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Seasonal Patterns of All-Cause & Malaria Mortality in Rural Burkina Faso 1998 - 2007

Bachelor Thesis

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Abbreviations

CI	Confidence Interval
COD	Cause of Death
CRSN	Centre de Recherche en Sante´ de Nouna
CSMF	Cause Specific Mortality Fraction
CSPS	Centres de Santé et de Sociale et de Promotion
CVD	Cardiovascular disease
DSA	Demographic Surveillance Area
HDSS	Health and Demographic Surveillance Systems
INDEPTH	International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries
InterVA	Interpretation of Verbal Autopsy
ITN	Insecticide-treated Bednets
MA	Moving Average
MDG	Millennium Development Goal
NHD	Nouna Health District
PCVA	Physician Coded Verbal Autopsy
RR	Rate Ratio
SES	Social Economic Status
SSA	Sub-Saharan Africa
VA	Verbal Autopsy
VER	Vital Event Registration

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Abstract

Background: To plan and develop health interventions targeted lessening mortality, reliable and correct empirical data on cause-specific mortality patterns is essential, but such information is still lacking in the developing world. Health and Demographic Surveillance Systems applying the verbal autopsy method allow to obtain longitudinal cause-specific mortality data of populations in poor countries. Physician Coded Verbal Autopsy (PCVA) is usually used to determine the cause of death, but recently the Interpreting Verbal Autopsy (InterVA) method, a computerized model, was alternatively introduced.

Objectives: The aim of this study is to determine the effect of season on all-cause and malaria mortality analyzing data of the period 1998 to 2007 obtained by the Nouna Health and Demographic Surveillance System with ~ 80,000 individuals in rural northwestern Burkina Faso and to compare seasonal malaria mortality patterns for the PCVA approach as well as for the InterVA model.

Methods: All-cause and cause-specific death rates were calculated overall and by age group. Seasonal mortality patterns were modeled using parametric Poisson regression analysis adjusted for sex, area of residence and year of death.

Results: Overall, 7,378 deaths were observed corresponding to an average mortality rate of 11.9 deaths per 1,000. InterVA assigned half as many deaths to malaria as physicians did. Both methods showed young children to be most affected by malaria whereas for adults and older people other causes of death played a major role. Despite few discrepancies, both methods showed comparable significant malaria mortality patterns in children with higher rates during the rainy season whereas for adults and old people the highest death rates occurred during the hot dry season for other causes of death. The effect of season is well explained by a parametric sinusoidal function. Under five mortality declined significantly for other causes of death over the years alongside stagnant malaria mortality.

Conclusions: This study adds further evidence to the seasonality of malaria mortality in malaria endemic regions of rural West Africa, shows the high impact of malaria on childhood deaths and emphasizes that it is still important to protect young children living in areas with high malaria transmission. Furthermore, it was shown that both the probabilistic InterVA model and PCVA determine reasonably well seasonal patterns of malaria mortality in a rural malaria holo-endemic area in Burkina Faso and are very valuable for the planning of health resources and activities, which should take into account seasonal variations in malaria mortality.

1 Introduction

High mortality levels in Sub-Saharan Africa are still a major public health problem. Children are the most affected group with malaria as one of the major causes of death in this region. To develop, implement and evaluate appropriate health policies and interventions for those at most risk and reduce mortality, information on mortality patterns is needed. But such data is scarce in developing countries, especially for adults and older people. Since most deaths occur at home and are therefore not registered in resource-poor countries, no information is available on time, location and cause of death. In order to support developing countries to determine health priorities and develop health policies, the International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries established a network of Health and Demographic Surveillance Systems in low- and middle-income countries that conduct research and provide health and demographic data on a longitudinal basis (1).

Despite the considerable number of studies analyzing mortality patterns in developing countries, relatively few set their focus on seasonal patterns. To contribute to the understanding of seasonality of malaria mortality, the aim of this study is to investigate the impact of season on all-cause and malaria mortality in different age groups analyzing data of a ten-year period obtained by the Nouna Health and Demographic Surveillance System (Nouna HDSS) in rural Burkina Faso. The Nouna HDSS provides cause-specific mortality data using the Verbal Autopsy method, which is interpreted by both physicians and recently by using a computerized model. Since the Nouna HDSS area is a malaria endemic region and physicians are known to overdiagnose malaria in such settings (2, 3), this study also compares seasonal patterns of malaria mortality between both methods.

The first part of this thesis gives an overview of mortality in Sub-Saharan Africa and describes the most common causes of death as well as the impact of season on mortality. Furthermore, Health and Demographic Surveillance Systems will be illustrated and the Verbal Autopsy method will be explained including its limitations.

The second part describes the study population analyzed in this study as well as both methods of interpreting Verbal Autopsy data used in the Nouna HDSS: physician coded verbal autopsy and a computer-based probabilistic model known as InterVA. Then, the management of this complex dataset for this study will be explained and methods used for data analysis will be presented.

The next part shows the results of data analysis beginning with a descriptive section presenting all-cause and cause-specific mortality estimates followed by a demonstration of seasonal patterns.

Finally, an interpretation of the results is given in the last part of this thesis and strengths and weaknesses of this study will be outlined.

2 Background

Seasonal variations on all-cause and cause-specific mortality rates are analysed for this thesis using data from a population under demographic surveillance, located in the Nouna district of the province Kossi in Burkina Faso, a country of the western part of Sub-Saharan Africa. An overview of mortality in Sub-Saharan Africa is given in the first part of this section. The second part explains how Health and Demographic Surveillance Systems using the Verbal Autopsy method to assign causes of death can provide mortality data in developing countries, which is the basis for this study. Cause-specific mortality is described in the third part and seasonal patterns of mortality in SSA are portrayed in the last part of this section.

2.1 Mortality in Sub-Saharan Africa

There are still high rates of mortality recorded in Sub-Saharan Africa (SSA). In 2010, 3,709,000 children under five years died in this region. Rates of under five mortality had fallen from 174 deaths per 1,000 live births in 1990 to 121 deaths per 1,000 live births in 2010 (4), but the disparity in mortality between SSA and other regions has grown. SSA still has the highest rates of childhood mortality with one in eight children facing a probability of dying before age five - that is more than 17 times the average in developed regions (5). Of the 26 countries with under-five mortality rates above 100 deaths per 1,000 live births in 2010, 24 are in SSA which accounted for 48.7% of all under five deaths worldwide (4). Four of five countries in this region have achieved the largest absolute reductions in under-five mortality, although SSA is combating the HIV/AIDS pandemic, that has affected countries in this region more than elsewhere in the world (6). However, the average rate of reduction in under-five mortality has doubled from 1.2% a year in 1990–2000 to 2.4% a year in 2000–2010 (4).

In 2010, many countries were on track to achieve the Millennium Development Goal (MDG) 4 of a two-thirds reduction of the under five mortality rate by 2015 compared to the rate in 1990, but in SSA childhood mortality has been decreasing too slowly during the past decades to achieve this target (6). With a decline by 30% in under five mortality in 1990-2010 it is less than half that is required to reach MDG 4 of 58 deaths per 1,000 live births (4). However, there is increasing evidence that MDG 4 can be achieved, but only if countries in SSA give high priority to reducing child mortality (6).

The highest levels of childhood mortality rates in SSA were in West and Central Africa where one out of six children died before age five in 2008 (2). Together with South Africa, West and Central Africa had strikingly lower rates of decline in under five mortality than other regions in SSA (3). For example, in Burkina Faso the under five mortality rate was 201 deaths per 1,000 live births in 1990 and decreased only by 17% to 166 deaths per 1,000 live births in 2009 (7).

High levels of fertility in SSA (8), combined with high levels of infant-mortality, have resulted in an increase of the absolute number of infant deaths from 2,273,000 in 1990 to 2,350,000 in 2010 but the infant mortality rate decreased from 105 per 1,000 live births in 1990 to 76 deaths per 1,000 live births in 2010 (9).

Whilst mortality in later childhood has been decreasing, the proportion of neonatal deaths has been rising (10). SSA, which accounts for more than a third of all global neonatal deaths, has the highest neonatal mor-

tality rate of 35 deaths per 1,000 live births in 2010 and has shown the slightest progress in lessening neonatal mortality rates by only 19% over the last two decades. 1,123,000 children younger than one month died, which represents one third of all under-five deaths in this region (6).

An underlying cause of a third of childhood deaths in SSA is malnutrition (11), increasing children's risk of dying from infections (12). Special efforts to combat infections by improving the nutritional status might prevent millions of childhood deaths (11). Other risks of dying depend on several factors. For instance, children in rural areas and with low social economic status (SES) face a higher risk of dying than children living in urban areas and rich households. In addition, children from well educated mothers have a two times lower risk of dying before age five than children of poorly educated mothers (11).

Besides, stillbirth is a huge neglected problem in SSA (13) with about 800,000 babies being affected each year (14). Since differentiation between stillbirth and neonatal deaths is problematic (14), estimation of such deaths is difficult.

Regarding maternal health, both globally and in SSA progress is insufficient to achieve MDG 5 to reduce the maternal mortality ratio by three quarters between 1990 and 2015, although reduction has more accelerated since 2000. The maternal mortality ratio decreased by only 26% from 870 per 100,000 live births in 1990 to 640 per 100,000 live births in 2008 (11). Thus, urgent action is needed to apply more proven interventions to improve reproductive and maternal health. Generally, maternal mortality rates are higher in West and Central Africa than in Eastern and Southern African countries (5).

Except for maternal mortality, little information exists about adult and old age mortality in developing countries. In 2010, mortality rates for men were at around 300 per 1,000 in some regions of SSA and show notably higher mortality risks than in other MDG regions. For women the break is at around 200 per 1,000 and only SSA and Oceania are in the highest risk category (9). Available adult mortality data for SSA show that three-quarters of the global burden of diseases attributable to unsafe sex is primarily a result of HIV/AIDS (15). Between 1970 and 2010 substantial increases in adult mortality occurred in SSA because of the HIV epidemic. However, in almost all regions of SSA adult male and female mortality has begun to decline since 2005, partly as a result of reductions in HIV seroprevalence and perhaps also because of increased access to antiretroviral treatment (9).

Yet, in many countries of SSA, reliable mortality statistics are of poor quality or barely available (11). Therefore, Health and Demographic Surveillance Systems have been established to provide longitudinal mortality data in developing countries, as described in detail in the following section.

2.2 Health & Demographic Surveillance Systems

Reliable information on the characteristics and health of certain populations is deficient in the developing world (16), which limits the understanding of global health and of changing morbidity and mortality. Cause-specific mortality data is very valuable for health policy makers to set health priorities for their population and to plan and establish appropriate and proven interventions (17). In the developed world such data is usually provided by well-established vital registration systems (18). In many developing countries with very limited resources such systems are weak and cause-specific mortality data often does not exist (16, 17). To provide empirical population and health data in developing countries, Health and Demographic Surveillance

Systems (HDSS) have been established and are linked by the International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries (INDEPTH), which is currently composed of 34 HDSS field sites in 19 countries located in Africa, Asia and Oceania (19). INDEPTH's mission is to focus on the need to collect and analyse reliable data from low and middle income countries and to support capacity building in these regions (20). Figure 2.1 shows countries with INDEPTH member centres running HDSSs.

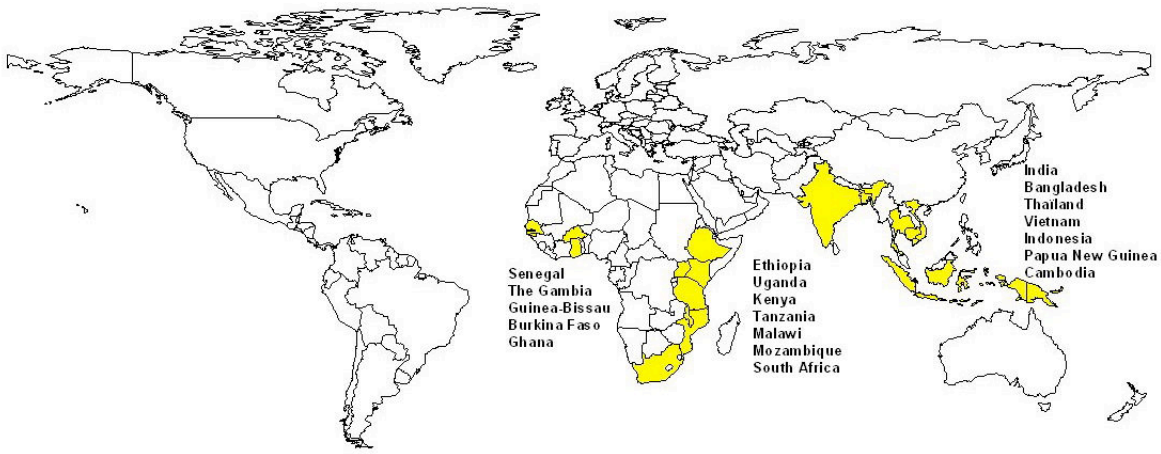

Figure 2.1: Countries with HDSS field sites in the INDEPTH Network (19)

The field sites generate longitudinal information on health of a population including key variables such as births, deaths, causes of death, population size and migration, which enables to identify levels, patterns, causes and trends of mortality (21).

2.2.1 Structures of Health & Demographic Surveillance Systems in the Developing World

One of the key characteristics of a HDSS is the measurement of demographic and health data on a longitudinal basis. Usually, HDSS data are collected on three different levels: individuals, households, and residential units (Figure 2.2).

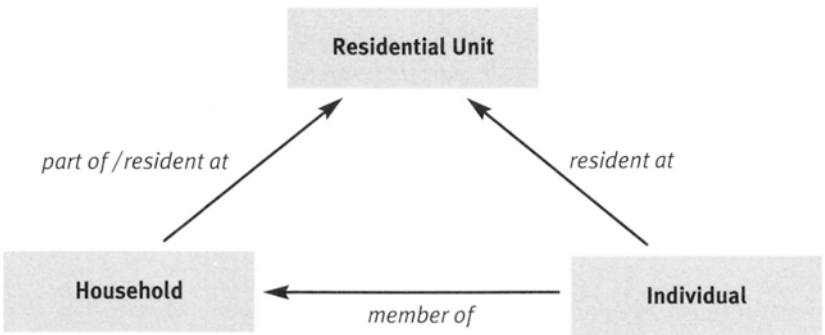

Figure 2.2: The three main HDSS subjects (22)

Their function is to be an informative unit in a predefined Demographic Surveillance Area (DSA), which is a clearly circumscribed geographic area and allows to make a clear distinction between the informative units that are included in the HDSS and those that are excluded (22).

The whole population that is resident of a DSA is included in the HDSS after being defined and registered by an initial census. The number of individuals between different HDSS sites varies between 5,000 and 212,000 persons. Equivalent to a dynamic cohort the cohort size increases by births and in-migration and decreases by deaths and out-migration After the first census, HDSSs collect attribute data on a prescribed set of characteristics by visiting registered and new individuals, households and residential units followed by regular update rounds (Figure 2.3) to record vital changes or events such as births or other pregnancy outcomes, marital status, deaths and migrations.

