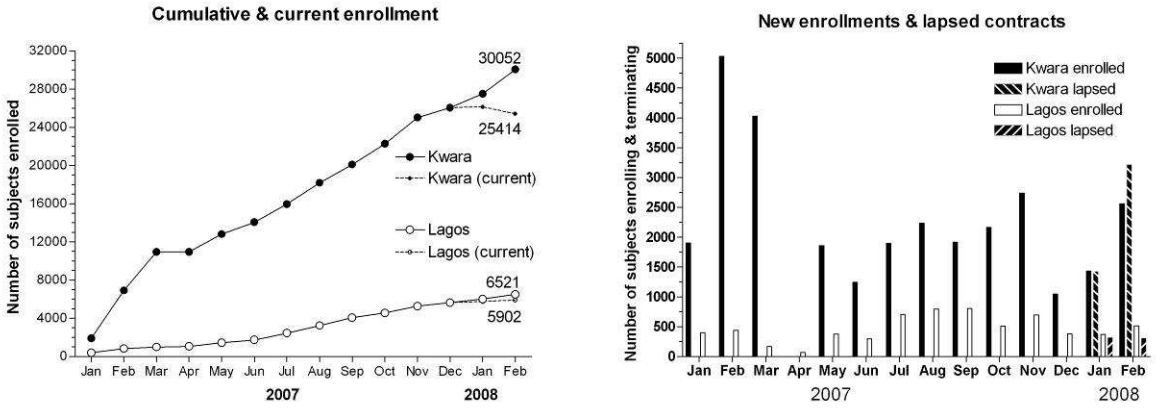


Figure legend. Left panel: "Cumulative enrollment" included all subjects ever to enroll in the Nigerian HIF program. The "current enrollment" is adjusted for lapsed contracts. Right panel: note that in March 2007 the program was not open for new enrollments in Kwara.

All enrolled subjects paid their insurance premium for 12 months in advance. As the first subjects enrolled in January 2007, the first renewals of the insurance were due in January 2008. Because not all subjects whose contracts lapsed have (yet) renewed their insurance, the numbers of subjects who are still insured in the HIF Nigerian program are leveling off. In the last month (February 2008) of the observation period the number of lapsed contracts in Kwara was actually larger than the number of new plus renewed insurances, causing a decline in the "current" number of subjects actually being insured. This is represented with the dashed lines in the left panel of Figure "Enrollment-1". The right panel of Figure "Enrollment-1" shows the absolute number of new enrollees and lapsed contracts per month.

In Lagos the number of lapsed contracts is offset by the number of newly recruited subjects. However, in Kwara the number of lapsed contracts is larger than the number of newly recruited subjects, which in the first months of 2008 has resulted in a slight drop of the total number of subjects covered by the insurance scheme. In Kwara the number of insurances that were due for renewal was 1,901 in January and 5,031 in February. The numbers of lapsed contracts in the same months were 1,425 in January and 3,214 in February, which is 75% and 64% of the total number of insurances due for renewal. Not all insurances that were due for renewal and that were not terminated, were actually renewed. For this analysis we used an optimistic scenario and considered these insurances to be renewed. The official number of renewed insurances is much lower, with 930 renewed insurances in Kwara and 80 in Lagos. Due to issues with lag times in updating the enrollment database by Hygeia, it is not unlikely that some of the lapsed contracts will actually be renewed in the near future. Therefore, no solid conclusions on the drop-out rates after the first year can be made as of yet.

The left panel of Figure "Enrollment-2" shows the cumulative number of subjects that were enrolled per participating clinic. In Kwara there are two large clinics, Ola-Oluwa and Shonga, each serving well over 10,000 subjects. The primary purpose of the Bacita clinic in Kwara is to serve as a referral center for Ola-Oluwa and Shonga, so therefore not many subjects use Bacita as their primary source of health care. There were obvious differences between hospitals in the relative numbers of subjects whose contract had lapsed and/or was not (yet) renewed (see Figure "Enrollment-2", right panel). Note that because for some hospitals the first subjects were recruited after February 2007, there are not yet any subjects in these hospitals which insurance is due for renewal (e.g. RAU Bacita, see Appendix "B1 – Enrollment" for the absolute and cumulative number of subjects enrolling per clinic per month).

We investigated if subjects whose insurance had lapsed had re-entered the program under another name. We coupled recently lapsed contracts with newly registered insurances using the following data points: calendar period during which the contract lapsed and new insurance was taken, geographic location, gender, date of birth, and family composition. Because of the large numbers involved, many people share the same date of birth, but it is far less likely for all individual members of two families to share the same date of birth. We could not match a single pair of families, one of which that had recently terminated their insurance and the other having just entered the program where two or more family members shared the exact same date of birth.
In Lagos many more clinics provide healthcare for the subjects enrolled in the HIF Nigerian program, resulting in far lower numbers of subjects per clinic. The three largest clinics are Chrystal, R-Jolad, and May with 2,561, 1,038, and 977 enrolled subjects, respectively.

Figure "Enrollment-2": Cumulative enrollment & lapsed insurance per clinic

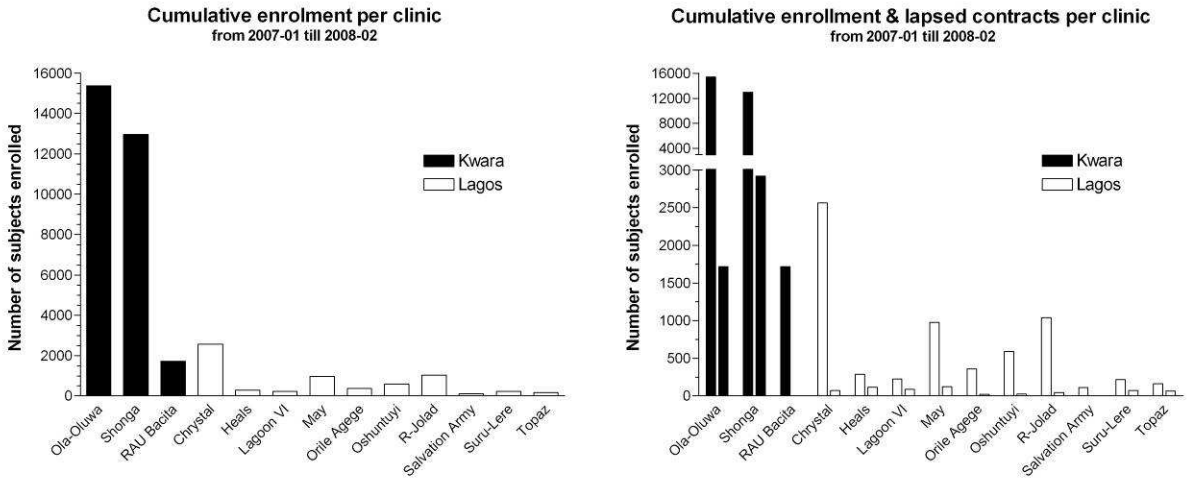


Figure legend. Left panel: it was not possible for subjects to register with the Bacita clinic in the first part of the program. Right panel: for each clinic two bars are shown. The left bar represents the cumulative number of enrolled subjects per clinic (which is the same as in Figure "Enrollment-3"). The right bar represents the cumulative number of subjects whose contract had lapsed. Note that the y-axis has been spit in two sections with vastly different scales, so the bars representing the cumulative number of subjects enrolled in Ola-Oluwa and Shonga are not proportional to all the other bars.

Demographics

Figure "Demographics-1" shows the absolute and relative numbers of adults, children and babies per state. Adults are over 16 years of age, children are between 1 and 16 years, and babies are less than 1 year old. In Lagos there was a far lower percentage of children (12.2%) and babies (2.6%) compared to Kwara (35.8% and 3.1%, respectively). The median age at enrollment was lower in Kwara compared to Lagos: 22.7 (interquartile range [IQR] 7.8 – 37.2) years and 36.4 (24.9 – 50.5), respectively. This reflects the larger proportion of children and babies in Kwara.

Figure "Demographics-1": Adults, children and babies

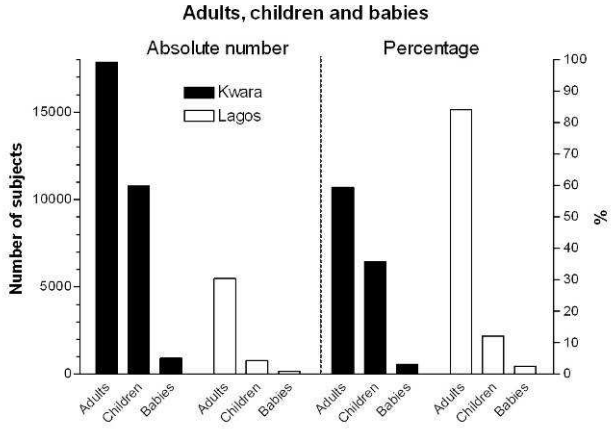


Figure legend. The bars in the left panel represent the absolute number of adults, children and babies enrolled in Kwara (black bars) and Lagos (white bars). The bars in the right panel represent the proportion for each age category compared to the total population in Kwara (black bars) and Lagos (white bars).

The proportion of elders (over 50 years of age) was 12.3%. There were many more elders in Lagos (26.1%) compared to Kwara (9.3%) as a proportion of the total insured population. This difference between the two states is only partly driven by the larger proportion of children and babies. When looking at the proportion of elders in the adult population only (instead of the proportion of elders in the entire population), there remained a deficit of elders in Kwara (15.6%) compared to Lagos (31.1%). It is possible that a considerably lower life expectancy in Kwara is responsible for the low proportion of elders in Kwara, although alternative contributing factors cannot be excluded.

The demographic trees for both Kwara and Lagos are shown in Figure "Demographics-2". The Kwara demographic tree, although slightly erratic and showing some overrepresentation of women, is very similar to the true demographic tree of the population in Kwara. However, the demographic tree of the insured population in Lagos is extremely thin, it is clearly lacking in young children and infants. Furthermore, like in Kwara only much more pronounced, there are many more women enrolled than men.

In Kwara the mean age of newly enrolled subjects was approximately 25 years during the entire period of observation. However, in Lagos the mean age at enrollment decreased from approximately 38 years in the first months of the program to approximately 34 at the end of 2007.

Figure "Demographics-2": Demographic trees of Kwara and Lagos

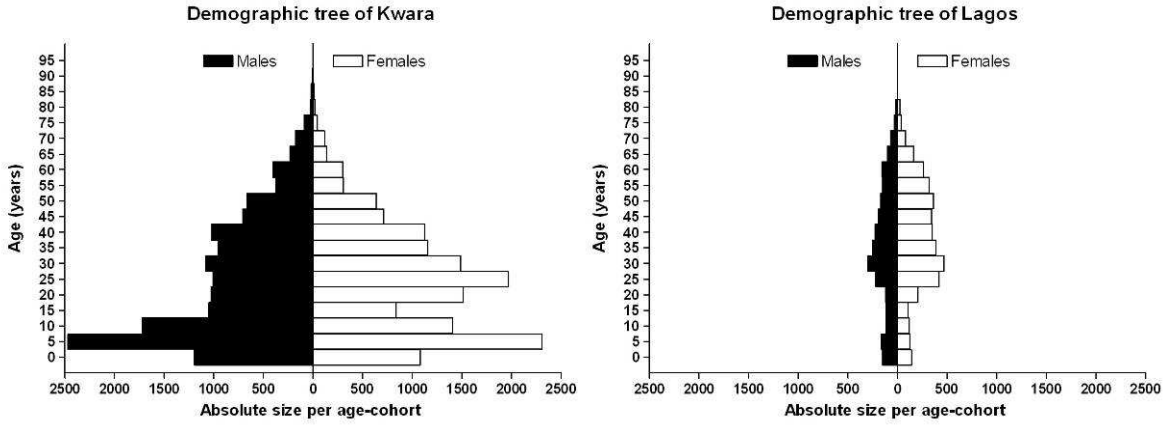
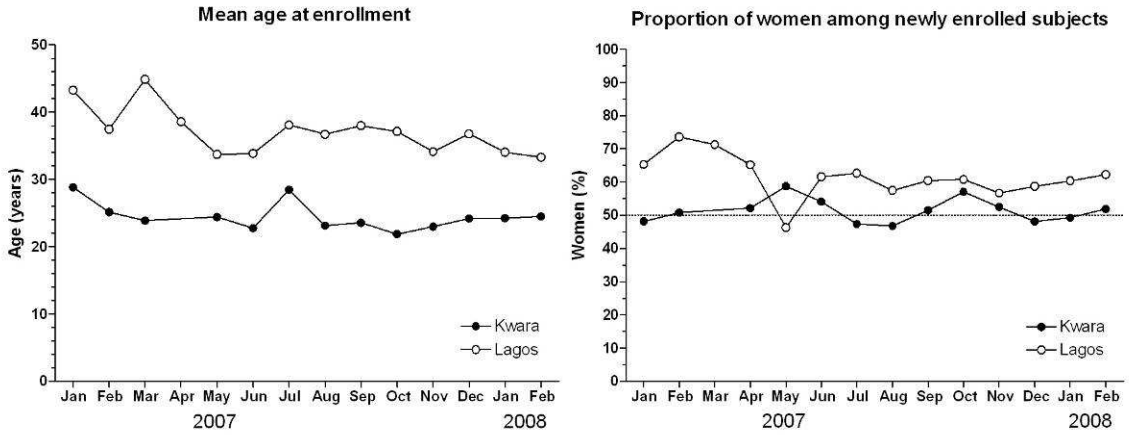


Figure legend. The left panel displays the demographic tree for the Kwara population, the right panel displays the demographic tree for the Lagos population. The black bars extending to the left represent the male population. The white bars extending to the right represent the female population. The size of each horizontal bar is proportional to the absolute number of subjects in that particular age category. The scale (x-axis) for Kwara and Lagos are equal.

