BANDIM HEALTH PROJECT

1978-2003

IMPROVING CHILD HEALTH?

Projecto de Saúde

BANDIM

BANDIM HEALTH PROJECT 1978-2003

BANDIM

The Bandim Health Project, 2003
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Thanks

To the mothers of the current mothers in Bandim, for whom the introduction of measles vaccine 24 years ago was a major change, showing that health problems could be controlled. Though we may have failed in some of our subsequent attempts to find other ways of improving health, the mothers of Bandim and the other study areas have continued to collaborate with the project appreciating the interest in the health of their children. Hopefully we can continue to demonstrate this concern.

To the numerous individuals who have worked for the project over the last 25 years, more than 300 Guinean assistants, drivers, accountants, laboratory technicians, nurses, and physicians, and more than 50 expatriate students, volunteers and experts. Without their help, interest, and critique the data would not have been collected. Hopefully the data will all be used.

To the individuals and foundations which have taken an interest in and supported our work, including Rådet for Udviklingsforskning (RUF), Grundforskningsfonden, SSVF, Novo Nordisk Fonden, DANIDA, SAREC, Forskerakademiet, EU-INCO, EU-ECHO (Folkekirkens Nødhjælp), Lundbeckfonden, MRC, Welcome, WHO, Thrasher Research Foundation, March of Dimes, Gates Malaria Partnership, Sight and Light, TDR/WHO, GPA/WHO, UNICEF-Bissau, Habitat, University of Copenhagen, University of Århus, Centre for International Health, University of Bergen, The Research Council of Norway, L. Meltzers Høyskolefond, Swedish Embassy, Bissau, SIDA, SMI, Stockholm, Michaelsen Fonden, Wedell-Wedellsborg Fonden, Fonden til Lægevidenkabens Fremme, Codan Fonden, Kong Christian den X's Fond, Augustinus Fonden, COWI, Tode Legatet, Figo fonden, Dagmar Marshalls Fond, W. Buhl Olesens Mindelegat, Ville Heises Legat, Dr. Louises Børnehospitals Forskningsfond, Carl P Petersens Fond, Eggert Petersens Mindelegat, Illum Fondet, Århus Amt, Direktør Jacob Madsen og hustru Olga Madsens fond, Fonden af 1870, Hans og Nora Buchards Fond, and VB5. Hopefully they will continue to do so.

To the late Jette Bukh, Ove Jessen, Henning Andersen, and Anja Vollmer who helped so much but sadly did not get a chance to see the process through.

To those who believed our results were impossible, unplanned, and biologically implausible and obliged us to document that the observations were reproducible. Hopefully they will plan to see for themselves.

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Bandim Health Project 1978-2003: Improving child survival?

This is a collection of summaries of major research themes investigated by the Bandim Health Project (BHP) through the last 25 years, as well as a bibliography of what has been published. Over the years, the BHP has developed collaborative relations with projects in other countries, in particular Medical Research Council Laboratories (MRC), The Gambia, and ORSTOM/IRD, Senegal. Where results from these collaborative projects are relevant to the research interest of the BHP, these have also been included in the list.

To set this in context, some major features of the development of the BHP have briefly been summarised below – and in Table 1. Most studies make use of the routine demographic and health data collection system described in a following chapter. Good mapping, numbering of houses, census and regular checking of the whereabouts of the individuals are necessary to make long-term follow-up possible in a country with no civil registration. These problems are particularly acute in urban areas such as Bandim and Belem where there is very high mobility. A central feature of the work in Guinea-Bissau has been the attempt to follow long-term consequences of various infections, health conditions and interventions. We are now examining the transfer of maternal antibodies from mothers who we vaccinated 25 years ago. Due to research career and funding structures, most international health research has a very short time horizon, usually 2-3 years. However, many health problems take years to detect, to understand, or to find a solution. One of the key advantages of longitudinal studies is that it is possible to pursue the inconsistencies and contradictions letting one project follow another and maybe eventually find a solution.

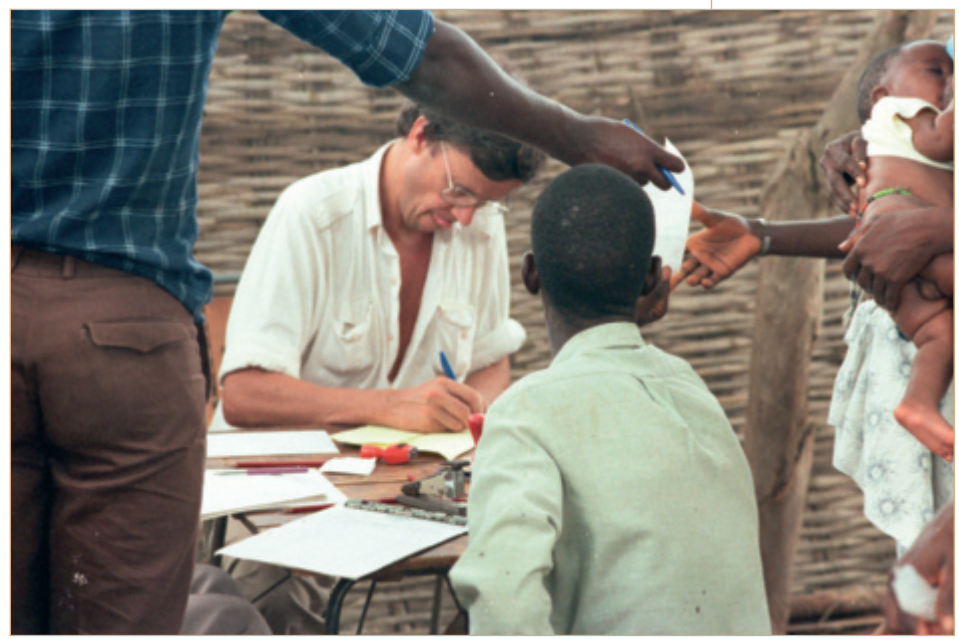
1978-1983: SAREC – Improving child nutrition and survival

In 1978, SAREC, the Swedish Agency for Research Cooperation with developing countries, sent an interdisciplinary team consisting of an anthropologist, a physician and a nutritionist to Guinea-Bissau on a one-year mission to examine the nutritional situation in the country and to suggest ways of improving nutrition and reducing child mortality. Guinea-Bissau had become independent only in 1974 and it was known from examinations of the age pyramid that under-5 mortality was probably in the range of 500-600/1000. SAREC considered the project an experiment in interdisciplinary research and in generating health through mobilising the population to change their nutritional practices. We were to collaborate with the local political institutions including political committees and youth organisations both in the collection of data and the implementation of research findings. The emphasis was clearly on poor nutrition as the main underlying cause of ill health. During 18 months, the project collected data in Bandim 1, an urban district in the capital of Guinea-Bissau with a population of 6,200, and in five rural areas. Though it was easy to work in Guinea-Bissau, it became clear that if we wanted reliable data on births and deaths we had to train our own assistants and to set up our own registration system as we could not rely on the political committees in this respect. However, more important was the frustration that our assumptions about malnutrition made no sense. The children were not severely malnourished, but childhood mortality was indeed 400-500/1000 during the first year of the study. In spite of relatively good nutritional status, measles infection had a case fatality rate of 21% in a large epidemic in 1979. It was evident that we did not really know what ought to be the priori-

ties in primary health care and what we should report back to the population. In response, we set up a system for continuing data collection after our departure so it would be possible to get a better understanding of the causes of high childhood mortality. SAREC did not appreciate our observations and interpretation that the real mechanism of high measles mortality was crowding, intensive exposure, and dose of infection; this was impossible, unplanned, and biologically implausible. Funding was stopped in mid-1981. However, as SAREC had not delivered a report to the ministry of health (MOH) in Bissau, the secretary of state requested that SAREC continue to fund the data collection infrastructure. This kept the basic data collection going until 1983.

1983-1988: IMCC – Improving measles vaccination and routine vaccination coverage

To continue the work on child mortality, we managed to get funding through Danchurchaid/DANIDA for two medical (IMCC) students per year to work in Bandim from 1983 to 1988. This funding permitted us to maintain the basic infrastructure for data collection from the SAREC period. We had four female assistants who registered pregnancies, births, growth, and deaths in the Bandim area, and one mobile team of nutritional assistants who continued bi-annual visits to the villages in the interior of the country. The mobile team identified the malnourished children or children who had grown poorly and discussed with the village committee and parents how to manage the children. Gradually, they also introduced routine vaccinations; measles vaccine from 1981 and DTP and OPV from 1984. In Bissau city, the IMCC students implemented two trials of Edmonston-Zagreb (EZ) measles vaccine to examine whether this vaccine was protective against measles already from 4 months of age. At the same time, we extended the registration system to the two neighbouring areas, Bandim 2 and Belem, to examine whether it was possible to combine outreach services with basic data collection, and whether vaccination coverage could be increased through outreach services. The data collection experiment in Belem failed miserably because the nurses did



not understand the need for reliable data but the outreach vaccination programme functioned well; the local political committee advised mothers to bring their children to a vaccination site at a specific day. Since the work during the first years had indicated that vaccinations had a marked effect on child survival, the IMCC students implemented a system for outreach vaccinations for the whole of Bissau city through the period 1985-1988. Each health centre had the responsibility for providing vaccinations to different districts in the capital. The vaccination coverage increased markedly in the process.

