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TIME SERIES ANALYSIS OF CHOLERA IN GUINEA-BISSAU, 1996-2008.

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Abbreviations

AR	Attack Rate
BHS	Basic Health Structure
CFR	Case Fatality Ratio
CTC	Cholera Treatment Center
CTU	Cholera Treatment Unit
CHU	Community Health Units
CHW	Community Health Worker
DGS	Public Health General Direction
ECHO	European Commission Humanitarian Aid
HBU	Health Base Units
INASA	Instituto Nacional de Saúde
LNSP	National Public Health Laboratory
MPH	Ministry of Public Health
MSF	Médecins Sans Frontières
MSF-OCBA	Medicos Sin Fronteras- Spanish section
NGO	Non-governmental organization
RDH	Regional Direction of Heal
SAB	Sector Autonomo de Bissau
SA	Sanitary Area
UNICEF	The United Nations Children's Fund
WHO	World Health Organization
WHS	Water, Hygiene and Sanitation

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Summary

Rationale: In July 2008, the government of Guinea Bissau officially declared a cholera epidemic and put in place a response plan. As there is often an inter-epidemic period after a large outbreak such as this, it is important to take the opportunity to learn lessons from previous outbreaks to better assess risks in the future. Analysis of available historical data on cholera epidemics in Guinea Bissau can help to develop a statistical model for risk assessment. Use of these models can help to ensure that there is a timely response of cholera outbreaks, thereby avoiding geographic spread, by identifying “signals” or indicators of when an outbreak is likely to occur or to predict the magnitude of an outbreak in an early stage.

Objectives: The general objective of this study was to implement a time series and a spatial analysis in order to help to the timely identification of cholera outbreaks adapted to each region of Guinea Bissau. The specific objectives of the study were: (i) to describe the historical cholera data and epidemics in Guinea-Bissau identifying long term trends and the seasonal pattern; (ii) to obtain a predictive model of the seasonal risk of finding cholera cases in each region of the country; (iii) to calculate a threshold to detect epidemics with potential to affect more than 0.5% of the population

Methods: We described the historical cholera data in Guinea-Bissau in terms of time and place. The data were analyzed on a daily basis and then aggregated in epidemiological weeks as defined by the WHO. Attack rates and case fatality ratios were computed for each epidemic. A sequential description of the outbreaks was performed.
Multviare analysis using a Poisson regression model was used both to assess the secular trend and the seasonal pattern. Three different criteria were analyzed to define situation with high potential to produce large outbreaks: : (i) the number of regions affected; (ii) the value of the decimal logarithm of the number of cases; and (iii) the observation of inflexion points on the logarithm curve. All three criteria have been associated with high burden epidemics.

Main findings: There is not a long-term defined trend in the occurrence of cholera epidemics in the country over the period investigated here. On the contrary, there is a seasonal pattern of cholera in the country: the risk of occurrence of cholera cases increases from April and is maximum in mid-September. There is a spatial pattern of cholera incidence in Guinea-Bissau: the most affected areas are the capital (Bissau), Biombo region and the Bijagos Islands. Other areas highly affected are São Domingos, Nhacra in Oio, Tite in Quinara and Bedanda and Catio in Tombali. The analysis provides a sufficient number of elements to create a decision framework to define situations that lead to high burden epidemics.

Recommendations
- To reinforce the cholera surveillance system beginning in April in order to improve the detection of epidemics in the country.
- To target preparedness and control activities to the areas repeatedly affected: Bissau, Biombo and the Bijagos Islands.
- To set-up a sentinel surveillance system including the three main cholera regions (Bissau, Biombo, Bijagos) and some of the other highly affected areas (São Domingos, Tombali, Nhacra and Tite) in order to improve the early detection of epidemics and its follow up.
- To use the decision algorithm to define situations with high potential to produce large epidemics to guide outbreak control and case management.
- To collect individual data including more detailed information regarding the residence of the patients to perform similar analyses of smaller geographical units.
- To reanalyze the data when data from additional outbreaks will be available and continuously update the decision framework with the new available information.

1 Background

The seventh cholera pandemic, which is still ongoing, started in 1961 in South Asia, reached Africa in 1971 and the Americas in 1991 [1]. The disease is now considered to be endemic, mainly in African countries, and the pathogen causing cholera cannot currently be eliminated from the environment [2].

Two serogroups of *V. cholerae* - O1 and O139 - can cause outbreaks. The main reservoirs are humans and aquatic sources such as brackish water and estuaries, often associated with algal blooms (plankton). Recent studies indicate that global warming might create a favourable environment for *V. cholerae* and increase the incidence of the disease in vulnerable areas. *V. cholerae* O1 causes the majority of outbreaks worldwide. The serogroup O139, first identified in Bangladesh in 1992, possesses the same virulence factors as O1, and creates a similar clinical picture. Currently, the presence of O139 has been detected only in South-East and East Asia, but it is still unclear whether *V. cholerae* O139 will extend to other regions. Careful epidemiological monitoring of the situation is recommended and should be reinforced. Other strains of *V. cholerae* apart from O1 and O139 can cause mild diarrhoea but do not develop into epidemics[3].

1.1 Clinical features

The disease is characterized in its most severe form by a sudden onset of acute watery diarrhoea that can lead to death by severe dehydration and kidney failure. The extremely short incubation period - two hours to five days - enhances the potentially explosive pattern of outbreaks, as the number of cases can rise very quickly. About 75% of people infected with cholera do not develop any symptoms. However, the pathogens stay in their faeces for 7 to 14 days and are shed back into the environment, potentially infecting other individuals. Cholera is a virulent disease that affects both children and adults. Unlike other diarrhoeal diseases, it can kill healthy adults within hours. Among people developing symptoms, 80% of episodes are of mild or moderate severity. Among the remaining cases, 10%-20% develop severe watery diarrhoea with signs of dehydration. If untreated, as many as one in two people may die. With proper treatment, the fatality rate is below 1%[4].

1.2 Epidemiology

Cholera is mainly transmitted through contaminated water and food and is closely linked to inadequate environmental management. The absence or shortage of safe water and sufficient sanitation combined with a generally poor environmental status are the main causes of spread of the disease. Typical at-risk areas include peri-urban slums, where basic infrastructure is not available, as well as camps for internally displaced people or refugees, where minimum requirements of clean water and sanitation are not met. The consequences of a disaster -- such as disruption of water and sanitation systems or massive displacement of population to inadequate and overcrowded camps -- can increase the risk of transmission [4].

Since 2005, the re-emergence of cholera has been noted in parallel with the ever-increasing size of vulnerable populations living in unsanitary conditions. Cholera remains a global threat to public health and one of the key indicators of social development. While the disease is no longer an issue in countries where minimum hygiene standards are met, it remains a threat in almost every developing country. The number of cholera cases reported to WHO recently rose dramatically. This increased number of cases is the result of several major outbreaks that occurred in countries where cases have not been reported for several years. It is estimated that only a small proportion of cases - less than 10% - are reported to WHO. The true burden of disease is therefore grossly underestimated [5].

1.3 Cholera in Guinea-Bissau

Cholera is endemic in Guinea-Bissau with the most recent epidemic occurring in 2008 when 14 220 cases and 225 deaths were notified. In 2005-2006, a large outbreak occurred with 25111 cases and 399 deaths reported (Figure 1). Previous outbreaks were also reported in 1994, 1996 and 1997. In many areas of Guinea-Bissau, basic infrastructure is insufficient and the overall quality of water and sanitation remains poor, thereby facilitating cholera transmission.

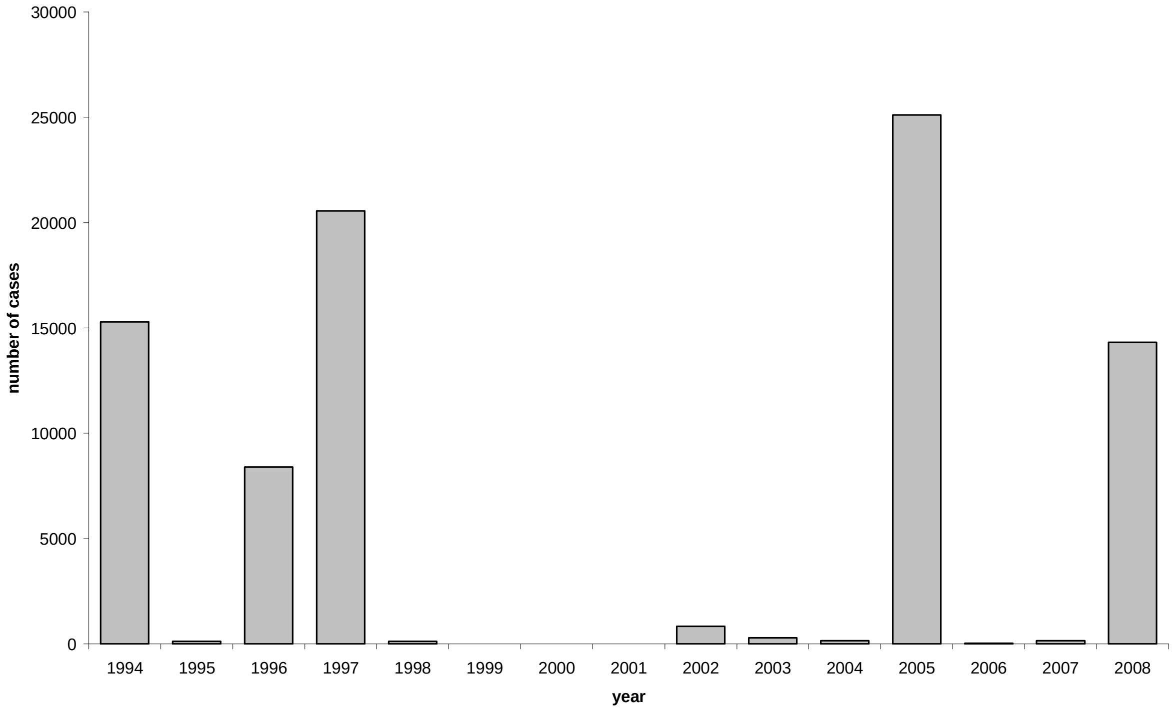


Figure 1. Number of cholera cases notified to the World Health Organization (WHO) in Guinea-Bissau. 1994-2008. Source: WHO weekly epidemiological report.

1.4 Rationale

In July 2008, the government of Guinea Bissau officially declared a cholera epidemic and put in place a response plan. As there is often an inter-epidemic period after a large outbreak such as this, it is important to take the opportunity to learn lessons from previous outbreaks to better assess risks in the future. Analysis of available historical data on cholera epidemics in Guinea Bissau can help to develop a statistical model for risk assessment. Use of these models can help to ensure that there is a timely response of cholera outbreaks, thereby avoiding geographic spread, by identifying “signals” or indicators of when an outbreak is likely to occur or to predict the magnitude of an outbreak in an early stage.

1.5 Objectives

The general objective of this study was to implement a time series and a spatial analysis in order to help to the timely identification of cholera outbreaks adapted to each region of Guinea Bissau

The specific objectives of the study were:

- To describe the historical cholera data and epidemics in Guinea-Bissau identifying long term trends and the seasonal pattern

- To obtain a predictive model of the seasonal risk of finding cholera cases in each region of the country

- To calculate a threshold to detect epidemics with potential to affect more than 0.5% of the population

2 Materials and methods

2.1 The cholera surveillance system in Guinea-Bissau

The main objective of the specific cholera surveillance system is the early detection of outbreaks in order to promptly respond to epidemics. Cholera surveillance is part of an "integrated surveillance system for health related events" (ISS) and covers the entire country.

The population under surveillance in the specific surveillance system for cholera is every person living in the country older than 5 years. The surveillance activities are running during the whole year and are reinforced when a cholera outbreak is declared.

The data collection is based in the basic health structures (BHS) and is coordinated by each Regional Direction of Health (RDH). The RHD has the responsibility to perform data collection and notify the Instituto Nacional de Saúde (INASA) of any cholera case detected in the respective RDH. There are two main sources of data: the health care structure and the community. When a health event, in this case watery diarrhea, is detected in the community, this event must be notified to the BHS. In this way all the information is centralized in the BHS and processed in hierarchical steps:

BHS → RDH → INASA → MPH and WHO

The data management is performed at the three levels. The data collection and the registration start in the BHS under the supervision of the RDHs. The number of cases and deaths are reported from the RDHs to INASA and here the information from all the regions is centralized, registered and checked.

2.2 Case definition

Two different health related events are under surveillance: cholera cases and cholera deaths.

- Suspected cholera case:
    - During non-epidemic periods: every person suffering from severe dehydration or dying of acute watery diarrhea
    - During epidemic period: every person suffering from acute watery diarrhea with or without vomiting.
- Confirmed cholera case: any suspected case with a positive stool sample to Vibrio cholera O1 or O139.

- Cholera deaths: any person dying from acute watery diarrhea.

2.3 Cholera data base

The legal authority for data collection is the Ministry of Public Health (MPH). Within the MPH, INASA is the structure who takes responsibility for data collection, analysis and interpretation of the information generated from the surveillance system. The responsibility for data collection is shared between the three administrative levels of the DGS: the Basic Health Structure (BHS), the Regional Direction of Health (RDH) and INSASA

The database used for the surveillance activities is an aggregated database where the total number of cholera cases and deaths are entered for each region. The program chosen for managing the database was MS Excel ® (Seattle, Washington).

Theoretically, cholera cases should be notified using a single form for every patient and this information should be available at INASA. Nonetheless, in practice, the notification of cases is done mainly by phone and only the total daily number of cases and deaths are registered in the MS Excel® database. No individual information is entered in the database.

2.4 Time series analysis

2.4.1 Description of historical data

We described the historical cholera data in Guinea-Bissau in terms of time and place. Central tendency (mean and medians) and dispersion parameters (standard deviation and interquartile range) were calculated for continuous variables, percentages and 95% confidence intervals for categorical variables. The data were analyzed on a daily basis and then aggregated in epidemiological weeks as defined by the WHO. Attack rates (AR) and case fatality ratios (CFR) were computed for each epidemic. A sequential description of the outbreaks was performed, considering the pre-peak period, the week of the peak and the post-peak period. When appropriate, epidemic curves by regions were drawn.

2.4.2 Seasonal risk analysis

The seasonal risk of cholera in Guinea-Bissau was evaluated for the whole country and for the three most affected regions: Bissau, Biombo and Bijagos. The dependent variable in these models was the number of cholera cases and the independent variable the day of the year (from 1 to 365).

The seasonal risk of cholera was analyzed by a Poisson regression model using a General Additive Model (GAM) framework (13). More specifically, let Y_t be the total number of cholera cases on day t. The Y_t are Poisson-distributed with expectation μ_t and with possible overdispersion φ. The general form of the model is

$$Yt \sim \text{Poisson}(\mu t)$$
$$Var(Yt)=\varphi\ \mu t$$
$$(\mu t) = s(day_t,df)\ (1)$$

where day_t is the day of the year. Cubic splines were used as the smoothing function, with smoothness defined as the approximate number of degrees of freedom (df) to be assigned to that particular term. A linear function has one df; increasing df increases flexibility in describing patterns in the data.

A sensitivity analysis was performed and no substantial differences were found varying df. The choice of the number of df for each non-parametric smoothing function was made based on adjusted R-square of the model.

Analysis were performed with R 2.8.0 (The R Foundation for Statistical Computing ©) using the mgcv library.

2.4.3 Threshold to define outbreaks with potential to produce large epidemics

In order to define thresholds to identity situations of high risk of large epidemic two types of information were available: the number of cases and the geographical spread (number of regions affected). Both data could be used to establish criteria to define high-risk situations.
In this regard, we use the cumulative number of cases as these data provide an indication of the cumulative risk of spread and are less affected by the instability of the daily notification. In order to help the interpretation of the graph and facilitate the comparability between epidemics we applied a decimal logarithm transformation to the data.

2.4.3.1 The decimal logarithm transformation

In statistics, data transformation refers to the application of a deterministic mathematical function to each point in a data set — that is, each data point z_i is replaced with the transformed value $y_i = f(z_i)$, where f is a function. Transformations are usually applied so that the data appear to meet more closely the assumptions of a statistical inference procedure that is to be applied, or to improve the interpretability or appearance of graphs. Nearly always, the function that is used to transform the data is invertible, and generally is continuous. The transformation is usually applied to a collection of comparable measurements.
The logarithm transformation is commonly used for positive data like cases counts. A common situation where a data transformation is applied is when a value of interest ranges over several orders of magnitude (like the cumulative number of cases in different epidemics). Power transforms, and in particular the logarithm, can often be used to induce symmetry in such data. The logarithm is often favored because it is easy to interpret its result in terms of "fold changes."

2.5 Ethical considerations

This study adhered to the principles that govern biomedical research involving human subjects. The Declaration of Helsinki was followed in order to assure that the rights, integrity, and confidentiality of participants were protected. All the analyzed data were anonymous and collected through the routine surveillance activities of the country. The study was implemented in collaboration with the Ministry of Health and with their approval.

3 Results

3.1 Historical cholera epidemics in Guinea-Bissau from 1996 to 2008

3.1.1 1996-1997 epidemic

From 1996 to 1997 two consecutive epidemics were notified in Guinea-Bissau with 26959 cases and 961 deaths at country level during this period. The first epidemic lasted from October 1996 to May 1997 and the second from May 1997 to January 1998.

3.1.1.1 October 1996-April 1997 epidemic

The first epidemic started in October 1996 and finished in April 1997 (30 weeks). During this outbreak 10844 cases and 108 deaths were reported (Figure 2). The overall estimated AR was 1% and the CFR was 1%.

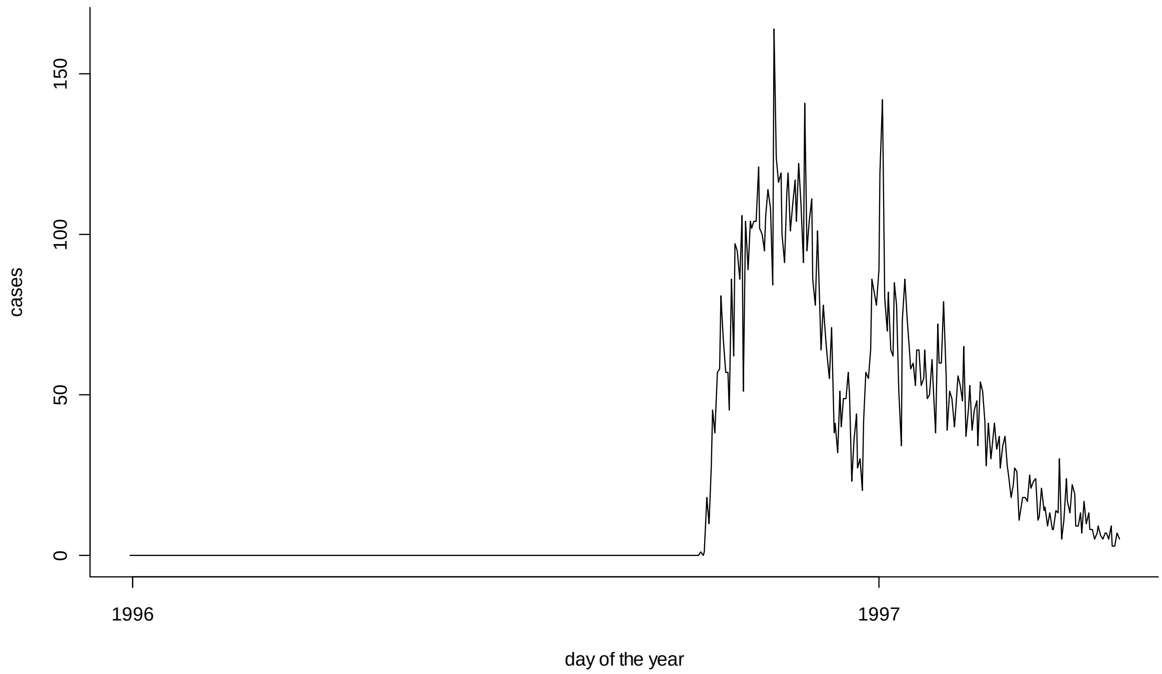


Figure 2. Daily number of cholera cases in Guinea-Bissau. October 1996 to April 1997.