In Kwara there were no changes during the first year regarding the proportion of males and females that enrolled in the program (Figure "Demographics-3", right panel), which was close to the 50%-mark during the entire observation period. In Lagos, there was a clear "excess" of women throughout the whole first year of the program. However, there seems to be a trend towards more equal numbers of males and females enrolling in the last quarter of 2007.

Figure "Demographics-3": Mean age of & proportion of women among new enrollees



legend. Left panel: mean age of newly enrolled subjects. Right panel: proportion of women among newly enrolled subjects. The horizontal dashed line at the 50%-level in the right panel represents the point where there are equal numbers of new males and females enrolling in the program.

Family-composition

The 36,579 enrolled were clustered into 11,733 families. Please note that the word "family" does not necessarily imply that all members of a family or "household" have enrolled into the program. Furthermore, some "extended families" have been enrolled with the same family-identifier (the largest family in Kwara has 41 members, probably consisting of several households). Therefore, the below mentioned statistics should not be interpreted as the true household composition. The number of subjects enrolled per family is shown in the left panel of Figure "Family-1." There are large differences between Kwara and Lagos with respect to the number of subjects enrolled per family. The mean number of enrolled family members is 4.3 in Kwara and 1.4 in Lagos. These means have been calculated for the total number of "subjects" enrolled into the HIF Nigerian project, not for the total number of "families". In Lagos 79.8% of families consist of a single subject, compared to only 28.3% in Kwara. In Kwara 21.3% of families had 7 or more insured family members, while in Lagos this was only 0.27%.

Figure "Family-1": Family size

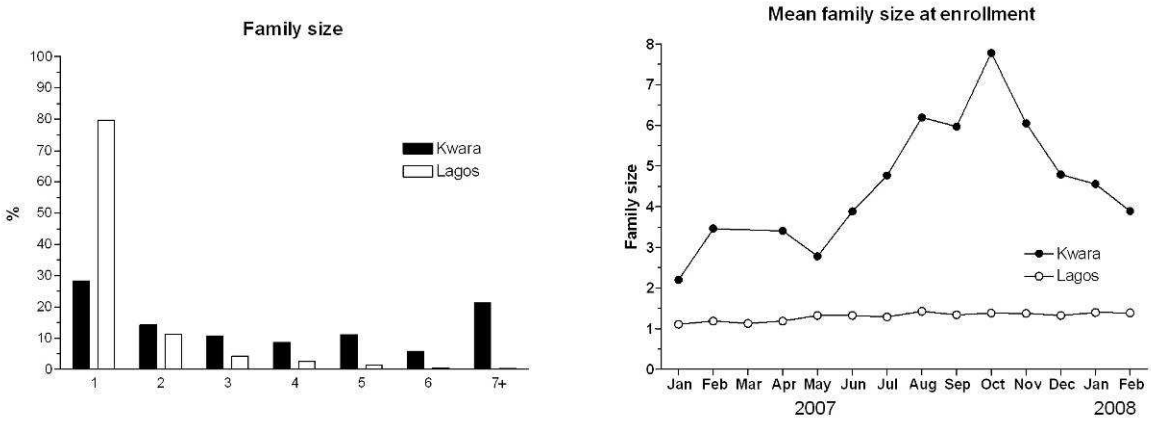


Figure legend. Left panel: all families with more than 7 members have been grouped in the bar marked "7+". Right panel: this panel shows the mean number of subjects enrolling at the same time per family. This analysis disregards any additional family members enrolling at a later time point.

Trends over time in the average size of a new family enrolling are shown in the right panel of Figure "Family-1". New family members enrolling at a later time point are disregarded in this analysis. In Kwara the mean size of a family enrolling was 2.2 at the start of the HIF Nigerian program in January 2007. It subsequently increased steadily until it peaked in October 2007 at 7.8 members per newly enrolled family. After that the mean family size steadily decreased until it was 3.9 in February 2008, which is the last month in this analysis. As of yet we have no explanation for the observed trends.

The pattern was remarkably different in Lagos. There were hardly any changes in mean family size during the entire 14 months of observation. At the start of the program the mean family size was 1.1, which seemed to increase ever so steadily but slowly to 1.4 in February 2008.

The left panel of Figure "Family-2" shows the number of adults, children (1-16 years old), and babies (less than 1 year old) per state. There were big differences between Kwara and Lagos with respect to the number of adults, children and babies. In Kwara 33% of families had only one adult enrolled, while in Lagos this was 84%. In Lagos less than 3% of families contained 3 or more adults, while in Kwara this was 38%. In the families with 3 or more adults there was only a slight excess of adult women, therefore indwelling adult children and/or (grand)parents are a more likely explanation than polygamy. In Kwara 48% of families had not enrolled any children, while this was almost 90% in Lagos. There were hardly any families with 3 or more children in Lagos, while this was 24% in Kwara.

In Kwara 11% of families enrolled 1 or more babies, while this was only 3.4% in Lagos. This does not necessarily indicate a lower fertility rate in Lagos, or a higher rate of twin births in Kwara. Actually the percentage of babies from the total insured population is almost equal in both states: 3.14% in Kwara and 2.56% in Lagos. The higher number of babies per family in Kwara is largely driven by the on average higher number of adults per family in Kwara.

Figure "Family-2": Demographic characteristics

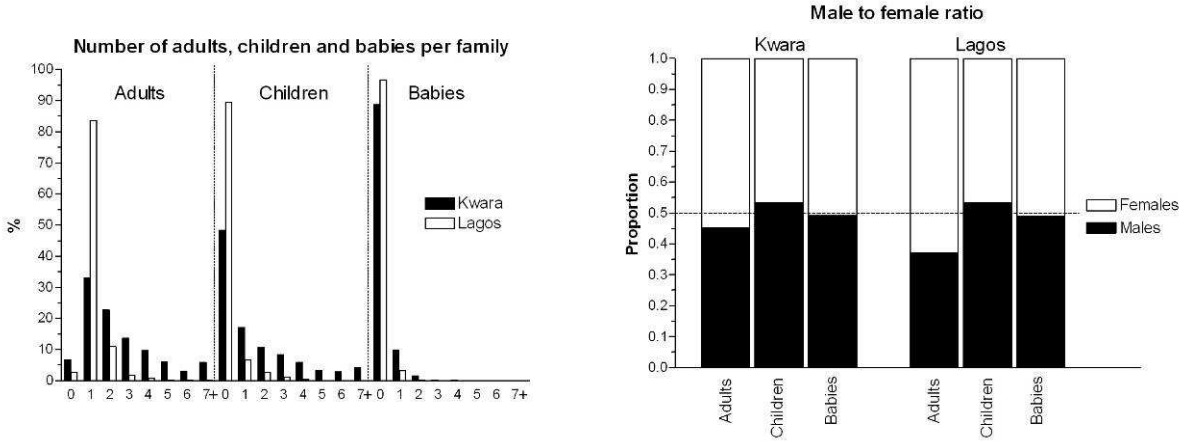


Figure legend. Left panel: group-sizes have been truncated at 7. Adults are individuals aged over 16. Children are those aged 1 to 16 years. Babies are less than 1 year old. Right panel: the dashed line at the level of 0.5 (50%) represents the point where there are equal numbers of males and females. Black bars extending higher than this dashed line represent an "excess" of males, and vise versa. Adults are individuals aged over 16. Children are those aged 1 to 16 years. Babies are less than 1 year old.

There was no evidence of preferential enrollment of males in the program: of the total population 53% was female and 47% male. In Kwara this was true for adults, children and babies (Figure "Family-2", right panel). The only exception was that in Lagos the number of adult males was far less than the number of adult females, while there were no differences in numbers of male and female children and babies. However, because there are so few children enrolled in Lagos, there are many more women the overall ensured population in Lagos. This should not be viewed as evidence for a surplus of females per family (polygamy) in Lagos. Instead it is caused by a large number of families consisting of single adult females. This most probably reflects the biased composition of the target groups: the lady mechanics and market women.

Sequential enrollment

We investigated the frequency with which new family members enrolled after the first family member(s) were enrolled. This analysis is limited to families with 2 or more family members enrolled for obvious reasons. Table "Sequential-1" shows that nearly 11% of families with 2 or more members enrolled in 2 or more enrollment steps. For this analysis the sequential enrollment of newborn babies is ignored.

Table "Sequential-1": Sequential enrollment of family members

	Total number of family members							
Number of sequential enrollments	**Size of the family**							
	1	2	3	4	5	6	7+	All family sizes ≥ 2
	Nigeria							
1	*5769*	1403 (91)	843 (89)	651 (90)	786 (94)	381 (89)	1260 (84)	5324 (89.3)
2	-	128 (8)	96 (10)	69 (9)	49 (6)	40 (9)	215 (15)	597 (10.0)
3	-	-	4 (0.4)	4 (0.6)	6 (0.7)	4 (1)	22 (1.5)	40 (0.67)
4	-	-	-	0 (0)	1 (0.1)	1 (0.2)	2 (0.1)	4 (0.07)
	Kwara							
1	*1975*	922 (93)	685 (92)	550 (92)	727 (94)	361 (89)	1252 (84)	4497 (89.9)
2	-	73 (7)	55 (7)	50 (8)	43 (5.4)	38 (9)	210 (14)	469 (9.4)
3	-	-	3 (0.4)	2 (0.3)	5 (0.7)	4 (1)	22 (1.5)	36 (0.72)
4	-	-	-	0 (0)	0 (0)	1 (0.3)	2 (0.1)	3 (0.06)
	Lagos							
1	*3793*	481 (90)	158 (79)	101 (83)	59 (88)	20 (91)	8 (62)	827 (86.2)
2	-	55 (10)	41 (21)	19 (16)	6 (9)	2 (9)	5 (38)	128 (13.3)
3	-	-	1 (0.5)	2 (1.6)	1 (1.5)	0 (0)	0 (0)	4 (0.42)
4	-	-	-	0 (0)	1 (1.5)	0 (0)	0 (0)	1 (0.10)

Table legend. Numbers represent the total number of families for each category. Numbers in brackets are column-percentages (each column adds up to 100%). The column marked 1 (families with one members) is only included as reference, and is not included in the final column marked "All family sizes ≥ 2". This analysis is done for the whole insured population in Nigeria (top), and repeated for Kwara (middle) and Lagos (bottom). The right-most column gives the overall numbers of families with a size greater or equal to 2 which members enrolled in 1, 2, 3, or 4 sequential steps.

There were no families in which case the family members enrolled in more than 4 separate enrollment steps. There was no clear trend for a higher number of sequential enrollments with larger family size, except for the very largest families. In Lagos there is some evidence of a trend were smaller families are more likely to sequentially enroll their individual members (see section on adverse selection).

Healthcare utilization

The top-left panel of Figure "Healthcare utilization-1" shows the number of clinic visits per patient per month. The weighted average number of clinic visits per patient per month for the entire Nigerian program is 0.157 visits per patient per month. There are large differences between Kwara and Lagos. The weighted average number of clinic visits in Lagos is more than twice that for Kwara: 0.280 versus 0.122. Because there are large differences in gender and age distribution between Kwara and Lagos we analyzed the data for the relevant sub-groups: adult males, adult females, children, and babies (see top-right and bottom-left panels of Figure "Healthcare utilization-1". For all these sub-groups there were more clinic visits per patient per month in Lagos compared to Kwara. The weighted average number of clinic visits for Kwara males and females were 0.100 and 0.180, respectively, while they were 0.253 and 0.318, respectively, for Lagos males and females. For children the same pattern emerged: 0.079 clinic visits per months for Kwara children and 0.179 for Lagos children. Because of the low numbers of babies in Lagos (a total of 167 babies have so far been enrolled in the entire program) it is difficult to get a reliable estimate of their number of clinic visits. In Kwara babies had an average of 0.195 clinic visits per month, while in Lagos this was 0.235. There are no signs for any seasonal trends.