Since measles had come under control due to the regular vaccinations, we started studies focusing on diarrhoea as the next major cause of child mortality. In 1986, the ministry of health requested that we conducted a study of the recently discovered HIV-2 virus, thus giving rise to the first community study of HIV-2 infection. Through this period we also initiated collaboration with projects in other countries, in particular MRC, The Gambia, IRD, Senegal, Bandafassi, Senegal, and the Machakos project, Kenya, to test whether our observations on measles mortality and crowding were reproducible elsewhere.

Mobile team 1988

1989-1993: DanChurchAid (DCA) – Improving monitoring of primary health care

From 1987-88, DCA assumed responsibility for a DANIDA-sponsored project for construction or renovation of health centres in Oio and Biombo, the two regions surrounding the capital, and supporting health services with technical advisors in these two regions as well as Bissau city. The DCA physician in Bissau should continue the work of the IMCC students, improving vaccination coverage in Bissau city. BHP was given the role as monitoring unit for the DCA project to assess the impact of the project on morbidity and mortality, and one physician was sponsored by the DCA project. As part of this process, we initiated a sample survey in Bissau city, a registration of all births at the maternity ward, and a registration of all hospitalisations at the paediatric ward from the study area. At the same time, we started surveillance in Biombo and Oio to monitor the changes in childhood mortality. Since UNICEF wanted a larger survey to assess neonatal mortality in the country, the surveillance was extended to Cacheu, Gabu and Bafata in 1990, covering the five largest regions, which represent 83% of the population outside Bissau city. With a sample of 100 clusters of 100 women of fertile age and their prospectively born children, this has become the best source of data on the childhood mortality level in the country. DCA changed its strategy and moved the medical advisor from Bissau to Biombo. The monitoring in Bissau city therefore remained of limited immediate utility, but the surveillance systems have later been used for pointing to important

health problems, e.g. maternal mortality, post-hospital mortality, ethnic differences, and impact of vaccinations. This period ended tragically with a boat accident in which the project physician and his wife, Henning Andersen and Anja Vollmer, DCA's construction manager, Knud Schumacher, and two Swedish teenage boys drowned.

In this phase, we started in Bissau city a breast-feeding intervention trial as a means to reduce diarrhoea morbidity and a trial of vaccinating contacts during outbreaks of measles to enhance protection against the disease. However, the dominating theme was the growing recognition since 1989 that something was wrong with the high-titre measles vaccine. Since we could follow the children who had taken part in these trials, we observed that girls who had received high-titre measles vaccine had a two-fold higher mortality than girls who had received the standard measles vaccine in both Bissau and Senegal. WHO responded as others had responded before that this was impossible, unplanned, and biologically implausible. The following year in 1992, when the same observation was made on Haiti, WHO was obliged to withdraw the recommendation of high-titre measles vaccine.

1993-1998: SSI - Improving research training and diversifying funding and the research agenda

DCA did not much appreciate research and did not want to continue to administer the BHP. As a compromise, the administration was subcontracted to Statens Serum Institut (SSI). From the late 1980s, it became easier to obtain funding, particularly since the funding institutions decided to emphasize PhD training. Through the 1990s, we were therefore able to strengthen the research agenda with several PhDs, the first funded from RUF, EU-INCO, and SSVF, but from 1994 also from the Danish National Research Foundation, permitting us to have several PhDs working both in Bissau and with Danish data. DANIDA, through the DCA contact, supported technical advisors for the training of Guineans, thus laying the foundation for later research training. In 1997, DANIDA provided funding for the first phase of a training programme (ENRECA) for Guinean researchers, which in the first phase sponsored one PhD and 7 MSc's. The basis for research training has been on-thejob-training; many have previously taken part in a research project in Bandim before assuming responsibility for one's own project. A large group of Guinean physicians, biologists, nurses and laboratory technicians have had a part-time job at the project, usually in the afternoon after official working hours in the ministry. For the academic staff, the project organised training courses in computers and English as well as practical courses in health research and collection and analysis of data. Since English training has been rudimentary in the Guinean schooling system, all Guinean candidates for research training have been sent to The Gambia for language training in order to be able to pursue more advanced studies abroad (England, Brazil, Denmark, and Sweden) (see Table). Several expatriate PhD students had previously worked in Guinea-Bissau as medical students.

Several new projects were started, including crowding and health, management of acute and

chronic diarrhoea, cholera control, rotavirus epidemiology and vaccination, epidemiology of diarrhoeagenic Escherichia coli, vitamin A supplementation and measles vaccine, measles vaccination strategies, additional measles vaccination campaigns, impact of routine vaccinations, transfer of maternal antibodies, RSV and respiratory infections, retrovirus epidemiology, TB and the impact of HIV-2, increased susceptibility to retrovirus infections among older women, respiratory infections, testing local malaria treatment schemes, national polio immunisation and hospital management of sick children. The main themes in this period were inherited from previous periods including the cause and treatment of diarrhoea, the role of retroviral infections, and the long-term consequences of measles infection and high-titre measles vaccinations. Many studies were attempts to pursue the implications of the previous studies on the role of the non-targeted effects of vaccinations for child survival. These studies came to an abrupt halt when civil war broke out in Bissau in June 1998; the expatriates had to be evacuated.

Bandim health Centre

1998-2003: SSI – Improving Guinean participation:War, humanitarian aid, further vaccine problems, and INDEPTH Network

During the war, BHP assumed responsibility for humanitarian aid to the numerous internally displaced persons from Bissau, following them first to their temporary residence on the Prabis peninsular just outside Bissau, where crowding reached incredible levels with an average of 104 persons per house; and then again when they returned to the capital in spite of general insecurity because living conditions were unbearable in Prabis, or because they wanted to protect their property in Bissau. The two years from mid-1998 to mid-2000 became dominated by humanitarian aid activities, including food distribution and water provision, management of clinical services and drug distribution, maintaining TB treatment, monitoring and treating malnourished and at-risk children, vitamin A distribution, bed net distribution, measles and meningitis vaccination campaigns, and distribution of building material to the 15% of the houses in the study area which had been damaged during the war. Through most of this period, the funding was from humanitarian aid, and DCA was once again the administering organisation. Though important, managing humanitarian aid was dreadful; there were always people trying to cheat and numerous dissatisfied people who did not get what they thought they were entitled to.

Though data had been collected in connection with the humanitarian aid activities, it was only from mid-2000 the main focus again became research and training. Several studies were initiated to examine the implications of the war.

Other studies examined the implications of exclusive breastfeeding, the long-term consequences of viral infections including measles and chickenpox infection, the environmental and genetic risk factors for TB, the policy of BCG vaccination, and the impact of vaccination status on hospital mortality. Once again, vaccination issues have become the main theme. In 2000, we published results suggesting that possibly some of the routine vaccinations (DTP) might have negative effects on child survival. WHO sent experts to review our data prior to publication and they found no fault. Nonetheless WHO's Global Advisory Committee on Vaccine Safety responded as others had done before; this was impossible, unplanned, and biologically implausible. WHO has subsequently sponsored four retrospective studies in other areas of the world, which did not find any negative effect of DTP. These studies have yet to be published. These studies were based on reanalyses of data, which were not designed to collect vaccination information. In contrast, we are continuing to find consistent non-targeted effects of vaccinations as described on the following pages. It is likely that vaccine issues will dominate the research agenda for years to come.

Through the 1990s there has been a growing number of longitudinal studies in low- income countries. In 1998, BHP was a founding member of the INDEPTH Network, which should strengthen the collaboration between these sites. INDEPTH has managed to coordinate and standardise many aspects of the methodology of longitudinal studies, e.g. verbal autopsy procedures, and to organise several working groups and collaborative projects.
Through 1998 to 2002, 8 Guineans finished their post-graduate PhD and MSc studies, and became the main group of trained people in the health sector in Guinea-Bissau. Many of these wanted to continue research and research training. Unfortunately, DANIDA has had its policy under reconsideration from 2001 to 2003, which has meant that not until the fall of 2003 has it been possible to proceed with research training. Grants from EU-INCO for trials of BCG and Gates Malaria Partnership secured the continuation of most BHP employees through 2002 and 2003. The Guinean researchers seem determined to maintain BHP as an autonomous research institution affiliated with the Ministry of Health. With the growth of the INDEPTH Network of longitudinal studies in several other African countries since 1998, there is hope that they may also count on regional support in this endeavour.