The first peak was observed after one month after cases were reported in epidemic week 46 with 798 cases. The average weekly case counts increased by 133 cases per week until reaching the peak. The highest increase was observed in the second week of the outbreak with an increase of 313 cases. A total of 23.0% of the cases were observed before the first peak, 7.3% occurred in the week of the peak and 69.7% in the 24 weeks with cases reported after the first peak. The epidemic curve showed a second peak in week 1 of 1997 with 658 cases (Figure 3)

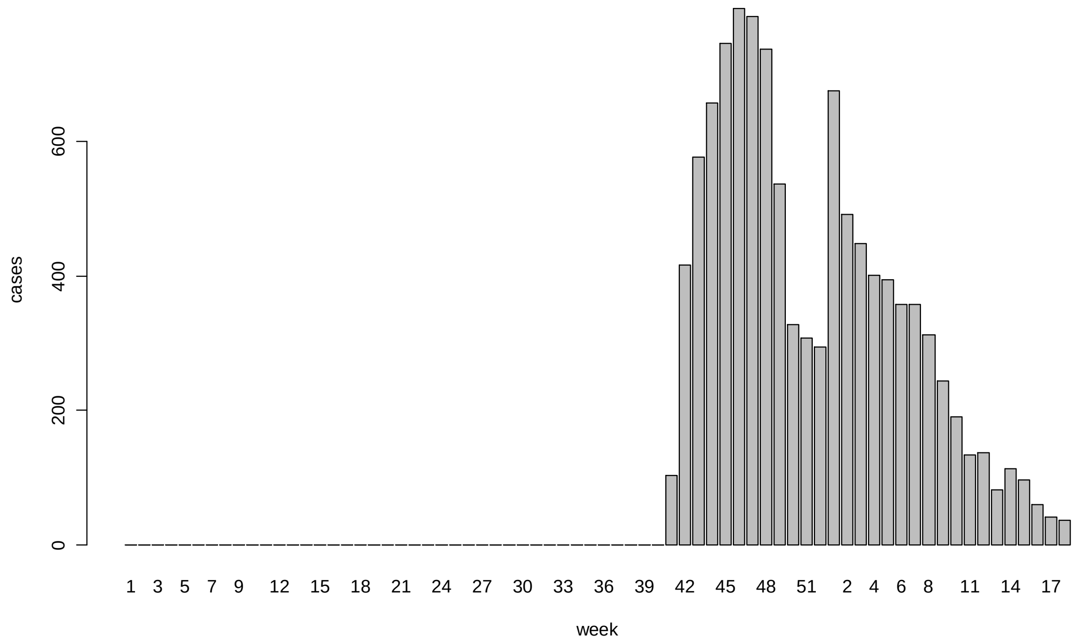


Figure 3. Weekly number of cholera cases in Guinea-Bissau. January 1996 to April 1997.

The Figure 4 shows that the October 1996-April 1997 epidemic affected mainly the capital, Bissau, with an AR over 4%. The second region most affected was Biombo , especially Prabis region with and an AR of 2.5%.

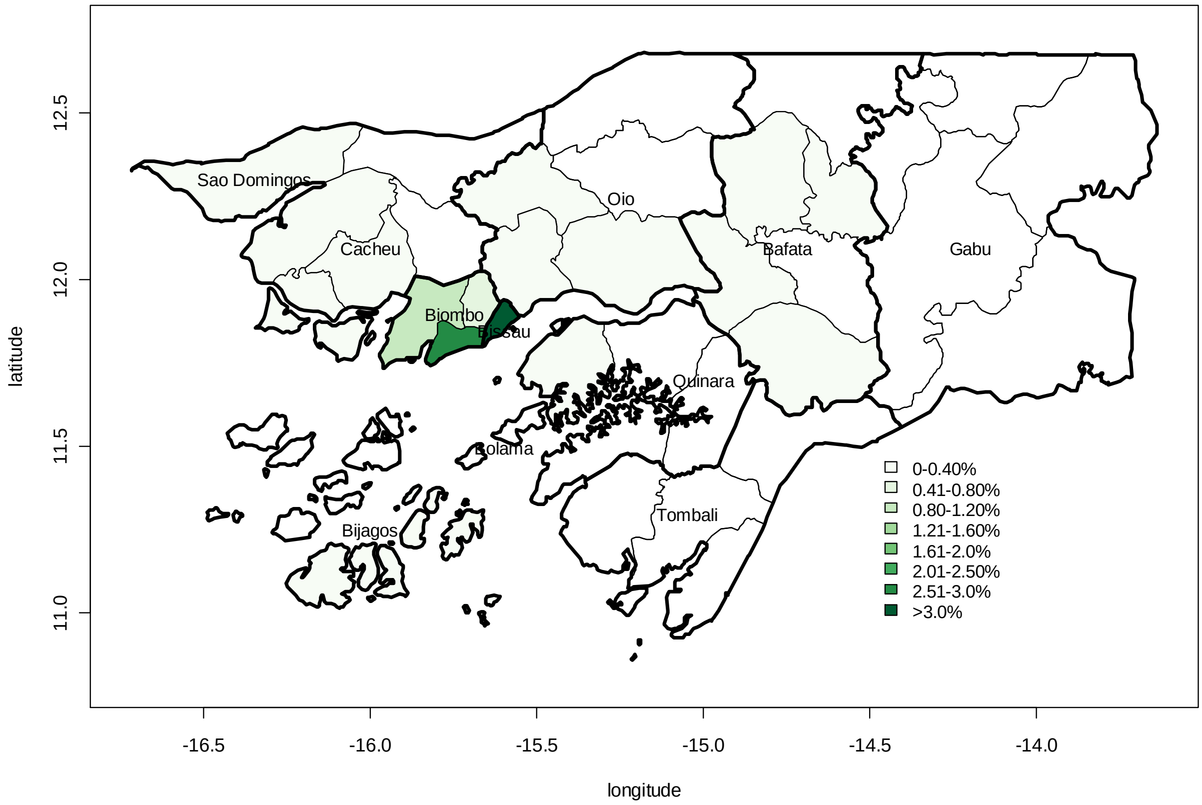


Figure 4. Cholera attack rates by sanitary area in Guinea-Bissau. October 1996 to April 1997.

The following graph shows the daily number of cases in Bissau and Biombo regions. In the capital both peaks (week 46 of 1996 and week 1 of 1997) were observed, but in Biombo only the first wave of 1996 was recorded.

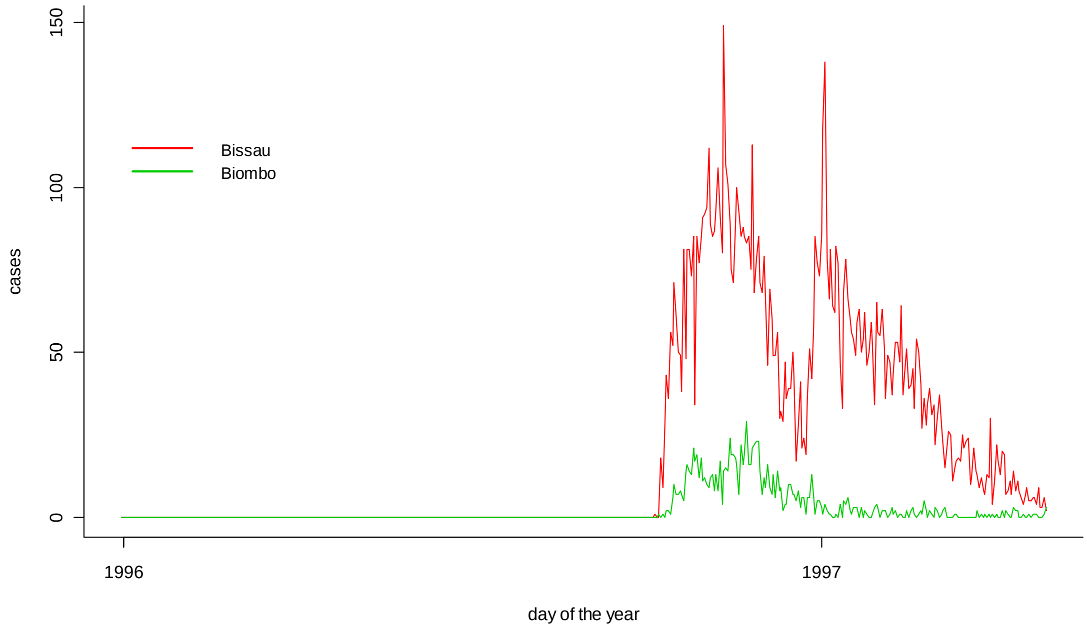


Figure 5. Daily number of cholera cases in Bissau and Biombo regions. January 1996 to April 1997.

3.1.1.2 May 1997-January 1998 epidemic

The second epidemic started in May 1997 and finished in January 1998 (38 weeks). During this outbreak 16115 cases and 853 deaths were reported (Figure 6). The overall estimated AR was 1.4% and the CFR was 5.3%.

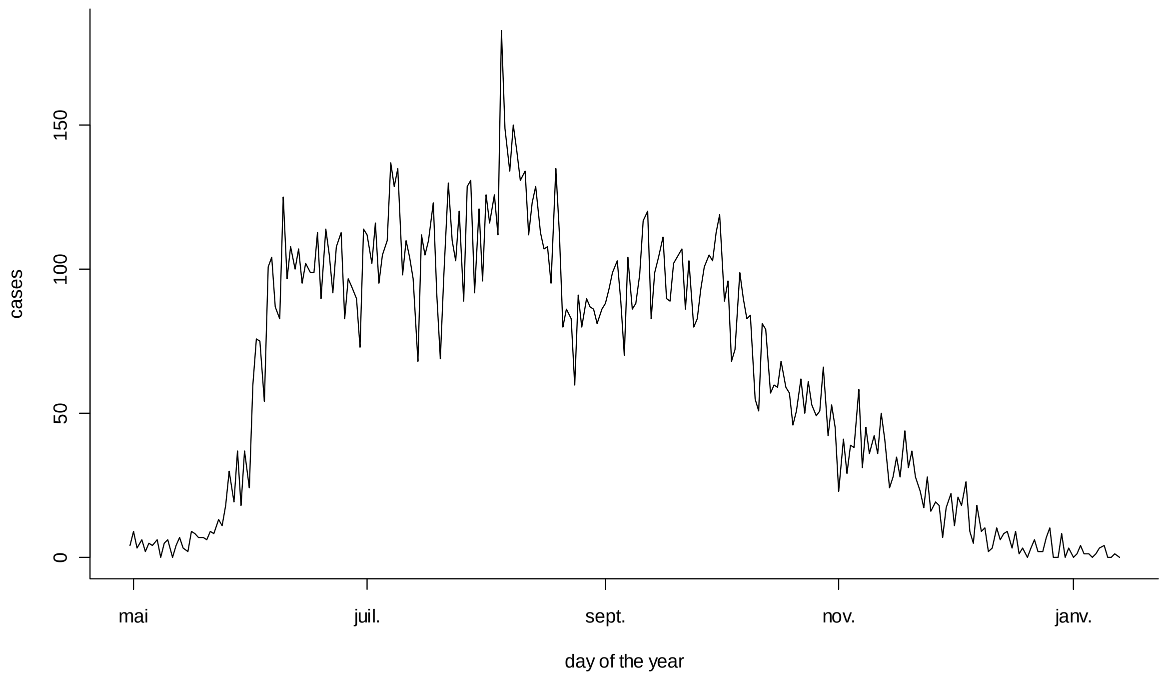


Figure 6. Daily number of cholera cases in Guinea-Bissau. May 1997 to January 1998.

The peak was observed after 14 weeks of epidemic (epidemic week 32) with 995 cases. The average weekly case counts increased by 74.4 cases per week until reaching the peak. The highest increase was observed in the fourth week of the outbreak with an increase of 374 cases. A total of 41.9% of the cases were observed before the first peak, 6.2% occurred in the week of the peak and 51.9% in the 24 weeks with cases reported after the first peak. (Figure 7). A second peak was observed form week 37 to 40.

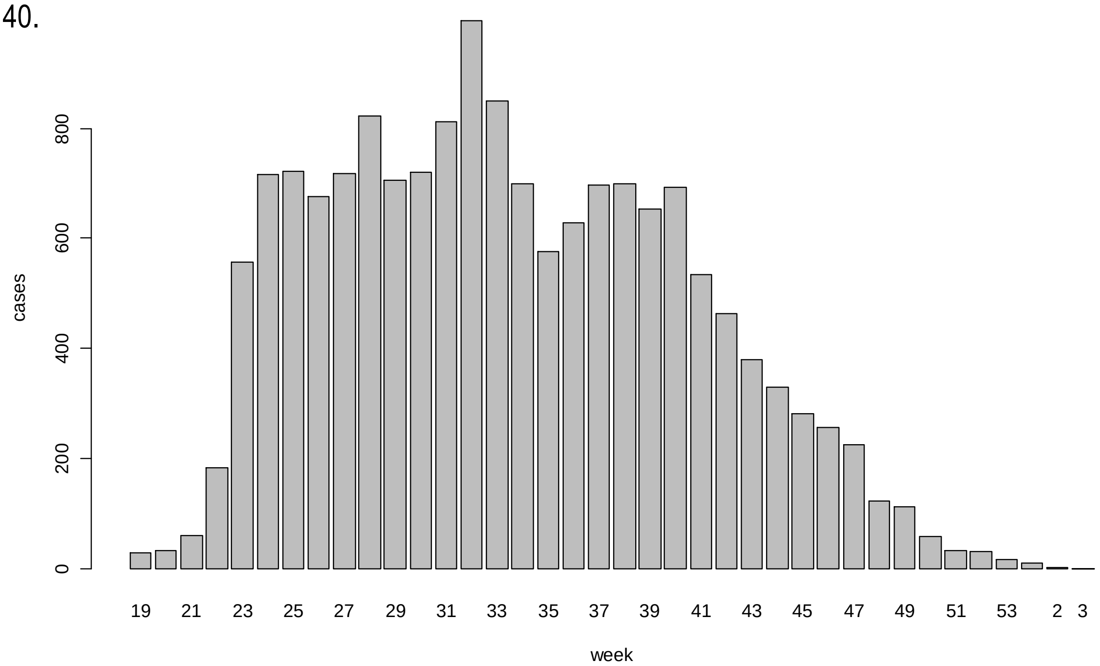


Figure 7. Weekly number of cholera cases in Guinea-Bissau. May 1997 to January 1998.

The next map shows the attack rates of the complete 1996-1998 epidemic considering the mid-period population (1997 population) as the total population at risk. The map shows that the epidemic affected mainly the capital (AR=8.2%), the Biombo region (AR=4.2%), and the Bijagos Islands (AR=4.6%).

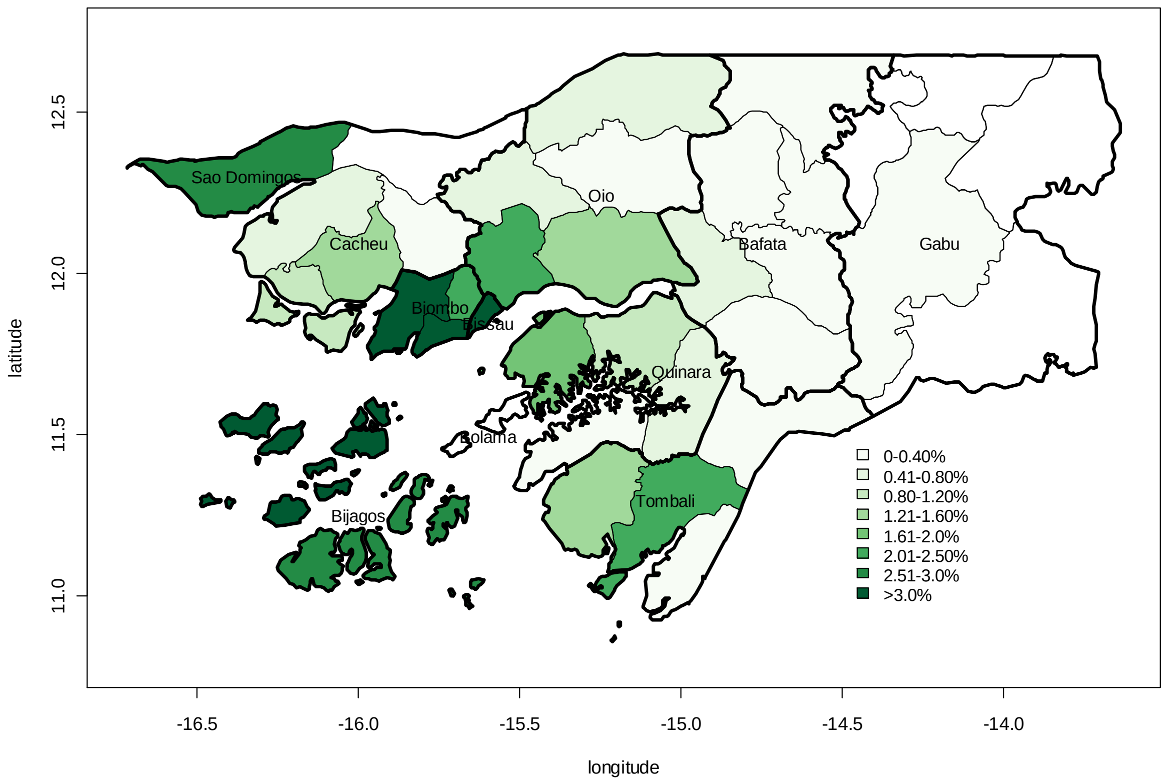


Figure 8. Cholera attack rates by sanitary area in Guinea-Bissau. 1996-1998 epidemic.

The most affected sub-regions particularly were Ondame, Quinhamel, Prabis, Bubaque, Caravelas, Uno, São Domingos, Nhacra in Oio and Bedanda in Tombali (Table 1).

Table 1. Cholera cases, deaths, attack rates and fatality by region. Guinea-Bissau. 1996-1998.