Figure "Healthcare utilization-1": Number of clinic visits per patient per month

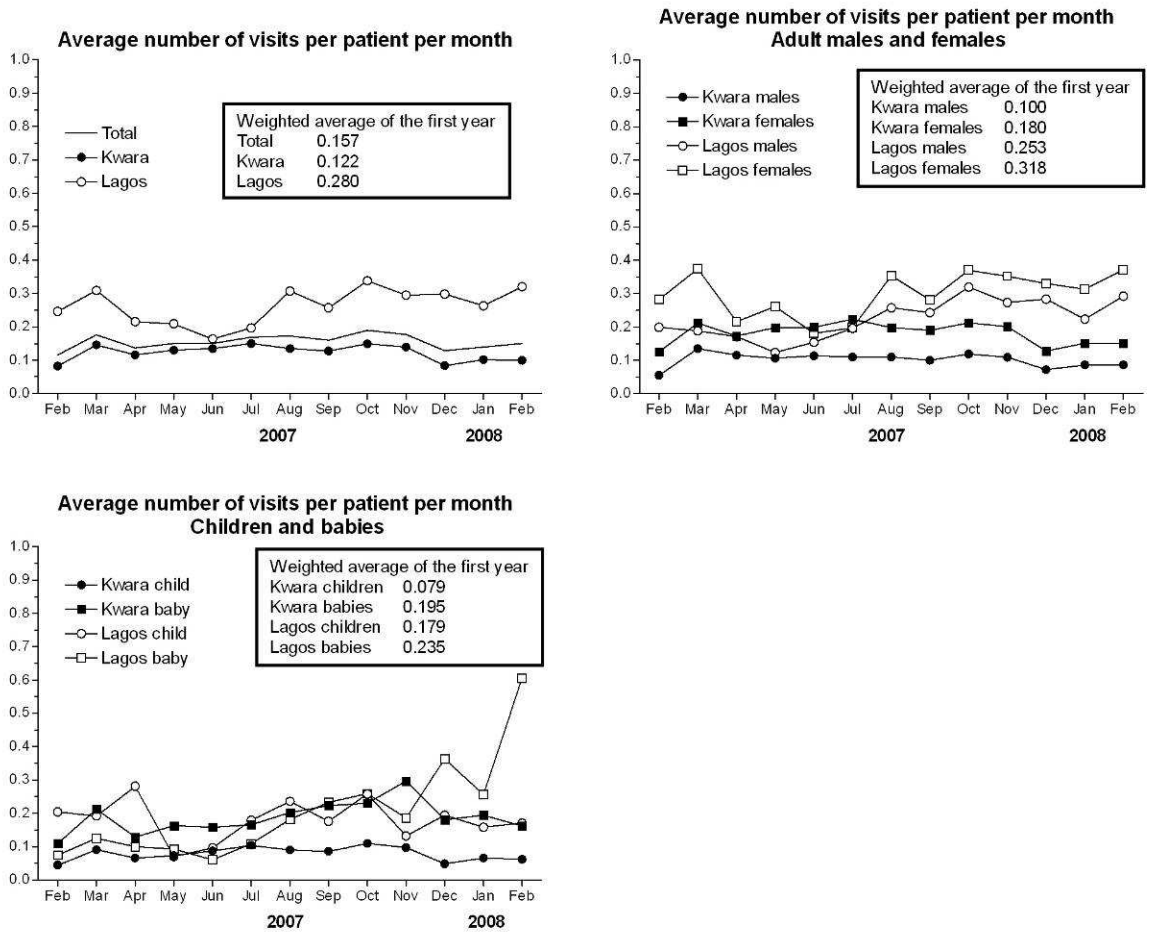


Figure legend. For each month the number of currently enrolled patients was used to calculate the visit rates. Note that the curves are much more variable in the early months of the program because of the far lower number of enrolled patients in that period compared to the later months of the program. Top left panel: the solid line without symbols represents the average for Kwara and Lagos combined.

To further characterize the patterns of clinic visits we did a sub-group analysis. We selected all subjects that enrolled in the period from January till June 2007 and determined for these subjects the number of clinic visits per subject for the period July till December 2007. Therefore all these subjects have the same observation period of 6 months. There were 11,774 subjects in Kwara that enrolled in this period: 7,185 adults, 4,249 children, and 340 babies. There were 1,463 subjects in Lagos that enrolled in this period: 1,268 adults, 135 children, and 60 babies. Because of the low number of children and babies in Lagos, no solid conclusion can be made for these groups. These 11,774 subjects made a total of 13,997 clinic visits. Figure "Healthcare utilization-2" shows the number of clinic visits for all sub-groups. Fifty-three percent of adults, 66% of children, and, remarkably, 50% of babies did not have a single registered clinic visit during this 6-month period. Eleven percent of the adults and the babies and 4% of the children made 4 or more clinic visits in this 6 month period. These subjects together were responsible for 8,960 of the 13,997 clinic visits (64%).

Figure "Healthcare utilization-2": Number of clinic visits per patient in a 6 month-period

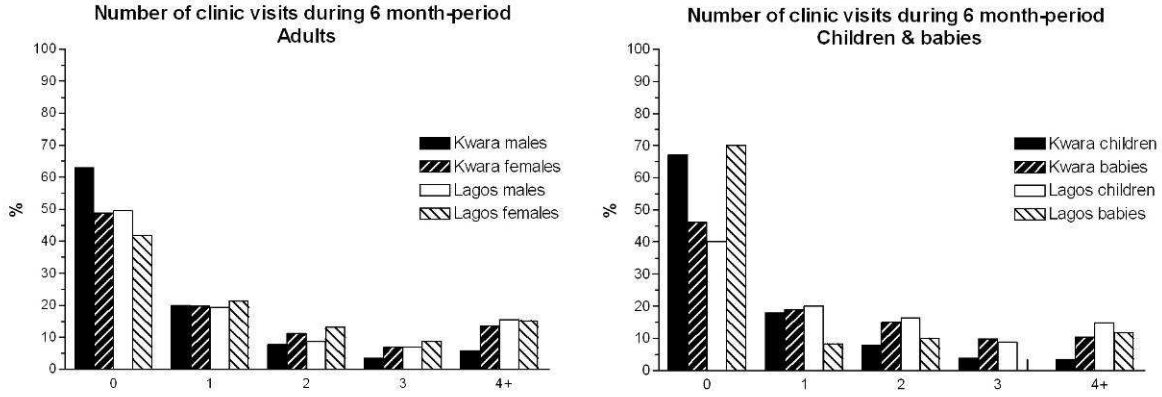


Figure legend. Sub-group analysis of all subjects that enrolled from January till June 2007. Healthcare utilization data are from July till December 2007. The categories on the x-axis represent the number of clinic visits an individual has made. All subjects that made more than 4 clinic visits are grouped in category "4+". The left panel shows the number of visits per adult males and females. The right panel shows the number of visits for children and babies. Note that there are only low numbers of children en babies from Lagos in this sub-group analysis.

Adverse selection

There are several clues that adverse selection might have taken place in Lagos. Compared to Kwara enrollment has been slow in Lagos (see Figure "Enrollment-1: Cumulative & current enrollment, lapsed insurance"). There is a much lower number of subjects enrolled per family in Lagos compared to Kwara (see Figure "Family-1"), with the majority of families in Lagos consisting of a single adult person. Although the average number of enrolled family members is lower, there is more sequential enrollment of family members in Lagos (see Table "Sequential-1: Sequential enrollment of family members"), and the members of the smaller families are even more likely to enroll sequentially than the members of the larger families. The demographic tree of Kwara is very unrepresentative for the Lagos population (see "Demographics-2: Demographic trees of Kwara and Lagos"). All demographic groups in Lagos have substantially higher rates of clinic visits compared to Kwara (see Figure "Healthcare utilization-1: Number of clinic visits per patient per month"). Although the Lagos population is roughly 1/6th of the insured population in Nigeria, they were responsible for 1/3rd of all diagnoses. Although it is expected that tuberculosis rates are higher in urban Lagos compared to rural Kwara, the observed tuberculosis incidence rate in Lagos of 6.1 cases per 1,000 pyr were much higher that what might have been expected.

Disease burden

During the period from February 2007 till February 2008 a total of 45,818 diagnoses were registered for all 36,579 subjects enrolled in the program: 30,813 diagnoses in 30,052 subjects in Kwara, and 14,994 diagnoses in 6,521 subjects in Lagos (note: 11 diagnoses in the database were linked to a patient registration number not containing an "area code"). Figure "Disease burden-1" shows the absolute and proportional number of diagnoses per age-category for Kwara and Lagos. These figures are much alike to the related graph "Figure "Demographics-1" which shows the number of enrolled subjects per age-group. In Lagos 16.7% of clinic visits yielded two or more diagnoses, with no differences between the sexes and between the age-categories. In Kwara, virtually all clinic visits yielded only a single diagnosis: note that this is an administrative issue.

Figure "Disease burden-1": Number of diagnoses per age-category

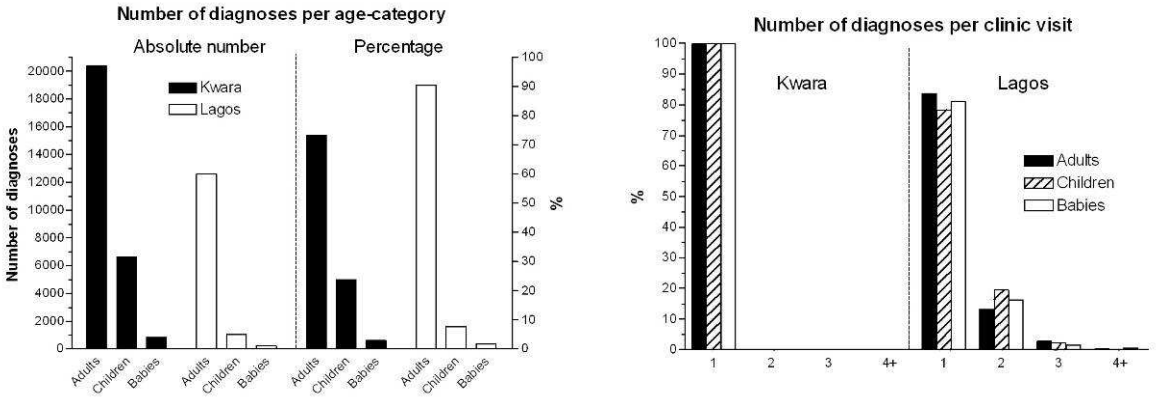


Figure legend. Left panel: the bars in the left panel represent the absolute number of diagnoses made for adults, children and babies enrolled in Kwara (black bars) and Lagos (white bars). The bars in the right panel represent the proportion for each age category compared to the total population in Kwara (black bars) and Lagos (white bars). Right panel: the categories represent the number of simultaneously made diagnoses per individual clinic visit. All clinic visits resulting in more than 4 diagnoses were grouped in the category "4+".

The specific diagnoses with the highest burden of disease, at least numerically, are shown in the following 3 Tables. Table "Disease burden-1" shows the 50 most frequently recorded diagnoses for the entire insured population in Nigeria (left column), Kwara (middle), and Lagos (right). This is a stratified analysis, therefore (the ranking of) the list of diagnoses is different for both locations. Note that percentages are calculated for the total number of recorded diagnoses (not people). Therefore, a single person can contribute the same diagnoses multiple times.

Overall, "malaria" was by far the most frequently recorded diagnosis in the program, and accounted for 25% of all recorded diagnoses. The other diagnoses that accounted for more that 5% of the total number of diagnoses were antenatal care (ANC), hypertension, (upper) respiratory tract infections, "follow up" visits (presumably for chronic diseases), and (osteo)arthritis. Comparing Kwara and Lagos there were several remarkable similarities and differences.

- Malaria, upper respiratory tract infections, (osteo)arthritis / musculoskeletal disorders and peptic ulcer disease were diagnosed equally frequently in Kwara and Lagos.
- ANC visits were much more frequent in Kwara, as was to be expected based on the demographic data of both insured populations.
- Enteric fever (typhoid) and metabolic diseases like (hypertension and diabetes mellitus) were more commonly diagnosed in Lagos.

- Remarkably absent from the "top 20" are TB (24th position in Kwara, 28th position in Lagos), and especially HIV (which is not even listed in the "top 50"). In Kwara 3 adult females, a single male, and 4 minors were reported HIV-seropositive, in Lagos 2 adult females and 2 males were reported to be HIV-seropositive.

Note that demographic differences between Kwara and Lagos have not been accounted for in this analysis and may explain some of the observed differences.

Table "Disease burden-2" shows the 50 most frequently recorded diagnoses for the adult populations in Kwara and Lagos, stratified by gender. Because adults make up the vast majority of the enrolled population Lagos the numbers change little here. But compared to the previous analysis some results shifted. With the children and babies excluded, hypertension was now equally frequent diagnosed in Kwara compared to Lagos. However, there remained more diagnoses of diabetes mellitus en enteric fever (typhoid) in Lagos compared to Kwara. In the adult population peptic ulcer disease was diagnosed more often in Kwara.

Pregnancy-related clinic visits make up a large proportion of the "diagnoses". As pregnancy is not a "disease" but contributes heavily to the denominator (total number of diagnoses), pregnancy was ignored (censored) in the analysis comparing males and females. The comparison of both genders has been done stratified for the Kwara and Lagos populations, therefore (the ranking of) the list of diagnoses is different for both locations. Note that also for this table percentages are calculated for the total number of recorded diagnoses (not people). Therefore, a single person can contribute more than one diagnosis and even the same diagnoses multiple times.

Comparing males and females, diabetes mellitus and injury / trauma appeared to more common in males. Remarkably, urinary tract infections were reported more often in males in both locations. Malaria was significantly less often diagnoses in males in Kwara: we speculate that high pregnancy rates in Kwara contribute to this trend. There were no other high-frequency diseases (defined as >1% of total number of diagnoses) that were much more common in women.

Table "Disease burden-3" shows the most frequently recorded diagnoses for children and babies in Kwara and Lagos. The comparison of Kwara and Lagos populations has been done stratified for children and babies, therefore (the ranking of) the list of diagnoses is different for both age-categories. Note that also for this table percentages are calculated for the total number of recorded diagnoses (not children/babies). Therefore, a single child/baby can contribute the same diagnoses multiple times.

In children malaria is by far the most frequently recorded diagnosis, closely followed by (upper) respiratory tract infections. Together these two diagnoses make up more than half of all recorded diagnoses in children. Enteric fever is remarkably more often recorded as a diagnosis in children in Lagos compared to Kwara: we expect this to be related to diagnostic practices. Anemia was remarkably rarely recorded, and so were parasitic infections: again this is probably underreported because of local diagnostic practices. As was to be expected (hoped) only a few diagnoses of vaccine-preventable diseases were recorded: a total of 38 cases of measles, almost all recorded in Kwara.

In babies malaria and (upper) respiratory tract infections together are also accountable for about half of all recorded diagnoses. Whereas in children in Lagos there were more (upper) respiratory tract infections, in babies the pattern was reversed. Because of the low number of babies in Lagos this can be a statistical fluke. (Gastro)enteritis was also much less frequent in Lagos, but again, this is based on low numbers of events.