Field assistants

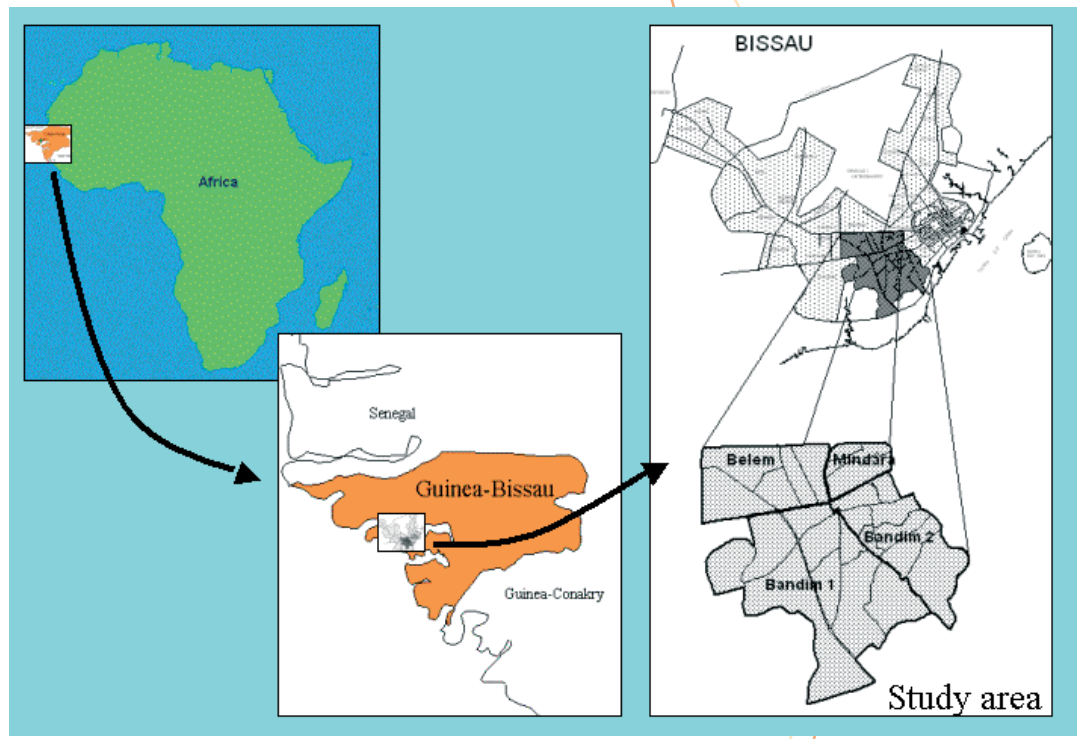
Table 1. Development of the Bandim Health Project and its main research activities through the past 25 years.

	1978-1983	1983-1988	1989-1993	1993-1998	1998-2003
Institutions	**MOH and SAREC, Sweden**	**MOH and IMCC, Denmark**	**MOH and DanChurchAid, Denmark**	**MOH and Statens Serum Institut, Denmark**	**MOH and Statens Serum Institut, Denmark**
Incorporation of new locations	Urban: Bandim 1 (1978-) Rural: Quinhamel, Oio, Cacheu, Tombali (1979-), Bubaque (1979-82)	Urban: Bandim 2 (1984-), Belem (1984-), Rural: Gabu (1984-)	Rural: National cluster sample: 100x100 women of fertile age (1990-) (Neonatal and childhood mortality)	Urban: Mindara (1994-), Rural: Caio (1993-) (HIV-2 study site)	Urban: Cuntum (1998-)
Population size	Urban: 6,300 Rural: 13,000	Urban: Bandim 2 (1984-), Belem (1984-), Rural: Gabu (1984-)	Urban: 36,000 Rural: 15,000 Survey of women and children: 10,000	Urban: 50,000 Rural: 23,000 Survey of women and children: 20,000	Urban: 85,000 Rural: 25,000 Survey of women and children: 25,000
Census	Bandim 1 (1978), Tombali (1979), Oio (1979)	Urban: 1984, 1986, Quinhamel: 1983, 1988 Oio: 1983	Urban: 1993-4, Quinhamel: 1993	Urban:1994-5, 1997 Quinhamel: 1994;Oio: 1995 Caio: Every year	Urban: 1999-2001, 2003 Caio: Every year
Routine data	Pregnancies, births, deaths Growth monitoring (weight, height) Breastfeeding Infections (measles, polio, whooping cough); Vaccines (tetanus, measles) Census: age, sex, family relations, schooling, occupation	Pregnancies, births, deaths Growth (weight) Breastfeeding, supplementary feeding Infections, Vaccines (tetanus, measles, BCG, DTP, Polio) Census: age, sex, family relations,	Pregnancies, births, deaths Growth (arm-circumference) Breastfeeding, supplementary feeding Infections, hospitalisations Living with pigs, living with mother Vaccines Census: bed-sharing, use of bed-net	Pregnancies, births, deaths Socio-economic status (SES), risk factors at birth Growth (arm-circumference) Breastfeeding, supplementary feeding Infections, hospitalisations, Vaccines, BCG scar Living with pigs, living with mother Census	Pregnancies, births, deaths Socio-economic status (SES), risk factors at birth Growth (arm-circumference) Breastfeeding, supplementary feeding Infections, hospitalisations, Vaccines, BCG scar Living with pigs, living with mother Census
Intervals for data collection	Urban: 3 months Rural: 6 month	Urban: pregnancies monthly, other data 3 months Rural: 6 months	Urban: pregnancies monthly, other data 3 months Rural: 6 months	Urban: pregnancies monthly, other data 3 months Rural: 6 months	Urban: pregnancies each month, other data 3 months Rural: 6 months
Mortality levels	Urban: IMR: 197/1000; <5: 454/1000 Rural: IMR: 200-250; <5: 500/1000	Urban: IMR: 97; <5: 215 (1987-90)	Urban: IMR: 107; <5: 200-250	Urban: IMR: 107; <5: 200-250	
Main studies	Malnutrition and child mortality	Child mortality, measles control, efficacy of high-titre measles vaccination, crowding, excess mortality of twins, cross-sex transmission of infection, long-term consequences of infections, T-lymphocyte analyses, diarrhoea and entero-pathogens in childhood, epidemiology of retrovirus infections	Child mortality, measles control, diarrhoea control and breastfeeding: use of health care services, treatment of diarrhoea, neonatal mortality, epidemiology of retrovirus infections, crowding, non-specific effects of immunisations, long-term consequences of infections, T-lymphocyte analyses, determinants of atopy, cellular immunity	Two-dose measles immunisation strategy, low-osmolality oral rehydration salt (ORS) and treatment of persistent diarrhoea, maternal mortality, crowding, non-specific effects of immunisations, long-term consequences of infections, T-lymphocyte analyses, respiratory infections, thymus growth, treatment of malaria, microbiological investigations of entero-pathogens, epidemiology of retrovirus infections, epidemiology of TB	Two-dose measles immunisation strategy, non-specific effects of immunisations, immunisation and hospital case fatality, long-term consequences of infections, treatment of malaria, rotavirus, use of health care services, consequences of the war, exclusive breastfeeding, retrovirus epidemiology, epidemiology of TB, epidemiology of meningitis, randomised trials of BCG to low birth children, of vitamin A with BCG, and BCG revaccination
Main interventions	Growth monitoring, tetanus vaccine, measles vaccine	Growth monitoring, tetanus vaccine, increasing vaccination coverage, efficacy of high-titre measles vaccination	Immunisation at exposure, preventing premature weaning, improved case management of diarrhoea	Two-dose measles vaccine strategy, vitamin A supplementation, cholera control, improved case management of diarrhoea, hospital case management	Two-dose measles vaccine strategy, introducing exclusive breastfeeding, prenatal supplementation, BCG trials, vitamin A supplementation, misoprostol for maternal bleeding,
Assistants	10 fieldworkers	10 fieldworkers, driver	40 supervisors, fieldworkers, laboratory technicians, drivers, clerks	150 supervisors, field workers, laboratory technicians, drivers, clerks	100 supervisors, fieldworkers, laboratory technicians, drivers, clerks
Academic staff	4 expatriates (2 anthropologists, 1 nutritionist, 1 physician)	2 medical students	3 Guineans (physicians), 4 expatriates (physicians, anthropologist)	20 Guineans (physicians, biologist, psychologist), 12 expatriates (5 physicians, 3 epidemiologists, anthropologist, 3 students)	2003: 15 Guineans (physicians, epidemiologist, biologist), 2 expatriates (1 physician, 1 anthropologist)
Expatriate research degrees		1 DMSc		5 PhD	4 DMSc's, 9 PhD's 8 PhD students ongoing
West African Research degrees				1 DMSc (Senegalese), 1 MSc (Guinean)	1 PhD, 8 MSc's (Guineans + 1 Senegalese),; 6 PhD students ongoing/planned, 3 MSc's ongoing/planned
Funding	SAREC	Core: DCA/DANIDA; Specialised studies: RUF	Core: DCA/DANIDA; Specialised studies: Danish Research Councils (measles, diarrhoea, HIV-2) , EU (measles, diarrhoea)	Core: DANIDA, Danish National Research Foundation; Specialised studies: Danish Research Councils (measles, diarrhoea, viral infections, respiratory infections, HIV-2) , Welcome (measles), British MRC (HIV-2), EU (measles, diarrhoea, HIV-2), NOVO (RSV, sonography), Thrasher (maternal antibodies)	Core: Danish Research Foundation, Novo Nordisk Foundation, DANIDA, Specialised studies: Danish Research Councils (measles vaccination, viral infections, vaccines) , British MRC (HIV-2), EU (maternal mortality, TB epidemiology, BCG trials), March of Dimes (BCG)