Region	Cases	Deaths	Populacion	AR(%)	CFR(%)
Total SAB	18547	227	237315	7.82	1.22
Total Biombo	2851	45	62504	4.56	1.58
Ondame	892	11	12478	7.15	1.23
Quinhamel	1004	13	27279	3.68	1.29
Prabis	751	15	13752	5.46	2.00
Safim	204	6	9050	2.25	2.94
Total Cacheu	1064	152	101452	1.05	14.29
Bula	96	10	27477	0.35	10.42
Cacheu	87	8	18945	0.46	9.20
Caio	180	13	16651	1.08	7.22
Canchungo	701	121	46693	1.50	17.26
Total Oio	1497	260	187068	0.80	17.37
Bissora	245	43	61526	0.40	17.55
Farim	260	46	40697	0.64	17.69
Mansaba	4	1	23702	0.02	25.00
Mansoa	496	75	34100	1.45	15.12
Nhacra	492	95	23308	2.11	19.31
Total Bafata	262	65	165466	0.16	24.81
Bafata	43	13	43849	0.10	30.23
Bambadinca	153	37	23867	0.64	24.18
Contubuel	3	0	39336	0.01	0.00
Galomaro	9	2	14632	0.06	22.22
Ga-do	47	11	20101	0.23	23.40
Xitole	7	2	12932	0.05	28.57
Total Gabu	5	0	166985	0.00	0.00
Boe	0	0	11864	0.00	-
Gabu	5	0	41757	0.01	0.00
Pirada	0	0	24674	0.00	-
Pitche	0	0	34063	0.00	-
So-co	0	0	53030	0.00	-
Total Bolama	0	0	10165	0.00	-
Total Bijagos	980	57	23260	4.21	5.82
Bubaque	290	22	9994	2.90	7.59
Caravelas	125	10	4277	2.92	8.00
Uno	565	25	8210	6.88	4.42
Total Quinara	478	55	59454	0.80	11.51
Buba	68	6	11629	0.58	8.82
Empada	1	1	17648	0.01	100.00
Fulacunda	98	14	9627	1.02	14.29
Tite	311	34	19248	1.62	10.93
Total Sao Domingos	687	50	70173	0.98	7.28
Bigene	0	0	40748	0.00	-
Sao Domingos	687	50	27512	2.50	7.28
Total Tombali	588	50	87899	0.67	8.50
Bedanda	156	12	7876	1.98	7.69
Catio	414	36	26716	1.55	8.70
Cacine	15	0	7978	0.19	0.00
Quebo	3	2	17002	0.02	66.67
Komo	0	0	11642	0.00	-
Calaque	-	-	12605	-	-
Sanconha	-	-	3772	-	-
Total Guinea-Bissau	26959	961	1200030	2.25	3.56

The following graph shows the evolution of the whole 1996-1998 epidemic. During the first weeks of the second epidemic (from May 1997), the outbreak spread again in Bissau and during the last part of 1997 affected Biombo and Bijagos.

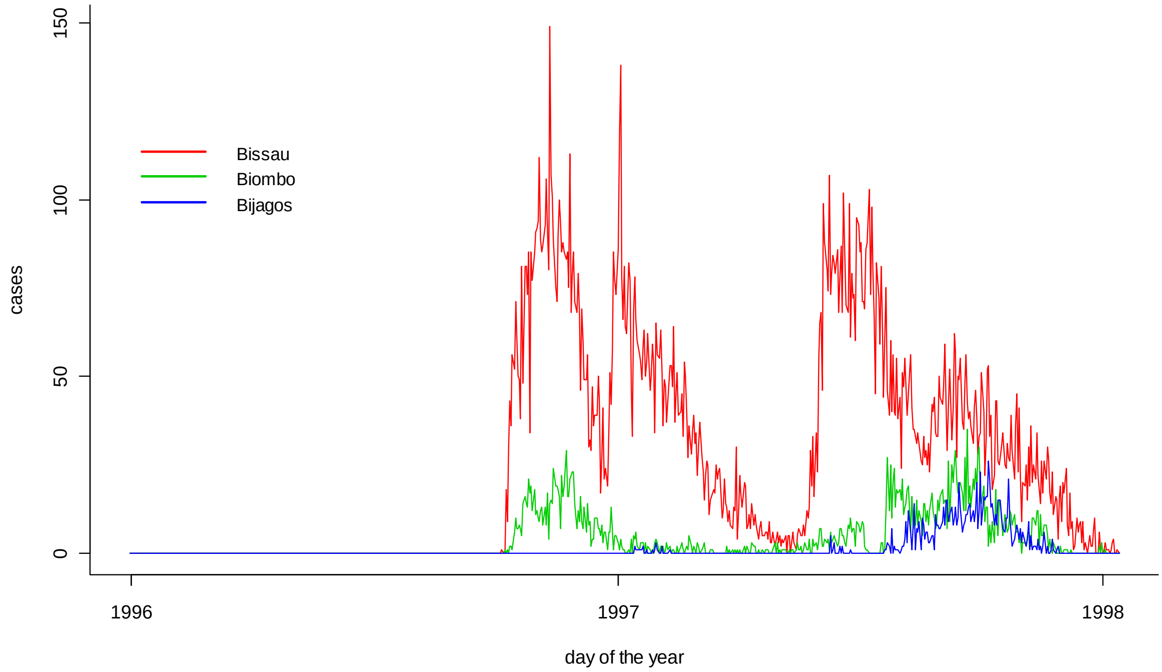


Figure 9. Daily number of cholera cases in Bissau, Biombo and Bijagos regions. May 1997 to January 1998.

The next figure shows the epidemic in the rest of sanitary areas with attack rates over 2%.

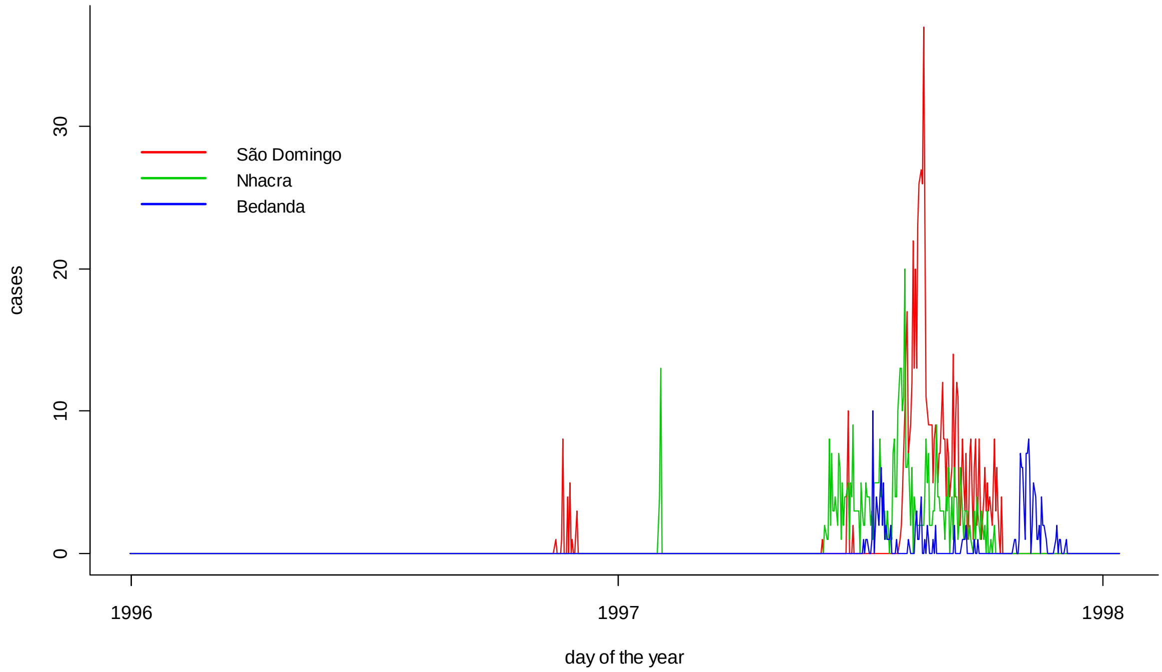


Figure 10. Daily number of cholera cases in São Domingos, Nhacra and Bedanda regions. May 1997 to January 1998

Annex 1 shows the evolution of the 1996-1997 epidemic in monthly steps.

3.1.2 2004 epidemic

In 2004, a smaller epidemic was notified in the Bijagos Islands with 227 cases and 3 deaths (Figure 11). The epidemic started in October 2004 and finished in December (11 weeks). The estimated AR was 0.95% and the CFR was 1.3% in the Bijagos Islands.

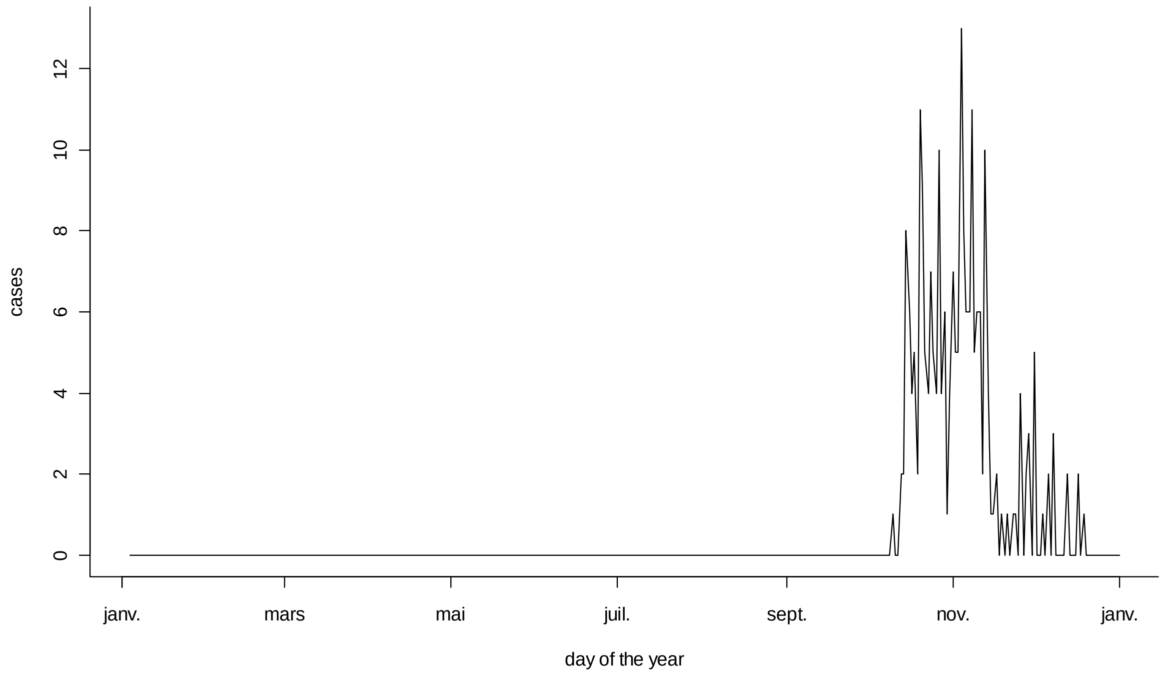


Figure 11. Daily number of cholera cases in Guinea-Bissau. 2004.

The peak was observed the fourth week of the epidemic in week 44 with 48 cases. The average weekly case count increased by 9.7 cases per week until reaching the peak. The highest increase was observed in the second week of the epidemic with an increase of 21 cases. A total of 42.3% of cases were observed before the peak, 21.1% occurred in the week of the peak and 36.6% in the week after the peak. A second peak was observed in week 48 with 11 cases (Figure 12).

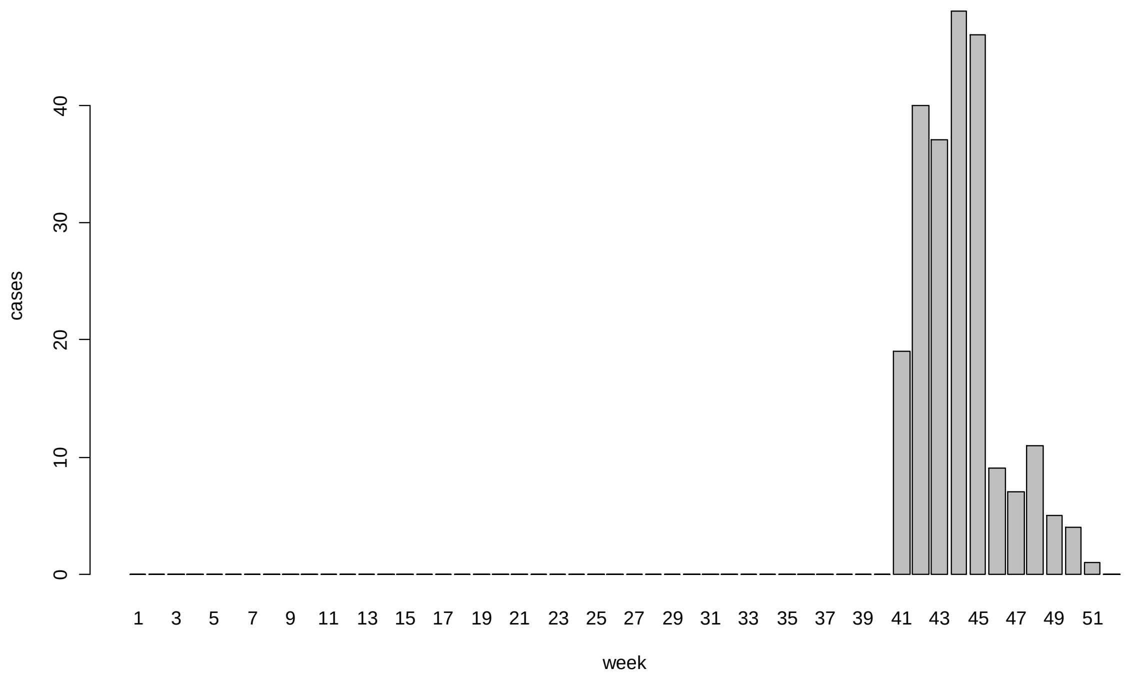


Figure 12. Weekly number of cholera cases in Guinea-Bissau. 2004.

The next map shows that the only area affected during this epidemic was the Bijagos Islands.

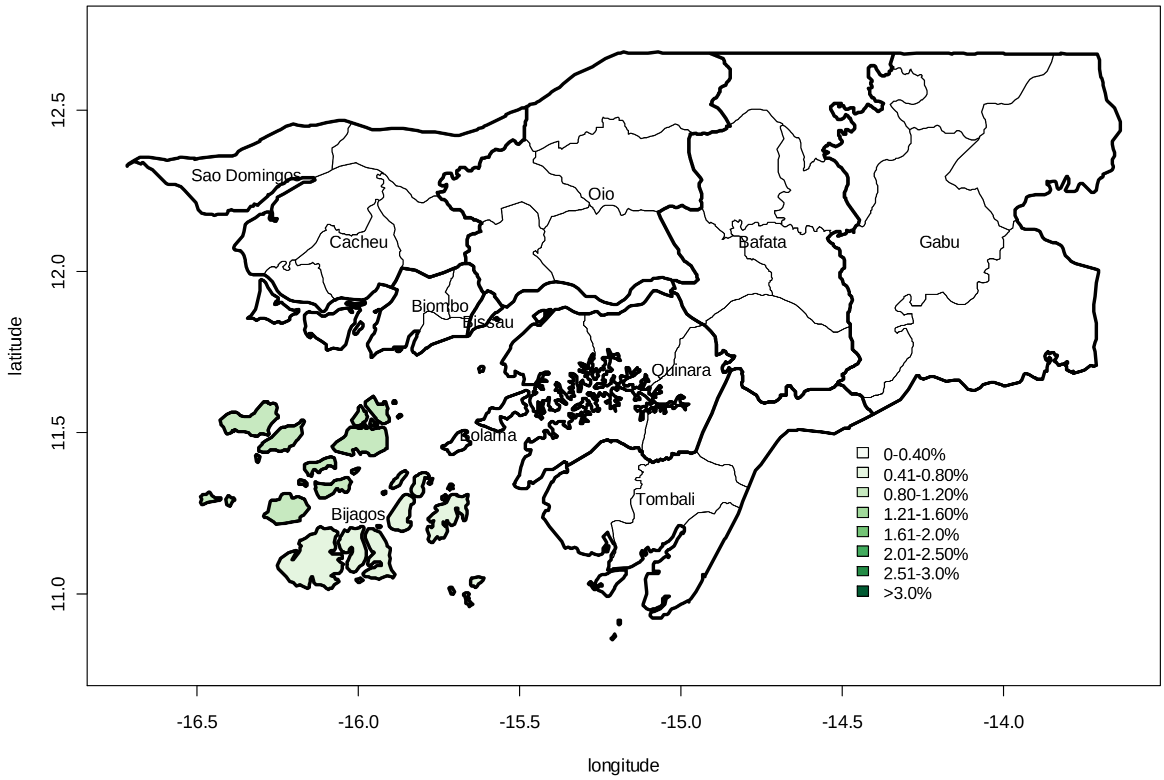


Figure 13. Cholera attack rates by sanitary area in Guinea-Bissau. 2004 epidemic.

The following table shows the attack rate and the CFRs the Bijagos Islands.

Table 2. Cholera cases, deaths, attack rates and fatality by region. Guinea-Bissau. 2004.

Region	Casos	Obitos	Populacion	AR(%)	CFR(%)
Total Bijagos	227	3	23167	0.98	1.32
Bubaque	76	0	9901	0.77	0.00
Caravelas	0	0	4187	0.00	NA
Uno	151	3	8245	1.83	1.99

3.1.3 2005 epidemic

The 2005 epidemic started in June 2005 and finished in February 2006 (35 weeks). During this outbreak 25282 cases and 397 deaths were reported (Figure 14). The estimated AR was 1.8% and the CFR was 1.6%.

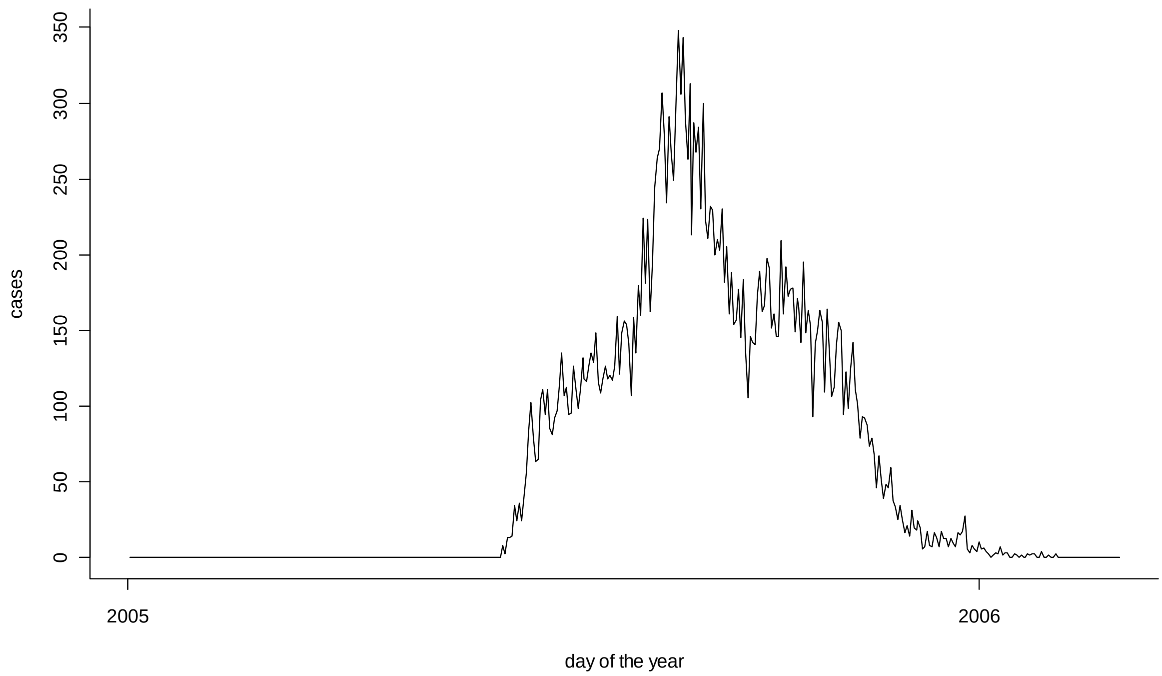


Figure 14. Daily number of cholera cases in Guinea-Bissau. 2005.