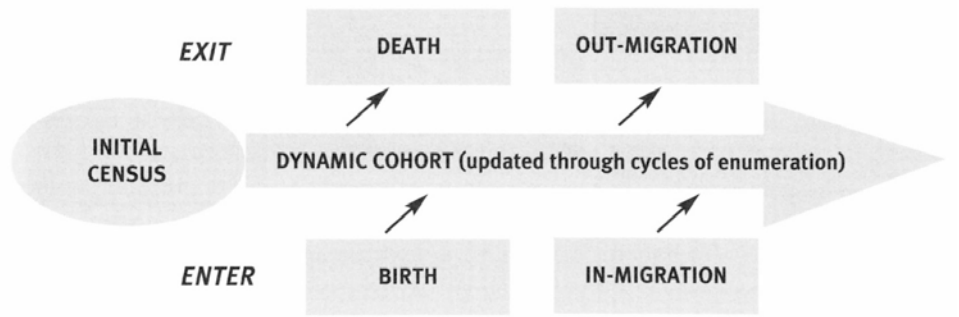

Figure 2.3: Prospective monitoring of demographic events (23)

Thus, the system provides data on the number of individuals under surveillance within the cohort at any time (21). But the larger the time interval for the rounds of visits is, the greater is the risk of under-reporting of vital events (24).

Vital events within a DSA can be described by the following demographic equation:

$$P_{t_1} = P_{t_0} + B_{t_0,t_1} - D_{t_0,t_1} + I_{t_0,t_1} - O_{t_0,t_1}$$

where P is the population, B is the number of births, D is the number of deaths, I is the number of in-migrants, O is the number of out-migrants and t_0,t_1 is the time interval between two update visits. All vital events of the whole study population are recorded, even if they occur outside the DSA. Conversely, vital events of individuals, whose place of residence is outside the DSA, are not recorded, even if they occur within the study area (22).

The consistent recording of vital events allows to estimate the total time spent by each individual in the study population called person-years, which is used as a denominator to estimate age-, sex-, and cause-specific mortality rates (23).

To maintain and improve the data quality obtained by HDSSs, a variety of quality controls is used at the field, data processing, and analysing stages. During regular visits to registered households, already collected data is checked and corrected if necessary, which makes HDSSs self-checking (23). In addition, trained supervisors check data quality by visiting households again, re-interviewing its individuals and checking forms (21).

Community key informants usually identify such events and obtain information on deaths. Thereby typical indices and outcome measures like all-cause and cause-specific mortality based on HDSS data can be generated. Detailed information like cause of death is generally obtained through verbal autopsies (21), a method to assign cause of death in developing countries.

2.2.2 Methods of Cause of Death Assignment in Developing Countries

In order to monitor the health situation of a population and to plan for suitable interventions, information and analyses on cause-specific mortality are essential. However, in many developing countries, cause-specific mortality data is sparse because most deaths occur outside health facilities and are therefore not registered. To obtain cause-specific mortality information in settings with weak vital registration systems, a widely used method to ascertain a probable cause of death (COD) is Verbal Autopsy (VA) (16).

After someone dies in such a setting, trained field staff conducts an interview with one of the closest relatives or another primary caregiver of the deceased about signs, symptoms, and circumstances preceding death that can be interpreted later to identify a probable COD (25). Thus, there might be bias in remembering, reporting and recording such information (26), which is more likely to occur with longer intervals between death and interview, worsening the repeatability of the VA procedure (27). Furthermore, the interviewed person can have an effect on the final identification of a probable COD such as mothers who are able to retrospectively report signs and symptoms of their child's illness, but maybe not distinguish between degrees of severity (28). This relates to one of the key underlying assumptions of VA, that each disease category has a distinct pattern of symptoms that can be recognized, recalled and reported accurately by lay respondents (29). Moreover, the comparability of VA data between different countries is limited by diverse questionnaire designs, different approaches of the interviewers and in interpreting the gathered information although efforts towards standardization have been made (30-32).

The VA method has high rates of sensitivity and specificity for diseases that manifest with a well-defined and unique set of symptoms such as neonatal tetanus, measles, and accidents, but this instrument is less able to discriminate between diseases with overlapping symptoms such as malaria and pneumonia or HIV/AIDS and tuberculosis (33, 34). It has been shown that VA can overestimate malaria deaths in both low and high transmission settings even where the proportional mortality of malaria among a particular population is very low (29, 35, 36).

Also, misclassification of mortality estimates from causes obtained by VA depends not only on the sensitivity and specificity of the VA questionnaire but also on the cause-specific mortality fraction (CSMF), the true proportion of deaths resulting from a particular cause. The same VA instrument can sometimes overestimate and sometimes underestimate deaths due to a specific cause depending on the underlying proportion of deaths due to that cause in the population in which the VA instrument is being used. If false positives excess over false negatives, the CSMF based on VA data is an overestimate. Conversely, the excess of false negatives over false positives results in an underestimate. If CSMF is low, specificity of the VA questionnaire is more important than sensitivity in estimating accurate results (33).

Besides variations in VA data collection, different methods in interpreting VA information to determine a probable COD are used such as physician review, algorithms or neural networks (37). Physician-Certified

Verbal Autopsy (PCVA) is still the most common approach to interpret VA data (38). Usually, two local physicians review the questionnaires and assign a probable COD. A third physician is involved in this procedure if the two previous physicians cannot agree on a final diagnosis. At least two of the three physicians have to agree on a final diagnosis otherwise no cause of death is recorded (36, 39-42).

Arguments against physician-based certification of COD from VAs are variations in interpreting VA data due to different training, experience, and/or perceptions of local epidemiology of the reviewing physicians and difficulties of maintaining quality work over long periods of time (43). Physicians may vary in their interpretation of VA data (44) hindering reliable comparisons of cause-specific mortality between different regions and periods of time (45, 46) and worsening the accuracy of estimated CSMFs.

Furthermore, PCVA is a time- and resource-intensive process (23) and in resource-constrained areas it may not seem appropriate to assign the few available physicians to review VA questionnaires. This may also lead to long delays in analysing the data, because finding and training physicians in VA interpretation is still a challenge in poor countries (32). Moreover, many deaths get lost during the VA procedure due to physicians not assigning a cause (25).

In many cases, the process of COD assignment from VA is simplified to a single cause per individual not considering further probable causes (47). If physicians reviewing VA questionnaires do not reach consensus on a final COD, no cause will be recorded although VA data is available on this particular death, which may result in underestimation of the burden due to a particular COD (48). In addition, the approach of agreeing on one final cause lacks a theoretical justification. When multiple opinions agreeing on the same COD for a particular case are interpreted as representing the "true" cause even if it is not, democratic fallacy can be manifested (32, 48). Thus, if two physicians derive different CODs, both suggestions should be recorded with a weighting of 50% to each as suggested by Byass et al (48). Furthermore, by assigning only one COD for each case, important vital information on possible interactions between diseases and comorbid conditions can get lost (49).

A new method to interpret VA data is a computerized model known as InterVA (Interpreting Verbal Autopsy), which is a more consistent approach than the PCVA method (47). Based on Bayes' probability theorem the InterVA model weights symptoms reported during the VA process in relation to specific CODs and determines up to three probable CODs and their corresponding likelihoods (49), thus reducing the effect of democratic fallacy (48). It may be also more suitable to asses comorbid conditions (49) and estimates the overall lack of certainty for a case (44). Further advantages are that InterVA does not relate to any particular setting or questionnaire and it can interpret information from different sources (49). It also needs only little human resources and is therefore a cheaper and faster method in comparison to PCVA. Besides, it is 100% consistent in interpretation, which allows special and temporal comparisons (27) and it is free available on the internet (50).

One limitation of this method and the VA method in general is the lack of a ''gold standard'' against which to validate diagnoses (37). In addition, interpretation of VA information by InterVA is less nuanced and detailed than physicians' reviews. An experienced and skilled physician going through VA questionnaires may better recognize atypical and conflicting information (44, 51, 52).

However, despite obvious limitations the VA method is at present the principle way to study COD information in the developing world.

2.3 Cause-Specific Mortality in Sub-Saharan Africa

Information on cause-specific mortality is sparse in SSA and presented by only few studies yet. Most research has been conducted in populations of children showing infections as leading COD during childhood (53). A review of reports from HDSS sites in SSA presented pneumonia, diarrhoea and malaria as the main causes of childhood mortality (54), which are preventable and also possible to treat (5). Incidences of diarrheal deaths varied widely among HDDS sites. The highest mortality estimates were found for West African sites and the most affected groups were young children as well as old people (55). A study analysing data from a malaria holoendemic area of north-western Burkina Faso for the time period 1999 to 2003 showed that malaria was with about 40% the most common COD with highest mortality rates among infants aged 6 – 11 months (56). Increases in funding and special efforts to fight and prevent malaria in SSA during the last decades have shown critical progress and a widespread reduction of malaria morbidity and mortality by developing and implementing proven and effective tools and interventions. But still about 90% of all malaria deaths worldwide occur in SSA with children under the age of five as the most affected group (57).

Over the period from 1990 to 2010 mortality among neonates increased by 17% (6) mostly attributable to infections including sepsis, pneumonia, tetanus, diarrhoea as well as complications during pregnancy and birth such as asphyxia and preterm births having the highest risk of dying (5).

A comparison of mortality profiles from surveillance sites during 1999–2003 showed, that malaria-related mortality was highest in West African sites, with AIDS-related mortality highest in South Africa (58). The most affected groups by age were the youngest children and young adults (55), although only 4% of all childhood deaths are attributable to HIV/AIDS in SSA (10).

During the past decades noncommunicable diseases such as cancer, diabetes and cardiovascular diseases have become more frequent (55) as major CODs especially among people age 65 years and above. In addition, mortality from chronic diseases increased with rising age during the period from 2000 to 2009 (59).

Mortality in adulthood was mainly due to cardiovascular diseases (60), injury deaths (15) and AIDS followed by complications of pregnancy among women in SSA (61). During 1997-2007, the main CODs for complications during pregnancy and childbirths were haemorrhage (34%) and hypertension (19%) (62), accounting for more than 50% of all maternal deaths in SSA (63). Other factors contributing to the high maternal mortality in SSA are consequences of malnutrition such as maternal anaemia or iodine deficiency as well as the high incidence of stillbirths and congenital anomalies (12). In addition, mothers infected with HIV face a ten times higher risk to die than HIV-negative mothers (10).

However, reliable and accurate cause-specific mortality data are limited among adults in this region (60). Uncertainty ranges were generally large for deaths from specific diseases. For example, the relative uncertainty for deaths from ischemic heart disease ranged from 25–35% (15) and highlights the need for improved population health measurement systems providing more accurate mortality data.

2.4 Seasonal Patterns of Mortality

There is only little information available on the seasonal effect on mortality in developing countries yet. To investigate seasonal variations in mortality, several studies have been conducted in SSA, for example in Burkina Faso (56, 64), Nigeria (65) or Senegal (66). An analysis on seasonal patterns of overall-mortality in the HDSS population of Nouna located in northwestern Burkina Faso reported consistently higher mortality during the hot dry season, which lasts from November to May, and lower death rates during the wet season from June to October except for infant mortality excessing at the end of the rainy season. It was the first study, which used a parametric sinusoidal function to describe all-cause mortality patterns. However, the variation observed for the older age groups was even seen in children aged one to five years (64). Another analysis of HDSS data from Burkina Faso found for children in that age group an intermediate mortality pattern with peaks at around the end of the rainy season but also during the early dry season (67). This contrasts with findings from other studies in SSA reporting higher all-cause mortality among children during the wet season as compared to the dry season (56, 65, 66).

Besides seasonal all-cause mortality patterns, data from the Nouna HDSS in Burkina Faso, a rural and a malaria holoendemic area, was analysed to investigate cause-specific mortality in children under five years of age during 1999 to 2003. They found significant higher malaria mortality rates in the rainy season in comparison to the dry season. Higher death rates during the dry season could be attributed to acute respiratory infections (56). The same pattern for respiratory infections was reported from a study in northern Cameroon analysing hospital deaths for the period 1993 to 2009 that occurred more frequently during the dry season. Besides malaria as COD, deaths from diarrheal diseases, malnutrition and anaemia were also more frequent during the rainy season (68).

Further evidence to consistently higher childhood mortality during and at the end of the wet season, when transmission intensity of malaria is at its highest, was added by a further analysis of HDSS data from Burkina Faso (69) also using a parametric sinusoidal function to describe the seasonal effect on mortality. It was the first time this approach was applied to investigate cause-specific mortality patterns influenced by the seasons for malaria. This study also adds further important information to the shortage of available data on CODs and seasonal patterns of mortality among adults and older people in SSA. The findings showed higher mortality rates during the dry season and are in line with previous analyses of data from the same HDSS on seasonal all-cause mortality variations among adults and older people (67, 70). In contrast to childhood mortality, high mortality rates in adults during the dry season are mostly attributable to other diseases than malaria (69). A following study in the Nouna HDSS region in Burkina Faso found in a more detailed analysis on cause-specific mortality that especially mortality from cardiovascular disease (CVD) increased in the hot dry season (71).

Regarding adult mortality patterns, a study evaluated the impact of malaria on maternal death through the analysis of retrospective data on seasonal variations at Maputo Central Hospital in Mozambique between January 2001 and December 2003. Maternal malaria mortality patterns varied by season with peaks at the beginning and the end of the malaria transmission season (72).

3 Study Population and Methods

3.1 Study Area and Population

Data analysed for this thesis was obtained by the Nouna HDSS located in the North-West of Burkina Faso and run by the Centre de Recherche en Sante´ de Nouna (CRSN) (73). The Nouna HDSS is a member of the INDEPTH Network (21) and part of the Nouna Health District (NHD), a rural area located in the poor province Kossi about 300 km away from Ougadougou, the capital of Burkina Faso (Figure 3.1).

In 1992, an initial population census was conducted to gather demographic data on all individuals within the study area. At the beginning, the HDSS covered three peripheral health facilities, Centres de Santé et de Sociale et de Promotion (CSPS), within 39 villages and a population size of 26,626 individuals (73). Additionally, passive Vital Events Registration (VER) started as a monthly activity by interviewing the key informant of each village by a trained interviewer and asking if any vital events had occurred since the previous visit. To check quality of data and add further information, two control censuses were carried out in 1994 and 1998. Since 1998, active VER was implemented. Instead of communicating with a key informant of a village, interviewers visit each registered household themselves every three to four months and collect information on key variables such as births, deaths, pregnancy status, migration and the corresponding dates (73, 74).

Figure 3.1: Geographical location of the Nouna HDSS in Burkina Faso (75)

A further census was conducted in 2000 adding two new villages to the study area as well as Nouna town, which is the capital of the NHD and served by one hospital, followed by a fourth census in 2004. In 2004, the study area was expanded again. 17 further villages were included, leading to a current total of 58 villages on 1,756km^2 in Kossi inhabited by about 81,500 inhabitants in 2008, and 13 additional health facilities in the surrounding villages (73).

The Nouna HDSS is mainly a rural area populated almost exclusively by subsistence farmers, living in rural villages. The village population varies from 121 to 2,346 persons. The distance from village to health centre ranges from 0 to 34 km (73). Generally, the main water sources are wells (76), with the exception of the town

of Nouna, a semi-urban area, which represented with about 23,902 inhabitants 30% of the HDSS population in 2008 (73) and has a running water supply for some of its inhabitants. Nouna also has a telephone system and an electric power supply (76), which serves the town 19 hours per day at present. The capital is not a well-developed city, but it is a provincial economic and political centre. Nouna's inhabitants benefit from a better transportation system and shorter distances to health facilities and have a relatively higher SES than those living in the surrounding villages (74).

The population pyramid of the Nouna HDSS is typical for SSA with a young demographic base and few old people (Figure 3.2). Both sexes are equally distributed in almost all age groups.