Table "Disease burden-1": Most frequently reported diagnoses

	Nigeria			Kwara			Lagos		
	Diagnosis	**n**	**%**	**Diagnosis**	**n**	**%**	**Diagnosis**	**%**	**%**
1	Malaria	11462	25.02	Malaria	7624	24.74	Malaria	3833	25.56
2	ANC	4802	10.48	ANC	4266	13.84	Hypertension	1672	11.15
3	Hypertension	4031	8.80	Follow up	3173	10.30	(U)RTI	1216	8.11
4	(U)RTI	3770	8.23	(U)RTI	2553	8.29	Enteric fever	802	5.35
5	Follow up	3633	7.93	Hypertension	2357	7.65	(Osteo)arthritis	588	3.92
6	(Osteo)arthritis	1634	3.57	Enteritis	1081	3.51	ANC	536	3.57
7	Pain	1329	2.90	(Osteo)arthritis	1045	3.39	Follow up	460	3.07
8	Peptic ulcer dis.	1260	2.75	Pain	909	2.95	DM	444	2.96
9	Enteritis	1219	2.66	Peptic ulcer disease	867	2.81	Pain	420	2.80
10	Enteric fever	1188	2.59	Cellulitis/dermatitis	460	1.49	Peptic ulcer dis.	392	2.61
11	Myalgia	800	1.75	Myalgia	419	1.36	Myalgia	381	2.54
12	DM	738	1.61	Delivery	400	1.30	Pregnancy	339	2.26
13	Cellulitis/dermatitis	631	1.38	Enteric fever	385	1.25	Dermatitis	171	1.14
14	Pregnancy	614	1.34	Urinary tract inf.	328	1.06	Trauma/injury	148	0.99
15	Delivery	464	1.01	Helmithiasis	314	1.02	Enteritis	138	0.92
16	Urinary tract inf.	446	0.97	DM	294	0.95	Conjunctivitis	122	0.81
17	Helmithiasis	344	0.75	Pregnancy	275	0.89	Urinary tract inf.	118	0.79
18	Trauma/injury	313	0.68	Conjunctivitis	165	0.54	Asthma	102	0.68
19	Conjunctivitis	258	0.56	Trauma/injury	165	0.54	Stress/anxiety	91	0.61
20	Asthma	212	0.46	Enteric f. / malaria	161	0.52	Candidiasis	84	0.56
21	Sepsis	208	0.45	Inguinal hernia	159	0.52	PID	84	0.56
22	PID	192	0.42	Sepsis	147	0.48	Lumbago	73	0.49
23	Inguinal hernia	178	0.39	No diagnosis	139	0.45	Delivery	64	0.43
24	TB	167	0.36	TB	113	0.37	Sepsis	61	0.41
25	Enteric f. / malaria	161	0.35	Asthma	110	0.36	Immunization	58	0.39
26	No diagnosis	139	0.30	PID	108	0.35	Allergy	55	0.37
27	Candidiasis	128	0.28	Otitis media	104	0.34	Eye problem	55	0.37
28	Anaemia	125	0.27	Fever	81	0.26	TB	54	0.36
29	Otitis media	123	0.27	Toothache/caries	77	0.25	Neuropathy	52	0.35
30	Stress/anxiety	109	0.24	Anaemia	76	0.25	Anaemia	49	0.33
31	Fever	108	0.24	Abdominal pain	75	0.24	Cataract	43	0.29
32	Toothache/caries	101	0.22	Tinea corporis	63	0.20	Insomnia	37	0.25
33	Abdominal pain	93	0.20	Menopause	59	0.19	Vaginitis	35	0.23
34	Allergy	84	0.18	Chicken pox	54	0.18	Uterine fibroid	34	0.23
35	Dysmenorrhea	80	0.17	Dysmenorrhea	52	0.17	Helmithiasis	30	0.20
36	Tinea corporis	76	0.17	Impetigo	50	0.16	Refractive dis.	30	0.20
37	Lumbago/sciatica	75	0.16	Schistosomiasis	49	0.16	Dysmenorrhea	28	0.19
38	Cataract	73	0.16	Headache	47	0.15	Fever	27	0.18
39	Headache	68	0.15	Mézales	47	0.15	Infertility	27	0.18
40	Neuropathy	68	0.15	Candidiasis	44	0.14	Haemorrhoids	25	0.17
41	Vaginitis	67	0.15	Lipoma	41	0.13	Obesity	25	0.17
42	Immunization	66	0.14	Surgery	37	0.12	Toothache/caries	24	0.16
43	Menopause	66	0.14	Mumps	33	0.11	Appendicitis	22	0.15
44	Chicken pox	63	0.14	Sickle cell (crisis)	33	0.11	Fatigue	21	0.14
45	Impetigo	53	0.12	Vaginitis	32	0.10	Headache	21	0.14
46	Insomnia	53	0.12	Stitches removal	31	0.10	Inguinal hernia	19	0.13
47	Lipoma	52	0.11	Cataract	30	0.10	Otitis media	19	0.13
48	Measles	51	0.11	Allergy	29	0.09	Abdominal pain	18	0.12
49	Schistosomiasis	49	0.11	Circumcision	29	0.09	Mental disorder	16	0.11
50	Eye problem	45	0.10	Admission	28	0.09	Esophagitis	15	0.10

Table legend. Most frequent diagnoses for the all enrolled subjects in Nigeria (left column), Kwara (middle column), and Lagos (right column). All ages are included in this table. Each individual column is ranked from the most frequent diagnosis to the 50th most common diagnosis. N = number of diagnoses. Percentages are column percentages, with the denominator being the total number of diagnoses (not subjects) for that group of subjects.

Table "Disease burden-2": Most frequent diagnoses for adult males and females

	Kwara					Lagos				
		Females		Males			Females		Males	
	Diagnosis	n	%	n	%	Diagnosis	n	%	n	%
1	Malaria	2620	26.59	1241	20.15	Malaria	2075	26.41	1024	26.67
2	*Follow up*	1267	12.86	924	15.00	Hypertension	971	12.36	537	13.99
3	Hypertension	1194	12.12	790	12.82	(U)RTI	570	7.25	295	7.68
4	(U)RTI	611	6.20	394	6.40	Enteric fever	438	5.57	249	6.49
5	(Osteo)arthritis	563	5.71	318	5.16	(Osteo)arthritis	409	5.21	127	3.31
6	Peptic ulcer disease	472	4.79	254	4.12	DM	247	3.14	156	4.06
7	Pain	413	4.19	261	4.24	*Follow up*	257	3.27	135	3.52
8	Enteritis	307	3.12	250	4.06	Pain	245	3.12	133	3.46
9	Myalgia	215	2.18	128	2.08	Myalgia	237	3.02	114	2.97
10	Enteric fever	181	1.84	91	1.48	Peptic ulcer disease	260	3.31	86	2.24
11	DM	133	1.35	122	1.98	Cellulitis/dermatitis	81	1.03	48	1.25
12	Urinary tract inf.	121	1.23	129	2.09	Trauma/injury	64	0.81	48	1.25
13	Cellulitis/dermatitis	114	1.16	115	1.87	Urinary tract inf.	53	0.67	44	1.15
14	Helmithiasis	111	1.13	86	1.40	Conjunctivitis	71	0.90	25	0.65
15	TB	50	0.51	54	0.88	Asthma	56	0.71	28	0.73
16	Inguinal hernia	17	0.17	82	1.33	Enteritis	61	0.78	22	0.57
17	*No diagnosis*	56	0.57	43	0.70	Stress/anxiety	67	0.85	16	0.42
18	Enteric f. / malaria	63	0.64	35	0.57	Candidiasis (unsp.)	64	0.81	15	0.39
19	Trauma/injury	38	0.39	55	0.89	PID	66	0.84	10	0.26
20	Conjunctivitis	53	0.54	39	0.63	Lumbago/sciatica	50	0.64	18	0.47
21	PID	75	0.76	12	0.19	Neuropathy	31	0.39	19	0.49
22	Asthma	50	0.51	35	0.57	Immunization	38	0.48	11	0.29
23	Abdominal pain	50	0.51	12	0.19	Allergy	36	0.46	12	0.31
24	Toothache/caries	37	0.38	18	0.29	Eye problem	25	0.32	21	0.55
25	Menopause	51	0.52	0	0.00	TB	12	0.15	29	0.76
26	Fever	23	0.23	22	0.36	Anaemia	32	0.41	8	0.21
27	Dysmenorrhea	35	0.36	-	-	Cataract	23	0.29	14	0.36
28	Headache	28	0.28	12	0.19	Insomnia	22	0.28	11	0.29
29	Lipoma	22	0.22	18	0.29	Sepsis	25	0.32	8	0.21
30	Anaemia	26	0.26	11	0.18	Uterine fibroid	31	0.39	-	-
31	Sepsis	23	0.23	10	0.16	Vaginitis	28	0.36	-	-
32	Otitis media	23	0.23	8	0.13	Dysmenorrhea	25	0.32	-	-
33	Tinea corporis	15	0.15	16	0.26	Helmithiasis	12	0.15	12	0.31
34	Candidiasis (unsp.)	19	0.19	11	0.18	Obesity	21	0.27	3	0.08
35	Schistosomiasis	4	0.04	26	0.42	Refractive disorder	19	0.24	3	0.08
36	Vaginitis	27	0.27	-	-	Fever	16	0.20	5	0.13
37	*Surgery*	11	0.11	15	0.24	Infertility	16	0.20	5	0.13
38	Cataract	19	0.19	5	0.08	Toothache/caries	15	0.19	6	0.16
39	Chicken pox	11	0.11	13	0.21	Appendicitis	18	0.23	2	0.05
40	Stitches removal	8	0.08	16	0.26	Fatigue	17	0.22	3	0.08
41	Allergy	14	0.14	9	0.15	Haemorrhoids	6	0.08	14	0.36
42	Dizziness	16	0.16	7	0.11	Headache	15	0.19	4	0.10
43	Admission	11	0.11	9	0.15	Abdominal pain	15	0.19	1	0.03
44	Eye problem	12	0.12	5	0.08	Inguinal hernia	2	0.03	14	0.36
45	Stress/anxiety	5	0.05	11	0.18	Otitis media	5	0.06	11	0.29
46	Weakness/dizziness	12	0.12	4	0.06	Mental disorder	11	0.14	3	0.08
47	Neuropathy	6	0.06	9	0.15	Esophagitis	10	0.13	3	0.08
48	Fatigue	12	0.12	2	0.03	Circumcision	11	0.14	1	0.03
49	Insomnia	7	0.07	7	0.11	Constipation	7	0.09	4	0.10
50	Appendicitis	4	0.04	9	0.15	Somatization	11	0.14	-	-

Table legend. Most frequent diagnoses for the all adult subjects in Kwara (left half), and Lagos (right half). The ranking of the individual diagnoses is based on the rank of each diagnosis in the overall adult population within each geographic locations. N = number of diagnoses. Percentages are column percentages, with the denominator being the total number of diagnoses (not subjects) for that group of subjects. Pregnancy-related clinic visits have been ignored in this analysis.

Table "Disease burden-3":

	Children					Babies				
		Kwara		Lagos			Kwara		Lagos	
	Diagnosis	n	%	n	%	Diagnosis	n	%	n	%
1	Malaria	2679	40.85	344	32.09	Malaria	244	30.39	62	25.73
2	(U)RTI	1037	15.81	218	20.34	(U)RTI	224	27.90	37	15.35
3	*Follow up*	558	8.51	32	2.99	Enteritis	110	13.70	9	3.73
4	Enteritis	285	4.35	33	3.08	*Follow up*	65	8.09	6	2.49
5	ANC	274	4.18	5	0.47	Cellulitis/dermatitis	19	2.37	5	2.07
6	Cellulitis/dermatitis	168	2.56	28	2.61	Sepsis	13	1.62	10	4.15
7	Enteric fever	81	1.24	68	6.34	ANC	7	0.87	5	2.07
8	Pain	91	1.39	17	1.59	Circumcision	11	1.37	-	-
9	Sepsis	84	1.28	10	0.93	Enteric fever	2	0.25	7	2.90
10	Helmithiasis	86	1.31	4	0.37	Pain	8	1.00	1	0.41
11	Peptic ulcer disease	71	1.08	10	0.93	Fever	8	1.00	-	-
12	Hypertension	61	0.93	15	1.40	Urinary tract infection	3	0.37	5	2.07
13	(Osteo)arthritis	54	0.82	13	1.21	(Osteo)arthritis	6	0.75	1	0.41
14	Conjunctivitis	50	0.76	17	1.59	Helmithiasis	6	0.75	1	0.41
15	Otitis media	64	0.98	1	0.09	*Immunization*	-	-	7	2.90
16	Trauma/injury	38	0.58	20	1.87	Conjunctivitis	4	0.50	2	0.83
17	Inguinal hernia	53	0.81	3	0.28	Malnutrition	2	0.25	3	1.24
18	Enteric f. / malaria	46	0.70	-	-	Measles	5	0.62	-	-
19	Urinary tract infection	32	0.49	9	0.84	Enteric f. / malaria	4	0.50	-	-
20	Anaemia	30	0.46	8	0.75	Anaemia	3	0.37	-	-
21	Measles	36	0.55	2	0.19					
22	Impetigo	35	0.53	1	0.09					
23	Myalgia	25	0.38	10	0.93					
24	*No diagnosis*	29	0.44	-	-					
25	Mumps	27	0.41	1	0.09					
26	Chicken pox	24	0.37	3	0.28					
27	Tinea corporis	23	0.35	2	0.19					
28	Fever	19	0.29	5	0.47					
29	Asthma	13	0.20	10	0.93					
30	Sickle cell (crisis)	16	0.24	1	0.09					

Table legend. Most frequent diagnoses for children (left half) and babies (right half) in Kwara and Lagos (right half). The ranking of the individual diagnoses is based on the rank of each diagnosis in the total population of children and babies in both geographic locations combined. N = number of diagnoses. Percentages are column percentages, with the denominator being the total number of diagnoses (not subjects) for that group of subjects.