The first peak was observed after almost three months after cases were first reported in epidemic week 34 with 2106 cases. The average weekly case count increased by 190.7 cases per week until reaching the peak. The highest increase was observed in the week preceding the peak with an increase of 528 cases. A total of 34.0% of the cases were observed before the first peak, 8.3% occurred in the week of the peak and 57.7% in the 23 weeks with cases reported after the first peak. The epidemic curve showed a second peak in weeks 40 and 41 with 1200 cases each (Figure 15).

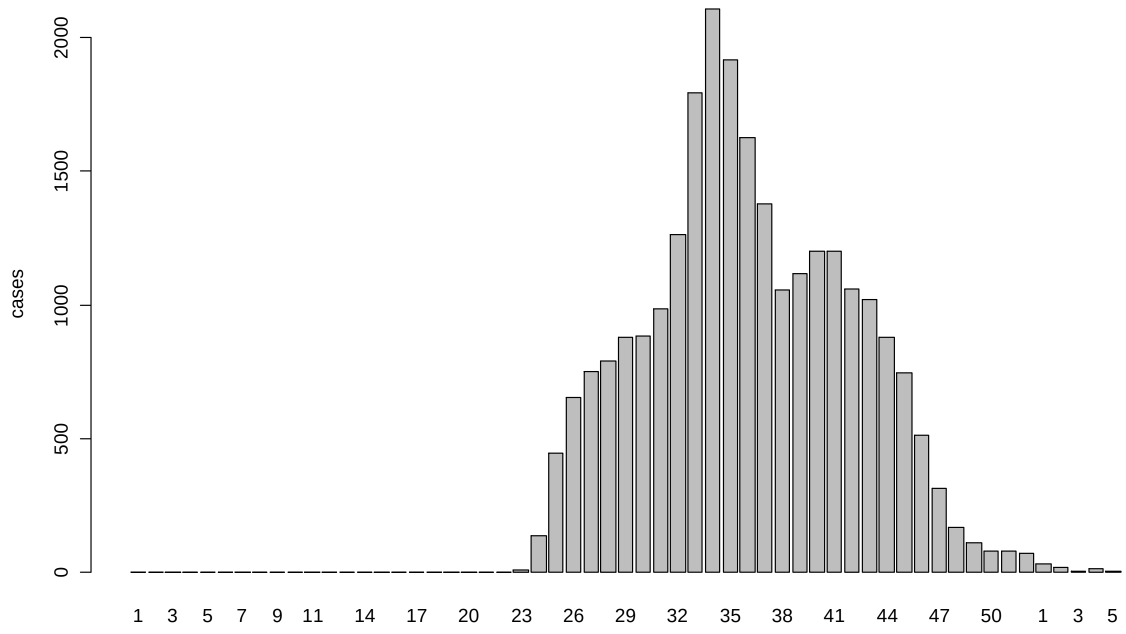


Figure 15. Weekly number of cholera cases in Guinea-Bissau. 2005.

The next map shows that the 2005 epidemic affected different areas of the country; nonetheless, the three most affected areas, as in previous epidemics, were Bissau, Biombo and the Bijagos Islands, with ARs of 4.1% 6.1% and 9.6% respectively. The entire coastal including sanitary areas from Tombali, Quinara, Oio, Cacheu and São Domingos were highly affected.

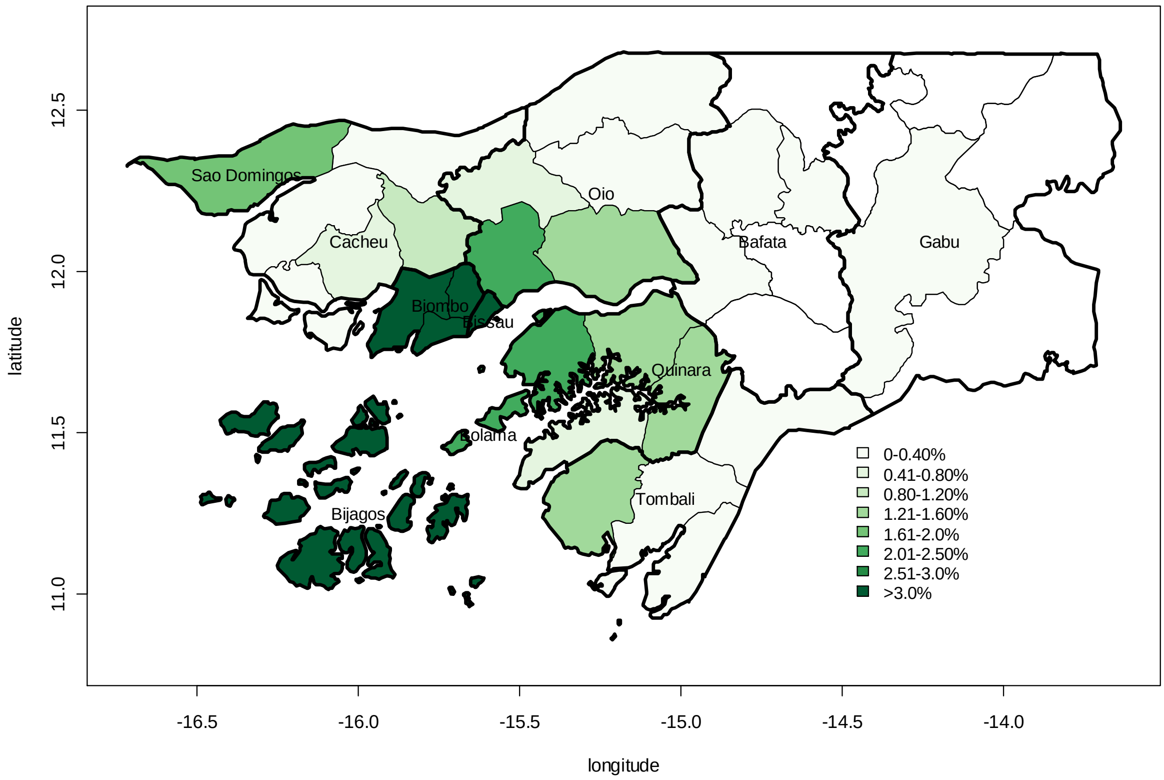


Figure 16. Cholera attack rates by sanitary area in Guinea-Bissau. 2005 epidemic.

The most affected sub-regions were Ondame, Quinhamel, Prabis, Safim, Bubaque, Caravelas, Uno, Bolama, Nhacra and Tite (Table 3).

Table 3. Cholera cases, deaths, attack rates and fatality by region. Guinea-Bissau. 2005.

Region	Cases	Deaths	Populacion	AR(%)	CFR(%)
Total SAB	14376	82	348804	4.12	0.57
Total Biombo	4028	39	65062	6.19	0.97
Ondame	1155	5	12485	9.25	0.43
Quinhamel	1612	16	27192	5.93	0.99
Prabis	944	12	15710	6.01	1.27
Safim	317	6	9651	3.28	1.89
Total Cacheu	807	30	109062	0.74	3.72
Bula	297	5	26634	1.12	1.68
Cacheu	74	8	19657	0.38	10.81
Caio	59	8	15785	0.37	13.56
Canchungo	377	9	49312	0.76	2.39
Total Oio	1340	68	204376	0.66	5.07
Bissora	320	38	66623	0.48	11.88
Farim	9	1	51798	0.02	11.11
Mansaba	52	3	24992	0.21	5.77
Mansoa	450	12	36985	1.22	2.67
Nhacra	509	14	22575	2.25	2.75
Total Bafata	194	16	191344	0.10	8.25
Bafata	191	16	58893	0.32	8.38
Bambadinca	2	0	29058	0.01	0.00
Contubuel	0	0	46161	0.00	-
Galomaro	0	0	16129	0.00	-
Ga-do	1	0	23685	0.00	0.00
Xitole	0	0	13746	0.00	-
Total Gabu	47	2	197886	0.02	4.26
Boe	0	0	11770	0.00	-
Gabu	47	2	56083	0.08	4.26
Pirada	0	0	29796	0.00	-
Pitche	0	0	41472	0.00	-
Sonaco	0	0	57936	0.00	-
Total Bolama	218	6	9932	2.19	2.75
Total Bijagos	2185	17	24018	9.10	0.78
Bubaque	1034	8	10769	9.60	0.77
Caravelas	598	6	5068	11.80	1.00
Uno	553	3	7933	6.97	0.54
Total Quinara	920	76	67095	1.37	8.26
Buba	222	17	15670	1.42	7.66
Empada	163	15	20727	0.79	9.20
Fulacunda	120	6	9806	1.22	5.00
Tite	415	38	20360	2.04	9.16
Total Sao Domingos	711	36	82482	0.86	5.06
Bigene	70	1	49126	0.14	1.43
Sao Domingos	641	35	32737	1.96	5.46
Total Tombali	456	25	103317	0.44	5.48
Bedanda	36	7	9449	0.38	19.44
Catio	372	15	30694	1.21	4.03
Cacine	28	1	11115	0.25	3.57
Quebo	20	2	20397	0.10	10.00
Komo	0	0	11763	0.00	-
Calaque	-	-	14400	-	-
Sanconha	-	-	5255	-	-
Total Guinea-Bissau	25282	397	1416304	1.79	1.57

The following graph shows the evolution of the epidemic in Bissau, Biombo and the Bijagos Islands. The epidemic started in Bissau, reaching more than 100 cases per day in the first days of the epidemic, after the epidemic spread to Bimbo and later to Bijagos, but the peak in the three areas was observed almost during the same dates in late August 2005.

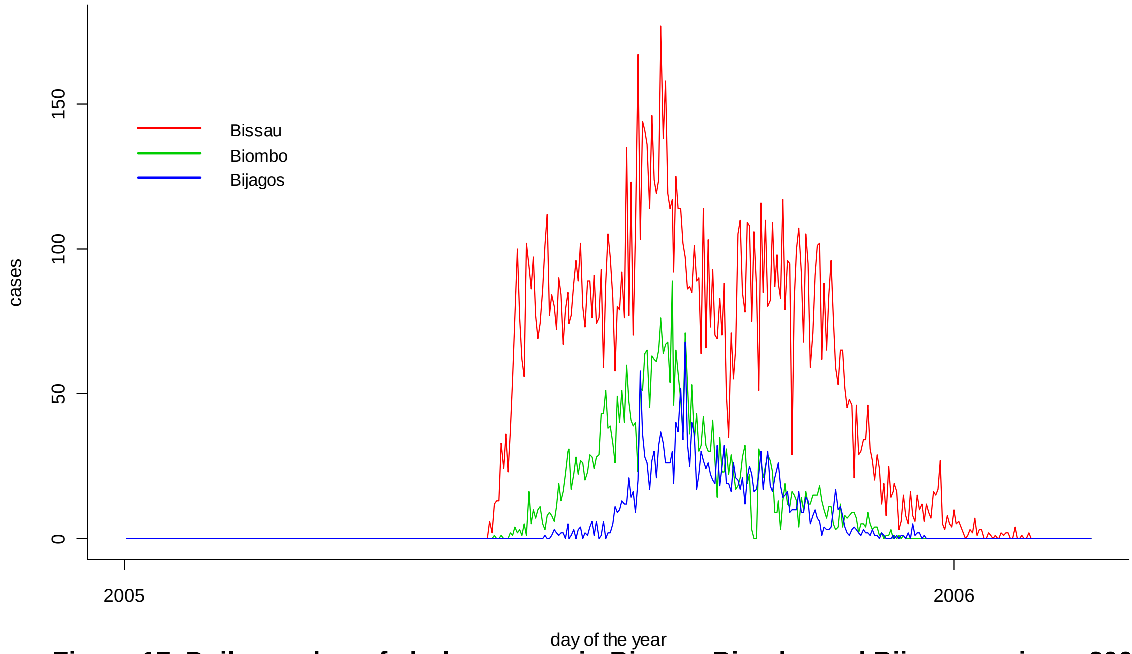


Figure 17. Daily number of cholera cases in Bissau, Biombo and Bijagos regions. 2005.

Other areas highly affected during the 2008 epidemic were Oio, Quinara, São Domingo and Tombali.

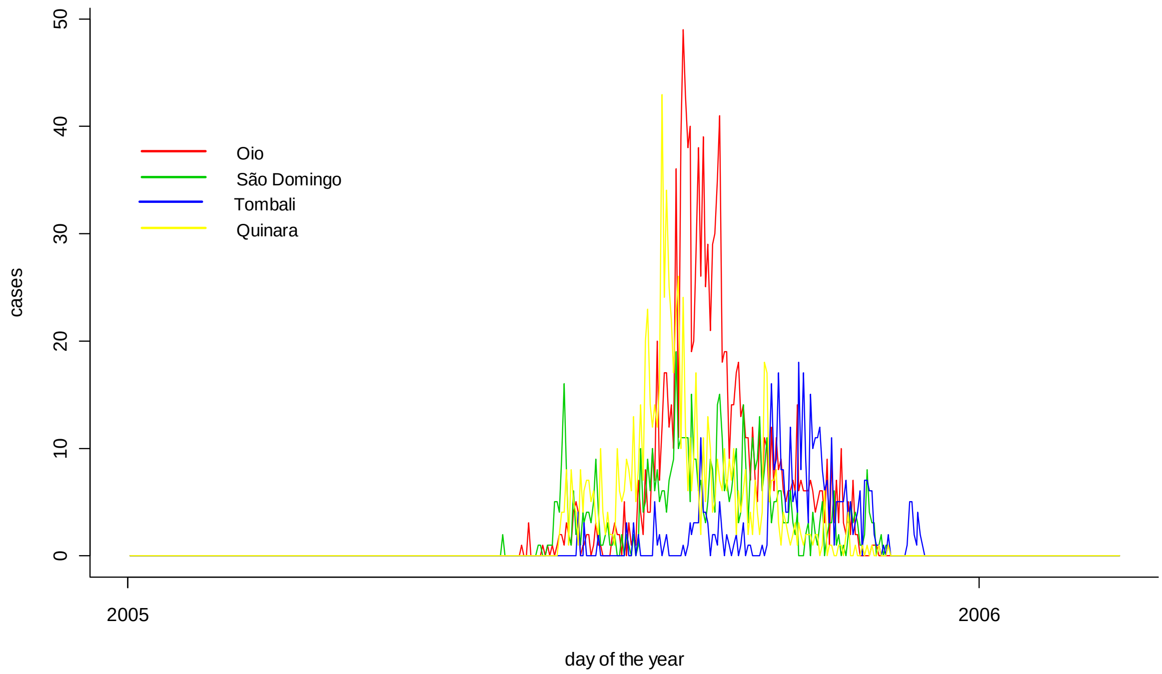


Figure 18. Daily number of cases in Oio, São Domingo, Tombali and Quinara regions. 2005.

Annex 2 shows the evolution of the 2005 epidemic in monthly steps.

3.1.4 2007 epidemic

In 2007, a small epidemic was notified in Tombali with 73 cases and 3 deaths (Figure 19). The epidemic started in October 2007 and finished 18 days later. The estimated AR was 0.07% and the CFR was 4.1%. In the Komo sub-region the AR was as high as 0.6%.

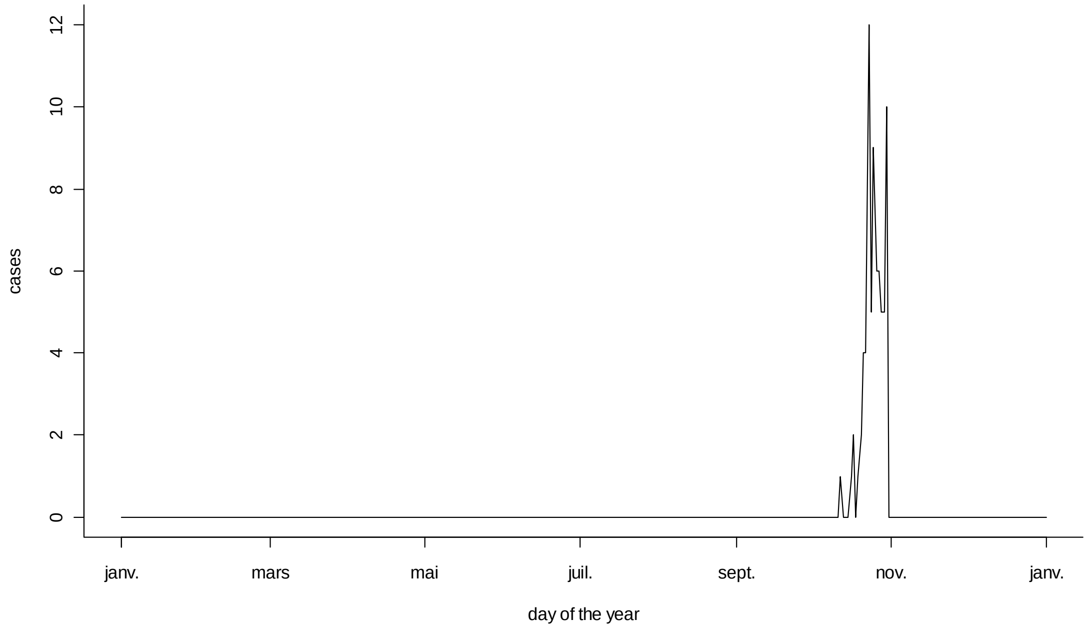


Figure 19. Daily number of cholera cases in Guinea-Bissau. 2007.

The peak was observed the third week of the epidemic in week 43 with 46 cases. The average weekly case counts increased by 22.5 cases per week until reaching the peak. The highest increase was observed in the week of the peak with an increase of 40 cases. A total of 9.6% of the cases were observed before the peak, 63.0% occurred in the week of the peak and 21.4% in the week after the peak. (Figure 20)

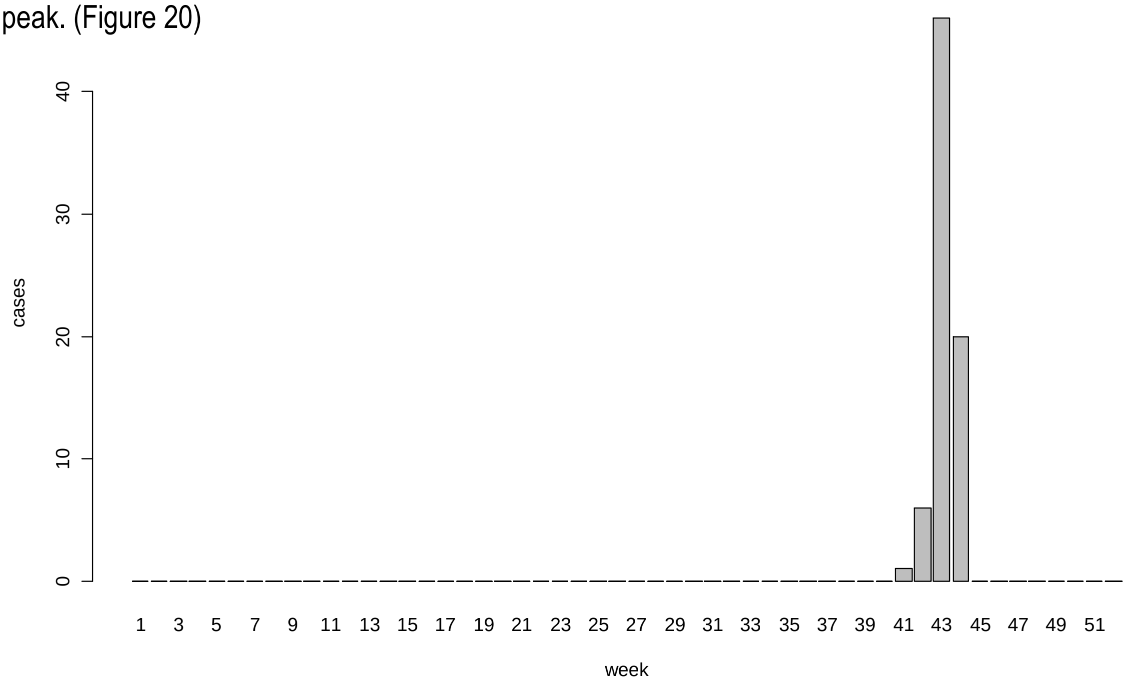


Figure 20. Weekly number of cholera cases in Guinea-Bissau. 2007.