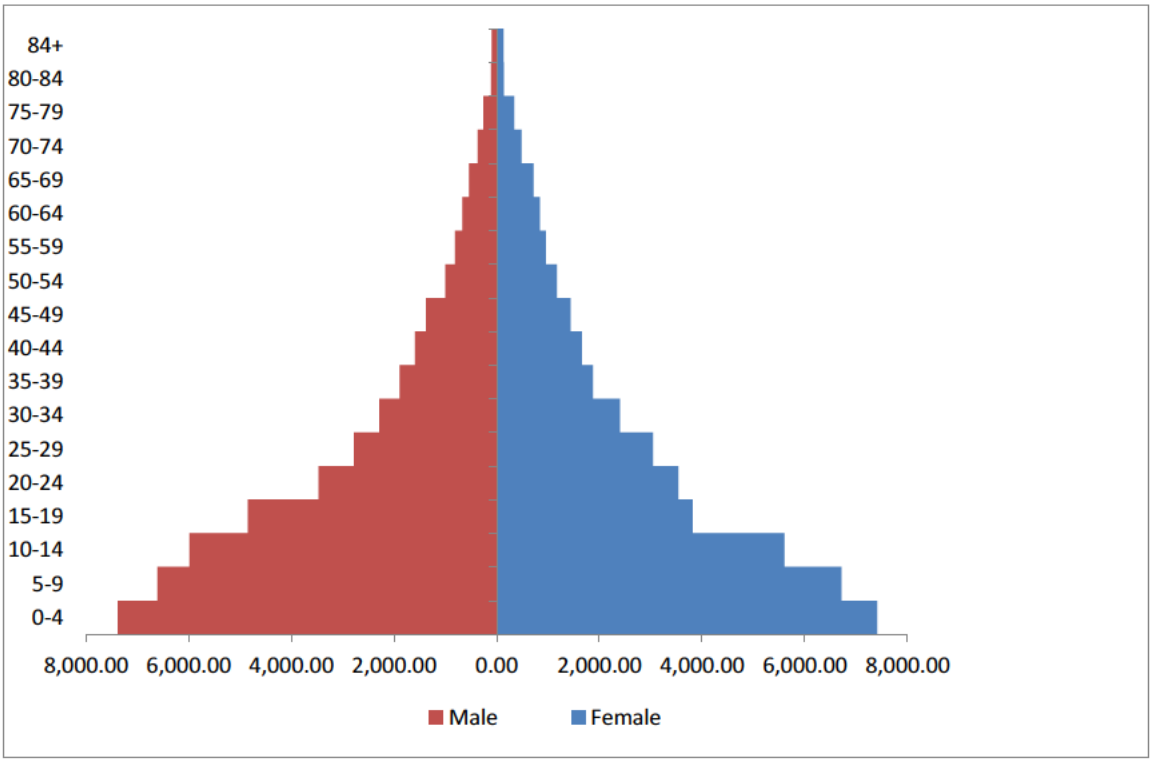

Figure 3.2: Nouna Population Pyramid, 2009 (75)

Different ethnic groups, Mossi, Bwaba, Marka (or Dafing), Samo and Peulh (or Fulani), inhabit the study area and the three main religions are Islam (62%), Christianity (32%), and traditional religions (6%). Besides the official language French, the Dioula language permits communication between different ethnic and religious groups (76).

A sub-Sahelian climate predominates the study area, which is a dry orchard savannah with two distinct rainy (June-October) and dry (November-May) seasons per year. During the rains, numerous roads are flooded and not passable (73, 76). Although malaria is holoendemic in this region, malaria transmission, morbidity and mortality are highest during and shortly after the wet season. The overall annual Entomological Inoculation Rate varies between the villages with 100 and 900 per year with approximately 95% emerging in the rainy season (56, 77).

All data obtained by the Nouna HDSS is entered into a Microsoft Access database (78), which has a system to check for data consistency and is updated regularly. The Institute of Public Health of the University of

Heidelberg receives updates of the Nouna HDSS database at least twice annually and routinely performs analyses of the data.

3.2 Procedures of Cause of Death Assignment

In addition to the regular VER visits, the Nouna HDSS applies the VA method to record COD data since 1993. The Nouna questionnaire is standardized, given in French and covers individual identification information, demographic data, and the clinical history up to the point of death by interviewing the relatives or primary caregivers of the deceased. Clinical history includes information on symptoms like diarrhoea, vomiting, convulsions etc., their duration and treatment. Additionally, further information not asked for in the structured section can be described in free-texts. After a death has occurred, trained interviewers, who have no medical background, visit the corresponding household and translate the questionnaire into local languages, for example Dioula, to conduct the VA interview after they have obtained oral informed consent. Most VA interviews are carried out between three to six months after death allowing for the mourning period. To ensure data quality, 5 to 10 % of the questionnaires are checked by supervisors revisiting households and re-interviewing respondents.
VA questionnaires are entered into the Microsoft Access database and sent back to the interviewers for correction in case of missing or unclear information. To derive probable CODs, local physicians trained on the VA method review the questionnaires. In addition, the InterVA method has been applied in the Nouna HDSS recently to provide CODs.

3.2.1 Physician Coded Verbal Autopsy

After a VA interview was conducted, usually two or three experienced and specifically trained local physicians code the 12-page questionnaires using ICD-10 after reading and completing them.
After assessing all information recorded in the questionnaire, the first physician derives the most likely COD according to his or her medical knowledge. A second physician, who is blinded of the diagnosis of the first physician, follows the same procedure. In case of discordance between both physicians a third one is involved and provides a probable COD independently of the two previous suggestions. At least two reviewing physicians have to agree on a final cause. In case of no consensus, the cause is classified as unknown.

3.2.2 Application of the InterVA Model

Besides the PCVA method, the InterVA-3 was applied here to the Nouna HDSS data to derive the most likely cause of 35 possible COD groups (Table 3.1). The InterVA model defines the probability of a cause (C) for a particular death given the presence of a specific disease indicator or symptom (I) using an automated Bayesian model (47).

The posterior probability P (C|I) for cause (C) given the indicator (I) can be derived as:

$$P(C|I) = \frac{P(I|C) \times P(C)}{P(I|C) \times P(C) + P(I|!C) \times P(!C)}$$

where P(!C) is the probability of not (C). The probability of an indicator given a specific cause P(I|C) and the a priori probability of a cause P(C) at population level has been estimated by an expert panel of physicians with extensive clinical experience in resource-poor settings (79). Thus, the a priori distribution of CODs at population level is not country-specific but a high degree of precision is not essential for these probabilities in order to build a workable model (47). InterVA is based on a matrix of these probabilities and adjusts the a priori probability P(C) of each possible cause by the above theorem according to this matrix of conditional probabilities of a set of indicators and of a set of causes and displays up to three likely CODs and their associated posterior probabilities P (C|I) for each death. The matrix consists of 35 columns corresponding to 35 COD groups and the rows are represented by 106 indicators or symptoms. To consider large variations of the prevalence of particular diseases such as HIV/AIDS and malaria between different regions, the a priori probabilities of CODs can be adjusted in the model.

Table 3.1: CODs included in InterVA-3 (80)

Accidental drowning	Malnutrition
Accidental poisoning	Maternity related death
Acute cardiac death	Measles
Acute respiratory disease not pneumonia	Meningitis
Bloody diarrhoea	Non-bloody diarrhoea
Chronic cardiac death	Other acute infection
Chronic respiratory disease	Other chronic infection
Congenital malformation	Other digestive disease
Diabetes	Other fatal accident
Disease of nervous system	Perinatal asphyxia
HIV/AIDS related death	Pneumonia/Sepsis
Haemoglobinopathy	Pre-term/small baby
Homicide	Stroke
Kidney or urinary disease	Suicide
Kwashiorkor	Tetanus
Liver disease	Transport-related accident
Malaria	Tuberculosis (pulmonary)
Malignancy	

Information from a VA interview was extracted from electronically available data of the VA questionnaire's structured section. An international team of physicians and epidemiologists assigned the obtained infor-

mation to a set of InterVA indicators. Overall, 69 (64.5%) indicators could be allocated to the gathered data from the Nouna VA questionnaire[1]. Information recorded in the free-text section of the questionnaire is not standardized and available electronically, thus it did not feed into the model. No data could be assigned to 16 indicators because they demand for a clinical diagnosis, which is impossible to gain from lay respondents at the household. In order to consider local epidemiology for important diseases in the Nouna HDSS region, the malaria and HIV/AIDS prevalence was set to "high" for malaria and to "low" for HIV/AIDS (81).
Information on CODs derived by the InterVA method is saved in an additional database, which is attached to the Nouna HDSS database.

3.3 Data Management and Analysis

For this thesis, the basis for data analysis is an extract of the complete database from the Nouna HDSS for the observation period January 1, 1998 to December 31, 2007. This includes all gathered information on the individuals in the study area such as date of birth, date of death etc. and COD information provided by physicians and InterVA. Data for Nouna town could only be analysed since January 1, 2000 after Nouna town was integrated into the DSA. Data management and analysis were carried out with the statistical software SAS, version 9.2.

3.3.1 Data Management

All individuals registered in the Nouna HDSS within the study period were included in the analysis except a few individuals (N=97) for whom no information on month of death were available. For age-specific analysis the following age groups were defined: infants (< 1 year), children (1 to < 5 years), youth (5 to < 14 years), adults (15 to < 60 years), and old people (60+ years).
The original dataset, consisting of one observation for each individual, was aggregated according to month, year, sex, age group, and area by a SAS macro. Thus, the aggregated dataset comprises 2,400 observations (12 x 10 x 5 x 2 x 2), one for each month, one for each calendar year between 1998 and 2007, one for each age group, for males and females, and for the rural area and Nouna town separately. To calculate mortality rates per month, the monthly population was estimated as the average of the population at the beginning and end of a month (mid-month population) for each observation as well.
For cause-specific analysis, six different COD categories were considered: three for each method of COD assignment. CODs derived by the PCVA method were assigned to malaria, other causes (non-malaria), and the group of ill-defined (including fever, abdominal pain, convulsions etc.) or missing causes. There can be two reasons for a missing cause. Either a complete VA questionnaire was missing or the questionnaire was reviewed but there was no consensus between the physicians on a definitive COD. All CODs not assigned to malaria as well as the ill-defined and missing group were considered as other causes[2].
For analysis of InterVA data, only the first probable CODs with the highest likelihood as displayed by the

[1] Table 8.3 in the appendix gives an overview of the extracted and all InterVA indicators.
[2] Table 8.1 in the appendix presents all possible causes, which can be assigned by physicians.

InterVA output were considered for this study. Causes derived by the InterVA model were allocated analogously to causes determined by physicians regarding the "malaria" and "other causes" category. All deaths with a missing VA questionnaire or where the model could not define a cause were considered as the group of undetermined and missing causes.

3.3.2 Descriptive Analysis

The main outcome in this analysis is mortality. Data were analysed descriptively overall and for different combinations of the categories COD, age group, sex, area, year and month. Besides the total number of deaths among different categories, the monthly all-cause and cause-specific mortality rates per 1,000 were calculated to analyse seasonal trends and estimated as

$$\mu = (D/M) * 1000$$

in which μ represents the mortality rate, D the number of observed deaths in a month and M an approximation of the person years, estimated by dividing the mid-month population by 12. The corresponding 95% confidence intervals (CI) were calculated as

$$CI\ 95\% = \mu \pm 1.96 \sqrt{[(D/M^2) * 1000^2]}$$

To assess the importance of malaria as a COD by month, the monthly proportion of malaria deaths of all deaths that occurred within the corresponding month was estimated. For graphical assessment of seasonal variations and long-term trends of mortality, a weighted five-month moving average (MA) of the mortality rates was used according to

$$MA_{month} = 0{,}4 * \mu_{month} + 0{,}2 * (\mu_{month+1} + \mu_{month-1}) + 0{,}1 * (\mu_{month+2} + \mu_{month-2})$$

3.3.3 Poisson Regression Models

Poisson regression is the method of choice to analyse the effect of covariables on a count variable (82). In order to assess the relative effect of month on death and to control for potential effect modification and confounding of covariates (sex, calendar year, and area), age group-specific Poisson regression models were fitted for all cause- and malaria deaths separately. The dependent variable in these models is the number of deaths, which are assumed to follow a Poisson distribution, an approximation of the binomial distribution applied in large samples, where the probability of an event (e.g. vital status at the end of an observation period) is small.

The natural logarithm of the person-years approximation (see above) was entered into the model as the so-called offset term. The regression equation for the first fitted model is

$$\ln [D (x_1, x_2, x_3, x_4)] = \ln (M) + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 \qquad \textbf{(Model I)}$$

in which D is the number of deaths in each month, M is the person-years approximation, x_1 is a vector with binary dummy variables for each month and x_2 represents a vector with binary dummy variables for each calendar year of observation. The variable for sex is denoted as x_3 and the variable for area of residence is represented by x_4. Instead of estimating an intercept, this model calculates an estimate for each month. In the second model

$$\ln [D (x_2, x_3, x_4)] = \ln (M) + \beta_0 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 \qquad \textbf{(Model II)}$$

no effect of month is estimated but an intercept β_0 of the overall effect is provided. The relative effect of month on mortality was calculated by the difference of the parameters $\beta_1 - \beta_0$ of the monthly effect of the first model and the overall effect of the second model.

In order to further investigate the seasonal trend, the monthly effect on mortality for malaria and other causes was estimated using Poisson regression with a sine-function of the form

$$g_1(x_1) = \sin (x_1 * \pi/6)$$

and a cosine-function of the form

$$g_2(x_1) = \cos (x_1 * \pi/6)$$

in which x_1 adopts a value between 1 and 12, corresponding to the months January to December. This resulted in the model

$$\ln [D (x_1, x_2, x_3, x_4)] = \ln (M) + \beta_0 + \beta_{11}\, g_1(x_1) + \beta_{12}\, g_2(x_1) + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 \qquad \textbf{(Model III)}$$

Estimating the monthly effect as a sine- and cosine-function in one model gives the best fit automatically. Results are shown as a parametric sinusoidal curve. To determine the significance of the monthly effect on mortality, the difference of the deviance of Model II and the deviance of Model III was calculated. Since two parameters (β_{11}, β_{12}) are estimated, the difference is asymptotically χ2-distributed with two degrees of freedom. P-values of less than 0.05 were considered significant. The seasonal effect is calculated as logarithmic rate ratio (RR). For graphical assessment of the validity of this approach, modelled rates were compared to the MA rates. For this, another model was fitted

$$\ln [D (x_1, x_2)] = \ln (M) + \beta_0 + \beta_{11}\, g_1(x_1) + \beta_{12}\, g_2(x_1) + \beta_2 x_2 \qquad \textbf{(Model IV)}$$

in which x_1 can take a value between 1 and 12 for each month and x_2 can adopt all values between 1 and 10, which corresponds to the years 1998 to 2007.

To allow for comparison to the MA rates, the logarithmic RRs were given as rates μ by the following equation

$$\mu = \exp(\beta_0 + \beta_{11} g_1(x_1) + \beta_{12} g_2(x_1) + \beta_2 x_2)$$

Since Nouna town was encompassed in the study area in 2000, 432 out of 480 observations, determined by all possible cross-classifications of the variables year, sex and area for which people were observed, were included in each model. For every model 48 observations were set missing, because the number of individuals in these observations was zero. Poisson regression was carried out with the SAS-procedure PROC GENMOD.