Diagnostic practices

During the period from February 2007 till February 2008 a remarkably low number of 13,410 (laboratory) investigations were performed during 43,537 clinic visits for all 36,579 subjects enrolled in the program. Although still only performed in a minority of clinic visits, it is clear that in Lagos relatively more frequently investigations are done compared to Kwara: 7,731 investigations in 30,052 subjects in Kwara, and 5,678 diagnoses in 6,521 subjects in Lagos (note: 1 investigation in the database was linked to a patient registration number not containing an "area code"). Figure "Diagnostic practices-1" shows the absolute and proportional number of investigations per age-category for Kwara and Lagos. In the vast majority of clinic visits no (laboratory) diagnostic procedures are performed: in 87.1% in Kwara and in 77.2% in Lagos. It is clear for both Kwara and Lagos that (laboratory) investigations are even more rarely done for children and babies compared to adults (compare the left panel of Figure "Diagnostic practices-1" with the left panel of Figure "Demographics-1").

Figure "Diagnostic practices-1": Number of investigations

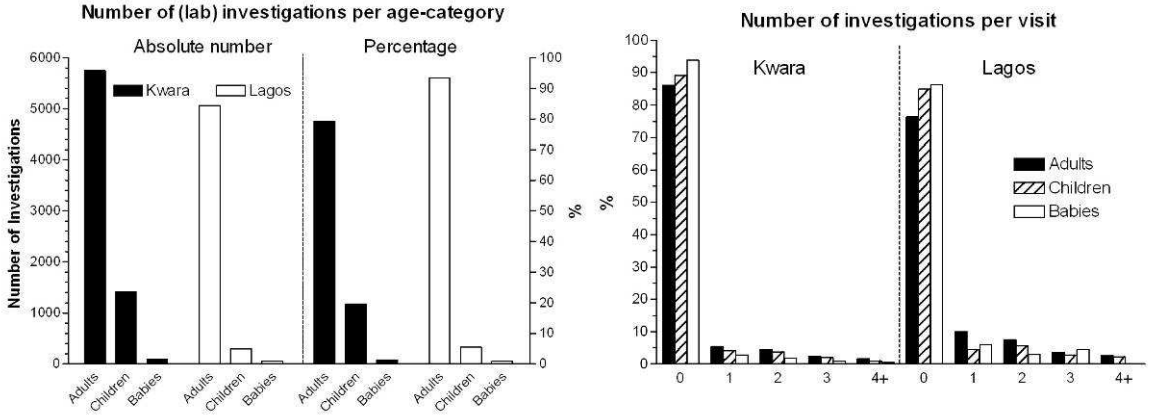


Figure legend. Left panel: the bars in the left panel represent the absolute number of (laboratory) investigations made for adults, children and babies enrolled in Kwara (black bars) and Lagos (white bars). The bars in the right panel represent the proportion for each age category compared to the total population in Kwara (black bars) and Lagos (white bars). Right panel: the categories represent the number of simultaneously made diagnoses per individual clinic visit. All clinic visits resulting in more than 4 (laboratory) investigations were grouped in the category "4+".

Table "Diagnostic practices-1" lists the most frequently used (laboratory) investigations. Generally speaking, the investigation to diagnose a particular disease is performed much less often that the disease itself is diagnosed. Therefore most diagnoses are either presumptive and/or are based on the findings from the anamnesis plus physical examination only. A prime example of this is malaria, which is the most frequently diagnosed disease which was recorded a total of 11,462 times, although just 503 malaria tests have been recorded. At this moment it is still difficult to estimate the extent of possible underreporting of laboratory investigations, although our experiences from site visits generally confirm the infrequent use of laboratory investigations to aid the diagnostic process.
Enteric fever / typhoid is a rare example of a disease that is tested for more often (n=1344) then it is diagnosed (n=1188). HIV-tests were apparently performed 473 times, although the diagnosis HIV-infection was recorded only 12 times. Note that only the fact that a test has been performed is recorded, not the test results itself.

Table "Diagnostic practices-1": Most frequently used (laboratory) investigations

Test	n	%
Widal (enteric fever)	1344	20.15
Urinalysis	1128	16.91
FBS (fasting blood sugar)	596	8.94
Ultrasound	551	8.26
Malaria	503	7.54
HIV	473	7.09
PCV	454	6.81
Blood group	197	2.95
Chest X-ray	92	1.38
Stool analysis	90	1.35
RSV (Respiratory Syncytial Virus)	84	1.26
Pregnancy test	81	1.21
RBS (random blood sugar)	77	1.15
Blood test, unspecified	71	1.06
Genotype (Hb)	71	1.06

URI	58	0.87
FBC (full blood count)	53	0.79
Lipid profile	51	0.76
Sputum M/C/S	49	0.73
Vaginal smear M/C/S	48	0.72
WBC (white blood cells)	40	0.60
VDRL	35	0.52

Table legend. N = number of diagnoses. Percentages are column percentages, with the denominator being the total number of diagnoses (not subjects) for that group of subjects.

Therapeutic practices

In sharp contrast to the low number of investigations, during the period from February 2007 till February 2008 a remarkably low number of 151,274 treatments were prescribed / performed during 43,537 clinic visits for all 36,579 subjects enrolled in the program. There were similar numbers of prescribed treatments per diagnosis in Lagos compared to Kwara: 106,975 treatments for 30,813 diagnoses in 30,052 subjects in Kwara, and 44,281 treatments for 14,994 diagnoses in 6,521 subjects in Lagos. Figure "Therapeutic practices-1" shows the number of prescribed treatments per clinic visit for Kwara and Lagos. The average number of prescribed treatments per separate diagnosis was 3.47 in Kwara and 2.95 in Lagos: this difference can be largely attributed to the very frequent prescription of multivitamins in Kwara. In just 7.3% of clinic visits no prescribed treatments are recorded: in 7.8% of clinic visits in Kwara and in 4.9% of clinic visits in Lagos. Note that in Kwara there is virtually always just a single diagnosis per individual clinic visit, but in Lagos 16.7% of clinic visits yielded two or more diagnoses (see Figure "Disease burden-1"). There were no obvious differences in the number of prescribed treatments per clinic visit between males and females (not shown), or between adults, children and babies. There was a trend for slightly more prescribed treatments per clinic visit in Lagos compared to Kwara. This might be explained by the slightly larger number of registered diagnoses per clinic visit in Lagos.

Table "Therapeutic practices-1" lists the most frequently prescribed treatments for all enrolled subjects in Nigeria, for the subjects enrolled in Kwara, and in Lagos. Multivitamins and paracetamol are by far the two most frequently prescribed treatments. Folic acid and iron are two other frequently prescribed drugs, but only in Kwara, not in Lagos.

Figure "Therapeutic practices-1": Number of prescribed treatments per clinic visit.

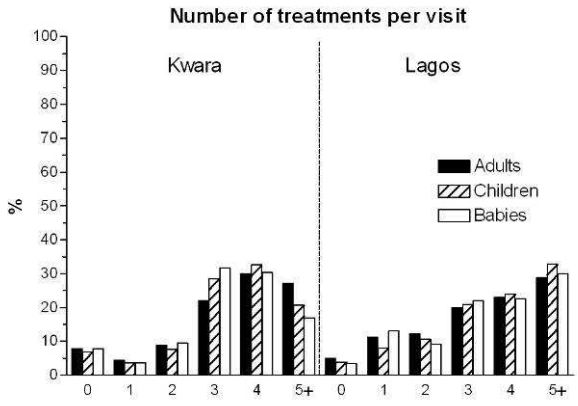


Figure legend. : The categories represent the number of simultaneously prescribed treatments per individual clinic visit. All clinic visits resulting in more than 5 treatments were grouped in the category "5+".

Table "Therapeutic practices-1": Most frequently prescribed treatments

	Nigeria			Kwara			Lagos		
	Treatment	**n**	**%**	**Treatment**	**n**	**%**	**Treatment**	**%**	**%**
1	Multivitamins	29082	19.22	Multivitamins	23388	21.86	PCM	6123	13.83
2	PCM	25014	16.54	PCM	18888	17.66	Multivitamins	5692	12.85
3	Folic acid	5811	3.84	Folic acid	5179	4.84	Fansidar	2208	4.99
4	Iron	5349	3.54	Iron	4608	4.31	Artesunate	1621	3.66
5	Chloramph.	4836	3.20	Chloramph.	4603	4.30	Diclofenac	1376	3.11
6	Cough syrup	3494	2.31	Co-trimoxazole	2579	2.41	Amoxycillin	1258	2.84
7	Moduretic	3464	2.29	Cough syrup	2567	2.40	Antihistamine	1243	2.81
8	Antihistamine	3345	2.21	Moduretic	2397	2.24	Ibuprofen	1114	2.52
9	Ibuprofen	3211	2.12	Antimycotic	2197	2.05	Moduretic	1067	2.41
10	Fansidar	3124	2.07	Metronidazole	2156	2.02	Cough syrup	926	2.09
11	Co-trimoxazole	3093	2.04	Antihistamine	2102	1.96	Nifedipine	882	1.99
12	Metronidazole	2965	1.96	Ibuprofen	2096	1.96	Asprin	835	1.89
13	Amoxycillin	2620	1.73	Tetanus vaccine	1834	1.71	Metronidazole	809	1.83
14	Artesunate	2418	1.60	Piroxicam	1640	1.53	Iron	741	1.67
15	Asprin	2306	1.52	Asprin	1471	1.38	Amodiaquine	708	1.60
16	Antimycotic	2294	1.52	Sulpha/pyrimeth.	1409	1.32	Folic acid	632	1.43
17	Nifedipine	2268	1.50	Nifedipine	1386	1.30	Ciprofloxacin	589	1.33
18	Tetanus vaccine	2031	1.34	Amoxycillin	1361	1.27	Routine drugs	567	1.28
19	Piroxicam	1794	1.19	Antacid	1333	1.25	Chloroquine	565	1.28
20	Diclofenac	1701	1.12	Ampiclox	1161	1.09	Co-trimoxazole	513	1.16
21	Ampiclox	1564	1.03	Ciprofloxacin	975	0.91	Methyldopa	489	1.10
22	Ciprofloxacin	1564	1.03	Fansidar	915	0.86	Quinine	408	0.92
23	Sulpha/pyrimeth.	1499	0.99	Methyldopa	877	0.82	Ampiclox	403	0.91
24	Antacid	1494	0.99	Tetramisole	876	0.82	Bromazepam	403	0.91
25	Methyldopa	1367	0.90	Artesunate	796	0.74	Diazepam	388	0.88
26	Chloroquine	1260	0.83	Chloroquine	693	0.65	Erythromycin	339	0.77
27	Routine drugs	1112	0.74	Buscopan	648	0.61	Metformin	326	0.74
28	Tetramisole	976	0.65	Gentamicin	595	0.56	Camosunate	300	0.68
29	Diazepam	902	0.60	Camosunate	587	0.55	Calcium	278	0.63
30	Buscopan	897	0.59	ORS	573	0.54	Atenolol	251	0.57
31	Camosunate	887	0.59	Cimetidine	562	0.53	Buscopan	248	0.56
32	Bromazepam	822	0.54	Routine drugs	545	0.51	Nitrazepam	240	0.54
33	Gentamicin	793	0.52	Diazepam	514	0.48	Chloramphenicol	233	0.53
34	Erythromycin	739	0.49	Bromazepam	419	0.39	Daonil	232	0.52
35	Amodiaquine	730	0.48	Promethazine	401	0.37	Farbitone	215	0.49
36	Cimetidine	724	0.48	Erythromycin	400	0.37	MMT	209	0.47
37	ORS	616	0.41	Daonil	377	0.35	Prednisolone	207	0.47
38	Daonil	609	0.40	No therapy	342	0.32	Gentamicin	198	0.45
39	Calcium	594	0.39	Diclofenac	325	0.30	Tetanus vaccine	197	0.44
40	Promethazine	542	0.36	MMT	323	0.30	Tab SP	185	0.42
41	MMT	532	0.35	Calcium	316	0.30	Fusidic acid	177	0.40
42	Prednisolone	454	0.30	Ampicillin	311	0.29	Cimetidine	162	0.37
43	Fusidic acid	430	0.28	Metoclopramide	311	0.29	Antacid	160	0.36
44	Quinine	427	0.28	Tramal	295	0.28	Piroxicam	154	0.35
45	Metformin	407	0.27	Diabinese	281	0.26	Promethazine	140	0.32
46	Ampicillin	399	0.26	Propen	257	0.24	Coartem	135	0.30
47	Tramal	384	0.25	Doxycycline	255	0.24	Methyl salicylate	124	0.28
48	Doxycycline	353	0.23	Fusidic acid	253	0.24	Omeprazole	116	0.26
49	Metoclopramide	349	0.23	Prednisolone	247	0.23	Salbutamol	114	0.26
50	No therapy	349	0.23	Streptomicin	221	0.21	Orphenadrine	110	0.25

Table legend. Most frequently prescribed treatments for the all enrolled subjects in Nigeria (left column), Kwara (middle column), and Lagos (right column). All ages are included in this table. Each individual column is ranked from the most frequently prescribed treatment to the 50th most common treatment. N = number of prescribed treatments. Percentages are column percentages, with the denominator being the total number of prescribed treatments (not subjects) for that group of subjects.