The next map shows that the only area affected during this epidemic was the Tombali region.

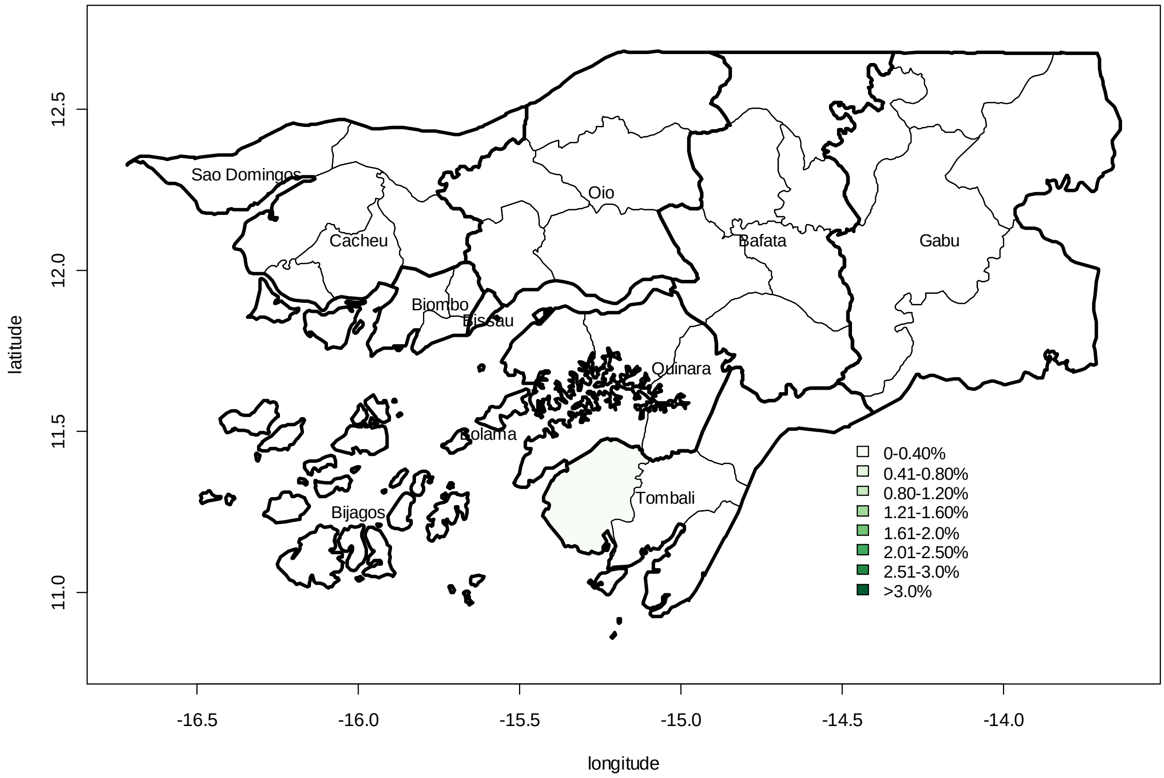


Figure 21. Cholera attack rates by sanitary area in Guinea-Bissau. 2007 epidemic.

The following table shows the attack rate and the CFRs in the Tombali region.

Table 4. Cholera cases, deaths, attack rates and fatality by region. Guinea-Bissau. 2007.

Region	Casos	Obitos	Populacion	AR(%)	CFR(%)
Total Tombali	73	3	107577	0.07	4.11
Bedanda	0	0	9889	0.00	NA
Catio	5	0	31778	0.02	0.00
Cacine	0	0	12076	0.00	-
Quebo	0	0	21347	0.00	-
Komo	68	3	11794	0.58	4.41

3.1.5 2008 epidemic

The 2008 epidemic started in May 2008 and finished in January 2009 (35 weeks). During this outbreak 14228 cases and 225 deaths were reported (Figure 22). The estimated attack rate (AR) was 0.9% and the CFR was 1.6%.

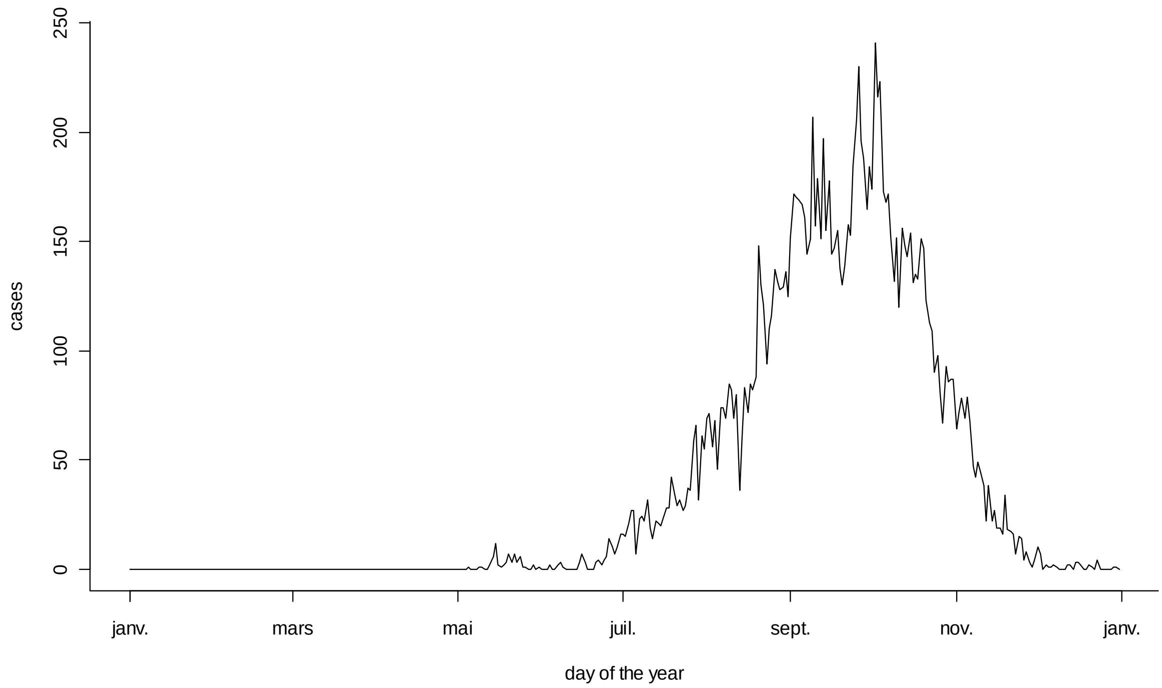


Figure 22. Daily number of cholera cases in Guinea-Bissau. 2008.

The first peak was observed 21 weeks after the first cases were reported in epidemic week 40 with 1391 cases. The average weekly case count increased by 66.1 cases per week until reaching the peak. The highest increase was observed in week 34 with an increase of 266 cases. A total of 59.3% of the cases were observed before the first peak, 9.8% occurred in the week of the peak and 30.9% in the 14 weeks with reported cases after the first peak. (Figure 23)

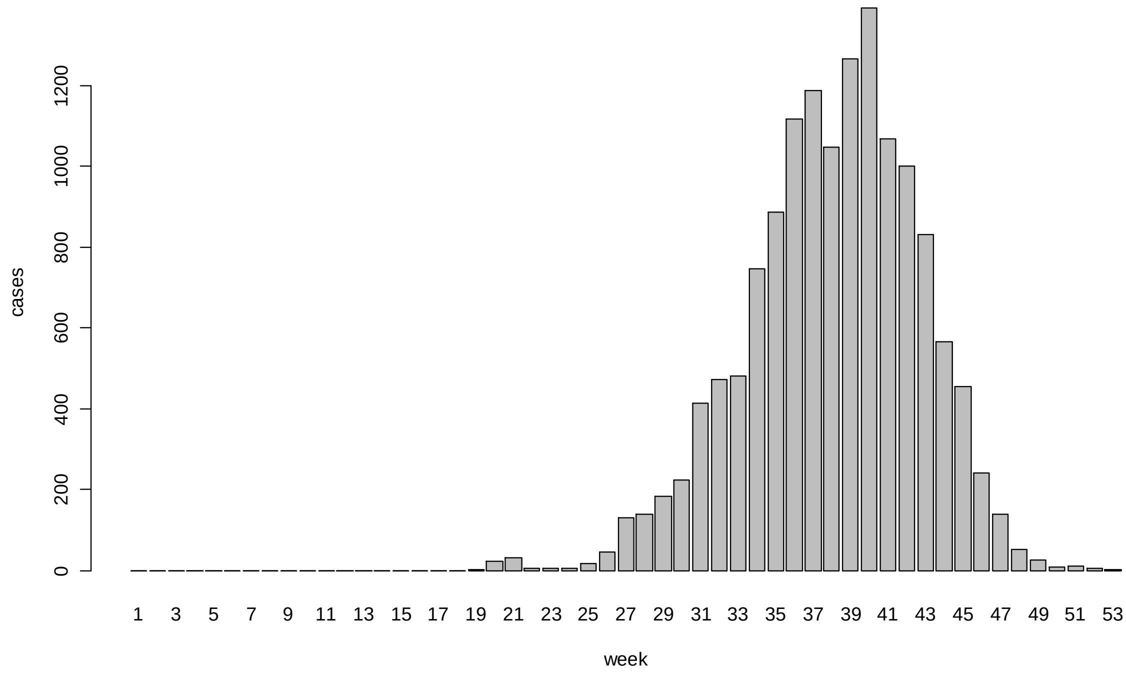


Figure 23. Weekly number of cholera cases in Guinea-Bissau. 2008.

The next map shows that the 2008 epidemic affected different areas of the country; nonetheless, the three most affected areas, as in previous epidemics, were Bissau, Biombo and the Bijagos Islands, with ARs of 2.3% 3.0% and 3.0% respectively.

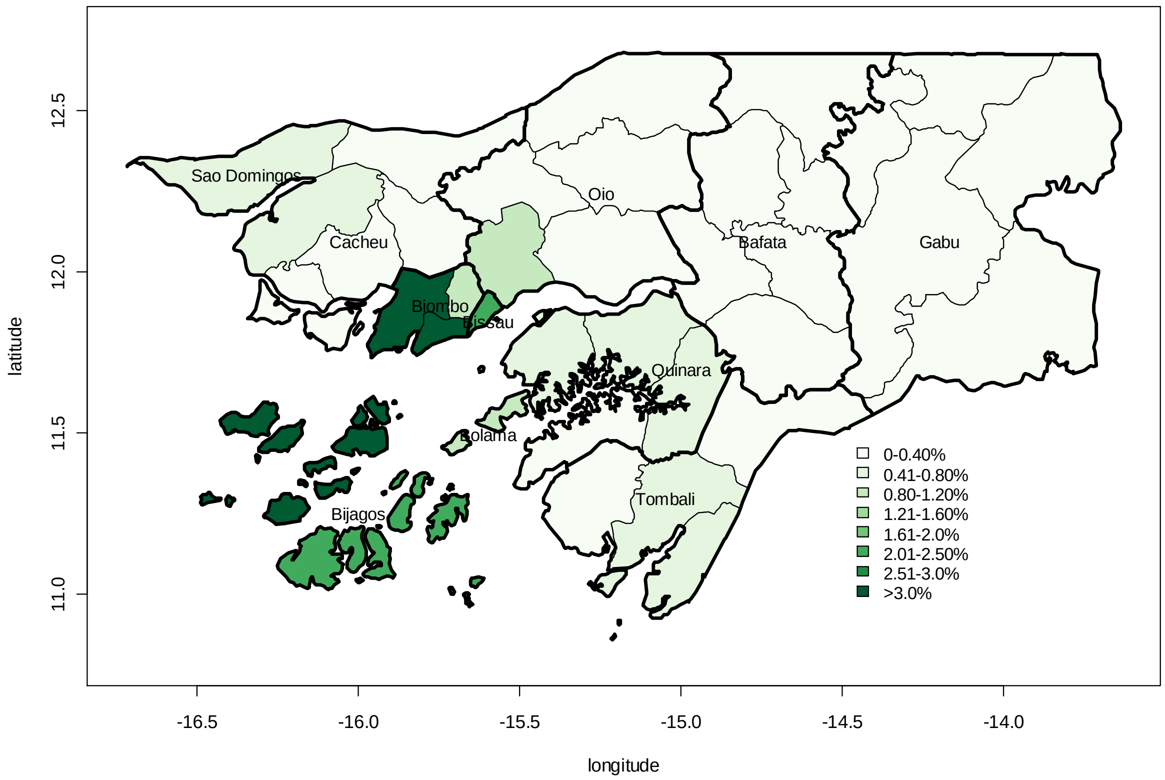


Figure 24. Cholera attack rates by sanitary area in Guinea-Bissau. 2008 epidemic.

The sub-regions particularly affected were Ondame, Quinhamel, Prabis, Safim, Bubaque, Caravelas, Uno, Bolama, Nhacra and Tite (Table 5).

Table 5. Cholera cases, deaths, attack rates and fatality by region. Guinea-Bissau. 2008.

Region	Cases	Deaths	Populacion	AR(%)	CFR(%)
Total SAB	9392	73	402998	2.33	0.78
Total Biombo	2004	20	66048	3.03	1.00
Ondame	533	0	12488	4.27	0.00
Quinhamel	855	9	27159	3.15	1.05
Prabis	521	8	16514	3.15	1.54
Safim	95	3	9886	0.96	3.16
Total Cacheu	358	20	112060	0.32	5.59
Bula	88	9	26325	0.33	10.23
Cacheu	100	8	19931	0.50	8.00
Caio	38	0	15472	0.25	0.00
Canchungo	132	3	50332	0.26	2.27
Total Oio	471	17	211272	0.22	3.61
Bissora	100	3	68641	0.15	3.00
Farim	4	1	56702	0.01	25.00
Mansaba	12	0	25493	0.05	0.00
Mansoa	139	8	38129	0.36	5.76
Nhacra	216	5	22306	0.97	2.31
Total Bafata	143	11	202061	0.07	7.69
Bafata	86	4	65781	0.13	4.65
Bambadinca	25	4	31283	0.08	16.00
Contubuel	4	0	49015	0.01	0.00
Galomaro	12	1	16729	0.07	8.33
Ga-do	15	1	25187	0.06	6.67
Xitole	1	1	14064	0.01	100.00
Total Gabu	256	13	210895	0.12	5.08
Boe	1	0	11735	0.01	0.00
Gabu	194	9	62642	0.31	4.64
Pirada	12	0	31979	0.04	0.00
Pitche	12	1	44648	0.03	8.33
Sonaco	37	3	59891	0.06	8.11
Total Bolama	108	1	9846	1.10	0.93
Total Bijagos	736	10	24309	3.03	1.36
Bubaque	260	0	11075	2.35	0.00
Caravelas	235	2	5402	4.35	0.85
Uno	241	8	7832	3.08	3.32
Total Quinara	323	29	70207	0.46	8.98
Buba	100	7	17525	0.57	7.00
Empada	17	1	22015	0.08	5.88
Fulacunda	44	9	9873	0.45	20.45
Tite	162	12	20794	0.78	7.41
Total Sao Domingos	268	22	87636	0.31	8.21
Bigene	39	7	52694	0.07	17.95
Sao Domingos	229	15	34942	0.66	6.55
Total Tombali	166	9	109773	0.15	5.42
Bedanda	54	2	10117	0.53	3.70
Catio	13	0	32334	0.04	0.00
Cacine	73	4	12587	0.58	5.48
Quebo	1	1	21839	0.00	100.00
Komo	25	2	11809	0.21	8.00
Calaque	-	-	15137	-	-
Sanconha	-	-	5951	-	-
Total Guinea-Bissau	14225	225	1507104	0.94	1.58

The following graph shows the evolution of the epidemic in Bissau, Biombo and the Bijagos Islands. The epidemic started in Bissau, reaching more than 50 cases per day in August, at this time the epidemic spread to Bimbo and later at the beginning of September to Bijagos. The peak was first observed in Biombo and later in Bissau and Bijagos.

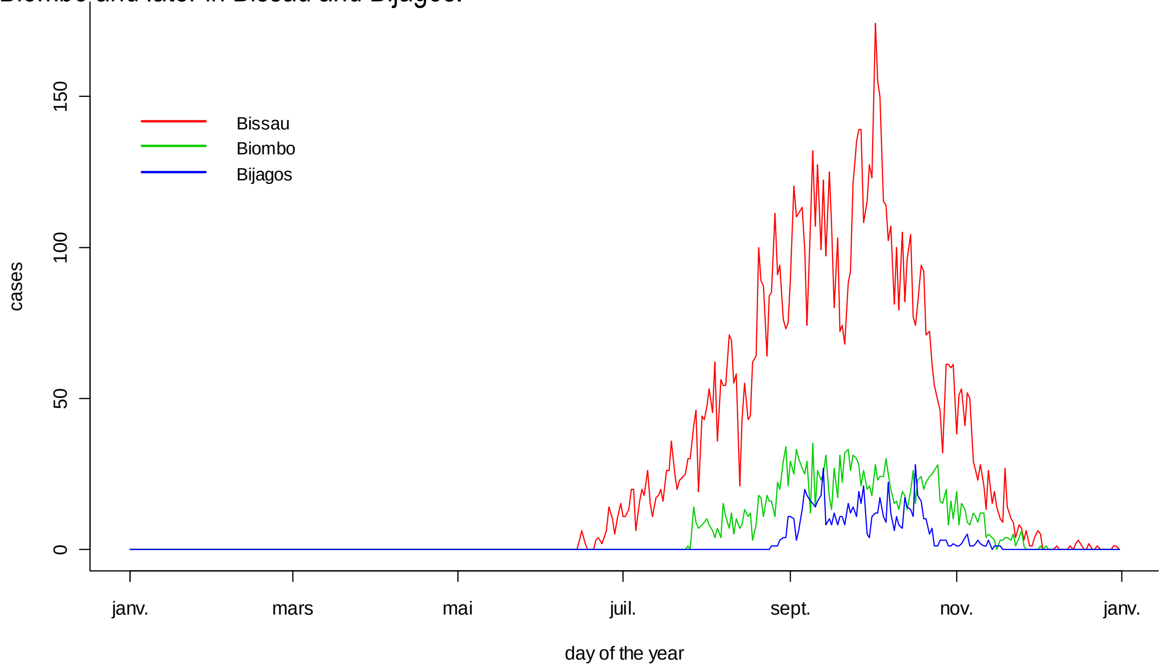


Figure 25. Daily number of cholera cases in Bissau, Biombo and Bijagos regions. 2008.