4 Results

4.1 Descriptive Analysis

The total population size of the Nouna HDSS increased steadily from 32,809 in 1998 to 80,382 in 2007 taken into account that Nouna town and two surrounding villages were integrated in 2000 and 17 further villages were included into the study area in 2004 (Table 4.1). The rural population rose steadily from 32,809 persons in 1998 to 56,051 persons in 2007. This was not seen for Nouna town where the population decreased by 16 persons or 0.7% from 2001 to 2002. However, for the period 2000 to 2007, the population in Nouna town showed an overall increase by 19.1% corresponding to a mean yearly growth rate of 2.58%.

Table 4.1: Annual population per area, Nouna HDSS, 1998 - 2007

	1998	1999	2000*	2001	2002	2003	2004**	2005	2006	2007
Rural	32,809	33,927	39,051	39,834	40,253	41,068	48,876	53,682	54,946	56,051
Nouna	-	-	20,432	21,544	21,528	21,569	22,130	22,525	23,597	24,331
TOTAL	**32,809**	**33,927**	**59,484**	**61,378**	**61,781**	**62,637**	**71,006**	**76,207**	**78,542**	**80,382**

* two villages and Nouna town were included
** 17 villages were included

4.1.1 All-Cause Mortality

During the whole study period from January 1, 1998 to December 31, 2007, 7,378 deaths occurred (3,573 female, 3,805 male), corresponding to a crude mortality rate for the overall population of 11.9/1,000 (95% CI 11.7-12.2). The crude mortality rate by sex was 11.6/1,000 (95% CI 11.2-12.0) for females and 12.3/1,000 (95% CI 11.9-12.7) for males. In the rural area, a total of 5,722 deaths were observed for the whole observation period and since the year 2000, in Nouna town 1,656 deaths occurred corresponding to crude mortality rates by area of 13.0/1,000 (95% CI 12.7-13.3) and of 9.3 deaths per 1,000 (95% CI 8.9-9.8), respectively.
The crude age-specific all-cause mortality rate over the whole study period was for infants 56.8/1,000 (95% CI 53.9-59.8) and for children aged one to four years 22.0/1,000 (95% CI 21.0-23.0). For young people be-

tween 5 to 14 years of age, an all-cause mortality rate of 2.5/1,000 (95% CI 2.3-2.7) was recorded. Adults (15–59 years) showed an all-cause mortality rate of 5.4/1,000 (95% CI 5.2-5.7) and for people 60 or older a rate of 56.3/1,000 (95% CI 53.8-58.8; Table 4.2) was estimated for the whole observation period.

Furthermore, table 4.2 shows the number of deaths and corresponding monthly all-cause mortality rates for each age group. The highest rate of mortality (85.4/1,000) for infants occurred in August in the middle of the wet season. Children showed a mortality peak in October at the end of the wet season with a mortality rate of (37.1/1,000) but rates for August, September, and November were relatively high as well. Mortality among the other age groups was higher during the dry season; especially for the oldest age group extremely high mortality rates were observed in April (80.8/1,000).

Table 4.2: Deaths (N), rates* per 1,000 and 95% CI by age group and month for all CODs, Nouna HDSS, 1998 – 2007

	Infants (<1)			Children (1-4)			Young (5-14)			Adults (15-59)			Old (60+)		
Month	**N**	**Rate**	**95%CI**	**N**	**Rate**	**95%CI**	**N**	**Rate**	**95%CI**	**N**	**Rate**	**95%CI**	**N**	**Rate**	**95%CI**
Jan	100	49.4	39.7-59.1	141	20.0	16.7-23.4	34	2.3	1.6-3.1	118	5.1	4.2-6.0	209	73.7	63.7-83.7
Feb	93	45.3	36.1-54.5	131	18.3	15.1-21.4	45	3.0	2.2-3.9	152	6.4	5.4-7.4	181	62.4	53.3-71.5
Mar	106	51.4	41.6-61.2	128	17.8	14.7-20.9	41	2.8	1.9-3.6	157	6.6	5.6-7.6	184	63.5	54.3-72.6
Apr	111	53.8	43.8-63.8	130	18.1	15.0-21.2	54	3.7	2.7-4.6	140	5.9	4.9-6.8	234	80.8	70.4-91.1
May	93	44.6	35.5-53.6	116	15.9	13.0-18.8	32	2.1	1.4-2.9	137	5.7	4.7-6.6	170	58.2	49.5-67.0
Jun	79	37.3	29.1-45.6	93	12.6	10.1-15.2	25	1.7	1.0-2.3	115	4.7	3.9-5.6	153	51.9	43.7-60.1
Jul	107	50.3	40.8-59.9	127	17.2	14.2-20.2	24	1.6	1.0-2.2	94	3.9	3.1-4.6	128	43.3	35.8-50.8
Aug	182	85.4	73.0-97.8	206	27.9	24.1-31.7	39	2.6	1.8-3.4	135	5.5	4.6-6.5	117	39.5	32.4-46.7
Sep	148	69.3	58.2-80.5	218	29.4	25.5-33.4	31	2.0	1.3-2.8	118	4.8	4.0-5.7	122	41.1	33.8-48.4
Oct	158	73.4	62.0-84.9	231	31.2	27.1-35.2	35	2.3	1.5-3.1	137	5.6	4.7-6.5	143	48.1	40.2-55.9
Nov	139	64.5	53.8-75.2	223	30.0	26.1-34.0	42	2.7	1.9-3.6	122	5.0	4.1-5.8	151	50.6	42.6-58.7
Dec	120	55.6	45.6-65.5	183	24.6	21.0-28.2	50	3.3	2.4-4.2	155	6.3	5.3-7.3	191	64.0	54.9-73.0
TOTAL	**1436**	**56.8**	**53.9-59.8**	**1927**	**22.0**	**21.0-23.0**	**452**	**2.5**	**2.3-2.7**	**1580**	**5.4**	**5.2-5.7**	**1983**	**56.3**	**53.8-58.8**

*Highest rates are highlighted in red.

4.1.2 Cause-Specific Mortality

Information on CODs was obtained by VA and 5,621 (76.2%) questionnaires were completed for all of the 7,378 deceased persons (2,650 or 78.8% for children less than 5 years) during the whole observation period. After a death had occurred, only 4.3% of all VAs were carried out during the first three months to allow for the mourning period. Since VER follows a three to four month cycle, 11.7% VA interviews were performed within a time interval of three to six months after a death and 84.1% VAs were carried out later than six months after death. Table 4.3 shows the numbers of missing VAs with highest proportions for infants and

young people. The amount of missing questionnaires for the oldest was the smallest (12.4%). The average proportion of missing VAs was 23.8%.

Table 4.3: Deaths and missing VAs by age group, Nouna HDSS, 1998-2007

	Infants (<1)	Children (1-4)	Young (5-14)	Adults (15-59)	Old (60+)	Total
Deaths	1436	1927	452	1580	1983	**7378**
Missing VAs	384	443	116	388	426	**1757**
% Missing VAs	26.7%	23.0%	26.7%	24.6%	12.4%	**23.8%**

In addition to missing VA questionnaires, no consensus between physicians who review the questionnaires is a further reason for a missing COD. Numbers for these missings were very similar for the first three age groups but increased for adults and old people (Table 4.4). Numbers of ill-defined CODs resulting from in-sufficient or unclear information were relatively small for children under age five but increased for the older age groups. The "undetermined" category encompasses all CODs, which could not be determined by the InterVA model. It is larger for infants and children (~ 6%) than in the ill-defined category determined by PCVA. For the older age groups, an opposite picture is shown. Here, the percentage of undetermined causes is smaller than in the ill-defined category.

Table 4.4: Missing causes due to no consensus between physicians, undetermined and ill-defined causes, Nouna HDSS, 1998-2007

	Infants (<1)	Children (1-4)	Young (5-14)	Adults (15-59)	Old (60+)	TOTAL
Deaths	1436	1927	452	1580	1983	**7378**
No consensus	64	98	25	125	174	**486**
No consensus %	4.5	5.1	5.5	7.9	8.8	**6.6**
Ill-defined	55	65	45	183	295	**643**
Ill-defined %	3.8	3.4	10.0	11.6	14.9	**8.7**
Undetermined	86	112	35	105	160	**498**
Undetermined %	6.0	5.8	7.7	6.6	8.1	**6.7**

Table 4.5 gives an overview of CODs by sex for the whole observation period of the Nouna HDSS. The proportion of deaths in the different COD categories is relatively similar between males and females but varies between the two methods of COD assignment. Overall, malaria is responsible for one quarter of all deaths according to CODs determined by physicians. In contrast, the InterVA model assigned Malaria only to 11.2% of all deaths. The proportion of other causes determined by InterVA is by ~ 20% larger than other causes derived by the PCVA method. Corresponding to the average amount of ill-defined and undetermined deaths in table 4.2, the proportion for the undetermined and missing group is smaller for InterVA for both sexes.

For malaria determined by InterVA, a slightly higher rate was recorded for females (1.4/1,000; 95% CI 1.3-1.5) but the difference between males (1.3/1000; 95% CI 1.1-1.4) and females was not significant. For PCVA, malaria mortality rates were the same for both sexes. A significant distinction between males and females was observed only for other causes derived by InterVA with higher mortality rates for males

(7.7/1,000; 95% CI 7.4-8.0) than for females (7.0/1,000; 95% CI 6.7-7.3).

Table 4.5: COD by sex, Nouna HDSS, 1998-2007

		Male				Female			
		N	%	Rate	95%CI	N	%	Rate	95%CI
PCVA	**Malaria**	927	24,4	3.0	2.8-3.2	919	25.7	3.0	2.8-3.2
	Other causes	1544	40,6	5.0	4.7-5.2	1361	38.1	4.4	4.2-4.7
	Ill-defined + missing	1334	35,1	4.3	4.1-4.5	1293	36.2	4.2	4.0-4.4
	TOTAL	**3805**	**100**	**12.3**	**11.9-12.7**	**3573**	**100**	**11.6**	**11.2-12.0**
InterVA	**Malaria**	392	10.3	1.3	1.1-1.4	433	12.1	1.4	1.3-1.5
	Other causes	2387	62.7	7.7	7.4-8.0	2170	60.7	7.0	6.7-7.3
	Undetermined + missing	1026	27.0	3.3	3.1-3.5	970	27.1	3.1	2.9-3.3

An overview of the distribution of CODs is presented in table 4.6 for each age group comparing both methods of VA interpretation. Among diagnoses identified by physicians, the main COD for infants and children was malaria. For adults, the proportion of malaria was the smallest (6.8%) and deaths assigned to the "other causes" category accounted for more than half of all adult deaths (52.6%).

Similarly, results of CODs determined by InterVA showed the highest proportion of malaria deaths in the two youngest age groups, but the smallest proportion of malaria deaths occurred in the oldest age group (2.7%), where other causes played a major role (71.7%). Corresponding to the results of table 4.5, less malaria causes were determined by InterVA than by PCVA except for adults. Here, the proportion of malaria deaths was larger (11.3%) than the proportion of malaria deaths assigned by physicians (6.8%). After stratifying by sex, 7.2% deaths were due to malaria for males according to InterVA and physicians assigned 6.9% of all male adult deaths to malaria corresponding to a malaria mortality rate of 0.4/1,000 (95% CI 0.3 – 05) for both methods. For females, a larger difference was found. 15.5% of all deaths assigned by InterVA are related to malaria whereas physicians determined only 6.7% malaria deaths. The corresponding malaria mortality rate was significantly lower among InterVA diagnoses (0.8/1,000; 95% CI 0.7 – 1.0) than for PCVA (0.4/1,000; 95% CI 0.3 – 0.4) [3].

Among all causes assigned by physicians, the malaria mortality rate was 20.7/1,000 (95% CI 19.0-22.5) for infants and 9.4/1,000 (95% CI 8.7-10.0) for children one to four years of age. For young people (5–14 years), a malaria mortality rate of 0.6/1,000 (95% CI 0.5-0.7) occurred and adults showed a malaria mortality rate of 0.4/1,000 (95% CI 0.3-0.4). For people aged 60 or older, a malaria mortality rate of 8.1/1,000 (95% CI 7.2-9.1) was estimated. For infants and children, a combined mortality rate of 11.9/1,000 (95% CI 11.3-12.6) was recorded (data not shown).

Except for adults, malaria mortality rates estimated for CODs derived by the InterVA model were significantly lower than rates estimated for causes determined by physicians. Here, the rate for infants was 8.0/1,000 (95% CI 6.9-9.1). For children, it was 3.9/1,000 (95% CI 3.5-4.3) and for young people the lowest rate was estimated (0.3/1,000; 95% CI 0.2-0.3). The rate for adults was significantly higher than the corresponding rate of malaria determined by PCVA. Here, the rate was 0.6 (95% CI 0.5-0.7), which is due to a significant difference among female deaths in this age category as already shown above. For children under

[3] Data is shown in table 8.2 in the appendix.

five, a malaria mortality rate of 4.8/1,000 (95% CI 4.4-5.2) was estimated (data not shown). A full analysis of COD is not intended here.

Table 4.6: Cause-specific deaths (N), proportions (%), rates per 1,000 and 95% CI by age group, Nouna HDSS, 1998-2007

			Infants (<1)	Children (1-4)	Young (5-14)	Adults (15-59)	Old (60+)	TOTAL
PCVA	Malaria	N	524	823	105	108	286	**1846**
		Rate	20.7	9.4	0.6	0.4	8.1	**3.0**
		95%CI	19.0-22.5	8.7-10.0	0.5-0.7	0.3-0.4	7.2-9.1	**2.8-3.1**
		%	36.5	42.7	23.2	6.8	14.4	**25.0**
	Other causes	N	458	563	178	831	875	**2905**
		Rate	18.1	6.4	1.0	2.9	24.8	**4.7**
		95%CI	16.5-19.8	5.9-7.0	0.8-1.1	2.7-3.1	23.2-26.5	**4.5-4.9**
		%	31.9	29.2	39.4	52.6	44.1	**39.4**
	Ill-defined + missing	N	454	541	169	641	822	**2627**
		Rate	18.0	6.2	0.9	2.2	23.3	**4.2**
		95%CI	16.3-19.6	5.7-6.7	0.8-1.1	2.0-2.4	21.7-24.9	**4.1-4.4**
		%	31.6	28.1	37.4	40.6	41.5	**35.6**
	TOTAL	**N**	**1436**	**1927**	**452**	**1580**	**1983**	**7378**
		Rate	**56.8**	**22.0**	**2.5**	**5.4**	**56.3**	**11.9**
		95%CI	**53.9-59.8**	**21.0-23.0**	**2.3-2.7**	**5.2-5.7**	**53.8-58.8**	**11.7-12.2**
InterVA	Malaria	N	203	342	49	178	53	**825**
		Rate	8.0	3.9	0.3	0.6	1.5	**1.3**
		95%CI	6.9-9.1	3.5-4.3	0.2-0.3	0.5-0.7	1.1-1.9	**1.2-1.4**
		%	14.1	17.7	10.9	11.3	2.7	**11.2**
	Other causes	N	806	1103	268	959	1421	**4557**
		Rate	31.9	12.6	1.5	3.3	40.3	**7.4**
		95%CI	29.7-34.1	11.8-13.3	1.3-1.7	3.1-3.5	38.2-42.4	**7.2-7.6**
		%	56.1	57.2	59.3	60.7	71.7	**61.8**
	Undetermined + missing	N	421	490	134	438	513	**1996**
		Rate	16.7	5.6	0.7	1.5	14.5	**3.2**
		95%CI	15.1-18.3	5.1-6.1	0.6-0.9	1.4-1.7	13.3-15.8	**3.1-3.4**
		%	29.3	25.4	29.6	27.7	25.9	**27.1**

Table 4.7 shows the seasonal variation of malaria deaths for each method of COD assignment by month and age group. According to both methods, the highest proportions of malaria deaths for infants and children occurred in the middle of the wet season whereas the picture is less clear for the other three age groups among physicians' diagnoses. In contrast, InterVA showed the highest proportions of malaria deaths also for the three oldest age groups during the rainy season. The percentage of malaria deaths derived by InterVA is lower for each age group and month except for adults. For this age group lower malaria proportions in comparison to the PCVA results were found only in April and May.