Bandim Health Project
A demographic and health surveillance system

Geography

The Bandim demographic surveillance system (DSS) is located in a suburban area of the capital Bissau in Guinea-Bissau, West Africa, a former Portuguese colony liberated in 1974 after a violent war. The Bandim DSS comprises five suburbs of the capital, and a mobile unit covers several rural populations. Guinea-Bissau is situated at 120 north latitude and 15° west longitude. Total population of the country is approximately 1,300,000. The climate is tropical. Mangrove vegetation covers the banks along the many rivers. Southern and northern parts are mainly forest while the rest of the country is wooded savannah; much of the country is under cultivation with rice fields and crops like peanuts, maize and manioc. The rainy season with high humidity lasts from June to October. Temperatures range from 20 to 36 °C.



The Bandim population

The BHP project covers a population of more than 100,000 in both urban and rural areas. Public water supply is available for some 35% of the population in the capital only, and drinking water is not boiled. There is no public sewerage system and all latrines are pit latrines. Major economic activities include small scale agriculture and petty trading with a large proportion of the population engaged only seasonally in selling cashew nuts, cashew wine, palm oil, fruits, vegetables or rice. Smaller domestic animals sleep inside the house. Houses are made of mud bricks and roofs are either thatched or covered with corrugated iron. The public sector has 36,000 employees, the majority being soldiers. Schools are primarily public, but in recent years a growing number of small private schools have appeared. In 1994, 25.6% of males and 45.1% of females over 10 years of age had no school education. In 2002, 9.8% of males and 27.3% of females over 20 years of age had no school education. The literacy rate is 13.0% in rural areas and 35.2% in urban areas.
In the urban Bandim area, the Pepel is the largest ethnic group (38%) followed by the Manjaco (15%) and various Muslim ethnic groups, mainly Fula and Mandinga, (12.4%). In the rural areas followed by the mobile team, Fula (25.8%) is the largest ethnic group followed by Pepel (22.7%), Mandinga (19.4%) and Balanta (18.4%). In urban areas most people speak Criolo, a local lingua franca based on Portuguese and African words and grammar. An increasing number of private clinics, hospital-like institutions and pharmacies reflects that the public health structures have been crumpling under changing donor interests and lack of funding over the past decade. There are three health centres in the study area, one of which was built by the project and has a 6-bed maternity ward and a laboratory. There is only one paediatric ward in the capital, which facilitates follow-up of children from the study area during and after hospitalisation. Of the children who died in Bandim in 1993, 49% were hospitalised and 90% were seen by a physician or nurse before death. Thirty-two percent of children with diarrhoea were brought to a health facility. In 1995, measles vaccination coverage in the urban area was 83.8% before 2 years of age. Since then, the coverage has been even higher due to a large measles vaccination project. Acute and persistent diarrhoea, pneumonia and malaria account for the majority of childhood morbidity and mortality. HIV-2 infection is still more prevalent than HIV-1. Including dual infections, the HIV-1 prevalence was approximately 5% in 1999. Cholera epidemics were observed for the first time in 1987 and again in 1994, 1996-97, and 2002.

Routines and procedures

After independence in 1974, an extremely high under-5 mortality rate (around 500/1000) prompted the Ministry of Health to approach SAREC (Swedish Agency for Research Co-operation with Developing Countries) to organise a study to define nutritional priorities in preventive health care. The nutrition and child health study was initiated in 1978 and a census was carried out with

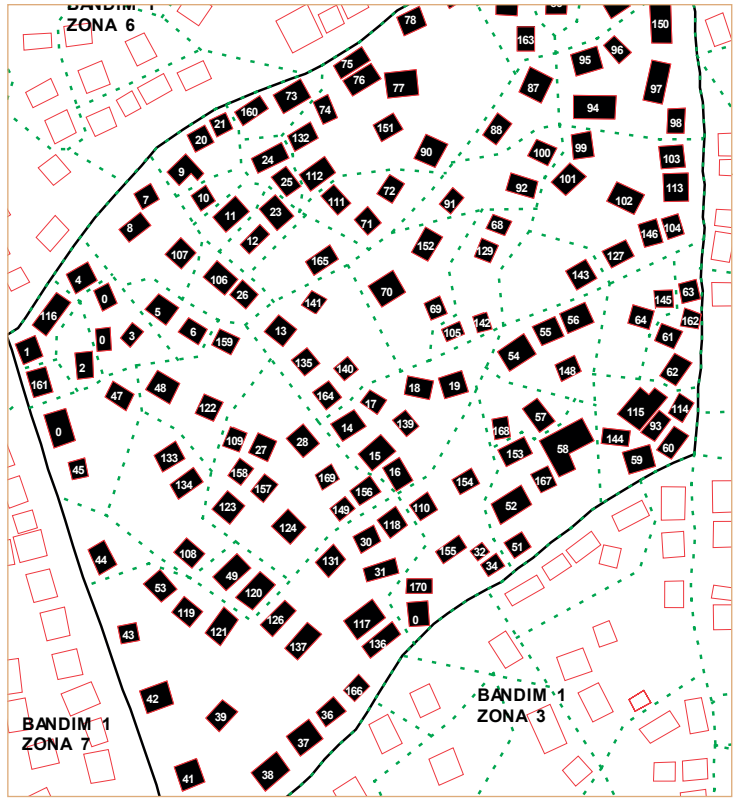
a subsequent anthropometric survey and organisation of antenatal care for all women found to be pregnant during the census. All new pregnancies were registered together with births, deaths and migrations. This became the basis for the ongoing registration of the population in the Bandim suburb. Distinct ecological zones were selected and regular rural population surveys covering 5 regions were initiated in the interior in 1979. A number of other suburban communities have been added over the years (Bandim 2 and Belem in 1984, Mindará in 1994 and Cuntum in 1999) and in 1990 a follow-up cluster survey of rural women of fertile age was initiated in 5 rural areas. In 1993, BHP took over the administration of a community study in the Caio sector in collaboration with the MRC laboratories in The Gambia.

The Bandim DSS covers an urban population of around 80,000 living in 6,035 houses in five suburbs, nearly 30% of the population in the capital Bissau. The rural population is 28,000 in five regions, as well as a survey of women in fertile age comprising 24,200 women and their 34,040 children. The study is presently monitoring nearly 12% of all births in Guinea-Bissau with around 6,000 registered births per year.

The site headquarters are situated in the Bandim suburban area of Bissau, where the main study population is found. A mobile team based in Bandim carries out the rural surveys. BHP is a collaborative project between the Ministry of Health and the Statens Serum Institut, Denmark, but has full financial and managerial autonomy. The site has close financial and training relations with the National Health Laboratory, where most immunological and biochemical analyses are carried out.

Data collection

Mapping. Mapping was originally done by hand, but was transferred to a GIS-based system (MAP-INFO) in 1995. Spatial analyses on cases of diarrhoea and on measles epidemics have been done. Maps are used daily by fields assistants to plan the walking route through the study area. Below is seen an example of the division of the Bandim suburban area into zonal areas within each of which houses are numbered.



Example of division into zonal areas and house-numbering

Initial census.
The first census was done in 1978. Over the years a number of censuses have been carried out in Bissau (1981, 1986, 1988, 1993, 1995, 1997, 1999) and in some of the rural areas, to keep track of the population and to document family structure. In the censuses, information is collected on names, date of birth or age, sex, household status and family relation, ethnic group, civil status, level of schooling, use of bed nets, use of common bed, and type of work.

Regular update rounds
Due to an increasingly mobile population after the economic liberalisation in the late 1980s, annual censuses in the urban areas would be desirable but has not been financially possible.