Annex 3 shows the evolution of the 2008 epidemic in monthly steps. The epidemic as in 2007 started in Tombali region.

3.1.5.1 Mapping of the 2008 epidemic in Bissau

The following information was collected by MSF-OCBA/Epicentre from the registers of the Cholera Treatment Centers and Units of the capital (SAB) and was previously reported in *Luquero FJ, Grais RF. Cholera outbreak in Guinea-Bissau. Bissau, October 2008. Epicentre. Paris, France.*

Information about the residence of the patients was obtained from 7 294 cases (94.1%), and from 4 987 (64.4%) the neighborhood of residence was also recorded. Differences were observed in the number of people coming from each Sanitary Area (SA) to receive treatment. Bandim was the SA with the highest number of total patients (24.1%) but also in relative numbers (AR=3.9%). Compared with Ajuda, people living in Bandim were 2.5 times more affected. Antula and Pefine had ARs over 2% and the rest of SAs between 1-2% (through 20/10/2008) (Table 6).

A Poisson regression model was used to account for possible confounding effects of age and sex on the crude estimations. The analysis showed that, in this case, there was no confounding effect of age or sex over the crude ARs by sanitary area (Table 6).

Figure 26 also reflects that the most affected area in SAB was Bandim. There was not a clear spatial pattern in the SAB, but all neighborhoods located in the southwest had ARs over 1.5%.

Table 6. Number of cases, population, attack rate per 100 people at risk (AR %), risk ratio (RR) and adjusted risk ratio (ARR) by Sanitary Area, age and gender in SAB until 20/10/2008.

Sanitary Area	Cases	Population	AR%	RR	ARR
Ajuda	160	10 429	1.53	Ref.	
Antula	640	30 778	2.08	1.36	1.37
Bandim	1 756	44 718	3.93	2.56	2.61
Bairro Militar	932	65 274	1.43	0.93	0.94
Belem	306	17 263	1.77	1.16	1.18
CIM	154	14 985	1.03	0.67	0.68
Cuntum	857	45 482	1.88	1.23	1.24
Luanda	219	25 236	0.87	0.57	0.58
Missira	516	38 838	1.33	0.87	0.87
Pefine	306	14 808	2.07	1.35	1.37
Plaque	380	27 633	1.38	0.90	0.89
Quelele	472	28 898	1.63	1.06	1.08
Sintra Nema	348	21 451	1.62	1.06	1.08
Santa Luzia	248	17 204	1.44	0.94	0.96

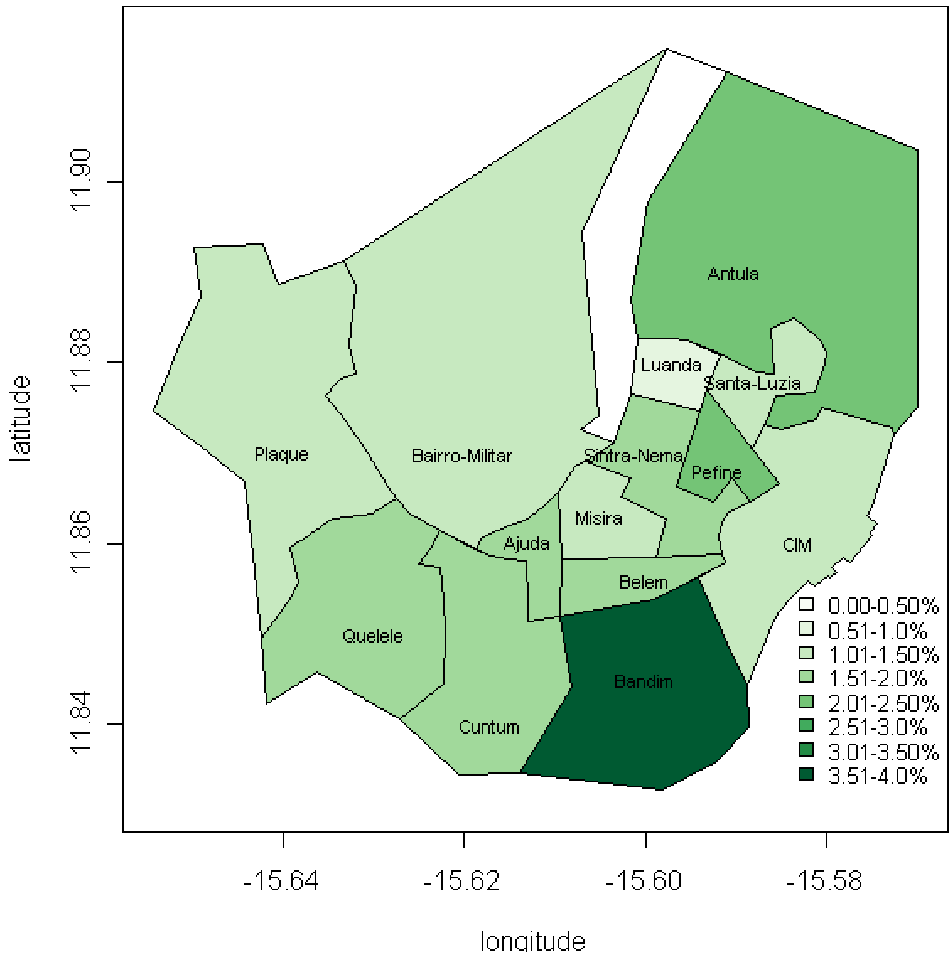


Figure 26. Attack Rates (%) by Sanitary Area in Bissau. 05/05/2008 to 20/10/2008.

The annex 4 contains one table and one figure showing the global overview of the 1996-2008 period.

3.2 Predictive model of the seasonal risk of cholera in Guinea-Bissau

The first objective of this study was to identify if there was a secular trend of cholera in Guinea-Bissau. We conducted a Poisson regression to check it, and this result did not indicate a trend and therefore we do not include it in the analysis. The second objective of this study was to assess the seasonal risk of cholera in Guinea-Bissau. The following graph shows that the cholera epidemics do not occur during every season. In fact, there are certain periods during the year that accumulate a higher number of cases. This period coincides with the rainy season in the country, although some epidemics like the 1996 epidemic occurred during the dry season (Figure 27).

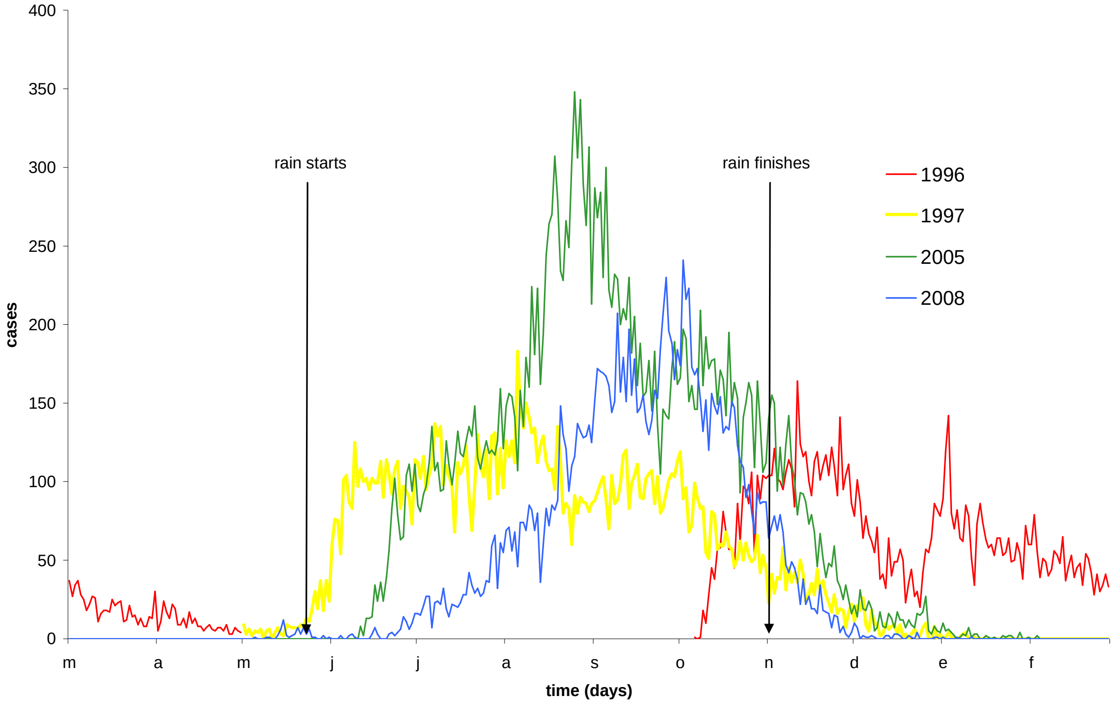


Figure 27. Daily number of cholera cases for the four largest epidemics in Guinea-Bissau.

The three largest epidemics in the country from 1996 started around week 20, which is the beginning of May. The fourth largest epidemic occurred in 1996 with a different epidemiological pattern, this epidemic started later in week 41 (Table 7) and affected the country during the dry season with cases reported over a 30 week period. The end of this epidemic coincided with the beginning of the 1997 epidemic. For epidemics with more than 10,000 cases notified, the duration was more than 30 weeks and more than 8 regions were affected. In small epidemics, only one region was affected, and the duration was shorter. The peaks of the different epidemics occurred from week 32 in 1997 to week 46 in 1996, which is the second half of the rainy season (Table 7).

Table 7. Seasonal description of cholera epidemics in Guinea-Bissau.

Epidemic	Starting week	Week of peak	Ending week	Duration	Number of regions affected	Cases	Deaths
1996-1997	41	46	18	30	8	10,844	108
1997-1998	19	32	2	37	10	16,115	853
2002-2003	-	-	-	-	-	1,132	8
2004	41	44	51	11	1	227	3
2005-2006	23	34	5	35	11	25,282	397
2007	41	43	44	4	1	73	3
2008-2009	19	40	1	36	11	14,228	225

Using multivariable techniques, we evaluated the seasonal risk of cholera for each day of the year for the country and for the three most affected regions: Bissau, Biombo and Bijagos.

3.2.1 *Risk model for Guinea-Bissau*

The following figure should the risk of cholera by date of the year. The day with a lowest risk of cases is day 89, which coincides to the 30th of March. So, the risk of cholera begins to increase in Guinea-Bissau from April. The risk is statistically significant greater than one from the 27th of April. The day with the highest probability of being the peak is day 259, which corresponds with the 16th of September (epidemic weeks 37-38).

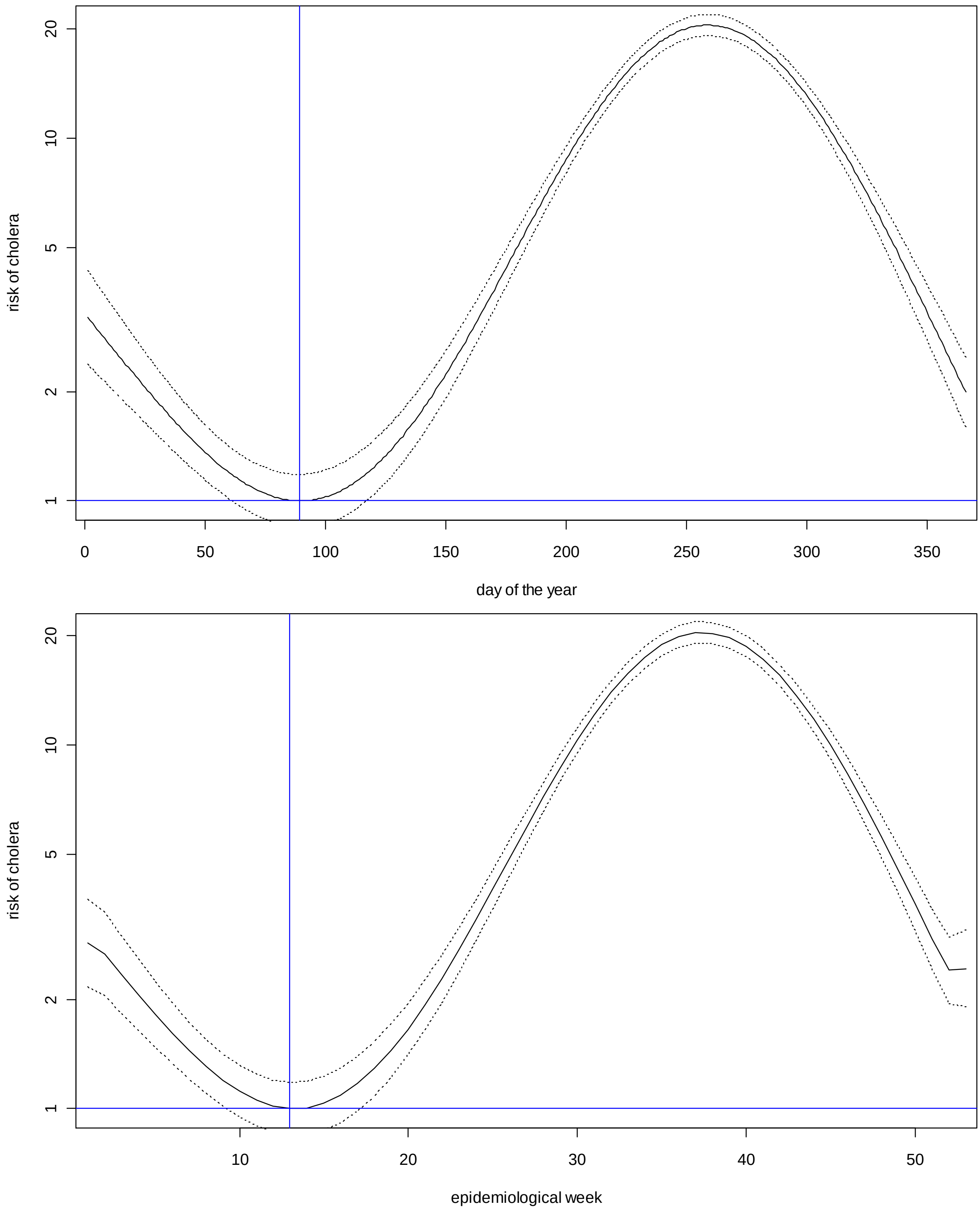


Figure 28. Seasonal risk of cholera in Guinea-Bissau obtained through a quasipoisson model with four degrees of freedom for the explanatory variable (day of the year). 1996-2008.

3.2.2 Risk model for Bissau-Sector

The next graph shows the risk of occurrence of cholera cases in Bissau, the capital. The day with a lowest risk of occurrence of cases is day 102 of the year that coincides with the 12th of April. So, the risk of cholera increases in the capital from mid-April. The risk is statistically significant higher than one from the 4th of May. The day with the highest probability of showing the peak is day 292, which corresponds with the 19th of October (epidemic weeks 42-43). There is another maximum of lower intensity in the 9th of August (epidemic week 32). The risk of the peak is between mid-August to mid-October in the capital.

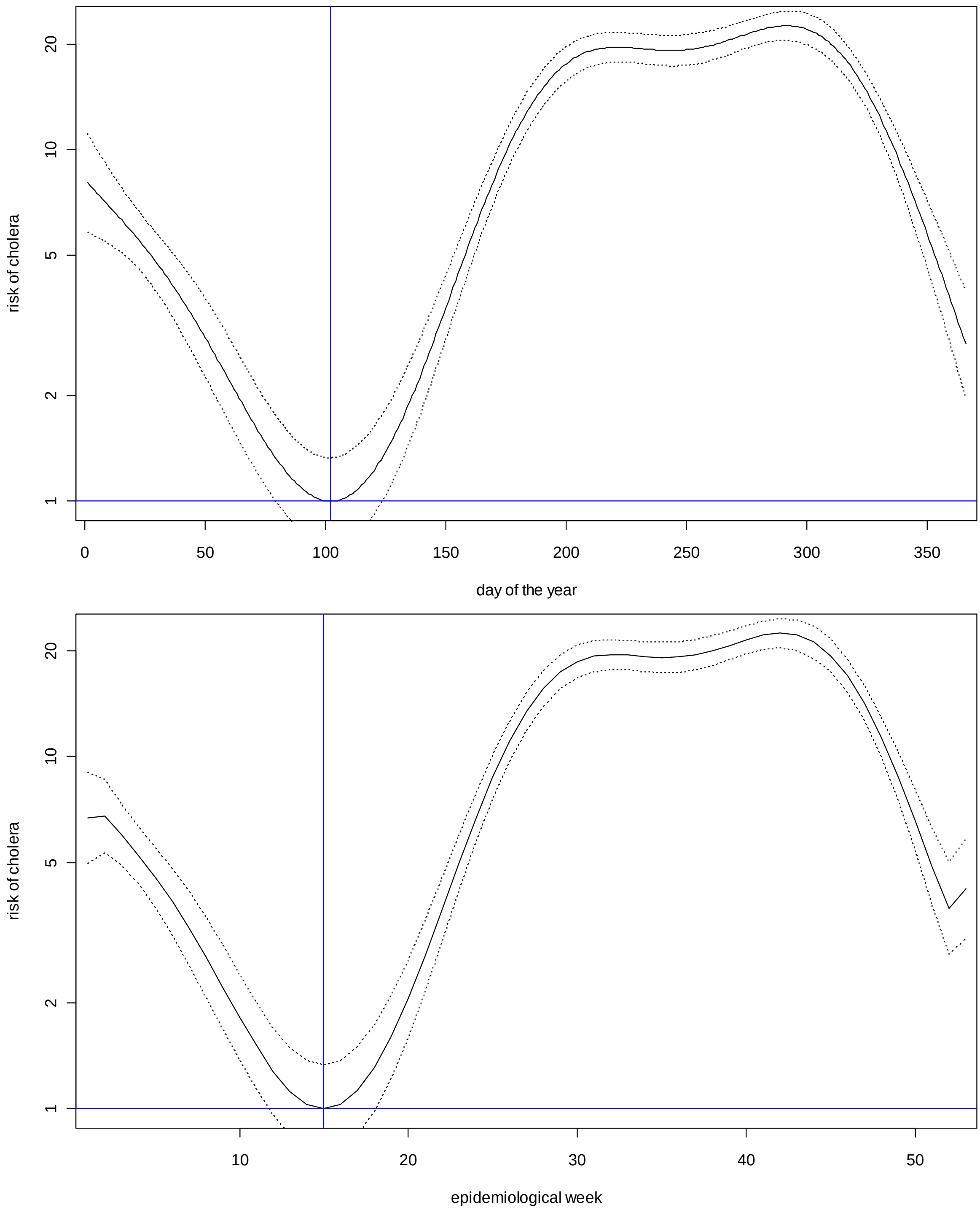


Figure 29. Seasonal risk of cholera in Bissau-Sector obtained through a quasipoisson model with seven degrees of freedom for the explanatory variable (day of the year). 1996-2008.

3.2.3 Risk model for Biombo region

This figure shows the risk of occurrence of cholera cases in Biombo. The day with the lowest risk of cases is day 89 that coincides with the 30th of March. So, the risk of cholera increases in Biombo from April. The risk is statistically significant higher than one from the 6th of May. The day with the highest probability of showing the peak is day 241, which corresponds with the 29th of August (epidemic weeks 34-35). The risk continues to be high through week 46, decreasing faster after this date.