In summary, the descriptive analysis showed a variation of cause-specific mortality by age group, sex, and month. Additionally, a significant difference in all-cause mortality by area of residence was found. To further investigate seasonal variations of mortality, trends of cause-specific mortality will be presented over the whole observation period for children under age five, most affected by malaria, and seasonal mortality patterns will be analysed in detail adjusting for sex, calendar year, and area and will be presented for each age group.

Table 4.7: Monthly proportions of malaria deaths by method of COD assignment and age group, Nouna HDSS, 1998 - 2007

	Infants (<1)		Children (1-4)		Young (5-14)		Adults (15-59)		Old (60+)	
Month	**PCVA**	**InterVA**	**PCVA**	**InterVA**	**PCVA**	**InterVA**	**PCVA**	**InterVA**	**PCVA**	**InterVA**
Jan	27.0	9.1	28.4	12.0	14.7	8.8	6.8	11.9	14.4	1.0
Feb	28.0	10.8	30.5	16.8	22.2	8.9	2.0	5.3	10.5	1.1
Mar	26.4	6.6	38.3	14.8	9.8	4.9	5.1	9.6	12.5	3.3
Apr	31.5	9.9	28.5	10.7	25.9	15.1	8.6	7.2	12.8	1.7
May	25.8	5.4	46.6	12.8	15.6	9.1	8.0	4.4	17.1	2.3
Jun	30.4	16.5	35.5	19.6	12.0	16.0	3.5	17.4	15.0	3.9
Jul	44.9	9.3	47.2	22.2	37.5	19.2	10.6	15.2	13.3	5.4
Aug	47.8	28.2	59.7	25.0	20.5	10.5	8.1	16.3	18.8	6.0
Sep	48.6	20.9	54.6	24.2	12.9	13.3	11.0	16.1	11.5	3.3
Oct	41.1	19.7	46.3	21.0	17.1	11.8	8.0	20.3	17.5	5.6
Nov	31.7	12.3	40.4	12.9	45.2	7.1	4.9	7.4	17.2	0.7
Dec	36.7	6.7	38.8	14.1	36.0	10.0	7.1	8.4	14.7	1.0
Total	**36.5**	**14.1**	**42.7**	**17.7**	**23.2**	**10.9**	**6.8**	**11.3**	**14.4**	**2.7**

4.2 Poisson Regression

4.2.1 Relative Effect of Month of Death on Mortality

All-cause mortality and the percentage of malaria deaths varied by season as presented before in the descriptive section. This corresponds with the relative monthly effect on all-cause and malaria mortality modelled with Poisson regression for each age group (Figure 4.1).

The top part of figure 4.1 presents the estimates for all-cause mortality. For infants and children, the logarithmic RRs were higher in the months of the wet season, whereas old people showed an opposite trend. The relative effect of month for young people (5-14 years) and adults is similar to the trend for the oldest, but the picture is less clear. The logarithmic RRs are slightly higher during the rainy season than for the oldest age group.

In the middle part of figure 4.1, malaria mortality for physicians' diagnoses is presented. Here, the pattern for infants and children shows higher logarithmic RRs from August until November during and shortly after the wet season and lower RRs in the dry season indicating that malaria might be responsible for the mortality pattern in these age groups. No clear trend could be found for young people. The relative effect for adults was high during both seasons but with a drop in June after the wet season had begun whereas for old people the highest RRs occurred during the dry season from January to April.

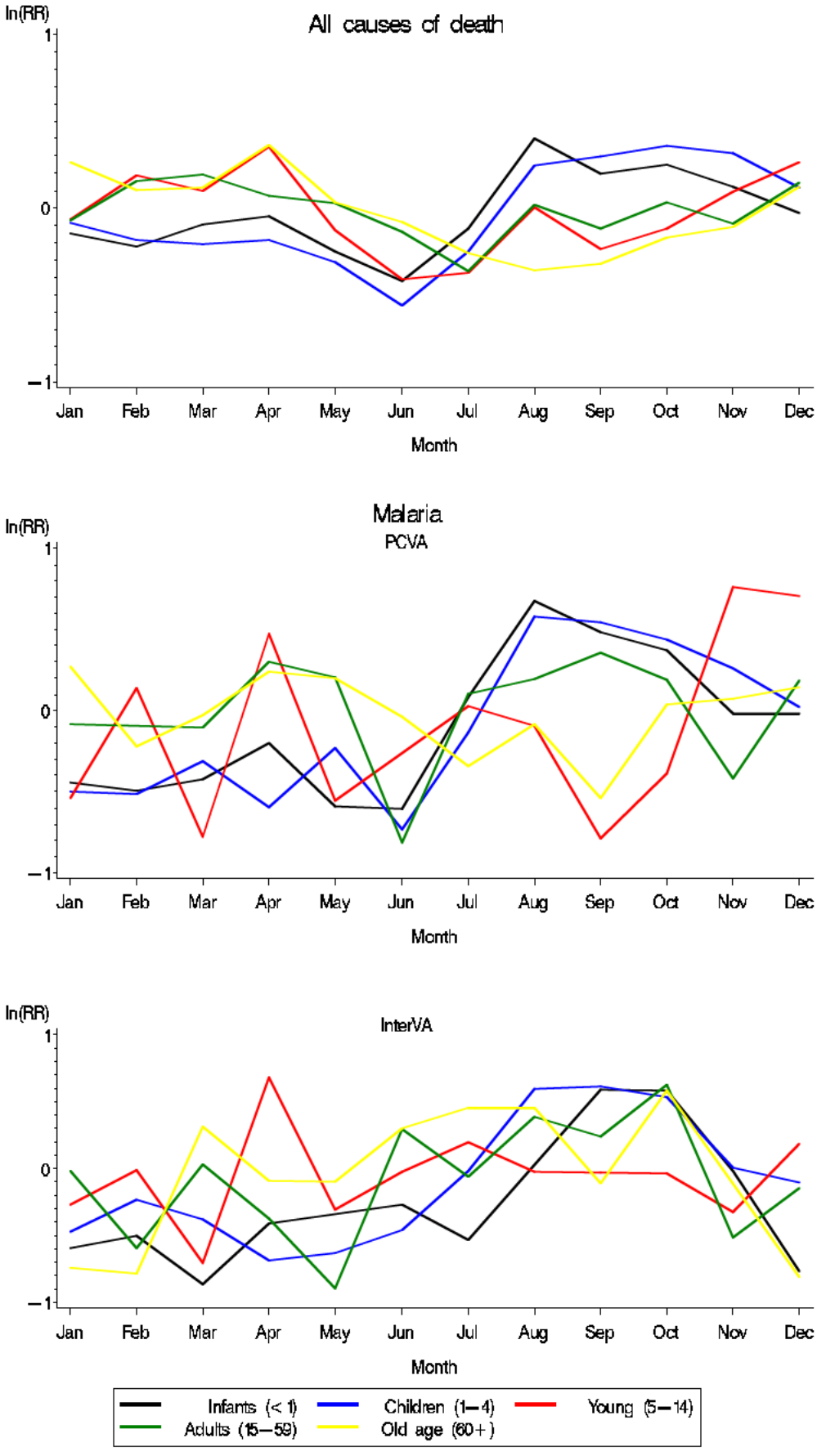

Figure 4.1: Relative effect of month of death by age group, Nouna HDSS 1998 – 2007

The last part of figure 4.1 presents the relative effect of month on malaria deaths obtained by InterVA. It shows similar trends for the two youngest age groups in comparison to the middle part of the figure, whereas young and old people showed slightly higher RRs during the rainy season than in the middle part of the figure. During the dry season, the picture is less clear for young people and adults. Old people showed relative high RRs during the second half of the dry season but very low RRs in the first half from December to February.

4.2.2 Further Assessment of the Seasonal Effect on Mortality

For further assessment of the seasonal effect on mortality, RRs were modelled with Poisson regression using a continuous function of month of death. Figure 4.2 shows the estimated age group-specific logarithmic RRs for each month and the modelled logarithmic RRs for malaria and other causes according to PCVA.
Infants and children showed a highly significant seasonal effect with a peak in September for malaria ($p < 0.0001$) whereas for the "other causes" category, higher RRs were recorded from October to February during the end of the wet season and the beginning of the dry season ($p = 0.02$ in infants and $p < 0.0001$ in children). For young people, no significant seasonal effect was seen for other causes ($p = 1$), whereas for malaria, higher RRs occurred from October to February ($p = 0.02$), but the deviance of the model fit was only about 278 with 418 degrees of freedom[4]. For adults, the seasonal effect on malaria mortality was not significant ($p = 0.37$), but RRs for other causes were slightly higher from December to April ($p = 0.01$). Old people showed a mortality peak for malaria in February, but this effect was not significant ($p = 0.14$). In contrast, the seasonal trend for other diseases was highly significant ($p < 0.0001$) with highest RRs in February and March.

[4] An overview of the goodness of fit for all models is given in table 8.5 in the appendix.

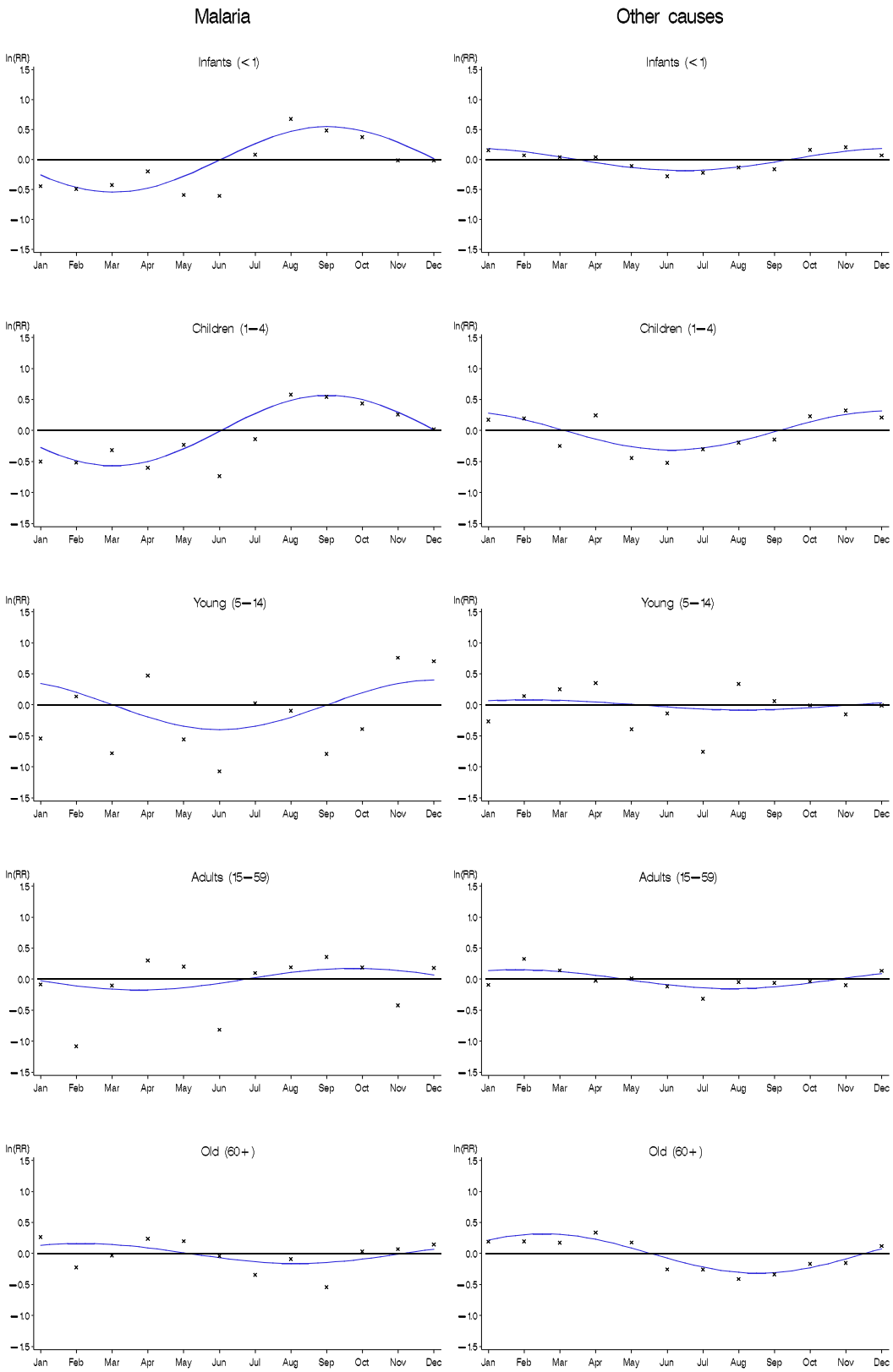

Figure 4.2: Discrete (x) and continuous (solid line) logarithmic RRs by month of death, Nouna HDSS 1998 – 2007. Poisson regression adjusted for sex, area, and calendar year. CODs derived by PCVA.

Figure 4.3 shows the seasonal patterns for CODs derived by InterVA. Again, results for each age group and for malaria and other causes are presented.