HIV-1

HIV-1 infection was rarely reported as a diagnosis. In Kwara 3 adult females, a single male and 4 minors were diagnosed with HIV-1, in Lagos 2 adult females and 2 males were reported to be HIV-1 seropositive. A total of 472 HIV-1 tests were reported to be performed. Unfortunately, at this moment we do not have the outcome of these tests available for analysis. In Nigeria HIV-1 treatment services are provided by designated HIV-clinics. None of the clinics participating in the HIF Nigerian program was such a designated HIV-clinic.

Tuberculosis

Tuberculosis was diagnosed relatively rarely in the Nigerian HIF-program. A total of 167 clinic visits for tuberculosis cases were reported in 70 individuals: 48 subjects in Kwara and 22 in Lagos. TB was diagnosed equally often in males compared to females. Four of the 70 cases were diagnosed in children. There are no signs for a seasonal trend in TB reporting in either Kwara or Lagos. The overall incidence rate for TB was 70 cases for 23,354 pyr of follow-up = 3.0 cases per 1,000 pyr for Nigeria, which is what was expected based on available data. There were huge differences between Kwara and Lagos: 48 cases / 19,738 pyr = 2.4 cases per 1,000 pyr in Kwara; and 22 cases / 3,615 pyr = 6.1 cases per 1,000 pyr in Lagos (see Figure "Tuberculosis-1").

Figure "Tuberculosis-1": Incidence rates of selected diseases

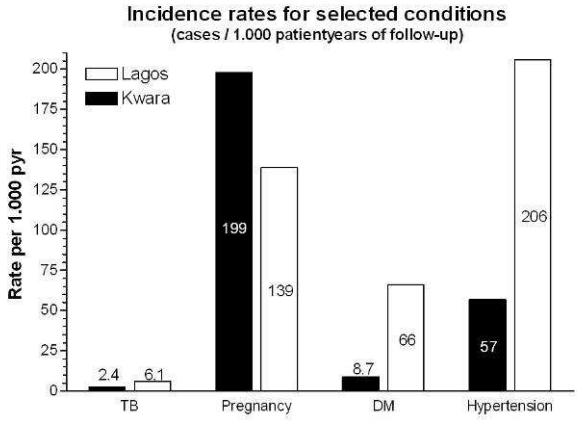


Figure legend. Incidence rates are expressed as the number of newly diagnosed cases per 1,000 personyears of follow-up. TB = tuberculosis, rate calculated for all age-categories. DM = diabetes mellitus. DM and hypertension rates calculated for adults only. Pregnancy rates calculated for adult females only.

The database captured few laboratory investigations at the moment tuberculosis was first diagnosed. Fifty-three percent of cases had no tests done to confirm the diagnosis of tuberculosis, in 23 cases (33%) a sputum smear was recorded, and 5 (7%) chest X-rays were made. In 13 cases (18.6%) an HIV-1 test was done (however, the results of these HIV-1 tests were not recorded in the database). There were no obvious differences between Kwara and Lagos with respect to diagnostic practices. Table "Tuberculosis-1" lists all (combination) regimens prescribed at the moment tuberculosis was first diagnosed. There were 24 different combination regimens with (adequate or inadequate) antituberculous activity. Only 29 patients were prescribed a regimen containing three or more drugs active against tuberculosis. Just 15 patients received the "standard regimen" containing ethambutol, INH, pyrazinamide, and rifampicin. For 19 subjects no

antituberculous treatment was recorded. Currently it is unknown if these patients have been referred to another clinic for treatment.

Table "Tuberculosis-1": Prescribed antituberculous regimens

Antituberculous agent	n	%
<no active drugs listed>	19	27.14
Ethambutol, INH, Pyrazinamide, Rifampicin	15	21.43
Ciprofloxacin	3	4.29
Erythromycin	3	4.29
Ethambutol, INH, Pyrazinamide, Rifampicin, Streptomicin	3	4.29
Isoniazid, Pyrazinamide, Rifampicin	3	4.29
Ethambutol, INH	2	2.86
Ethambutol, Pyrazinamide, Rifampicin, Streptomicin	2	2.86
INH, Pyrazinamide, Pyridoxine, Rifampicin	2	2.86
Rifampicin	2	2.86
Streptomicin	2	2.86
Ciprofloxacin, Ethambutol, INH	1	1.43
Erythromycin, INH, Pyrazinamide	1	1.43
Ethambutol	1	1.43
Ethambutol, INH, Pyrazinamide, Pyridoxine, Rifampicin	1	1.43
Ethambutol, INH, Rifampicin	1	1.43
Ethambutol, Pyrazinamide, Rifampicin	1	1.43
Ethambutol, Pyrazinamide, Streptomicin	1	1.43
Ethambutol, Pyrazinamide, uncoded:RIF.INH	1	1.43
Ethambutol, Rifampicin	1	1.43
Ethambutol, Rifampicin, Streptomicin	1	1.43
INH	1	1.43
INH, Pyrazinamide, Rifampicin, Streptomicin	1	1.43
Lincomycin	1	1.43
Ofloxacin	1	1.43

This table lists the antituberculous regimens prescribed at the moment tuberculosis was first diagnosed. N = number of prescribed treatments. Percentages are column percentages, the denominator being the total number of cases (70).

Malaria

The left panel of Figure "Malaria-1" shows the mean monthly rate of malaria in Kwara and Lagos for adults. The rate in Lagos is more than twice that in Kwara: 4.9% and 1.9%, respectively of the entire adult population each month is diagnosed with malaria.

Figure "Malaria-1": Monthly incidence rates of malaria in adults and children

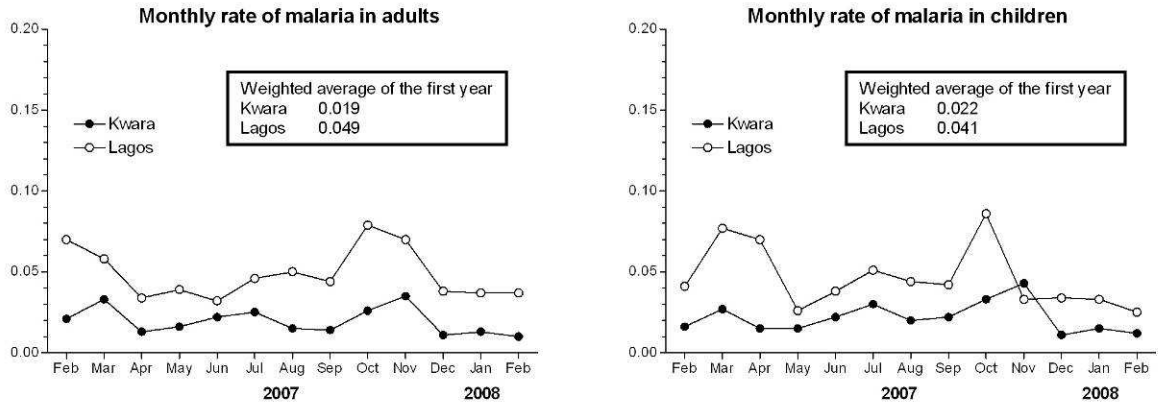


Figure legend. For each month the number of currently enrolled patients was used to calculate incidence rates. The left panel displays results for adults, the right panel for children.

In children (aged 1 to 16 years) the incidence rates were very similar to the adults. The weighted mean incidence rates for malaria in babies were 4.1% in Kwara and 4.7% in Kwara. In southern Nigeria, where Lagos is located, the two separate rainy seasons are: i) the long rainy season which starts in March and lasts to the end of July, with a peak period in June over most parts of southern Nigeria, which is followed by a short dry season in August; and ii) the short rainy season follows the brief wet period in August and lasts from early September to mid-October, with a peak period at the end of September. These two rainy seasons seem to be reflected in the incidence rates of malaria in Lagos for both adults and children (source: http://www.srh.noaa.gov/jetstream//tropics/itcz.htm).

In 608 of 7485 (8.1%) first malaria episodes a malaria blood smear was performed, the remaining 91.9% were presumptive diagnoses. In 407 malaria episodes also a Widal (typhoid) test was performed.

Table "Malaria-1" lists the most commonly used antimalarial drugs for the treatment of the first recorded malaria episode of the 7485 subjects who had one or more recorded episode of malaria. These 4349 antimalarial agents were used in 3452 regimens. The ten most commonly used regimens are listed in Table "Malaria-2". Slightly more than half (53.9%) the malaria episodes were not treated with an antimalarial drug: 4033 out of 7485 episodes. These episodes were usually treated with NSAID and multivitamins.

Table "Malaria-1": Most frequently prescribed antimalarial agents

Antimalarial agent	n	%
Fansidar	1149	26.42
Artesunate	920	21.15
Sulphadoxine/pyrimethamine	672	15.45
Chloroquine	584	13.43
Artesunate/amodiaquine	328	7.54
Amodiaquine	282	6.48
Quinine	142	3.27
Ampiclox	115	2.64
Artemether/lumefantrine	88	2.02
Arthemeter	69	1.59

Table legend. N = number of prescriptions per antimalarial drug. Percentages are column percentages, with the denominator being the total number of prescribed antimalarial drugs (4349).

Table "Malaria-2": Most frequently prescribed antimalarial regimens

Antimalarial regimen	n	%
Symptomatic treatment	*4033*	*53.88*
Sulphadoxine/pyrimethamine	602	8.04
Fansidar	476	6.36
Artesunate	429	5.73
Chloroquine	395	5.28
Artesunate/fansidar	344	4.60
Artesunate/amodiaquine	302	4.03
Amodiaquine	118	1.58
Chloroquine/fansidar	118	1.58
Amodiaquine/fansidar	88	1.18
Artemether/lumefantrine	86	1.15

Table legend. N = number of prescriptions per antimalarial drug. Percentages are column percentages, with the denominator being the total number of malaria cases (7485).

A considerable number of cases (41.6%) concurrently received antibiotics apparently aimed at treating typhoid (see Table "Malaria-3") reflecting the widespread practice of making presumptive diagnoses and treating a febrile patient for both malaria and typhoid simultaneously. Because in Kwara only one diagnosis is reported for each clinic visit, these "presumptive cases" of typhoid do not show up in the database.

Table "Malaria-3": Concurrent "*typhoid treatment*"

Antibiotic	n	%
Chloramphenicol	2286	27.4
Co-trimoxazole	532	6.4
Amoxycillin	408	4.9
Ciprofloxacin	210	2.5
Ampicillin	40	0.5

Table legend. N = number of prescriptions per antibiotic. Percentages are column percentages, with the denominator being the total number of "malaria" episodes (8351).

Adult & childhood respiratory tract infections

A total of 2894 subjects experienced 3770 episodes of (upper) respiratory tract infection. This analysis considers the first episode per subject only. The left panel of Figure "(U)RTI-1" shows the mean monthly rate of (upper) respiratory tract infections in Kwara and Lagos for adults. The rate in Lagos is three times the rate in Kwara: 1.79% and 0.59%, respectively, of the entire adult population each month is diagnosed with (U)RTI. The right panel of Figure "(U)RTI-1" shows the mean monthly rate of (U)RTI in Kwara and Lagos for children. Like for the adults, the rate of (U)RTI in children in Lagos is also three times the rate in Kwara: 2.83% and 0.93%, respectively. Like for malaria, the two rainy seasons in Lagos (see section "Malaria") are apparently reflected in the incidence rates of (U)RTI in Lagos for children, but less so for adults.

Figure "(U)RTI-1": Monthly incidence rates of respiratory tract infections in adults and children

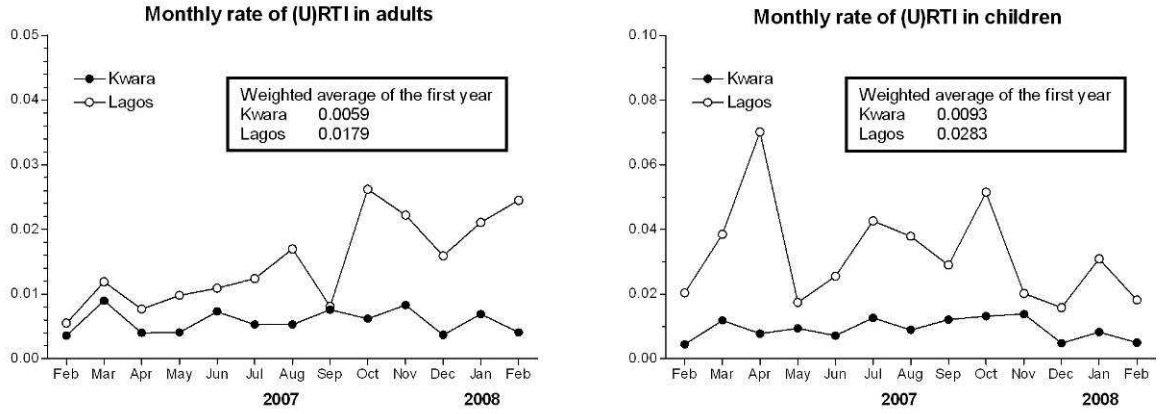


Figure legend. For each month the number of currently enrolled patients was used to calculate incidence rates. The left panel displays results for adults, the right panel for children.