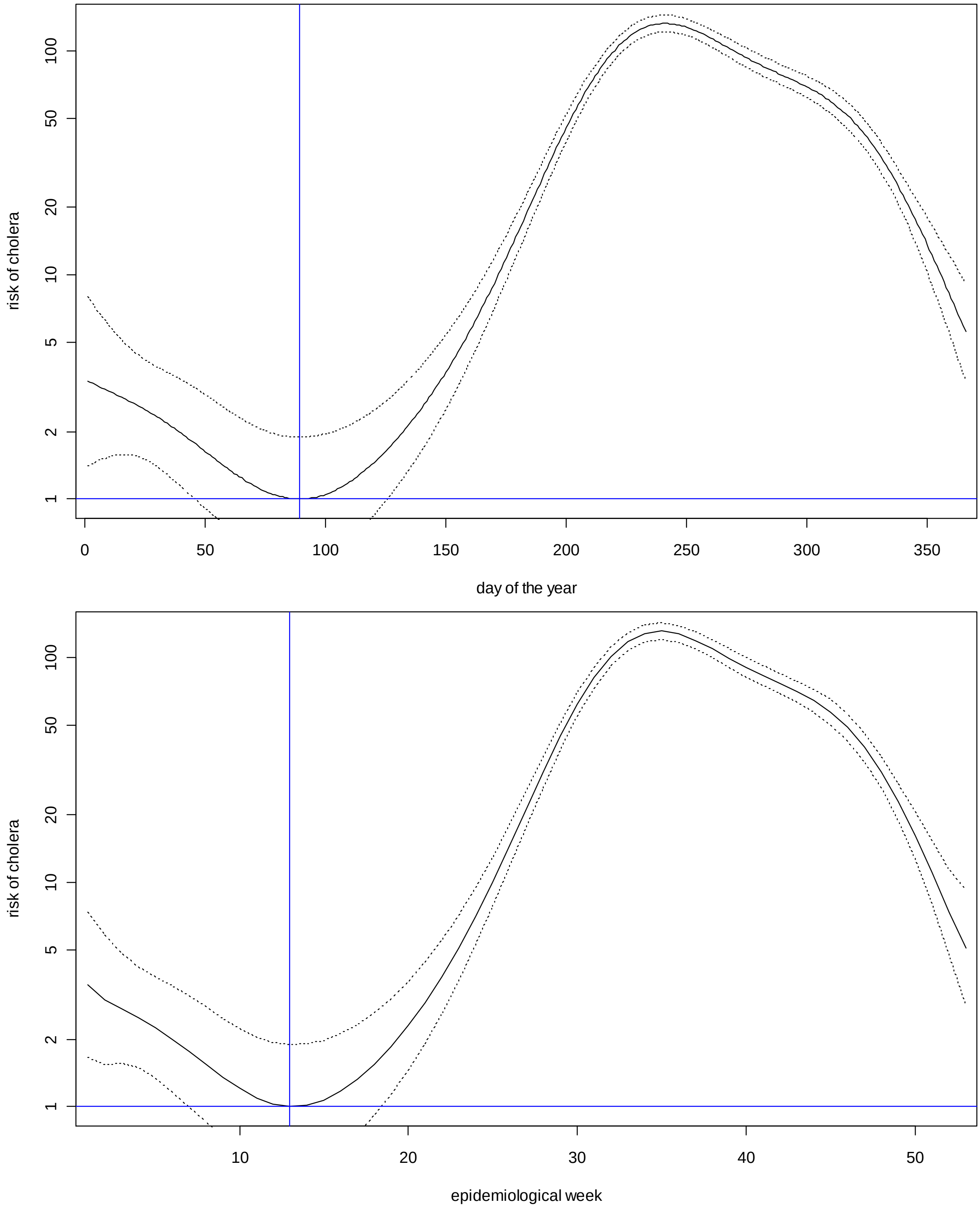


Figure 30. Seasonal risk of cholera in Biombo region obtained through a quasipoisson model with nine degrees of freedom for the explanatory variable (day of the year). 1996-2008.

3.2.4 Risk model for Bijagos Islands

The next graph shows the risk of occurrence of cholera cases in the Bijagos Islands. The day with a lowest risk of cases is the day 120 of the year that coincides with the 30th of April. So, the risk of cholera increases in the Bijagos Islands from May. The risk is statistically significant higher than one from the 31st of May. The day with the highest probability of showing the peak is the day 264, which corresponds with the 21st of September (epidemic weeks 38-39).

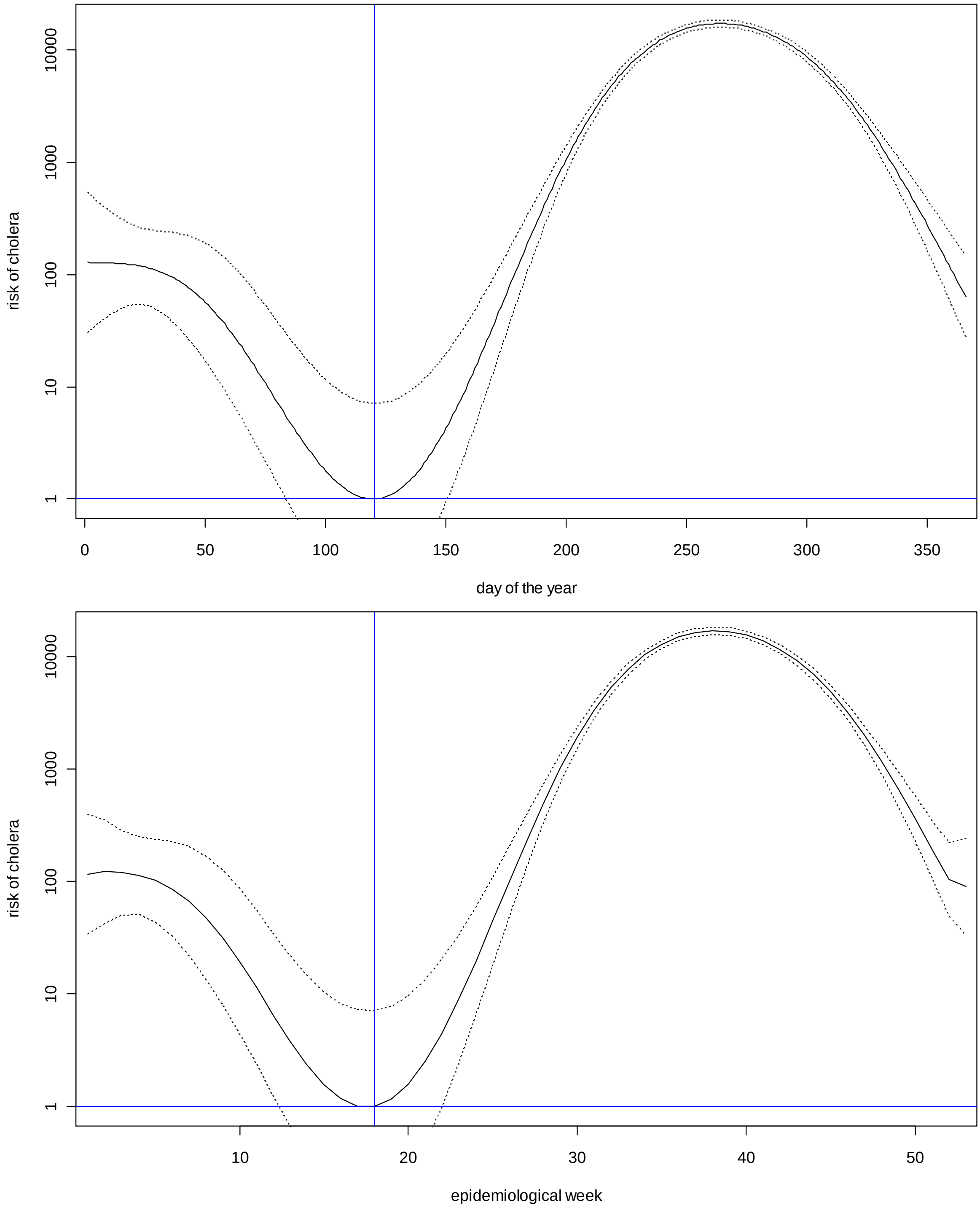


Figure 31. Seasonal risk of cholera in the Bijagos Islands obtained through a quasipoisson model with seven degrees of freedom for the explanatory variable (day of the year). 1996-2008.

3.3 Decision framework to define situations with high epidemic potential.

In order to create a decision framework to define situations with high epidemic potential, we have available two sources of information: the spatial analysis and the time series analysis.

We define high incidence epidemics as those epidemics with more than five cases per thousand inhabitants at the end of the outbreak.

The decision framework is useful at the beginning of epidemics in order to assess the potential of each epidemic to produce a high disease burden. Therefore, we are mainly interested in establishing differences between epidemics in the first weeks after the first cholera notification. Thus, we are going to use the first 60 days of each epidemic to find differences and assess the potential risk.

The next table describes the main attributes of each epidemic regarding the number of areas affected and the duration of each outbreak. We have classified the epidemics considering the AR at the end of the epidemic to distinguish in between high burden epidemics and low burden epidemics. Four epidemics met the 5 cases per thousand threshold and three under this limit.

Epidemic	Starting week	Week of peak	Ending week	Duration	Number of regions afeected	Cases	Deaths	AR
1996-1997	41	46	18	30	8	10,844	108	> 5 ‰
1997-1998	19	32	2	37	10	16,115	853	> 5 ‰
2002-2003	-	-	-	-	-	1,132	8	< 5 ‰
2004	41	44	51	11	1	227	3	< 5 ‰
2005-2006	23	34	5	35	11	25,282	397	> 5 ‰
2007	41	43	44	4	1	73	3	< 5 ‰
2008-2009	19	40	1	36	11	14,228	225	> 5 ‰

In the following paragraphs, we distinguish between high and low burden epidemics in terms of place and time to create the decision framework.

3.3.1 Spatial differences in the first 60 days of epidemic

As is reflected in the previous table, high burden epidemics affected more than one region at the end of the epidemic, showing greater geographic spread in terms of place. This spread is observed the first two months of the epidemic. The following graph shows the cumulative number of regions affected in each epidemic in the first 60 days. In high burden epidemics, four or more regions were affected in the first 60 days. In low burden epidemics, only one region was affected in the first 60 days. A number of affected regions between 2 and 4 can be used as an alert threshold indicating risk of high burden epidemic. We can obtain a more sensitive threshold with two regions and a more specific with four regions.

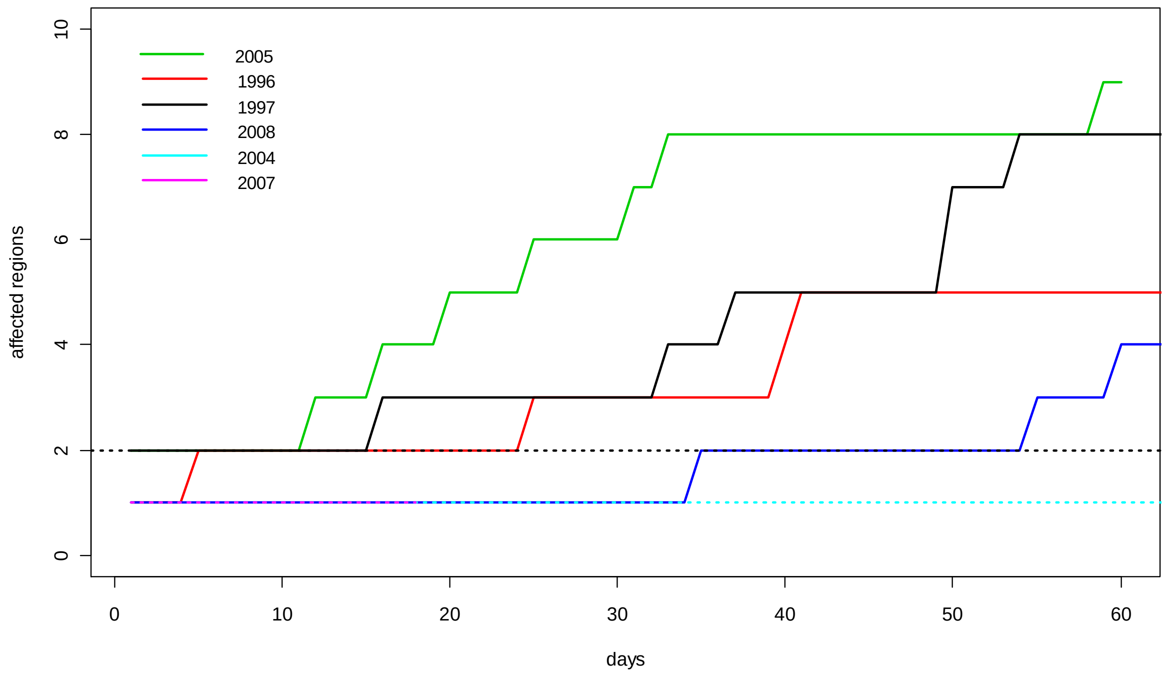


Figure 32. Cumulative number of affected region in Guinea-Bissau during cholera outbreaks in the first 60 days of epidemic. 1996-2008.

3.3.2 Time differences in the first 60 days of the epidemic.

The following graph shows the evolution of the different epidemics since the date o the first notification. The graph below represents the logarithm of the cumulative number of cases over the whole epidemic.

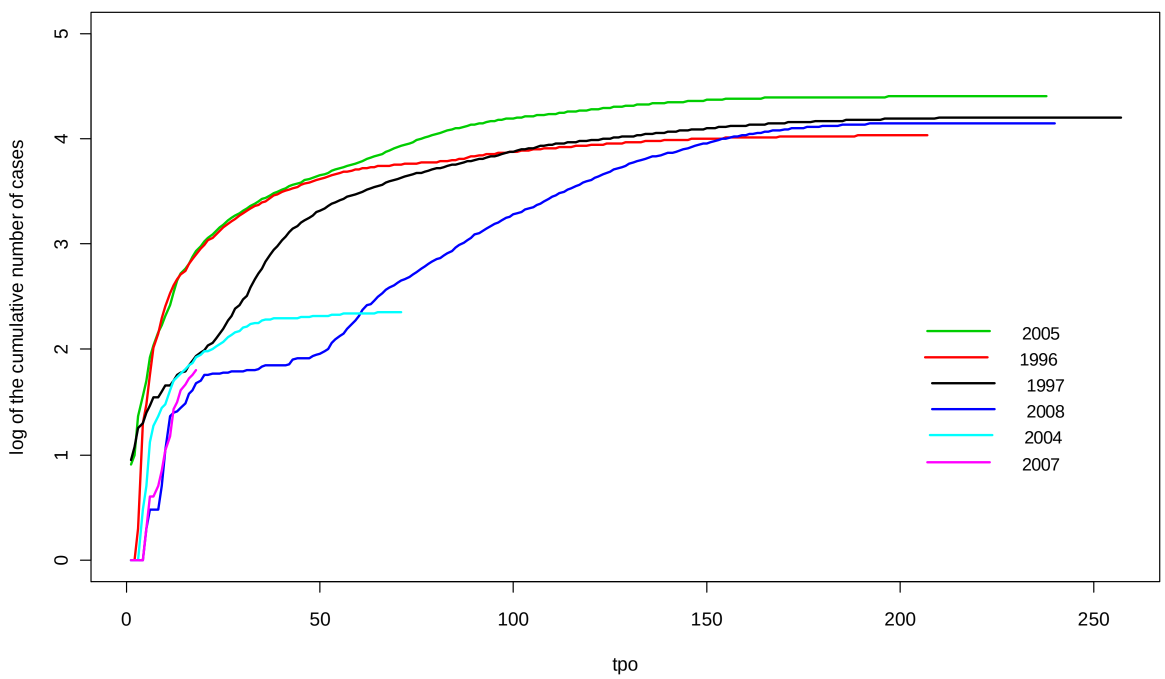


Figure 33. Decimal logarithm of the cumulative number of cases in Guinea-Bissau during cholera outbreaks. 1996-2008.

When looking at the graph below, we can distinguish three different patterns in cholera epidemics.
(i) The 2005 and 1996 epidemics showed a very quick exponential increase in the cumulative number of cases. (ii) The 1997 and 2008 epidemics showed three different phases with two inflexion points: a first increase, a plateau, and a new increase. The final AR at the end of these four epidemics was over 5‰. (iii) The other two epidemics (low burden epidemics) had just one inflexion point: a first increase and plateau without a second increase. We can identify the same observations in the first 60 days of epidemic (Figure 34).

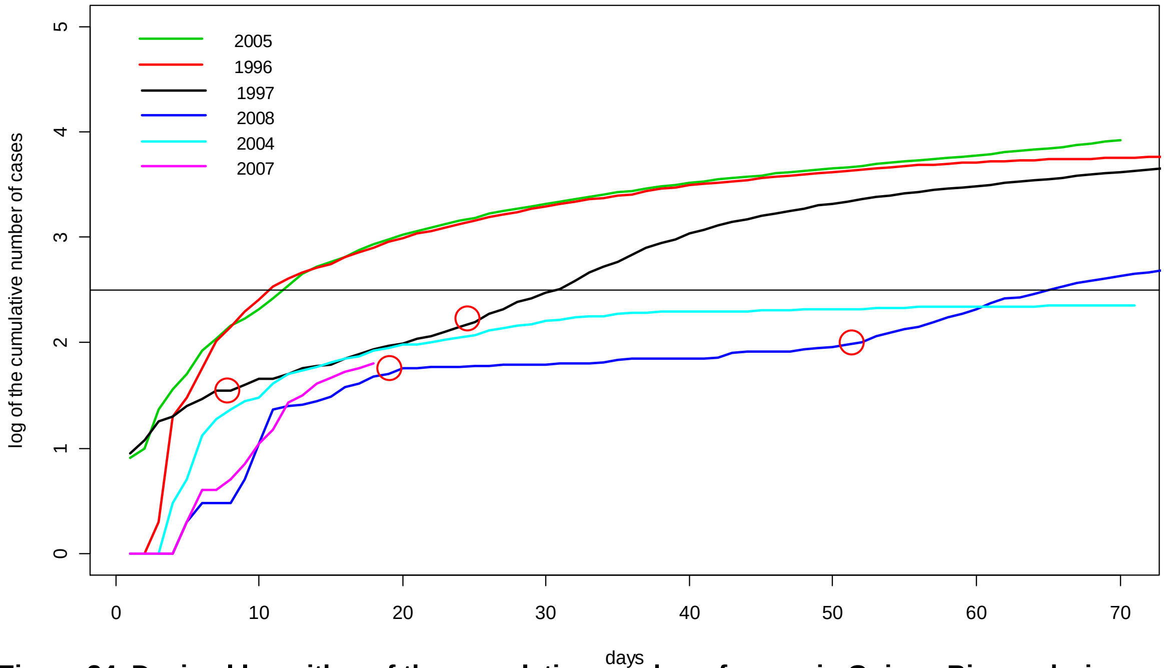


Figure 34. Decimal logarithm of the cumulative number of cases in Guinea-Bissau during cholera outbreaks in the first 60 days of the epidemic. 1996-2008.