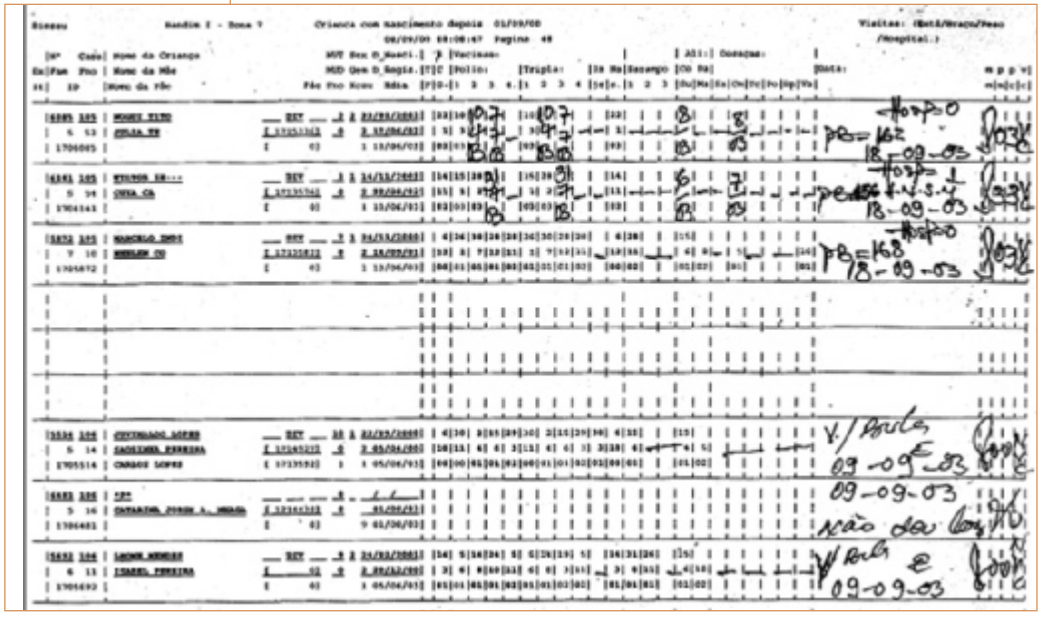


Fig. 1.
Child list used for household visits to follow-up children every 3 months.

Migrations are tracked within the urban study area, and in certain studies migrations are traced outside the study area as well.

Continuous child surveillance
With a focus on maternal and childhood health, registration of all pregnancies has been a key element of the data collection system. Field assistants visit all households once a month to enquire about new pregnancies and register women who have already given birth. In the urban districts, children are followed with 3-monthly home-visits from birth to 3 years of age. The type of child list utilized by the field assistants during their household surveys is shown in *figure 1*.

The interval between routine visits in the rural areas is 6 months. Often children are followed more closely due to specific studies, such as weekly morbidity surveys of respiratory and diarrhoeal diseases. Information is gathered on anthropometry (weight, height and arm-circumference), immunizations, feeding and breast-feeding, infections and hospitalisation, various socio-economic indicators and migrations and deaths. In Bissau, data on hospitalisation of children from the study area are collected routinely at the hospital and all vaccinations are documented at the three health centres in the study area. Information about children is usually obtained from mothers or caretakers.

Deaths
Death certification is carried out with a brief

verbal autopsy-like questionnaire conducted by 1-2 specialised field assistants usually 2 weeks to 3 months after the death (one questionnaire for children and a different one for adults). Expatriate and national medical doctors have carried out more thorough verbal autopsy surveys in 1987,1993 and 1999.

Supervision and quality assurance

There is one supervisor for each 2-3 field assistants and the supervisor is also responsible for questionnaire checking and data entry. Each assistant is supervised weekly in the field.

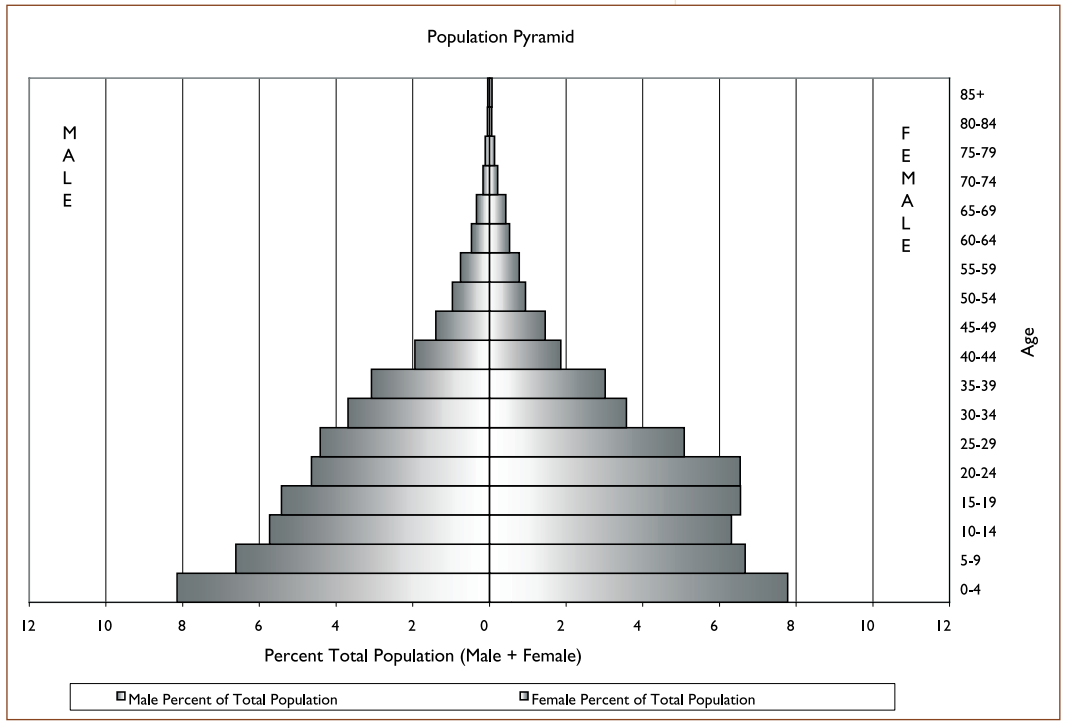
Data management

Data are entered on laptops into a menu based DBASE program designed specifically for the Bandim site. The database program has built-in control and validation features. Once a month a report of inconsistent or lacking information is printed out for correction. Each supervisor checks questionnaires before data entry. National supervisors, Guinean physicians and expatriates carry out field supervision.

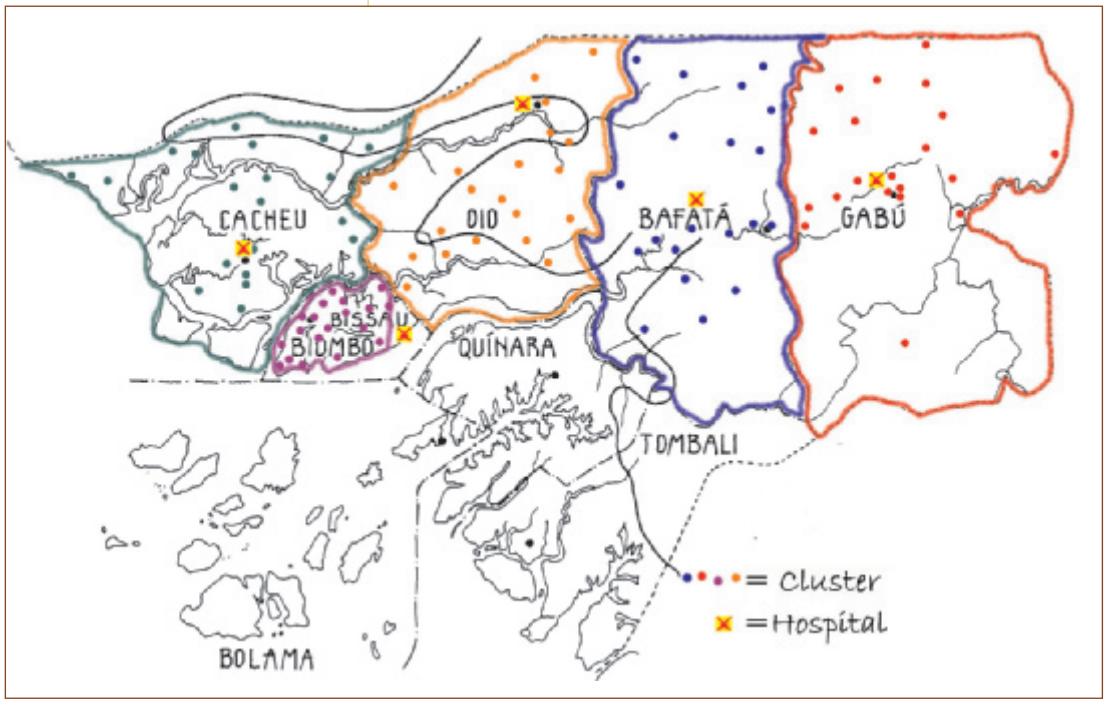
The mobile team: Data collection

The mobile team has since the beginning in 1978 followed around 500 children under five years of age in each of 5 regions in the interior. The size of villages is different for different ethnic groups and the number of villages followed in the different regions varies between 4 and 10. Since 1990 the main focus of the mobile team has been to follow a cohort of 100 clusters of 100 women in the five major regions (see map). Over the years, the cohort of women has included 24,200 women and their 34,040 children. Villages are visited every six months. Each compound has been mapped and is revisited every time to identify new pregnant women, document what happened to previously registered pregnancies and to all the children less than 5 years of age. As in the urban area, information is collected on growth, breastfeeding, infections,

Fig. 2.
Population pyramid of person years observed at the Bandim Health Project, 1995-1997.