Very few (laboratory) investigations for each case of (U)RTI were recorded in the database: in 94.7% of cases no investigations were performed (97.6% in Kwara, 87.6% in Lagos). Most of these (U)RTI cases will have been cases of common cold or other viral infections. Because we have no information on the severity of the individual cases, it is difficult to estimate in how many

cases additional diagnostics should have been performed because of moderate to severe disease. Just 14 chest X-rays and 13 sputum examinations were performed.

In sharp contrast to the lack of investigations is the large number of treatments: 10,444 individual drugs were prescribed for these 2894 individuals. In just 197 cases (6.8%) not a single treatment was prescribed. The most frequently prescribed treatments (> 1%) are listed in Table "(U)RTI-1". The three most frequently prescribed treatments were multivitamins, paracetamol and cough syrup. Together these three treatments constitute nearly 50% of all prescribed treatments. In a small percentage of (U)RTI cases antimalarial drugs were concomitantly prescribed.

Table "(U)RTI-1": Most frequently prescribed treatments for respiratory tract infections

Treatment	n	%
Multivitamins	2135	20.44
PCM	1785	17.09
Cough syrup	1223	11.71
Co-trimoxazole	885	8.47
Antihistamine	365	3.49
Amoxycillin	305	2.92
Fansidar	235	2.25
Erythromycin	204	1.95
Chloramphenicol	199	1.91
Acetylsalicylic Acid	177	1.69
Artesunate	160	1.53
Ibuprofen	149	1.43
Ampiclox	146	1.40
Multivitamins	2135	20.44

Table legend. N = number of prescriptions per treatment. Percentages are column percentages, with the denominator being the total number of prescribed treatments (10,444).

Table "(U)RTI-2": Most frequently prescribed antibiotics for respiratory tract infections

Antibiotic(s)	n	%
No antibiotics prescribed	*1036*	*5.80*
Co-trimoxazole (CTX)	663	22.91
Amoxycillin	254	8.78
Erythromycin	177	6.12
Ampiclox	120	4.15
Chloramphenicol, CTX	91	3.14
Chloramphenicol	71	2.45
Ciprofloxacin	71	2.45
Ampicillin	66	2.28
CTX, sulphadoxine/pyrimethamine	44	1.52
CTX, gentamicin	33	1.14
Metronidazole (Flagyl)	23	0.79
CTX, metronidazole	22	0.76
Doxycycline	20	0.69
Sulphadoxine/pyrimethamine	19	0.66
Amoxycillin, metronidazole	18	0.62
Gentamicin	14	0.48
Cephalexin	12	0.41

Table legend. N = number of antibiotic regimens per case of (U)RTI. Percentages are column percentages, with the denominator being the total number of (U)RTI cases (2894).

Of all 2894 cases of (U)RTI a total of 1036 (35.8%) cases did not receive antibiotic treatment, but only supportive / symptomatic treatment. The remaining 1858 (64.2%) cases were treated with one of over 70 different combinations of antibiotics (see Table "(U)RTI-2").

Adult & childhood diarrhea

A total of 1,219 cases of (gastro)enteritis occurred in 1,060 individuals. We analyzed the first cases for each individual only. The incidence rate of (gastro)enteritis was higher in Kwara compared to Lagos: 0.40% and 0.30%, respectively, of the entire population was diagnosed with (gastro)enteritis each month. Babies had the highest incidence rate, 2.08% in Kwara and 0.95% in Lagos. In Kwara there was no difference in incidence of enteritis between adults and children: 0.35% and 0.29%, respectively. In Lagos among adults there was a lower incidence compared to children: 0.21% and 0.65%. Note that because of the low number of children and babies in Lagos the incidence rates over time are very variable; no line is drawn for babies in Lagos because in total there were just 11 registered cases of (gastro)enteritis is the entire first year of the program. There were no gender differences at any age-category. No clear seasonal trends were apparent. There appeared to have been a short epidemic of some sort amongst babies in Kwara in November 2007 when there were 24 cases amongst babies instead of the average 8 monthly cases.

Figure "Entertis-1": Monthly incidence rates of (gastro)enteritis in adults, children and babies

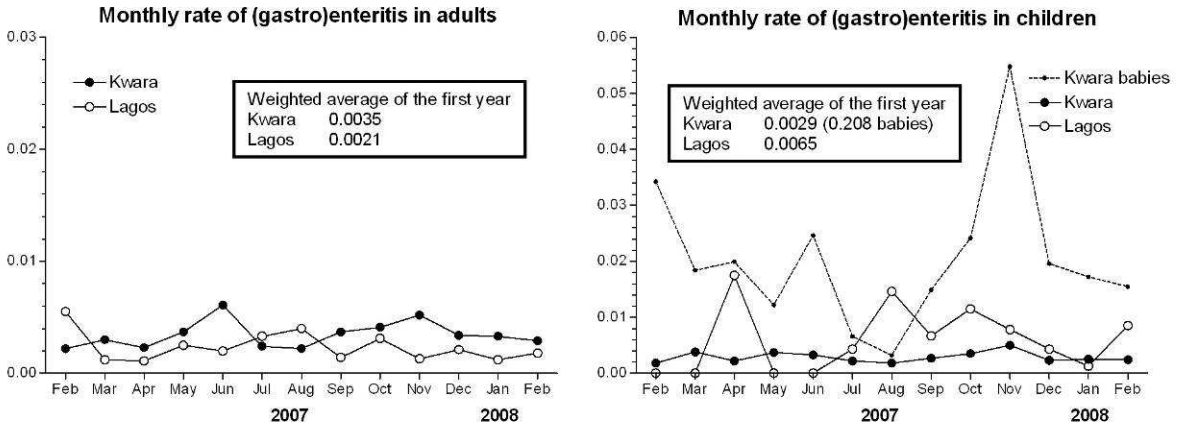


Figure legend. For each month the number of currently enrolled patients was used to calculate incidence rates. The left panel displays results for adults, the right panel for children.

In total just 10 stool samples were analyzed. In over 95% of (gastro)enteritis cases no (laboratory) investigations were performed. Just 74 (7.0%) of cases was not prescribed any treatment. A total of 3,756 different treatments were prescribed for the 1,060 individual cases. The most frequently prescribed treatments are listed in Table "Enteritis-1". Multivitamins and paracetamol together accounted for one third of all prescribed treatments. Oral rehydration solution was prescribed in 184 (17.4%) of 1,060 cases. Only 34.2% of cases were not prescribed any antibiotics. The remaining 698 (65.8%) of cases were treated with more than 40 different (combinations of) antibiotics (see Table "Enteritis-2" which lists the antibiotic regimens prescribed to more than 1% of cases).

Table "Enteritis-1": Most frequently prescribed treatment for enteritis

Treatment	n	%
Multivitamins	625	16.64
PCM	614	16.35
Metronidazole (Flagyl)	533	14.19
Co-trimoxazole	231	6.15
ORS	184	4.90
Amoxycillin	102	2.72
Buscopan	84	2.24
Piroxicam	81	2.16
Chloramphenicol	77	2.05
Cough syrup	67	1.78
Fansidar	55	1.46
Ibuprofen	54	1.44
Folic acid	47	1.25
Antacid	42	1.12
Ciprofloxacin	42	1.12
Tetramisole	40	1.06
Doxycycline	39	1.04
Artesunate	38	1.01
Gentamicin	37	0.99

Table legend. N = number of prescriptions per treatment. Percentages are column percentages, with the denominator being the total number of prescribed treatments (3,756).

Table "Enteritis-2": Most frequently prescribed treatment for enteritis

Antibiotic(s)	n	%
No antibiotics prescribed	*362*	*34.15*
Metronidazole (Flagyl)	216	20.38
Co-trimoxazole / metronidazole	136	12.83
Amoxycillin / metronidazole	61	5.75
Co-trimoxazole	52	4.91
Amoxycillin	30	2.83
Doxycycline / metronidazole	29	2.74
Chloramphenicol	25	2.36
Ciprofloxacin	23	2.17
Chloramphenicol / metronidazole	17	1.60
Chloramphenicol / co-trimoxazole / metronidazole	14	1.32
Ciprofloxacin / metronidazole	14	1.32
Co-trimoxazole / gentamicin / metronidazole	12	1.13

Table legend. N = number of antibiotic regimens per case of (U)RTI. Percentages are column percentages, with the denominator being the total number of (gastro)enteritis cases (1,060).

Antenatal care

In this analysis episodes of antenatal care (ANC) are considered to include the diagnosis of i) pregnancy, ii) check-ups during pregnancy, iii) delivery, and iv) care to mother & child in the first months after delivery. The data on pregnancy and delivery available for analysis are not very detailed and contained many missing data, limiting the possibilities for performing analyses. In this analysis we only considered the first clinic visit per person for one of the above mentioned reasons (pregnancy, ANC, delivery), which provides us with an approximation of the pregnancy

rate of the adult female population. A total of 1546 pregnancies were recorded: 1275 in Kwara and in 271 Lagos. On average in Kwara 1.66% and 1.17% of adult women became pregnant each month: 1275 cases per 6,443 pys = 197.9 cases per 1,000 pyr in Kwara; 271 cases per 1,953 pyr = 138.8 cases per 1,000 pys in Lagos (see Figure "Tuberculosis-1"). Often women did not (yet) deliver in the clinic: just 452 deliveries in the clinics were recorded: 443 vaginal deliveries, and 9 caesarean sections. Because we have data on just a one-year period, and the duration of pregnancy at first presentation is unknown, it is difficult to estimate how many of these pregnancies should already have ended. However, as often the pregnancy is already progressed into the third trimester at the moment of first presentation for ANC, most of the recorded pregnancies should already have ended.

A total of 772 HIV-1 test were recorded in the database. However, the results of these HIV-1 tests were not captured, and the same applies to the results of the syphilis and hepatitis B virus serology. Syphilis was serologically tested in 81 cases. Hepatitis B virus serology was tested for 16 times. The blood group was investigated in 568 cases. Ultrasounds were performed 489 times. Random and fasting blood sugars were performed 40 times.

Diabetes mellitus

There were 305 subjects (who made 738 clinic visits) in the database for which a diagnosis of diabetes mellitus was recorded: many more (both relatively and numerically) diagnoses of DM were made in Lagos (202) compared to Kwara (103). DM was reported for 295 adults, 7 children, and 3 babies. This yields incidence rates of DM 7.6 times higher in the adult population in Lagos compared to the adult population in Kwara: 0.51% per patient per month in Lagos and 0.06% per patient per month in Kwara. Expressed differently: 202 DM cases / 3,061 adult patientyears of follow-up = 66.0 cases per 1,000 pyr in Lagos, and 103 DM cases / 11,902 adult patientyears of follow-up = 8.65 cases per 1,000 pyr in Kwara (see Figure "Tuberculosis-1").

A total of 152 (random or fasting) blood glucose levels were measured.

Counseling and lifestyle advice were not recorded in the database. The 305 DM cases were treated with many different (combinations of) antidiabetic agents (see Table "DM-1"). We have no information on the efficacy of these treatments in lowering the blood glucose levels.

Table "DM-1": Treatments for diabetis mellitus

Antidiabetic agent(s)	n	%
<no active drugs listed>	168	55.08
Daonil (glibenclamide) / metformin (glucophage)	53	17.38
Metformin (glucophage)	34	11.15
Daonil (glibenclamide) / diabinese (chlorpropamide)	27	8.85
Daonil (glibenclamide)	11	3.61
Glyburide-metformin	7	2.30
Diabinese (chlorpropamide)	3	0.98
Daonil (glibenclamide) / insulin	1	0.33
Insulin	1	0.33

Table legend. N = number of antidiabetic regimens per case of diabetes mellitus. Percentages are column percentages, with the denominator being the total number of DM cases (305).

Hypertension

There were 1,574 subjects (who made 4,031 clinic visits) in the database for which a diagnosis of hypertension was recorded: 860 diagnoses of hypertension were made in Kwara compared to 714 in Lagos. Hypertension was primarily reported in adults: 677 adults in Kwara and 630 in Lagos. This yields incidence rates of hypertension 3.6 times higher in the adult population in Lagos compared to the adult population in Kwara: 1.73% per patient per month in Lagos and 0.48% per patient per month in Kwara. Expressed differently, 677 adult hypertension cases / 11,902 adult patientyears of follow-up = 56.9 cases per 1,000 pyr in Kwara, and 630 cases / 3,061 pyr = 205.8 cases per 1,000 pyr in Lagos (see Figure "Tuberculosis-1"). We have no information on the severity of the hypertension.

In 86% of the 1,574 cases no (laboratory) investigations were done. Urinalysis was done 74 times, an ECG was made 22 times. Counseling and lifestyle advice were not recorded in the database. The 1,574 hypertension cases were treated with many different antihypertensive agents that were used in many different combinations (see Tables "Hypertension-1 & 2"). We have no information on the efficacy of these treatments in lowering blood pressure.

Table "Hypertension-1": Most frequently used antihypertensive agents

Antihypertensive agent	n	%
Moduretic	729	40.10
Nifedipine (Adalat)	508	27.94
Methyldopa (Aldomet)	406	22.33
Atenolol	83	4.57
Captopril (Capoten)	26	1.43
Propranolol	18	0.99
Furosemide (Lasix)	15	0.83
Clopamide (hypertension)	12	0.66
Lisinopril (ACE inhibitor)	12	0.66
Amlodipine (Norvasc)	9	0.50

Table legend. N = number of prescriptions per treatment. Percentages are column percentages, with the denominator being the total number of prescribed treatments (1,818).