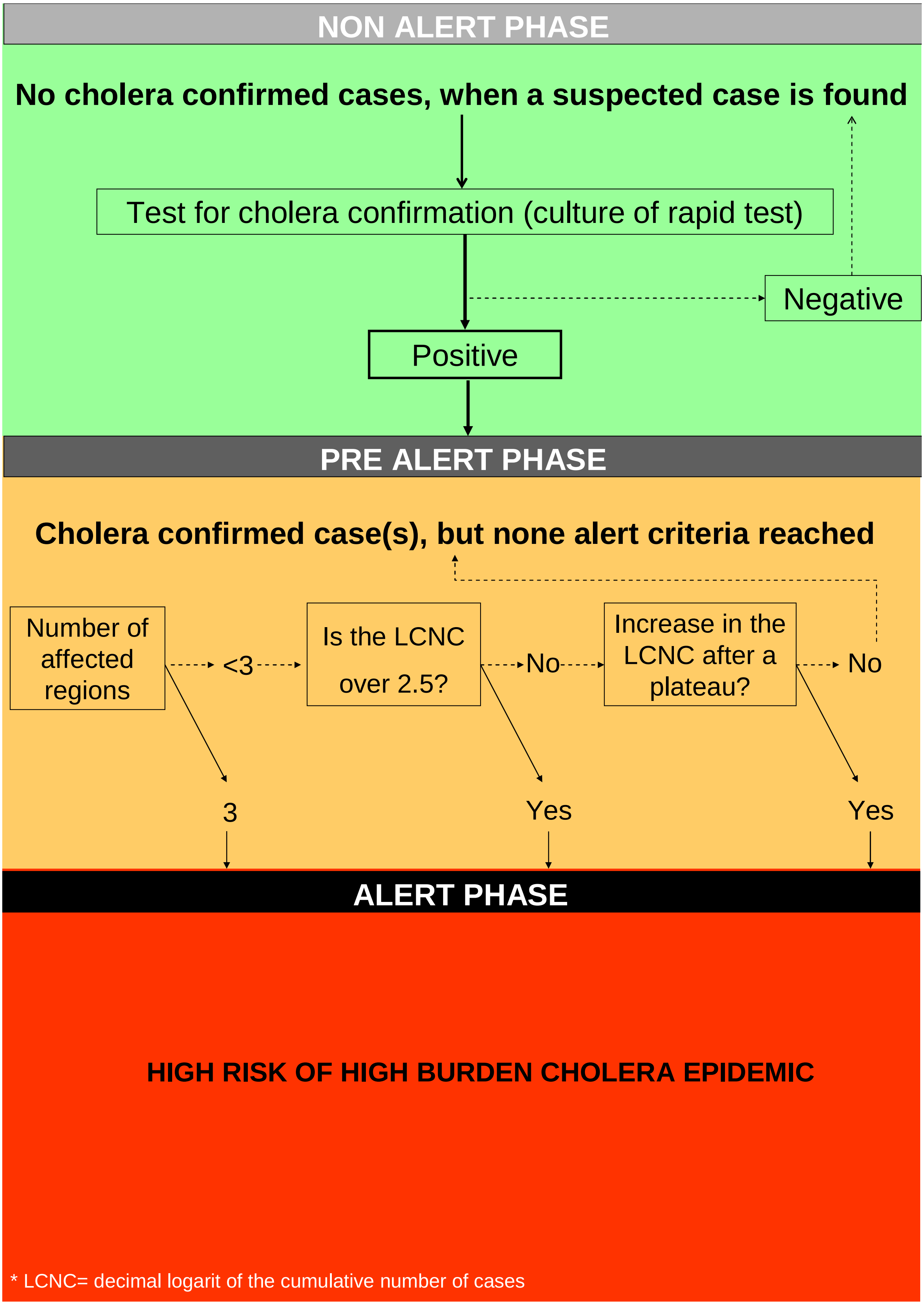
Two possible criteria can be used to define epidemics with high epidemic potential: the value of the decimal logarithm of the cumulative number of cases and the observation of an increase in the number of cases after one plateau. A possible value than can differentiate epidemics of high burden is the 2.5 logarithm. This value, when is reached before the day 60 is specific to high burden epidemics, as well as a second inflexion point on the log cumulative graph is indicative of high burden epidemic.

3.3.3 Decision framework

Based on the previously explained criteria to define situations with a high potential to produce high burden epidemics, we have created a possible decision framework. This decision framework contains three phases: a non-alert phase, a pre-alert phase and an alert phase:

1. To pass from the non-alert phase to the pre-alert phase, confirmation of cholera is needed (by culture or rapid test)
2. To pass from the pre-alert phase to the alert phase, one of the following criteria must be reached:
    a. Three or more regions affected in the country
    b. More than 2.5 log-cumulative number of cases
    c. A increase in the log-cumulative number of cases after one plateau

This decision tree is illustrated in the next figure:



4 Discussion

Although there were different electronic files containing information on cholera epidemics at the Instituto Nacional de Saude (INASA), this information was not merged in a unique data set. As a result, for this analysis, we created a unique data set containing all the information available regarding cholera in Guinea-Bissau from 1996 to 2008.

At least four large epidemics and two small outbreaks were detected from 1996 to 2008 in Guinea-Bissau. Our analysis did not identify any trend in the number of notified cases and there is not a fixed inter-epidemic period between epidemics in the country. The last epidemic occurred with a shorter inter-epidemic period compared with the previous ones. During the civil war and post-war periods (1998-2001) there were no notifications to the surveillance system; this gap limits the analysis.

Considering the four largest epidemics in the country from 1996, we observed some similarities. In all four outbreaks (1996, 1997, 2005 and 2008) more than 10,000 cases were notified with ARs of 1%, 1.4%, 1.8% and 0.9% respectively. Fatality varied between 5.3% in 1997 to 1.6% in 2008. The duration was more than 30 weeks and more than 8 regions were affected in all four epidemics. Three of these epidemics (1997, 2005 and 2008) started around week 19, which is the beginning of May. The fourth largest epidemic occurred in 1996 with a different epidemiological pattern; this epidemic started later, in week 41, and affected the country during the dry season over a 30-week period. In the small epidemics, only one region was affected, and the duration was shorter (without considering the data from 2002-2003). The peaks of the different epidemics occurred from week 32 in 1997 to week 46 in 1996, which is the second half of the rainy season.

Regarding the geographical spread, it is possible to identify three main areas affected in Guinea-Bissau: Bissau (the capital), Biombo and the Bijagos Islands. These three areas accumulated most of the notified cases in previous epidemics and this is expected to be similar in future outbreaks. Within the capital, Bairro Bandim was especially affected during the last epidemic [6]. When considering other areas or interest, the coastal area, including São Domingos, Cacheu, Oio (Nhacra), Quinara (Tite) and Tombali (Bedanda and Catio), presents a higher risk of cholera epidemics. São Domingos regions has been repeatedly affected showing high attack rates in the four large outbreaks, and Tombali has been the region with the first notified case in the last two epidemics (2007 and 2008).

Regarding the seasonal pattern of cholera in Guinea-Bissau, this analysis confirms that the high-risk season starts with the beginning of the rains in April. The seasonal pattern differs slightly among regions with an increased risk from the beginning of April in Biombo, mid-April in the capital and May in the Islands.

Two elements have been identified to quantify the risk of occurrence of a high burden epidemic: the number of regions affected and the cumulative number of cases. We propose an algorithm to facilitate risk assessment in the first phase of the epidemic after the confirmation of the first cases. This algorithm considers three phases: first, the non-alert period when there is not confirmation of cholera cases; the pre-alert period when a cholera confirmation has occurred; and the alert period when at least one criteria of high risk has been met.

This division reflects different levels of concern. It is important to realize that the confirmation of cholera in the country is already a very important criterion to start response activities. Nonetheless, when some cases are confirmed sometimes is difficult to assess how the situation is evolving and what will be the final extent of the epidemic. The proposed algorithm tries to help in this assessment on a daily basis.

The algorithm helps to identify situations with potential to produce high burden outbreaks. On this type of situations, the decision makers should activate all the components of the response plan (which should have started with the detection of the first case) and demand international aid if necessary. To do so, we propose three different criteria: (i) the number of regions affected; (ii) the value of the decimal logarithm of the number of cases; and (iii) the observation of inflexion points on the logarithm curve. All three criteria have been associated with high burden epidemics. We propose that at least three regions should be affected to increase the specificity of the definition, but that spread to two regions could be enough to alert a high-risk situation. Indeed, the lack of information regarding the 2002-2003 outbreaks limits this proposed decision framework in this respect. Regarding the limit of 2.5 logarithms, this value can vary in the sensitivity and specificity depending of the area affected. For instance, the threshold can be very sensitive if an epidemic starts in Bissau, but the sensitivity of the criteria will decrease if the outbreak starts in a small community of Tombali. Because of this, it is important to interpret this value considering the other criteria, the number of inflexion points. A single inflexion point will mean that a plateau phase has been reached, but a second inflexion point will mean a new increase in the number of cases. When the 2.5 log threshold is crossed with an increasing trend in the logarithm function this is much more suggestive of a high-risk situation. We propose to work with this sensitive value and try to adapt it when more information will be obtained in future epidemics.

This analysis has several limitations. First, as commented above, there is a period of missing data, which would be very useful to define intermediate situations. We are in contact with INASA to try to obtain this information, which will be included in, an addendum to the report, if possible.

Second, there are limitations stemming from the source of information. As the data used are from surveillance, both selection and information bias may be present. For instance, the ability of each region to collect and notify information can introduce bias regarding the geographical or even the seasonal pattern. On the other hand, this information is the most accurate information available in the country and the strongest evidence to guide future outbreak response.

In addition, changes in the notification pattern can introduce bias. The MPH and the other partners collaborating on cholera control in Guinea-Bissau are aware of the importance of early detection of the first cholera cases. There are available tools to improve the early detection that can be introduced soon in the country, like the rapid diagnostic test. The early detection of cholera cases will increase the duration of the pre-alert phase since periods of limited transmission will be detected, and thus the risk algorithm proposed here should be adapted consequently. Another issue for the use of the algorithm is the transmission pattern. It is possible, that the transmission pattern changes during epidemics in the country – from a point-source transmission to predominantly person-to-person transmission. This will result in a longer pre-alert phase. If this hypothesis in confirmed, the algorithm may need to be revisited in the very early phase of the epidemic to increase sensitivity. However, it is probable that changes in the trend after plateau periods (third criteria of the algorithm) will remain suggestive of a high-risk situation independent of transmissibility. Transmission patterns should be always be assessed in the event of a future outbreak.

Finally, we have also to acknowledge the small number of epidemics that we have available for the analysis. The aim of the decision framework is to distinguish between high burden and low burden epidemics and we have information from four and two respectively. Stratified sub-analysis by region and collection of further information can help to strengthen the findings presented here.

5 Conclusion and recommendations

5.1 Conclusion

- There is not a long-term defined trend in the occurrence of cholera epidemics in the country over the period investigated here.

- There is a seasonal pattern of cholera in the country: the risk of occurrence of cholera cases increases from April and is maximum in mid-September.

- There is a spatial pattern of cholera incidence in Guinea-Bissau: the most affected areas are the capital (Bissau), Biombo region and the Bijagos Islands.

- Other areas highly affected are São Domingos, Nhacra in Oio, Tite in Quinara and Bedanda and Catio in Tombali. The first cases in last two epidemics were notified in Tombali.

- The analysis provides a sufficient number of elements to create a decision framework to define situations that lead to high burden epidemics.

5.2 Recommendations

- To reinforce the cholera surveillance system beginning in April in order to improve the detection of epidemics in the country.

- To target preparedness and control activities to the areas repeatedly affected: Bissau, Biombo and the Bijagos Islands.

- To set-up a sentinel surveillance system including the three main cholera regions (Bissau, Biombo, Bijagos) and some of the other highly affected areas (São Domingos, Tombali, Nhacra and Tite) in order to improve the early detection of epidemics and its follow up.

- To use the decision algorithm to define situations with high potential to produce large epidemics to guide outbreak control and case management.

- To collect individual data including more detailed information regarding the residence of the patients to perform similar analyses of smaller geographical units.

- To reanalyze the data when data from additional outbreaks will be available.

- To continuously update the decision framework with the new available information.

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6 ANNEX

6.1 Evolution of the 1996-1998 epidemic

See additional file: evolution_1996_1998.pps

6.2 Evolution of the 2005 epidemic

See additional file: evolution_2005.pps

6.3 Evolution of the 2008 epidemic

See additional file: evolution_2008.pps

6.4 Annex 4: Global overview of the 1996-2008 period

Region	Cumulative cases	Cumulative deaths	Cumulative Annual Population	AR(%)	CFR(%)
Total SAB	**42315**	**382**	**4410588**	**0.96**	**0.90**
Total Biombo	**8883**	**104**	**899705**	**0.99**	**1.17**
Ondame	**2580**	**16**	**174763**	**1.48**	**0.62**
Quinhamel	**3471**	**38**	**381069**	**0.91**	**1.09**
Prabis	**2216**	**35**	**211448**	**1.05**	**1.58**
Safim	**616**	**15**	**132498**	**0.46**	**2.44**
Total Cacheu	2229	202	1493723	0.15	9.06
Bula	481	24	376575	0.13	4.99
Cacheu	261	24	272090	0.10	9.20
Caio	277	21	224790	0.12	7.58
Canchungo	1210	133	678952	0.18	10.99
Total Oio	3308	345	2785969	0.12	10.43
Bissora	665	84	910531	0.07	12.63
Farim	273	48	677454	0.04	17.58
Mansaba	68	4	344263	0.02	5.88
Mansoa	1085	95	505231	0.21	8.76
Nhacra	1217	114	319262	0.38	9.37
Total Bafata	599	92	2566699	0.02	15.36
Bafata	320	33	760140	0.04	10.31
Bambadinca	180	41	384410	0.05	22.78
Contubuel	7	0	616714	0.00	0.00
Galomaro	21	3	219300	0.01	14.29
Ga-do	63	12	316078	0.02	19.05
Xitole	8	3	188897	0.00	37.50
Total Gabu	308	15	2636770	0.01	4.87
Boe	1	0	165190	0.00	0.00
Gabu	246	11	723869	0.03	4.47
Pirada	12	0	395023	0.00	0.00
Pitche	12	1	548638	0.00	8.33
So-co	37	3	789758	0.00	8.11
Total Bolama	326	7	140068	0.23	2.15
Total Bijagos	**4128**	**87**	**332943**	**1.24**	**2.11**
Bubaque	**1660**	**30**	**147393**	**1.13**	**1.81**
Caravelas	**958**	**18**	**67534**	**1.42**	**1.88**
Uno	**1510**	**39**	**112277**	**1.34**	**2.58**
Total Quinara	1721	160	906164	0.19	9.30
Buba	390	30	202097	0.19	7.69
Empada	181	17	276851	0.07	9.39
Fulacunda	262	29	136495	0.19	11.07
Tite	888	84	280193	0.32	9.46
Total Sao Domingos	1666	108	1101489	0.15	6.48
Bigene	109	8	651584	0.02	7.34
Sao Domingos	1557	100	435726	0.36	6.42
Total Tombali	1283	87	1379722	0.09	6.78
Bedanda	246	21	125492	0.20	8.54
Catio	804	51	412471	0.19	6.34
Cacine	116	5	142242	0.08	4.31
Quebo	24	5	270896	0.01	20.83
Komo	93	5	164154	0.06	5.38
Calaque	NA	NA	193812	NA	NA
Sanconha	NA	NA	67250	NA	NA
Total Guinea-Bissau	**66766**	**1589**	**18892683**	**0.35**	**2.38**

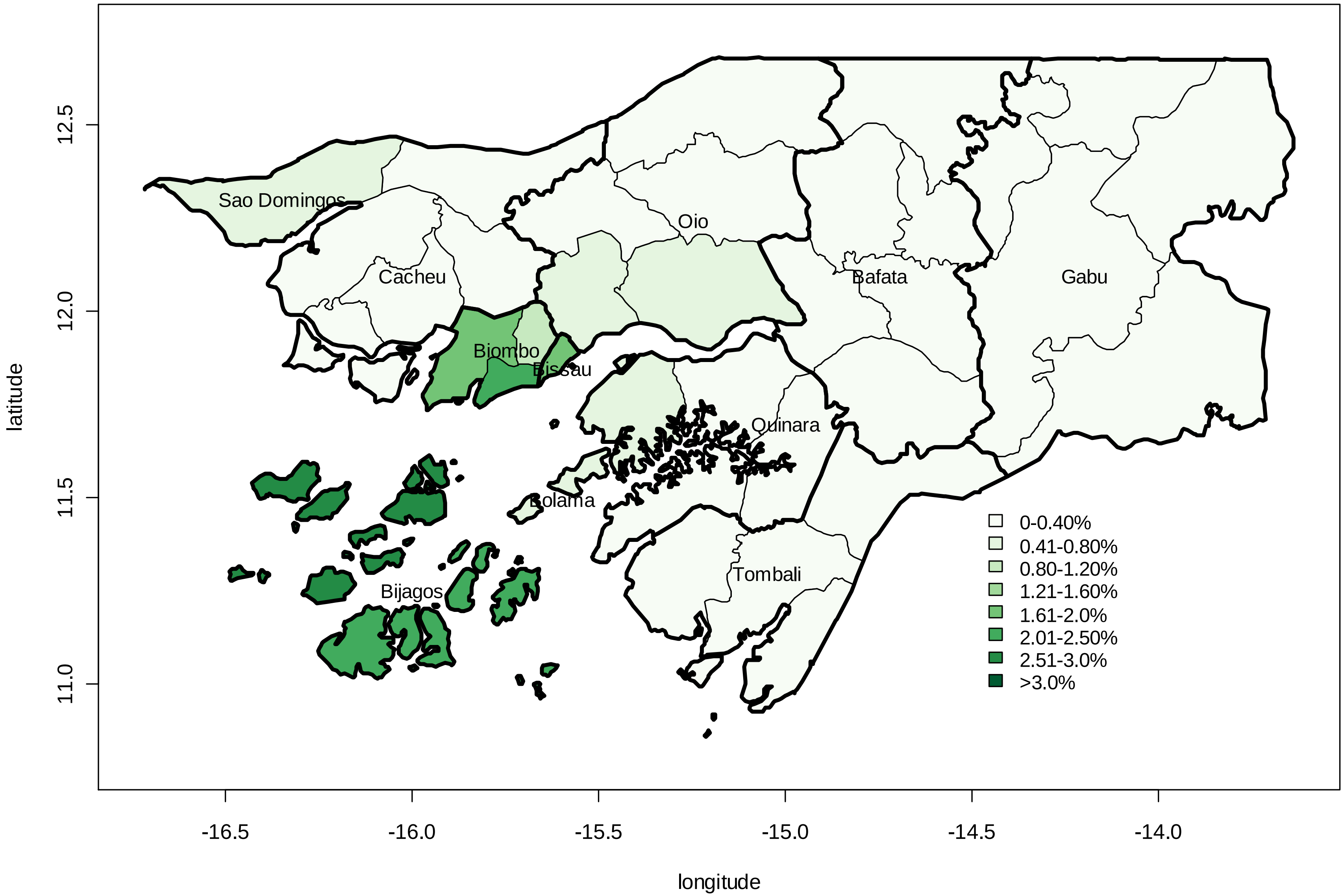

Figure 1. Cumulative attack rates from 1996 to 2008. Calculated using the cumulative number of cases and the cumulative annual population at risk.