Mobileteam: Cluster villages by region



hospitalisations and vaccinations. At each visit, around 60-65% of the children are seen and their vaccination card inspected.

Bandim project: Basic outputs

The Bandim DSS has over 100,000 people under continuous monitoring (80,000 urban and 28,000 rural). In urban areas, infants are 3-4% of the population, 13% are 1-4 years old, 25% are 5-14 years, 57% 15-64 years and 2% are 65 years or older (Fig.1).

The age dependency ratio is 82 and the male:female ratio is 0.92. There is a large excess of women between 15 and 30 years of age due to male out-migration from Guinea-Bissau. The total fertility rate for women aged 15-49 is 5.8 for urban and 6.8 for rural areas. The infant mortality rate is around 100 per 1000 live births in the urban areas and around 140-150 per 1000 live births in rural areas (Figs. 2 and 3).

The under-5 mortality ratio is around 280 per 1000 live births in the national cluster survey followed by the mobile team. Child mortality is generally higher in the rainy season compared with the dry season (Fig. 4). The maternal mortality ratio is 818 per 100,000 live births. The average household size is 4.57 and there is an average of 3½ households per house. In the urban area, 67.1% of males and 40.7% of females are literate by age 15 or over.

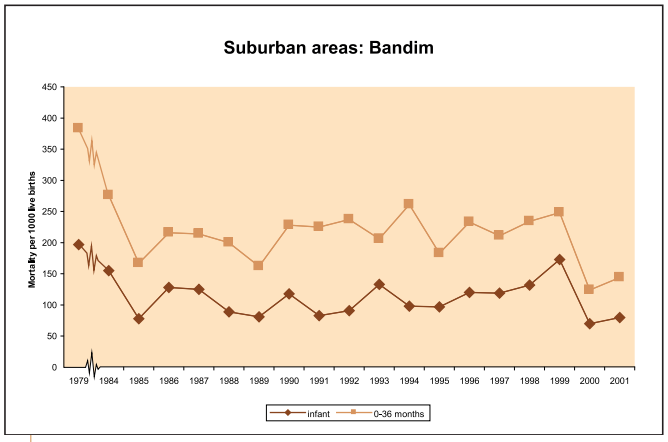


Fig. 2.
Infant- and child mortality by year, 1979-2001. Suburban study population, Bandim.
Note: The analysis included 12,616 children registered prior to birth of whom 2,047 died before 3 years of age.

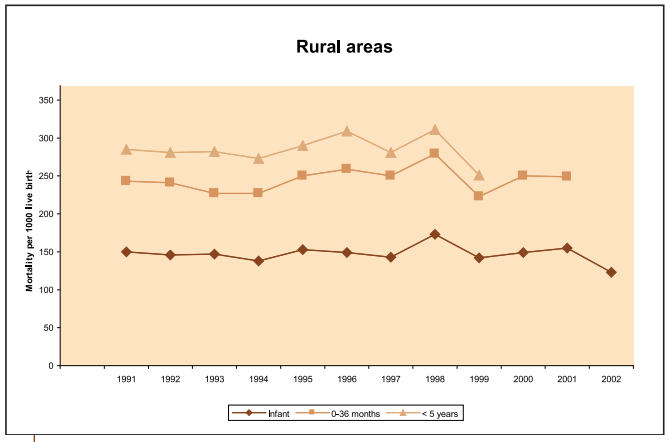


Fig. 3.
Infant- and child mortality by year, 1991-2002. Rural study population, Guinea-Bissau.
Note: The analysis included 20,407 children registered prior to birth of whom 4,644 died during follow.

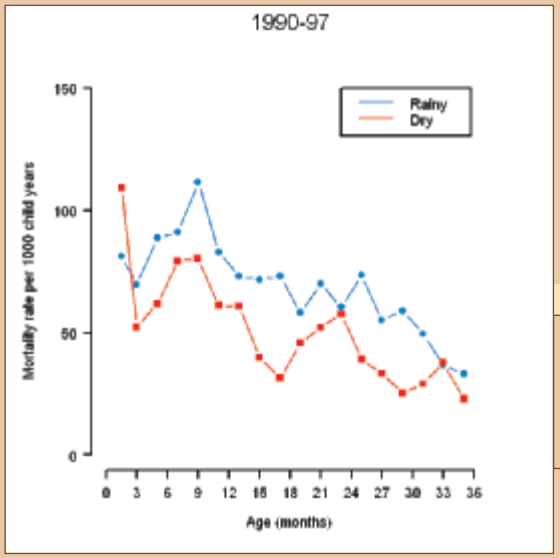


Fig. 4
Seasonal variations in age-specific child mortality, 1990-1997, Bandim Health Project.

Statisticians Without Limits

Background

Longitudinal epidemiological studies at the Bandim Health Project (BHP) in Guinea-Bissau are generating data that needs to be analysed carefully. Longitudinal studies often have repeated measurements of the same individual. The collection of data on individuals is not always a collection of independent data, as we may have a grouping of individuals at different levels (e.g. family, household, house). Data from repeated measurements or related individuals calls for more specialised statistical methods. Below are given examples of statistical methodological challenges from BHP.

Recurrent Disease Events:
To determine risk factors for episodes of diarrhoea, an open cohort of children was followed by weekly diarrhoea recall interviews (119, 175). Each child can contribute with more than one episode of diarrhoea and the analysis of risk factors using a standard Poisson regression showed that the Poisson assumption was not met. Instead a fully parametric random effect model (negative binomial regression) was used (119) giving a much better fit. The interpretation of the effect of the risk factors, i.e. the relative risk (RR), in this model is, however, conditional on the child-effect, thus an effect within the same child. A more useful method when assessing risk factors for public health is the method of Generalised Estimating Equations where the interpretation of RR is between any two children (175).

Growth and Cryptosporidium infection:
A major cause of acute and persistent diarrhoea is cryptosporidium. To investigate whether occurrence of cryptosporidium infection has an influence on growth, an open cohort of children was followed by weekly diarrhoea recall interviews with anthropometric measurements and

stool samples. To model growth, e.g. weight as a function of age and the effect of cryptosporidium on growth, a generalised linear mixed model was used (183). This flexible model allows for modelling of individual growth curves instead of using e.g. simple means for different ages. Modelling of other important factors for growth, such as seasonality, are easily included. The models used and developed in (183) have since been used in e.g. (251, 354).

Multivariate Survival Data:
A longitudinal study of women and their offspring was started in 1990 in rural Guinea-Bissau using a cluster (100 villages) sampling approach. Survival times from the offspring were used to investigate the effect of routine vaccinations on child survival (241). In the survival analysis we need to control for village, which was done using a stratified Cox regression, stratifying on village. However, this approach is not good in the case of highly stratified data. The results were therefore compared with a random effect model, the shared gamma frailty model. Having left-truncated data (not all children followed from birth) it was necessary to correct the frailty model to handle left truncation, which was studied in detail in (279). In this data the stratified Cox regression performed well.

Evaluation of humanitarian aid:
In wartime, like the 1998-99 armed conflict in Guinea-Bissau, or complex emergencies, almost everyone is affected leaving no direct reference for an evaluation of impacts on e.g. mortality. During the conflict in Guinea-Bissau, BHP organised several interventions such as supplementary feeding for malnourished children and distribution of bednets to pregnant women. To evaluate these interventions a reference is needed. Methods for projecting (forecasting) population-based data into time of emergency based on information obtained before the conflict have been compared to create a local-line reference (362). If time-at-risk during the forecasted period is known forecasting can be done using Poisson regression. In the forecasting it is important to adjust for epidemics and calendar-time fluctuations (season). Analyses of the interventions are ongoing.

References to statistical work:
56, 83, 119, 175, 183, 241, 251, 279, 354, 362

Measles and malnutrition

Background

When the original SAREC-sponsored project was planned and initiated in 1977-78, it was known from the age pyramid among children in Guinea-Bissau that under-5 mortality had to be around 500/1000. The leading concept to understand high mortality was the underlying malnutrition aggravating common infectious diseases like measles, diarrhoea and pneumonia. When the work started in the fall of 1978, the plan was to do anthropometric surveys of children under 5-6 years of age to study the prevalence and risk factors of malnutrition. Through 1978 and 1979 surveys were carried out in Bandim 1, a district in the capital of Guinea-Bissau, and in clusters of villages in five rural areas covering the major ethnic groups and ecological zones in the country (1).