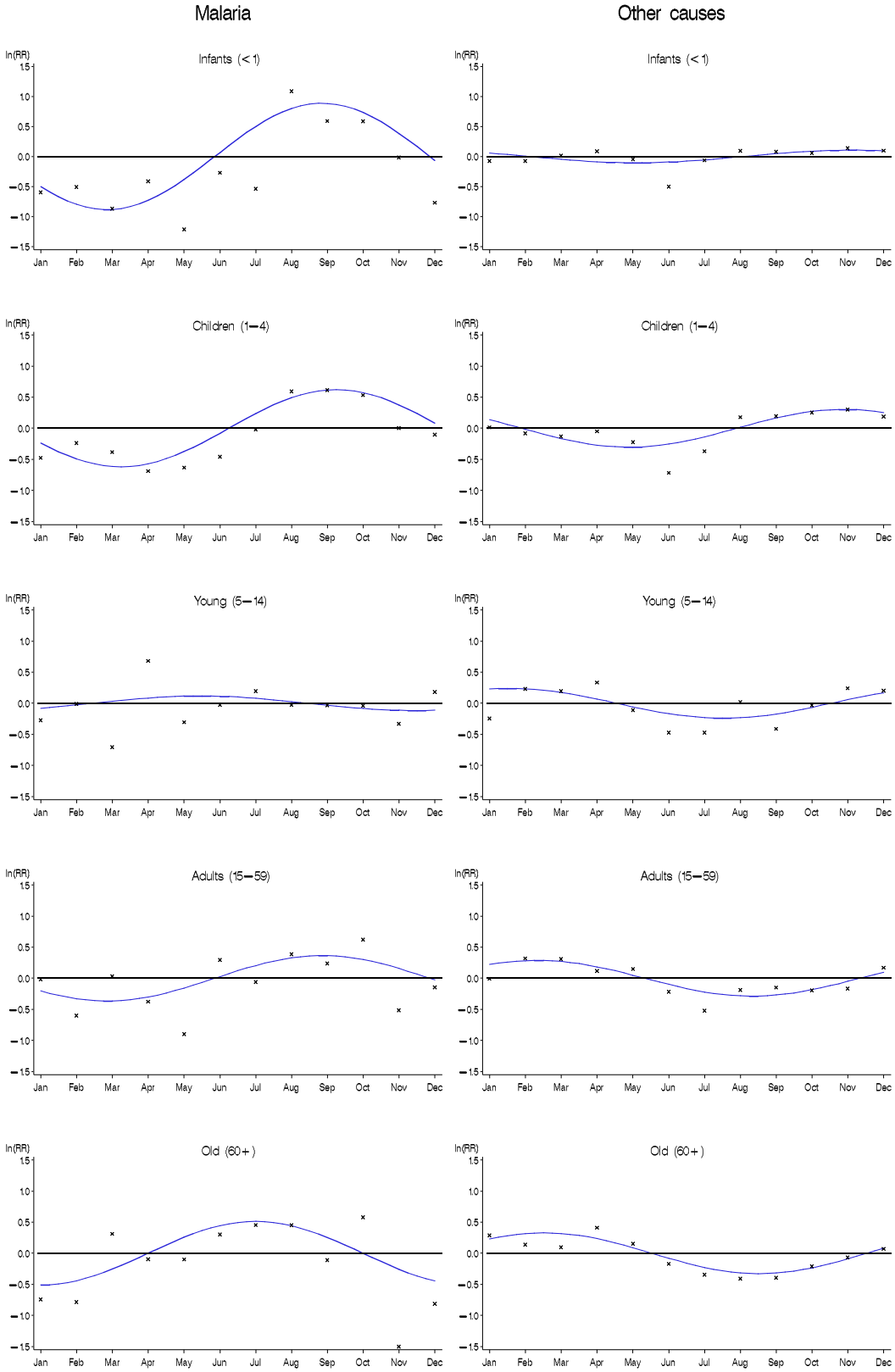

Figure 4.3: Discrete (x) and continuous (solid line) logarithmic RRs by month of death, Nouna HDSS 1998 – 2007. Poisson regression adjusted for sex, area, and calendar year. CODs derived by InterVA.

For malaria, infants and children showed again highly seasonal effects ($p < 0.0001$ for both) during and at the end of the rainy season from July to November with highest RRs in September, except that logarithmic RRs for infants were twice as high as in figure 4.2, but the seasonal effect for other causes was not significant ($p = 0.08$). Here, higher RRs for children occurred from September to January, the end of the rainy and the beginning of the dry season ($p < 0.0001$). In comparison to the pattern of PCVA, young people showed an opposite trend. The seasonal effect for malaria was not significant ($p = 1$), but higher RRs were seen during the dry season for other causes ($p = 0.02$). A clear distinction of the seasonal effect of mortality for malaria and other causes between the rainy and the dry season occurred for adults ($p = 0.002$ in malaria and $p < 0.0001$ in other causes) with higher RRs for malaria from July to November and higher RRs for other causes from December to March. The seasonal effect on mortality of other causes for the oldest age group is similar to the seasonal trend of other causes coded by physicians ($p < 0.0001$), but for malaria, the highest RRs occurred in July at the beginning of the rainy season ($p = 0.03$).

The following two figures illustrate over the whole study period estimated mortality rates for each month for malaria (Figure 4.4) and other diseases (Figure 4.5) determined by both methods separately, the MA of the rates and the modelled rates after converting the logarithmic RRs estimated by model IV into rates. This analysis focuses intentionally upon infants and children as the most sensitive and critically affected. To increase the sample size for this analysis, infants and children were combined.

Among all deaths, 3,363 occurred for children under age five alone with an average mortality rate of 29.8/1,000 (95% CI 28.8-30.9) for the whole observation period. According to PCVA, the seasonal pattern for malaria was very similar during the whole study period with higher rates in the rainy and lower rates in the dry season. The highest peak of malaria mortality could be observed during the wet season in 2003. In the last year of the observation period, VAs were completed only for 61.3% of all deaths for children under five[5], which corresponds to the low MA rates recorded in 2007. Since active VER was first implemented in 1999, lower malaria rates also appeared in 1998, while the amount of completed VAs of all deaths for children less than five years was 84%. During the whole study period, no clear long-term trend occurred for malaria as reflected by the non-significant corresponding parameter β_2 for the effect of year in the model ($p = 0.33$). The modelling approach is further supported by the high similarity of the MA trend compared to the modelled estimates.

Seasonal analysis of InterVA causes showed a comparable pattern for malaria over the observation period but with lower mortality rates than estimated for PCVA. Again, for the years 1998 and 2007, lower rates were recorded. In contrast to PCVA, a slightly decreasing trend of malaria mortality was observed for the observation period ($p = 0.0001$).

[5] An overview of the frequencies of VAs of all deaths for children less than five years old is given by year in table 8.4 in the appendix.

For other causes determined by physicians, a clear but opposite seasonal trend occurred with higher death rates during the dry season and lower mortality rates in the wet season. In contrast to the malaria results, a decreasing trend over the observation period was observed with a highly significant effect of calendar year on mortality ($p < 0.0001$). As for malaria, the estimates for the MA and the modelled rates were very similar.

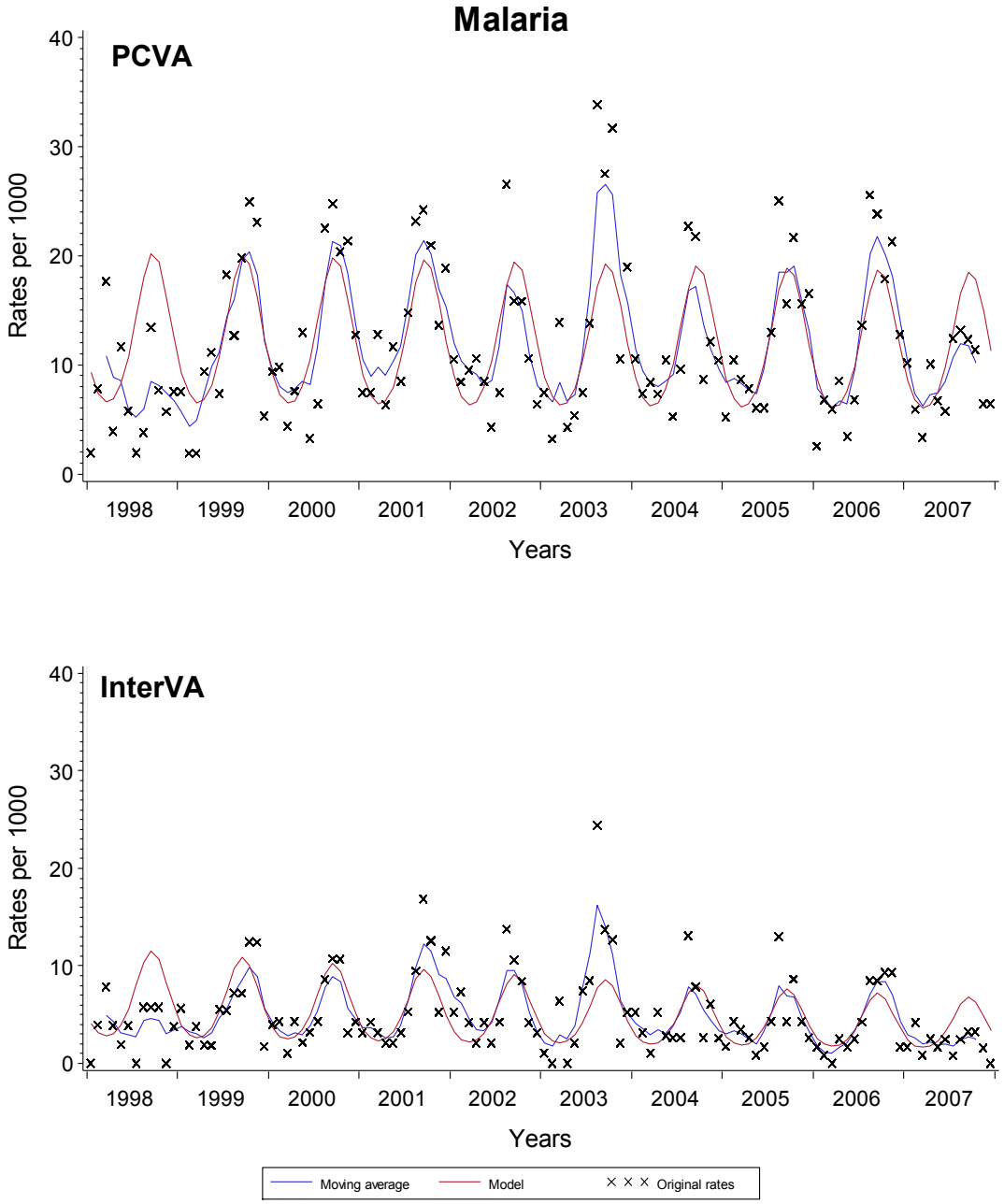

Figure 4.4: Malaria mortality rates by method of COD determination for children less than five years of age by year, Nouna HDSS, 1998 – 2007.

For InterVA, higher mortality rates were estimated for other causes over the observation period with a similar mortality pattern compared to PCVA. Again, the decreasing trend of mortality from 1998 to 2007 was highly significant ($p < 0.0001$). As for PCVA, the MA and the model curve showed a similar result.

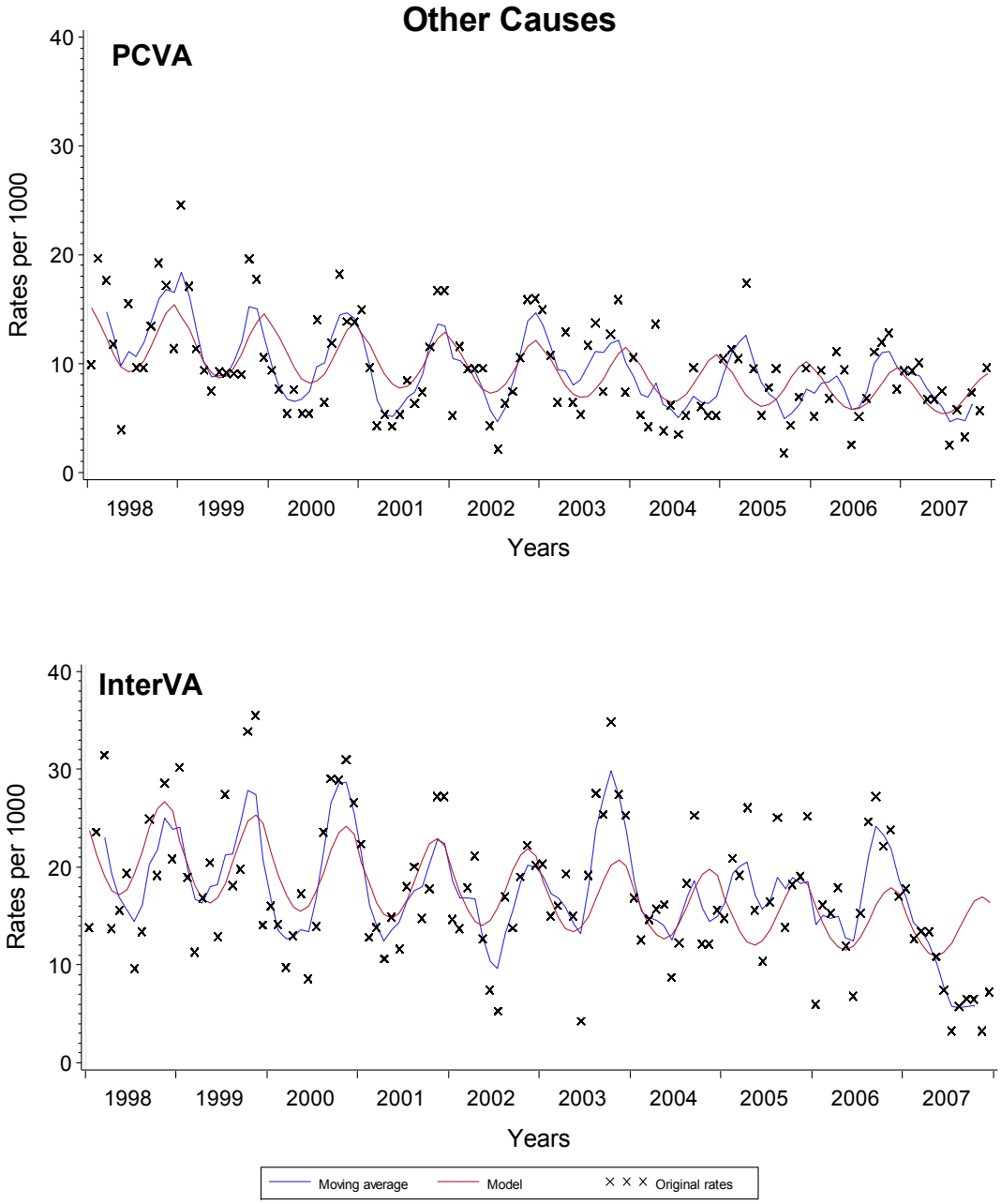

Figure 4.5: Mortality rates for other causes by method of COD determination for children less than five years of age by year, Nouna HDSS, 1998 – 2007

5 Discussion

5.1 Major Findings

The aim of this study is to present seasonal patterns of malaria and all-cause mortality in a malaria-holoendemic region. In the Nouna HDSS area, ~ 80,000 individuals were under demographic surveillance in 2007. Thus, COD data obtained by a French VA questionnaire was constantly collected over a ten-year period and could be compared using two different methods of COD determination for all age groups.

Overall, 7,378 deaths occurred during the whole study period. All-cause mortality was significantly lower in Nouna town compared to the surrounding villages and decreased by age for the three youngest age groups. However, levels of all-cause mortality for infants, children, and even for the elderly were relatively high compared to those for young people and adults. Between males and females, no significant difference was observed in all-cause mortality.

Cause-specific mortality rates could be obtained only for 5,621 deaths for which a completed VA questionnaire was available, corresponding to 76 % of all deceased. The two different methods to determine CODs showed similarities but also discrepancies for different sub-groups and seasons. Overall, physicians assigned one quarter of all deaths to malaria, whereas InterVA allocated only half as many deaths to this disease. Between males and females no significant difference was observed in cause-specific mortality according to PCVA. In contrast, a difference in cause-specific mortality by sex was only detected for other causes according to InterVA with significantly higher mortality rates for males.

Striking differences in cause-specific mortality were found by age: both PCVA as well as InterVA showed mortality from malaria to be highest in childhood. But it is noteworthy that physicians assigned more deaths to malaria for the oldest age group than InterVA did. Mortality rates estimated for malaria determined by physicians were significantly higher for all age groups compared to InterVA malaria rates except for adults. Here, the InterVA assigned significantly more deaths to malaria among adult woman than physicians did.

Furthermore, a strong association between mortality and season was demonstrated based on Poisson regression analysis. All-cause mortality for infants and children was higher in the rainy season. Young and old people as well as adults showed a trend in the opposite direction but the trend for young people and adults was less clear.