Table "Hypertension-2": Most frequently used treatments for hypertension

Antihypertensive agent(s)	n	%
<no active drugs listed>	*519*	*32.97*
Moduretic / nifedipine	248	15.76
Methyldopa / moduretic	195	12.39
Moduretic	139	8.83
Nifedipine	117	7.43
Methyldopa	87	5.53
Methyldopa / moduretic / nifedipine	72	4.57
Atenolol / moduretic	35	2.22
Methyldopa / nifedipine	33	2.10
Atenolol	24	1.52
Captopril / moduretic	13	0.83
Atenolol / nifedipine	9	0.57
Clopamide	9	0.57

Table legend. N = number of antihypertensive regimens per case of hypertension. Percentages are column percentages, with the denominator being the total number of hypertension cases (1,574).

Childhood anemia / malnutrition / intestinal parasites

The database only captured very few of these diagnosis, which we suspect does not reflect the local true prevalence of these conditions in the infant population. In Kwara helmithiasis was recorded 92 times, anemia 33 times, and malnutrition 2 times in 117 unique individuals. For Lagos these figures are 5, 8, and 3 times in 15 unique individuals. Helmithiasis was usually treated with tetramisole (n=70) and metronidazole (30). Anemia was usually treated with iron suppletion (9), folic acid (17), and sometimes blood transfusion (14).

Deaths

Currently data on (cases of) death are not systematically collected in the HIF Nigerian program.

Quality of patient records

A pilot study into the quality of the documentation of medical information in the clinical patient records in all participating clinics has been performed. The objective of this pilot study was to demonstrate:

- The adequacy of medical record keeping (could the medical case notes of randomly selected patients quickly be retrieved from the hospital archive?),
- The quality of the documentation in the medical case notes,
- Check diagnostic and therapeutic practices for selected diseases,
- Determine the feasibility of the 2nd (in-depth) phase of the CPCD operational research for which collecting additional data from the patient notes will be necessary.

The Nigerian HIF database has been used to randomly select cases from all participating clinics. A fixed number of cases were selected for the following 9 indicator diseases: malaria, tuberculosis, HIV-1 infection, infant and childhood respiratory infections, infant and childhood diarrhea, hypertension, diabetes mellitus, maternal health, neonatal health. During a routine Monitoring and Evaluation (M & E) exercise in January 2008, 14 clinics were visited. Although the personnel in the clinics knew beforehand that an M & E visit would take place, they were not informed about this pilot study. During the M & E visit they were requested to fetch the pre-selected clinical patient records from their medical records archive. These patient records were then examined by one of our medical doctors, who completed a score form for each patient record. The score form contained a 'general part' that focused on the general aspects of correct documentation of a clinic visit, and for each disease specific items were scored. The general issues that were scored were: anamnesis, physical examination, (laboratory) investigations, differential diagnosis, treatment, and follow-up. The specific issues to be scored for each of the above mentioned indicator diseases are listed in Appendix A1. The reporting of the results was both narrative / qualitative (Appendix A2), and quantitative (Appendix A3). A total of 201 patient records were screened. The six categories of general medical documentation were scored according to the rating scheme in Table "Quality-1". For each category the mean score was tabulated in Table "Quality-2". Generally speaking the categories anamnesis, physical examination, treatment, and follow-up are well documented. Documentation of investigations and the differential diagnosis is usually poorly done, reflecting the pervasive tendencies to rely on presumptive diagnosis. Note that adequate documentation of these categories does not necessarily

mean that for instance the correct diagnosis has been made or that adequate treatment has been instituted.

Table "Quality-1": Rating scheme for the six categories of general medical documentation

Score	Description
0	Not available, but not required
1	Not available, but required
2	Shortage, or no system, or not up to date
3	Available, and a system, and up to date, but not structurally maintained
4	Systematically organized / protocol available, structurally maintained, and kept up to date
5	Systematically evaluated, and continuously improved

Table legend. Note concerning the specific wording of the above rating scheme: for reasons of comparability this is a verbatim copy from the rating scheme in use by PharmAccess for rating all items covered in their Monitoring & Evaluation efforts in the HIF Nigerian program.

Table "Quality-2": Mean scores for the general medical documentation

	Mean score	1	2	3	4	5
Anamnesis	2.30	15	47	30	8	0
Physical examination	2.04	42	19	26	11	0
(Lab) investigations	2.04	42	19	26	11	0
Differential diagnosis	1.61	51	27	17	2	0
Treatment	3.02	1	13	69	17	0
Follow-up	2.40	27	18	38	16	0

Table legend. Mean = mean score for all patient notes. 1,2,3,4,5 = percentage of patient records that scored in this specific category.

Sixty-three cases malaria were investigated. The diagnosis of malaria was laboratory confirmed in less than half the cases (43%). Seventeen percent was documented to be moderate or severe disease. Many different regimens were used for treating malaria. The outcome of treatment was not recorded in 70% of cases.

- Tuberculosis was rarely diagnosed in the HIF program in Nigeria. Of the 4 cases that we could examine all 4 were laboratory confirmed. All were cases of pulmonary TB, all were treated with combination therapy. All 4 had (bi-)weekly follow-up visits to the clinic. Compliance was checked and documented. There were no drop-outs. Treatment response was adequately monitored. However, there was no (documentation of) screening of the family members. Only 2 of the 4 cases were offered an HIV-1 test (both tested HIV-1 negative.
- HIV-1 infections are also rarely diagnosed in the HIF program in Nigeria. Were could examine 5 cases. In none of them a CD4 count could be measured locally. Two were asymptomatic, 1 reported weight loss, 1 had diarrhea and fever, and 1 had oral candidiasis. All 5 were referred for further evaluation and treatment to a designated HIV-1 treatment center. Two patients received counseling and 2 patients disclosed their serostatus to their families.
- 15 cases of infant and childhood respiratory infections were investigated. In only 1 case an X-ray was made. Supportive treatment was instituted in only 1 case (iv fluids). Many different

antibiotics were used to treat the infection in 14 of the 15 patients. Outcome was not documented in 6 cases.

- 15 cases of infant and childhood diarrhea were investigated. In 3 cases aspecific diagnosis was made: 2 amoeba infections, and 1 case of typhoid. 10 cases received supportive treatment: 9 received ORS, and 1 was referred. 14 patients received antibiotics, many different regimens were used. Outcome was not documented in 6 cases.
- We investigated 43 cases of hypertension. Eleven had systolic pressure greater than 180 mmHg, 16 had diastolic pressure greater than 110 mmHg. Most were mildly symptomatic, and complained of headache, palpitations, and dizziness. In 32 there was no documentation of complications, however it is unknown to us if this could be interpreted as evidence of the absence of complications. There were many different regimens in use to treat the hypertension. 12 patients received life-style advises. Thirty-nine patients were in regular follow-up. 38 had their compliance checked. 21 had a well-controlled blood pressure at the last clinic visit.
- We investigated 25 cases of diabetes mellitus, all of which were lab-confirmed with a fasting blood sugar. In two cases it was documented that the presence of complications was investigated. Nineteen did not receive life-style advice. Twenty-three patients received treatment, 4 of those received injections with insulin, and the rest was treated with oral tablets. Compliance was checked in 23 patients. In 5 cases there were no further blood glucose measurements. 11 of the last blood glucose measurements were below 140 mg/dL (8 mmol/L), 8 were above 140 mg/mL.
- Twenty-two cases of pregnant women were investigated. Thirteen started antenatal care before the 30th week of pregnancy. Five were not offered an HIV-test (the local physicians estimate that about 8% of the pregnant women are HIV-1 positive). 13 were not offered a syphilis test. There was 1 documented complication during pregnancy (diabetes mellitus). There were no premature deliveries, 3 emergency cesarean sections, and 13 normal vaginal deliveries (the remaining 6 cases were still pregnant at the time of the pilot study). There were 2 complications during labor (1 prolonged labor, 1 hypertension). There were no recorded complications after the delivery, and no still births.
- 14 newborns who received antenatal care were investigated. One was less than 2.5 kg at birth. There were 3 cases of neonatal morbidity: 1 conjunctivitis, 1 jaundice, 1 respiratory tract infection. All had received at least 2 follow-up visits. Most had received multiple vaccinations.

Quality of malaria thick smears

As part of the pilot study into the quality of the medical case notes, we also performed a small pilot study into the quality of malaria thick smears. The local personnel was asked to prepare thick smears, which were collected and taken to our own hospital were they were examined by dr. Tom van Gool of the parasitology department in the Academic Medical center of the University of Amsterdam. About half the slides were of such bad quality that they could not be used to reliably demonstrate the absence or presence of malaria parasites in the blood sample.

Household survey

As part of the household survey performed by the AIID, a medical questionnaire, anthropometrics and blood tests for anemia, glucose, HIV-1 and malaria will be performed. This research is in the preparatory stages.

Recommendations to the HIF

The findings of the AMC-CPCD in the first year of the HIF Nigerian program lead to the following recommendations to the HIF:

Organizational

- Improve the collection and management of data. Good-quality data are vital for the management and evaluation of the project.
    - Coding of investigations, diagnoses, and treatments
    - Cross-checks between enrollment and utilization datasets
    - Build-in checks in the data-entry system, e.g. dates, correct IDs, to minimize the risk of data entry errors
    - Better registration of lapsed contracts, terminations and renewals of insurances
- Investigate 'adverse selection' in Lagos. With the currently available data it can not be excluded that 'adverse selection' is taking place in Lagos with preferential enrollment of sick(er) individuals. This is evidenced by the remarkably low number of enrolled subjects per family and the considerably higher number of clinic visits per subject in Lagos compared to Kwara. This threatens the sustainability of the program in Lagos. This topic should receive considerable attention, the recruitment strategies in Lagos should be adjusted to avoid adverse selection as much as possible. The strategy should be to enroll whole groups of people at once, or at the least whole families. The household survey will provide us with more adequate data on household composition in both Lagos and Kwara. Target group selection procedures might need to be re-evaluated.
- Investigate reasons for termination of insurances. A large percentage of subjects both in Kwara and in Lagos do not renew their insurance in the first two months of the second year of the program.
- Improve reporting of diagnoses in Kwara: only 'single' diagnoses are reported in Kwara.

Data collection & management

- Register (causes of) deaths.
- Perform case note-investigations regularly (and randomly). This should be part of routine M & E (Monitoring & Evaluation) of the healthcare providers by PharmAccess. This allows for i) monitoring of progress in the improvement of documentation of provided healthcare, ii) monitoring of the quality of the data entered into the project database, and iii) it provides some degree of protection against fraud where non-existing provided care is claimed.

Clinical practice

- Encourage the use of investigations to confirm diagnosis. This applies to routine laboratory investigations, but also to microbiology tests, serologic screening and physical diagnostics like X-rays. We acknowledge that indiscriminate testing should be avoided, but the current underutilization of the laboratory facilities can only result in misdiagnoses and therefore inadequate treatment of disease. The low utilization-rate of the diagnostic facilities also hinders the laboratory analysts from gaining adequate experience with testing methods, which

contributes in a negative way to the vicious circle of basing clinical management on presumptive diagnoses. The very frequent presumptive diagnosis of “malaria / typhoid”, which is often followed by empirical treatment for both diseases simultaneously, is the most prominent example of this practice.

- Emphasize protocollized treatment. Treatment for a specific disease differs greatly between healthcare providers, and even between patients for the same healthcare provider. However, it is unlikely that the patient population and/or disease organisms are much different. The healthcare providers should make much more use of protocols for the diagnosis and treatment of certain conditions. This is accepted good clinical practice and should be more vigorously enforced.
- Formularies of the pharmacies should be updated and standardized. Sometimes archaic and/or substandard treatments are used.

Future plans

Infectious diseases

- Malaria research will focus on making a proper laboratory-assisted diagnosis, this research will be performed in the larger setting of management of patients presenting with fever of unknown origin.
- Tuberculosis appears to be relatively rare, and is often managed in designated TB treatment centers. Therefore, in our in-depth studies we will only focus on screening / diagnosing TB and on the indiscriminate use of antibiotics with antituberculous activity for other diseases.
- For HIV-1 infection the same applies, it is relatively rarely diagnosed, and treatment is done outside the HIF Nigerian program in designated treatment centers. For HIV-1 we will focus on improved screening of sentinel groups, like pregnant women presenting for antenatal care.
- Our research into infant and childhood diarrhea will be extended with infant and childhood respiratory diseases as these infections also represent a heavy burden of disease in children. Our research will focus on diagnostic and therapeutic practices.
- Vaccine-preventable diseases are rarely diagnosed in this cohort, the application of vaccine other than tetanus shots is also rarely captured in the database. From the current data it is unclear if this low number of cases is because of a true low incidence of disease, or because of problems with adequate diagnosing of these diseases and capture of vaccinations in the database. Initially we will integrate our research into vaccine preventable diseases in the research into antenatal care.

Metabolic diseases

- Metabolic diseases like diabetes mellitus and hypertension are frequently diagnosed. Incidence rates are much higher in Lagos compared to Kwara. Our in-depth research into metabolic diseases will go ahead as originally planned.

Maternal and pediatric issues

- Screening for and diagnosis of sexually transmitted diseases is rarely done. Apparently screening is only done as part of antenatal care for pregnant women, and not even in all pregnant women. Our in-depth studies will therefore, just as for HIV-1, focus on appropriate screening methods in the setting of antenatal care.
- Family planning was originally short-listed as focus for further in-depth studies. Family planning is currently an integral part of the household survey of the AIID.
- As expected, pregnancy rates are high. Our in-depth research into antenatal care will go ahead as originally planned. Other major issues in reproductive health will receive proper attention as well: vaginal fistulae, incidence of complications before / during / after labor.
- The disease cluster “anemia, malnutrition, enteric parasites in children and babies” will be added to the list of indicator diseases.