Results

During the first year of the study, mortality was indeed 500/1000. However, severe malnutrition was very uncommon, in 1200 children examined in Bandim we had found no kwashiorkor and only two marasmic children. However, during the dry season of 1979 a severe epidemic of measles swept through Bandim. The nutritional project had not been set up for epidemiological surveillance and case detection of specific diseases. In spite of the relatively good nutritional status of children in Bandim, the case fatality was 21% for children less than 5 years of age. Surprisingly, there was virtually no association between the nutritional status we had measured just a few months before the epidemic and the likelihood of dying of measles infection (4).
A severe epidemic of measles was also observed during 1979 and 1980 in Quinhamel, the region just outside the capital Bissau. Measles was

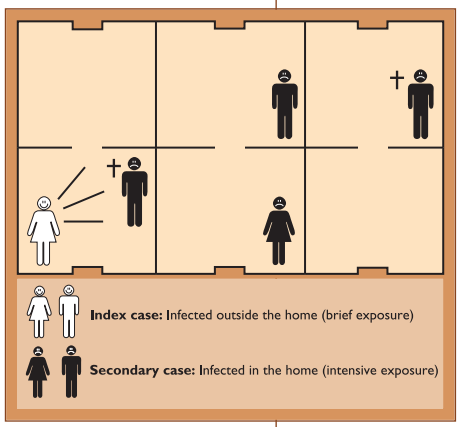
again extremely severe with a case fatality of 34% for children under five years of age. Again there was no association between the state of nutrition and likelihood of dying of measles (11). Following the introduction of measles vaccine in December 1979 (13), the case fatality declined but measles continued to occur and there continued to be no association between the nutritional status and the likelihood of dying of measles (32).
In retrospect, the data previously used to argue that nutritional status or nutritional intervention programmes determined measles mortality turned out to be very slim (33, 47). A general consideration of global nutritional patterns and mortality levels in measles infection should have suggested that malnutrition could not be the main cause; measles mortality was high in Africa where nutritional status was relatively good and low on the Indian subcontinent where nutritional status was poor (47).

Public health implications

The malnutrition paradigm had many consequences; for example, child mortality preventive activities focused on growth monitoring, and there was little belief in vaccinations because the "weak" children likely to die from measles would probably die from something else if saved from measles by vaccination. An emphasis on other factors was clearly needed to explain high mortality in common infections (33)

References on measles and malnutrition:
1, 3, 4, 6, 7, 9,11, 17, 22, 26, 29, 32, 33, 34, 47, 50, 51, 66, 106, 126

Measles, Overcrowding and principles of severe disease



Background

Observations during the first registered measles epidemic in Bandim suggested that the case fatality was higher when there were several cases in the same house. We therefore conducted retrospective interviews about the pattern of disease transmission in both the epidemic in Bandim (4) and in a rural area (11).

Subsequently, we conducted studies in other areas and studies of historical records to establish the general importance of overcrowding as a determinant of severe disease.

Results

Clustering of cases and overcrowding:

The principle that clustering cases increased the case fatality turned out to be systematic not only in Bissau (11, 12) but also in other countries (33, 54, 59) and in historical records (18, 31, 88). In fact, most historical and geographical variation in severity could be explained by variation in the clustering of cases (33).

Intensity of exposure:

Apparently the mechanism underlying the importance of clustering was that intensive exposure – i.e. being a secondary case (see Figure) – increased the case fatality (33). Hence, these data clearly supported the emphasis in historical records on overcrowding and large family size as risk factors for severe measles infection (85). Numerous subsequent studies have found intensity of exposure to be important and we have also been able to establish that the intensity of exposure is important for severity of polio (252,274,276), whooping cough (268) and varicella (308).

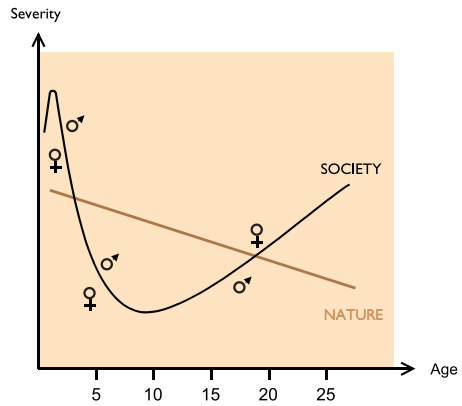
Dose of infection and length of incubation:

Studies in both measles (17, 78) and polio (252) have suggested that severity is associated with

length of incubation making it likely that dose of infection is a determining principle for severity.

Amplification of severity: Severity is transmissible and secondary cases are therefore even more severe when the transmitting cases had severe infection. This gives rise to a pattern in which the case fatality increases with each new generation of cases in close institutions (59, 66, 78, 88). This is presumably the explanation of the extremely high case fatalities experienced in virgin soil epidemics (15) and institutions such as military barracks, immigrant ships, refugee camps, and child institutions (85).

Cross-sex transmission:
Inadvertently, the data from Bandim suggested that measles was more severe when contracted from the opposite sex (19). This has subsequently been found in many studies in other countries and historical records (61, 68-70, 81, 84, 86, 88). Apparently the same principle applies to polio infection (274), varicella and possibly to respiratory syncytial virus (364).
Age and sex patterns of severe disease: The pattern of transmission of infections varies by age and sex with the lowest proportion of secondary cases among children aged 3-10 years old, the precise age depending on social institutions like kindergarten and schools. This gives rise to the characteristic U-formed curve of severity found in many transmissible infections (see Figure) that is in fact also a curve of the proportion of secondary cases in different age groups (8,24,85,194). The same pattern may explain gender differences in severity of infection. At younger ages, girls are contracting infections more easily and boys are therefore more likely to become secondary cases and have higher case fatality (88,194). However, at older ages teenage girls and young women are more likely to become secondary cases and have more severe disease than males (194). In societies, which are restricting the movements of women, this pattern will be inversed; boys will bring home infections and girls will have higher mortality.



Note: Nature curve represents the age response to the same dose of exposure (vaccine).
The Society curve is the observed severity of infectious diseases by age.

Public health implications

With crowding as a major determinant of high child mortality levels in both Africa now and in

Europe at the turn of the 20th century much stronger emphasis should probably have been put on improving housing and reducing family size. For example, we have consistently found bed crowding to increase transmissibility and severity of many infections and to increase child mortality. Much more ought to be done in this area. However, the importance of crowding and dose of infection also contradicted the emphasis on "weak" children as being the cause of high mortality and hence strengthened the possible role of disease-specific prevention.

Immunisations became the immediate and cheapest solution to substantially reduce child mortality levels. Through the 1980s, BHP in collaboration with Danish IMCC (International Medical Cooperation Committee) established routine immunisation services in the study area but also a system of outreach vaccination services, visiting all of the districts in Bissau city regularly.
International health experienced a similar change in focus towards immunisations through the 1980s – not because of the observations on crowding – but because the smallpox eradication campaign showed that final solutions were possible and the same infrastructure could eventually be used to control other infections.

References on crowding and principles of severe disease:
5, 8, 9, 11, 12, 14, 15, 17-19, 22, 24, 25, 29-35, 38-41, 45, 47, 50, 51, 54, 55, 57, 59-62, 66, 68-75, 78, 81, 83-89, 105, 106, 126, 131, 133, 134, 152, 154, 159, 161, 174, 184, 194, 195, 214, 216, 269, 308, 363

Poliomyelitis: Acute Severity and Long-term Consequences

Background

Several studies on measles have revealed that severity of infectious diseases is associated with transmission factors such as intensity of exposure and dose of virus. Severity seems to be particularly high among secondary cases (cases infected by someone in the household) compared to index cases (the first case in the household). As adults and infants are at higher risk of being infected as secondary cases, a U-formed association between the acute severity of diseases and age is expected. It has furthermore been suggested that intensity of exposure is associated with later health consequences following the virus infection. We therefore decided to test whether the transmission model could be applied to other viral diseases such as poliomyelitis and to examine the association between acute severity of poliomyelitis and later mortality and morbidity.

Methods

Approximately 6000 patients treated for poliomyelitis at the Blegdamshospital, Copenhagen, in the period 1919 to 1954, were identified. Basic information including severity of the polio infection (non-paralytic, paralytic, respiratory polio and fatal polio) was extracted from the hospital records. The CRS numbers of more than 90% of the polio patients were identified through the local municipal registers and the civil registration system. Late mortality and morbidity was analysed through a linkage procedure with the Danish Cancer Register, the Register of Multiple Sclerosis, the Danish Hospital Discharge Register and the Causes-of-Death Register using the CRS number as the key. The observed morbidity and mortality was compared with the expected using either population-based incidence rates (when available) or a non-polio cohort.

Results

We found a U-formed association between severity and age, as both adults and infants had a high risk of developing paralytic polio (Figure). Short incubation period and being infected by another family member also tended to increase the severity of polio (252, 274, 276).