Proportions of malaria diagnoses by both methods of COD assignment were highest amongst infants and children during the wet season. Correspondingly, Poisson regression showed a stronger relative monthly effect on malaria mortality for infants and children as compared to the all-cause mortality trend showing malaria as the underlying COD for the patterns in these age groups. This is further supported by continuous modelling of the seasonal pattern for malaria in infants and children as presented by the sinusoidal curve with a highly significant mortality peak during the rainy season and lower rates in the dry season. Mortality due to other causes was higher at the end of the wet season and the start of the dry season. Compared to PCVA, the seasonal effect for malaria in infants was stronger among InterVA diagnoses, but no significant pattern was seen for other causes. For children, the curve for malaria was shifted left by one month.

Comparing both methods, no clear pattern was seen for young people. Here, no significant effect was found for other causes determined by PCVA and the effect for malaria was significant but showed a poor model fit.

Seasonal patterns for InterVA data presented an opposite trend. For malaria, no significant seasonal trend was detected but the seasonal effect for other causes was significant with higher mortality rates during the dry season.

Adults and old people had a significant seasonal effect for other causes with higher RRs during the dry season according to PCVA coding. According to InterVA, adults showed significant higher rates for malaria during the wet season and higher rates for other causes during the dry season. The seasonal trend for old people and other causes was similar to the trend among physicians' diagnoses but rates for malaria were higher at the end of the dry season and during the wet season.

According to PCVA, no decrease in malaria mortality for children under five years of age was seen during the whole observation period, while mortality due to other causes showed a highly significant declining trend for both methods. InterVA showed a slightly decreasing and significant trend for malaria as well.

5.2 Interpretation of the Findings

Reliable and accurate information on mortality patterns is needed by health policy makers to identify the health needs of their population and for planning and evaluation of appropriate public health activities. In addition, studies on seasonal mortality patterns can contribute to the investigation and monitoring of the relation between climate and disease, which is becoming more important because of global warming (83). Such information is especially needed in developing countries where only sparse epidemiological and demographic data exist. Therefore, this study adds important information on cause-specific mortality data in SSA and contributes to the knowledge on seasonal mortality in Burkina Faso. This study also adds detailed data on malaria mortality among adults in SSA. However, as adult mortality is mainly due to CODs other than malaria, detailed patterns of malaria mortality among adults are difficult to investigate due to small sample size.

Not surprisingly, all-cause mortality in Nouna town was significantly lower than in the rural area in this study since mortality in urban areas is often lower than in rural regions (84-87). The most likely explanation for this large difference might be better access to health facilities in Nouna town as compared to the rural areas (88, 89).

Rates of all-cause mortality decreased with age among the three youngest age groups. The decline in mortality during the first five years of life is in line with mortality patterns in similar countries with high childhood mortality levels (90-92). However, childhood mortality has been remaining high in many developing countries.

Cause-Specific Mortality

This study adds further evidence to the huge impact of malaria on mortality in rural malaria endemic regions of SSA (55, 56, 90, 93-97) especially among children, which is consistent with still high levels of childhood mortality in other areas of this region (55, 56, 94, 98). High all-cause and malaria mortality in childhood may be due to the poor nutritional status of children, which enhances their risk of dying from infectious diseases such as malaria (96, 99). A study from Navrongo, Ghana, showed that malaria affects all age groups, but its

impact on mortality reduces over time due to an increase in immunity against malaria (100) well reflected by relatively low malaria mortality rates among young people and adults in this study.

According to PCVA, there was a higher proportion of malaria deaths among the oldest, which is in line with malaria mortality estimates from West Africa showing declining malaria mortality rates in late childhood and young adulthood but a rise with increasing age (55). In India, it was shown that malaria mortality rates increased by age though the malaria epidemiology of this region might not be comparable to Burkina Faso (101). The assumption of a weakening immune system among the elderly might lead physicians to diagnose more malaria. However, this would probably lead to an increase of other infections besides malaria. In contrast, lower malaria proportions among InterVA diagnoses for the oldest are in line with results reported elsewhere showing a steadily decreasing malaria mortality trend by age for the whole SSA region (102). One possible explanation supporting the hypothesis for a decreasing trend among the elderly may be immunity acquired over time by people living in malaria-endemic areas (77, 103).

Overall, physicians assigned more deaths to malaria than InterVA did, possibly due to physicians' tendency to overdiagnose malaria in malaria-endemic areas (2, 3). An exception could be seen in female adults. Most non-pregnant women in SSA have been exposed to falciparum malaria and are semi-immune to this disease, but they lose much of their immunity during pregnancy and become more susceptible (104) resulting in a higher risk of dying from malaria (105). Given that most adult women in this study were of reproductive age (15-49) this might explain the higher malaria mortality levels according to InterVA diagnoses for female adults as compared to PCVA coding (106). In contrast, local physicians might expect pregnant women living in malaria holoendemic regions to be semi-immune and tend to diagnose other infections than malaria. However, no records of pregnancy status were available for this study and explanations remain speculative.

Excluding the free-text sections of the VA questionnaire when applying the InterVA approach in malaria-endemic regions can not explain the observed differences in malaria proportions between physicians and the model as shown by several studies (106-108).

Seasonal Patterns

The data available for this thesis provides additional evidence to the seasonal effect on mortality during the rainy season in this part of SSA, which is mostly attributable to malaria (67, 69, 92) as shown by the significant seasonal pattern in malaria mortality in infants as well as in children according to both methods of COD assignment. This trend was presented in the regression model with a peak in the wet season, which can be modelled by a parametric sinusoidal curve, and supported by the results of the descriptive analysis (Table 4.6). Despite a smaller amount of malaria deaths, the seasonal effect in infants was stronger for InterVA, which is more consistent in interpretation than PCVA. Physicians may tend to overdiagnose malaria during the whole year in a malaria-holoendemic region and not just during the wet season, diluting the seasonal effect (81).

Results for young people did not show a clear seasonal pattern for malaria: although physicians' diagnoses showed a significant pattern for malaria, the model fit was poor and among InterVA diagnoses no significant seasonal effect in malaria mortality was seen. In this age group, people may already have acquired immunity against malaria. But results should be interpreted with caution because the number of observations in the young subgroup was sparse for reasonable modelling. InterVA showed a significant mortality pattern for

other causes with the highest mortality rates in the dry season. The same pattern of mortality was seen in adults and old people as well, even among physicians' diagnoses. Main CODs are HIV/AIDS and tuberculosis for adults and pneumonia/sepsis and diarrhoea among old people, as reported by Ramroth el al. who investigated COD distributions in the Nouna HDSS for the same study period (81). Kynast-Wolf et al. presented seasonal mortality patterns of cardiovascular disease for adults and the elderly in the same study area with higher death rates during the dry season (71). However, since the "other causes" category in the present study contains many CODs, an explanation for these patterns remains difficult without a more detailed COD analysis.

In adults, a significant seasonal pattern of malaria mortality with a peak during the rainy season was only seen for InterVA, likely due to more deaths assigned to malaria by the model than by physicians and the model's better consistency in interpretation as already discussed above.

Results regarding seasonal malaria mortality patterns in old people are contradictory. The seasonal malaria mortality pattern for PCVA was not significant. Instead, InterVA showed a significant pattern with the highest rates in July. Although a peak in malaria mortality at the end of the dry season is not plausible, this pattern may be due to the limitations of the VA method and its poor sensitivity and specificity (29).

Furthermore, this study provides information on long-term trends of seasonal variations in mortality of malaria and other causes for children under the age of five monitored by the Nouna HDSS. During the whole study period, malaria mortality peaked consistently at the end of the rainy season when the malaria transmission intensity usually reaches its maximum. No decreasing trend was seen for malaria mortality over the whole study period among physicians' diagnoses, but it has to be taken into account that multiple physicians involved in the coding process over the years differ in their tendency to diagnose malaria. In contrast, the model approach showed a slightly but significantly declining trend for malaria mortality over the years. However, the decrease in malaria mortality was very small. One possible reason for underestimation of a reduction could be an increase of missing CODs by year. However, subsequent analyses did not show any increasing trend for missing causes (including missing VA questionnaires and missings because of no consensus between physicians) or any decreasing trend for the amount of completed VA questionnaires for children under the age of five over the years (Appendix Table 8.4).

Furthermore, this study showed a highly significant decrease in mortality for other CODs, which is in line with trends of childhood mortality from other parts of SSA (109, 110). Both methods showed a significant decline in under five mortality for other causes over the whole study period, possibly due to the positive impact of public health research over two decades in the CRSN area. Thus, although since the year 2000, two large insecticide-treated bednet (ITN) trials have been conducted in the CRSN study area distributing ITNs for protection of infants and children (111, 112), the decrease in under-five mortality was mainly due to the decrease in mortality of other causes but not due to a decrease of malaria.

Despite the high percentage of conducted VAs in 1998, relatively low malaria mortality rates for children under five were recorded. It is unlikely that mortality rates doubled in 1999. Since active VER was first implemented in 1999, data due to the former passive VER may be incomplete for 1998 (113) resulting in underestimation of mortality rates.

The validity of the modelling approach was checked graphically by comparison to MA of the rates, which were quite similar to the modelled rates. A previous study analysing PCVA data of the Nouna HDSS area on seasonal mortality patterns showed that this is an appropriate approach to investigate seasonal mortality patterns (69).

Overall, although the proportions of deaths among the different COD categories showed discrepancies between InterVA and PCVA, both methods revealed fairly similar seasonal mortality patterns. Thus, both InterVA and PCVA are useful methods for assessments of seasonal mortality.

5.3 Findings in Research Context

This thesis is one of the first studies comparing malaria diagnoses assigned by physicians to InterVA causes in a malaria endemic region, showing additional seasonal COD patterns. Besides this work, Ramroth et al analyzed COD distribution with InterVA and physician coding in the Nouna HDSS area from 1998 to 2007 and found 63.2% agreement between both methods (81). Fottrell et al investigated maternal mortality in the Nouna HDSS area by comparing PCVA to diagnoses derived by a specific version of the InterVA model for maternal deaths (InterVA-M) and found approximately 60% to 80% agreement between physicians and the model (106). Other studies comparing PCVA and InterVA were conducted in non-malaria endemic study areas in South and East Africa or Asia and focused more on HIV as the study areas have been considered as HIV endemic (44, 51, 59, 108, 114-116). One study from Nairobi, Kenya, compared PCVA with InterVA diagnoses and found InterVA assigning more deaths to malaria than physicians did. Since the malaria prevalence is less than 0.5% in their study population (117), physicians may tend to assign other CODs more frequently than malaria.

The impact of season on mortality in SSA has been investigated and reported only by few publications yet. Seasonal patterns of malaria mortality in the Nouna HDSS area were studied in a previous analysis (69) using COD data interpreted by physicians only. Although Becher et al analysed a shorter period from 1999 to 2003, their results are very similar to the PCVA findings of this study covering a prolonged period. As it was hypothesized that physicians overdiagnosed malaria in their analyses of VA information, this study compares seasonal malaria mortality patterns for InterVA data to PCVA coding. In addition, a larger observation period including more recent data was analysed for this study taking into account the effect of year on mortality, which was not done in the previous analysis.

Age-specific seasonality of all-cause mortality patterns in the Nouna HDSS area was analysed for an earlier period from 1993 – 2001 (67). Their results are similar to the results of this study except for children aged one to four years. In their analysis, children showed an intermediate pattern with highest mortality rates around the end of the rainy season but in addition also during the early dry season. They assumed pneumonia to be the major COD and responsible for the mortality peak in one to four year old children in February. Since the present study analyzed more recent data and health research might have had a positive impact on health within the study area, child deaths caused by pneumonia might have declined. In addition, resistance against the malaria first line drug chloroquine in the area has been increasing (118, 119) and may have led to an increase of malaria child deaths. This is supported by the shift of the sinusoidal curve towards the rainy season in this study (Figures 4.2 and 4.3), since malaria mortality is higher during the rainy season. Further-

more, it has to be taken into account that different physicians were involved in the coding process in the Nouna HDSS over this long period of time, varying in their tendency to assign malaria and other causes. Moreover, Kynast-Wolf et al did not adjust their analysis by year and area. Differences in rainfall over time and different malaria transmission intensities between Nouna town and the rural areas might have also influenced mortality. However, without a more detailed analysis of the other causes category explanations for this difference remain speculative.

An earlier analysis of the Nouna HDSS data on seasonal patterns of all-cause mortality from 1993 to 1998 (70) considering seasonal trends of CVD mortality from 1999 – 2003 (71) in adults and old people identified a seasonal trend in all-cause and CVD mortality with higher rates during the dry season. These findings are supported by the all-cause mortality patterns in adults and old people and the seasonal pattern among old people for other causes of this study since CVD may be a possible COD during the hot dry season.

Higher mortality rates during the rainy season for infants and children under age five were also found in a rural population under demographic surveillance in Senegal (66). Furthermore, a retrospective review of the period 1993 to 2009 for infants and child death records from a rural public hospital in Cameroon showed that deaths due to malaria were most common during and just after the rains (68).

5.4 Strengths & Limitations of the Study

One of the limitations of this study is the high proportion of unknown CODs due to missing VA questionnaires. Insufficient VA data results in the assignment of the "ill-defined" category by physicians or the "undetermined" category by InterVA. Furthermore, scarce information makes no consensus between reviewing physicians more likely leading to a recording of a missing cause as well. It is very likely that among deaths assigned to the "ill-defined"/"undetermined" categories or with unknown cause some were due to malaria. Therefore, an adjustment of malaria mortality rates for missing causes would result in higher malaria mortality estimates for both methods. In contrast, due to physicians' tendency to overdiagnose malaria in malaria endemic regions, it is unlikely that, except for female adults, rates among PCVA diagnoses are underestimated, as explained above.

Moreover, there are well-known limitations of the VA method itself relating to the validity of CODs, especially for diseases with non-specific symptoms like malaria. On the one hand, overlapping symptoms between malaria and diseases such as acute respiratory infection may lead to misclassification of diagnoses and affect the accuracy of the results. On the other hand, such inaccuracies might additionally be due to variations in VA sensitivity for malaria deaths, depending in areas of high transmission intensity more on the incidence and prevalence of malaria than on exact diagnostic definition. The decrease in VA specificity for malaria with increasing malaria proportional mortality (94) is accompanied by lower sensitivity of VA for other CODs in sites with intense malaria transmission (46). Thus, use of VA data makes it difficult to estimate the entire impact of malaria on mortality in high transmission settings due to lower specificity and sensitivity. Performance of VA in determining CODs may be better in areas where malaria play only a minor role.

Further limitations of the VA method are related to the interpretation of VA data. Physicians working in areas with high malaria transmission intensity tend to overdiagnose malaria as shown by a study from Tanzania (120). This misclassification of malaria diagnoses is best represented in the present study by relatively

high malaria mortality rates in old people when determined by physicians possibly expecting a weak immune system among the oldest as already mentioned above. Although other studies found similar results (55), high malaria mortality levels are not plausible among old people living in malaria endemic areas, since this age group may have acquired immunity (77, 103). In addition, reliable temporal comparison of PCVA data is questionable due to variations of physicians over time.

A relatively new approach to interpret VA data is the InterVA method (47), which is more consistent in interpretation than PCVA. The model displays up to three possible CODs with corresponding likelihoods, which is a further advantage to the PCVA method simplifying COD assignment to one cause. A further limitation of this study is that only one COD with the highest likelihood was included into the analysis, possibly leading to a distortion of the estimates of COD proportions among InterVA causes. However, the overall pattern of CODs did not change when comparing the weighted InterVA approach to the one considering only the most likely COD (121).

The InterVA method does have limitations as well. The VA questionnaire was not designed with the InterVA input indicators in mind. For example, not all indicators built into InterVA are available in the Nouna VA data and similarly, not all information gathered by the Nouna VA questionnaire can be utilized by InterVA. The consequences of this are likely to lead to lower overall certainty of derived CODs. Deaths with more available VA data usually result in higher likelihoods and a higher certainty (106). In addition, the model is not able to detect fine logical inconsistencies that reviewing physicians might recognize.

Unfortunately, no gold standard is available yet against which both methods could be validated. Thus, the true CODs are impossible to be obtained (122) and uncertainty levels with either procedure are high (81) in particular for malaria, which is difficult to diagnose accurately without parasitic evidence (123, 124). Hence, mortality statistics based on VA have to be interpreted with caution. Nevertheless, VA is at present the best possible method to obtain cause-specific information on death in resource-constrained regions despite obvious limitations (34) and has consequently been applied in a number of countries (55).

Moreover, reporting bias cannot be excluded, as conducting interviews during the rainy season is more difficult than during the dry season for many reasons such as weather conditions and availability of household members owing to agricultural work. Since VER is carried out only every 3rd to 4th month, about 80% of all VAs were conducted after six months. Thus, recall bias is likely to be stronger in the Nouna HDSS compared to HDSS sites with on-going VER (e.g. The Gambia) (92). However, other HDSS sites might experience the same problem as the Nouna HDSS.

Besides, this study does not standardize estimated mortality rates, which would allow for comparing the results to other countries. Anyhow, the main aim of this study was to analyse seasonal patterns of mortality using two different methods of COD determination for this region only. Furthermore, data on potential confounders such as SES, access to health facilities, malaria control programs, drug resistance and nutritional status were not available. Additionally, it was impossible to link malaria mortality to climatic conditions directly, because no rainfall measurements were available. However, such analyses would go beyond the possibilities and given time frame of a bachelor study like the present one.

One of the strengths of this study is that the study population is representative for populations in rural malaria-endemic regions of West Africa, even though the study population was not selected by randomisation from

the population of Burkina Faso. As this analysis is based on longitudinal data, it has to be taken into account that changes concerning the study population such as migrations, deaths etc. can occur over time and might result in confusion and inaccuracies of the data. To resolve these problems, individuals were tracked over such a long period by keeping their ID regardless of household affiliation, which provides a precise estimate of the denominator and deaths among different subgroups for this study.

Despite the difficulties caused by the dynamic study population and area, the inclusion of the complete population is a further strength of this study, compared to publications based only on a subsample of deceased persons or hospital visits. Also, the prospective cohort design is known to be superior to case-control or cross-sectional studies. An additional strength of the present study is the comparability between the descriptive analysis and the regression model, which are explained and reinforced by each other. Besides, a standardized questionnaire was applied to conduct VA interviews, which is consistent in itself. Moreover, Poisson regression was an appropriate and convenient approach to analyse and graphically illustrate seasonal mortality patterns.

Despite the limitations mentioned above, this study provides a solid description of seasonal mortality patterns of malaria in a malaria holoendemic area and adds evidence to the seasonality of malaria mortality. The Nouna HDSS has collected data since 1992, with continuous improvement of data quality over years, giving much confidence on data quality for this study. This allows to extrapolate these findings to other rural highly malaria endemic areas with similar living conditions.

6 Conclusions

The present study adds further evidence to the seasonality of malaria mortality in malaria endemic regions of rural West Africa by comparing cause-specific data obtained by two different methods. Furthermore, it confirms the high impact of malaria on mortality in children in rural Burkina Faso with excess at around the end of the rainy season. In contrast, mortality in adulthood and among the elderly is high during the dry season most probably explained by other CODs. The patterns are in line with other studies reporting an association between season and mortality.

Since efforts have been made towards malaria eradication in many areas of Africa, malaria mortality is anticipated to decline in these regions (125). However, an overall decline in childhood mortality of other causes but alongside stagnant malaria mortality indicates that Burkina Faso will not meet the expectations in the near future. This study shows that despite interventions in this region to fight malaria, the seasonal pattern and malaria mortality over time has not changed. Thus, it is still important to support public health efforts in malaria high transmission areas of SSA and to work on acceleration achieving towards MDG 4, which is to reduce under-five mortality by two-thirds between 1990 and 2015.

It was shown that both the probabilistic InterVA model and PCVA determine reasonably well seasonal patterns of malaria mortality in a rural malaria endemic area in West Africa. Both methods may potentially inform health policy makers and monitor progress and drawbacks of health program interventions in resource-limited settings where reliable estimates of morbidity and mortality are lacking. Such information on seasonal patterns is valuable for the planning of health resources and activities.

A more detailed analysis of other CODs could add data to the scarce information of cause-specific mortality in SSA, especially for adults and old people. For this, data from different HDSS sites can be combined to increase the sample size among COD- and age-specific subgroups if necessary, which would also allow for comparisons between different populations, regions, climates, cultures etc. To understand the true relationship between seasonality and patterns in mortality, further analyses should include information on health influencing factors such as SES, access to health services, malaria control programs, and drug resistance as well as seasonally dependent environmental factors like climate data and nutritional status, that could potentially explain mortality trends.

Moreover, a joint analysis of different HDSS sites would allow an investigation of seasonal malaria mortality patterns based on longitudinal data between different transmission settings, which may enable locally appropriate targeting of interventions to those most at risk aimed at lessening the burden of seasonal diseases.

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8 Appendix

SAS applications developed and used for data analysis are stored on the enclosed CD. Data analysed for this study can be requested from the Institute of Public Health Heidelberg, Prof. Dr. Heiko Becher, heiko.becher@urz.uni-heidelberg.de.

Table 8.1: CODs used for PCVA

NomFranc	ICD10	NomFranc	ICD10
Valeur par défaut	_00	Toux, Bronchite	J20
Aucune maladie	_00	Pneumonie	J18
Paludisme	B50	Convulsions	_00
Paludisme (non specif.)	B54	Accident	X00
Fièvre	B54	Rage	A82
Diarrhée aigue	A05	Conjonctivite chlamydiae	A74
Diarrhée (non specif.)	A09	Conjonctivite (non specif.)	H10
Dysenterie	A07	Douleurs pelviennes	_00
Choléra	A00	Varicelle	B01
Maux de ventre	_00	Oreillons	B26
Gastroentérite infectieuse	B26	Piqûre d'insecte	X11
Déshydratation	A09	Laryngite, Croup	J05
Infarctus de coeur	_00	Grippe	J11
Accident vasculaire cérébral	I21	Oedème aigue du poumon	J81
Intoxication (non specif.)	I61	Hémorragie gastro-intest.	K51
Ingestion de subst. toxique	_00	Autre maladie aigue	_00
Intoxication alimentaire	X08	Maladie aigue non specif.	_00
Occlusion intestinale	X09	Rougeole	B05
Hépatite	K56	Coqueluche	A37
Morsure de serpent	B16	Méningite	A39
Fièvre jaune	A95	Constipation	_00
Tuberculose	A15	Hoquet	R06
Tétanos néonatal	A33	Diabète	E14
Tétanos (sauf néonatal)	A35	Trypano	B56
Tétanos (sans specific.)	_00	Maux de coeur	_00
Fièvre typhoïde	A01	Rhumatisme	M25
Polio	A80	Hémorroïdes	I84
Autre maladie vaccinable	_00	Trachome	A71
Mal. vaccinable non specif.	_00	Onchocercose	B73
Lèpre	A30	Cécité	H54
Cécité nocturne	E50	Sida	B20
Cataracte	H25	Jaunisse (non specif.)	_00
Glaucome	H40	Malnutrition (non specif.)	E43
Goitre	E07	Plaie	_00
Enflement	_00	Épilepsie	G40
Éléphantiasis	B74	Folie, maladie mentale	F99
Paralysie	G83	Envenimation ancienne	_00
Maux des os (a supprimer)	_00	Vertiges	_00
Hernie	K46	Fissure anale	K60
Bilharziose	B65	Maux de dents	_00
Surdité	H91	Asthme	J45
Borgne	H57	Hépatopathie, cirrhose	K74
Maux d'oreille	00	Cardiopathie	I38
Maux de rein	00	Hématurie	00
Maux des os et articulations	_00	Hypertension artérielle	I10

NomFranc	ICD10	NomFranc	ICD10
Maux de dos	_00	Glomérulo-néphrite	N00
Maux de côtes	_00	Syndrome néphrotique	N04
Stérilité masculine	N46	Alcoolisme	F10
Ver de guinée	B72	Anémie	D53
Teigne	B86	Gangrène	R02
Diarrhée chronique	A06	Cancer non spécifié	_00
Tumeur maligne de la langue	C02	Autre maladie chronique	_00
Tumeur cérébrale	C71	Malad. chronique non specif.	_00
Cancer primitif du foie	C22	Suites d'avortement	O06
Cancer des voies respirat.	C39	Saignement vaginal	_00
Tumeur maligne du sein	C50	Dystocie, travail prolongé	O79
Tum. m. des organes génitaux	C55	Pertes vaginales	_00
Cancer digestif	C26	Endométrite	N71
Cancer peau et extrémités	_00	Hémorragie ante partum	O20
Autre cancer	_00	Hémorragie post partum	O46
(Pré-)Éclampsie	O15	Maladie de femmes non spec.	_00
Gross. multiple, jumeaux	O30	Mort né (sans specific.)	_00
Fièvre puerpérale	O86	Prématurité, hypotrophie	P07
Douleurs pelv. de la femme	N73	Malformation congénitale	Q99
Stérilité féminine	N97	Ictère néonatal	P59
Autre cause ante partum	O49	Malnutrition (néonatale)	P92
Autre cause post partum	O99	Affecté par troubles mater.	P00
Autre complicat. maternelle	_00	Asphyxie	P03
Complic. matern. non specif.	Z95	Infection de l'ombilic	P39
Autre maladie de la femme	_00	Hémorragie ombilicale	P51
Autre maladie de nouveau né	_00	Autre maladie	_00
Mal. de nouveau né non spec.	P99	Non applicable	_00
Assassinat, homicide	Y01	Pas d'information exploitable	Z99
Suicide	Y02	Maladie indéterminée	Z98

Table 8.2: Malaria deaths and proportion by method of COD assignment and sex for the five age-groups, Nouna HDSS, 1998 - 2007

		PCVA				InterVA			
		Malaria	%	Rate	95%CI	Malaria	%	Rate	95%CI
Infants (<1)	**Males**	251	34.8	20.1	17.6-22.6	102	14.1	8.1	6.5-9.7
Children (1-4)		452	43.7	10.3	9.4-11.3	176	17.0	4.0	3.4-4.6
Young (5-14)		62	25.5	0.7	0.5-0.8	30	12.3	0.3	0.2-0.4
Adults (15-59)		55	6.9	0.4	0.3-0.5	58	7.2	0.4	0.3-0.5
Old (60+)		107	10.6	6.6	5.3-7.8	26	2.6	1.6	1.0-2.2
Infants (<1)	**Females**	269	38.0	21.4	18.9-24.0	101	14.3	8.0	6.4-9.5
Children (1-4)		374	41.5	8.5	7.6-9.3	166	18.4	3.8	3.2-4.3
Young (5-14)		44	21.2	0.5	0.4-0.7	19	9.1	0.2	0.1-0.3
Adults (15-59)		52	6.7	0.4	0.3-0.4	120	15.5	0.8	0.7-1.0
Old (60+)		180	18.3	9.4	8.0-10.8	27	2.7	1.4	0.9-1.9

Table 8.3: InterVA indicators

was this an elder 65+ years	did final illness last at least 3 weeks
was this an adult 50-64 years	did final illness last < 3 weeks
was this a female 15-49 years	was death very sudden or unexpected
was this a male 15-49 years	was death during wet season
was this a child 5-14 years	was death during dry season
was this a child 1-4 years	was s/he in a transport accident
was this an infant 4 wks - 1yr	did s/he drown
was this a neonate < 4wks	had s/he fallen recently
was she pregnant at death	any poisoning, bite, sting
did pregnancy end within 6 weeks	was s/he a known smoker
any obvious recent injury	any stiff neck
was s/he known to drink alcohol	any oral candidiasis
was any suggestion of homicide	any rigidity /lockjaw
any convulsions or fits	abnormal hair colouring
any diagnosis of epilepsy	any coughing with blood
was the fontanel raised	any chest pain
was the fontanel or eyeball sunken	was there a cough for > 3wks
any headache	was there a cough for up to 3 wks
was there paralysis on both sides	any productive cough
any paralysis on /weakness on 1 side	any rapid breathing
any breathlessness on exertion	any chest indrawing
any breathlessness lying flat	any difficulty breathing
any breast lump or lesion	any wheezing
any cyanosis	any abdominal pain
any abdominal mass	any diarrhoea with blood
any vomiting	any vomiting with blood
any yellowness /jaundice	any acute diarrhoea (< 2wks)
any abnormality of urine	any persistent diarrhoea (2-4 wks)
any urinary retention	any chronic /recurrent diarrhoea (4+w)
any haematuria	any abdominal swelling
any swelling of ankles /legs	no bilateral swelling of ankle
any skin lesions or ulcers	any herpes zoster
any rash (non measles)	any measles rash
any excessive night sweats	any excessive water intake
any excessive urination	any acute fever
any excessive food intake	any persistent fever (>2wks)
any enlarged /swollen glands	any facial swelling
any anaemia/ paleness	was there a comma > 24hrs
any drowsiness	any weight loss
any delayed / regressed development	any diagnosis of hypertension
any diagnosis of asthma	been discharged from hospital very ill
any diagnosis of diabetes	any suggestion of suicide
any diagnosis of heart disease	any surgery just before death
any diagnosis of HIV/AIDS	any diagnosis of TB
was she adequately vaccinated	any diagnosis of liver disease
any diagnosis of measles	any diagnosis of cancer
any diagnosis of kidney disease	any diagnosis of stroke
any diagnosis of haemoglobinopathy	any diagnosis of malaria
were there convulsions during delivery	any delivery complications
was the baby born early < 34 wks	any heavy bleeding before/after delivery
was the baby small < 2500g	was there prolonged labour >24 hrs
was there difficulty breathing at birth	was this a multiple birth
any congenital malformations	any umbrical infection

Highlighted indicators could be extracted from the Nouna questionnaire.

Table 8.4: Deaths, VAs and missings (PCVA) for children under five, Nouna HDSS, 1998 -2007

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	Total
Deaths	175	238	354	355	297	374	369	410	391	400	**3363**
VAs	147	188	287	294	256	326	263	326	318	245	**2650**
VAs%	84.0	79.0	81.1	82.8	86.2	87.2	71.3	79.5	81.3	61.3	**78.8**
Missings (PCVA)	36	63	88	78	55	73	127	104	88	163	**875**
Missings (PCVA) %	20.6	26.5	24.9	22.0	18.5	19.5	34.4	25.4	22.5	40.8	**26.0**

Table 8.5: Goodness of fit

			Malaria	Other causes
	Model	**Degrees of freedom**	**Deviance**	
PCVA	**Infants**	418	514	434
	Children	418	540	457
	Young	418	278	376
	Adult	418	322	463
	Old	418	453	529
InterVA	**Infants**	418	377	513
	Children	418	479	517
	Young	418	203	406
	Adult	418	343	507
	Old	418	214	549