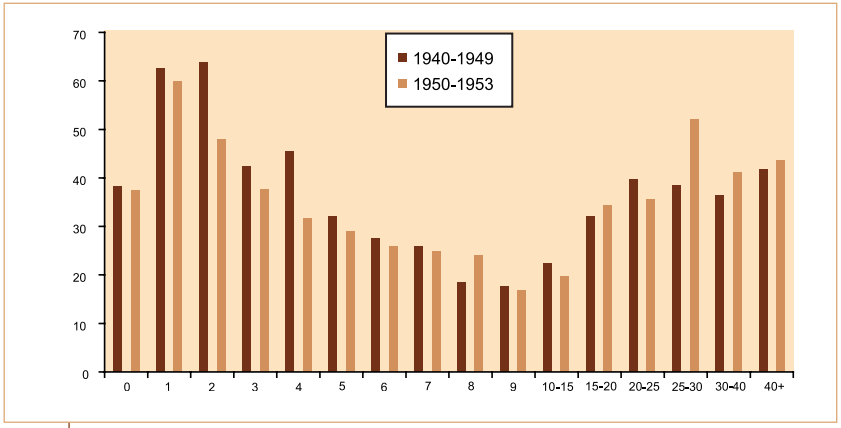


Figure: Proportion of paralytic polio patients compared to all polio patients by age and period

Followed to the present day, polio patients had a 14% overall increase in mortality, 11% risk of cancer and between 10 to 30% increased risk of being hospitalised with cardiovascular diseases, lung diseases, gastrointestinal disorders or diseases of the locomotive apparatus (243,254,284,328, 349). Excess mortality and the occurrence of secondary health problems seemed associated with the acute severity of poliomyelitis. Paralytic polio patients had a 20% higher mortality (SMR= 1.21 (1.1-1.3)) compared with the Danish population and excess mortality rose with progressively more severe stages of paralysis, patients with respiratory polio having the highest mortality (SMR= 2.71 (2.2-3.4)) (328). This group of patients also had the highest risk of lung diseases (IRR=3.51 (2.5-4.9)) (349). However, despite no remaining physical problems after the poliovirus infection, non-paralytic polio patients also had an increased risk of being hospitalised and a slightly increased mortality (SMR=1.09 (1.00-1.7)), mainly due to gastrointestinal diseases and suicide (363). This was a late-onset effect since mortality for non-paralytic patients had actually been significantly lower in the first 20 years after hospitalisation for polio infection.

Public Health Implications

Crowding and intensive exposure are likely to be among the determinants of the severity of poliomyelitis. Furthermore, the occurrence of long-term consequences after poliomyelitis and the excess mortality seem to be associated with the acute severity of poliomyelitis. The mechanism behind the increased morbidity among non-paralytic polio patients is, however, unknown. Worldwide an estimated 10 to 20 mill persons are currently paralysed by polio. Hopefully a better knowledge about the frequency and type of secondary health problem following poliomyelitis will lead to a better and more careful treatment of previous polio patients.

References to poliomyelitis:
198, 232, 243, 252, 254, 268, 274, 276, 278, 284, 328, 349, 363

Chickenpox in Guinea-Bissau

Background

Chickenpox, the classic childhood disease caused by Varicella Zoster Virus (VZV), is common between 2 and 8 years of age in industrialised countries and more than 90% of adults have had the infection (1). The epidemiology of VZV infection is different in many low-income countries. Asian studies had reported a low age-adjusted sero-prevalence and many severe cases in adults. Few studies have been performed in Africa. Intensity of exposure has previously been shown to be a determinant of severity of measles, polio, and pertussis infections. To study the epidemiology and to identify the risk factors for severity of chickenpox in Guinea-Bissau, a household study was performed. All cases of chickenpox virus were identified in the study area: Bandim 1, Bandim 2, Mindara and Belem. A clinician examined all cases and the history of exposure was documented.

Results

During 2000-2001, a total of 1539 cases were examined, nearly all cases occurring in an epidemic in the dry season of 2001. The median age of chickenpox infection was 4 years of age. Secondary cases had significantly more pox (table) and the duration of the incubation period was related to the intensity of exposure. An infant and a young adult man died of chickenpox.

Pneumonia was diagnosed in 10.3% of the cases. The frequency of children with pneumonia was significantly higher for secondary cases ($p < 0.01$) and they were younger (median 1.7 years). Secondary cases had higher fever ($p<0.01$). Skin infections were common (nearly half of the cases) and also related to intensity of exposure. Antibiotic was given to one third of all cases most commonly due to skin infection or pneumonia. No correlation to nutrition measured by

Number of elements	<20	20-49	50-99	100-199	>200	All
Exposure						
Index case	47 (5%)	177 (20%)	342 (38%)	233 (26%)	100 (11%)	899 (100%)
Secondary cases	18 (3%)	53 (10%)	127 (23%)	172 (31%)	181 (33%)	551 (100%)
TOTAL	65	230	469	405	281	1450

Number of cases according to number of pox and exposure status as index or secondary case.

Number of elements	Exposed in same bed	Exposed in same room	Exposed in same household	Exposed in same house	Unclassified exposure inside the house	All
<20	0	1 (1%)	3 (3%)	14 (7%)	0	18
20-50	7 (5%)	6 (5%)	6 (7%)	33 (17%)	1 (33%)	53
50-100	15 (10%)	16 (14%)	25 (26%)	71 (37%)	0	127
100-200	47 (32%)	38 (34%)	39 (41%)	47 (24%)	1 (33%)	172
>200	77 (53%)	52 (46%)	22 (23%)	29 (15%)	1 (33%)	181
All	146 (100%)	113 (100%)	95 (100%)	194 (100%)	3 (100%)	551

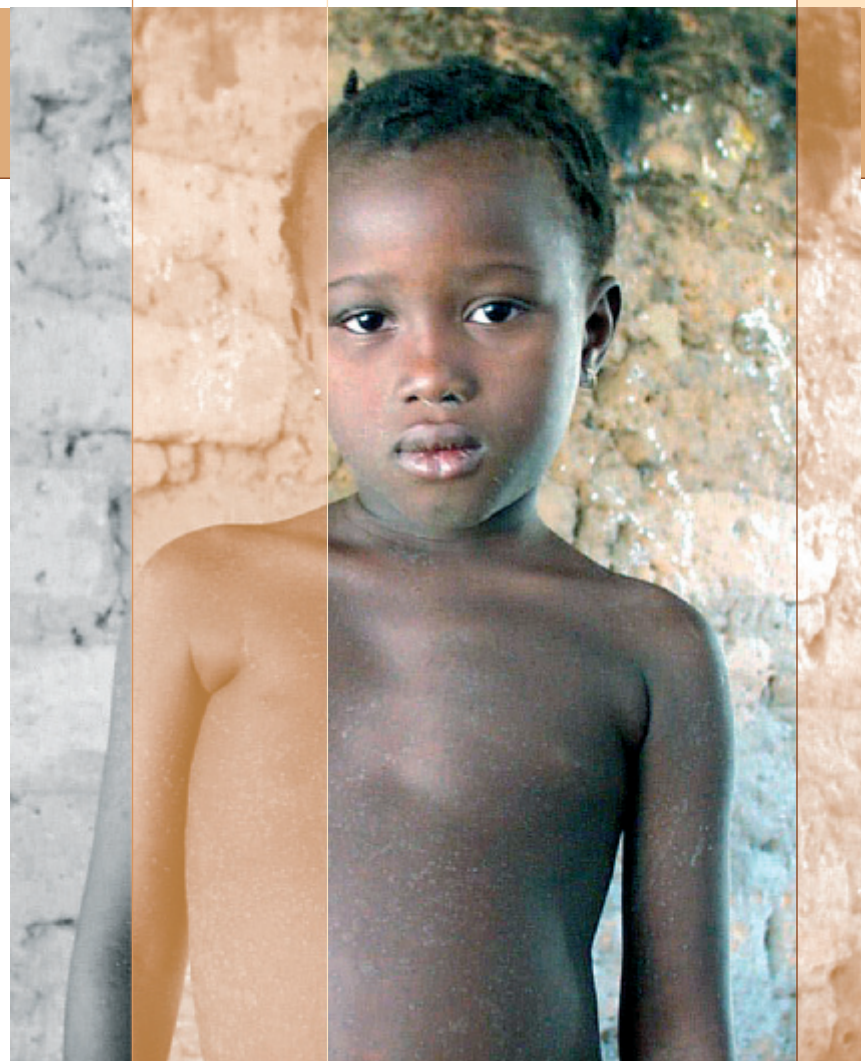
Number of pox for secondary cases according to history of exposure inside the house.

middle upper arm circumference was found. Chickenpox was associated with a marked increase in eosinophil cells (384).

Conclusion

The age distribution of VZ-infections in Guinea-Bissau was similar to high-income countries. Intensity of exposure was an important determinant of severity of chickenpox infection. Though mortality was low, it may be higher in environments with less access to medical care and the severity may increase as the HIV epidemic is progressing.

References on chickenpox:
307,308,318,384



Respiratory syncytial virus (RSV) infection

Background

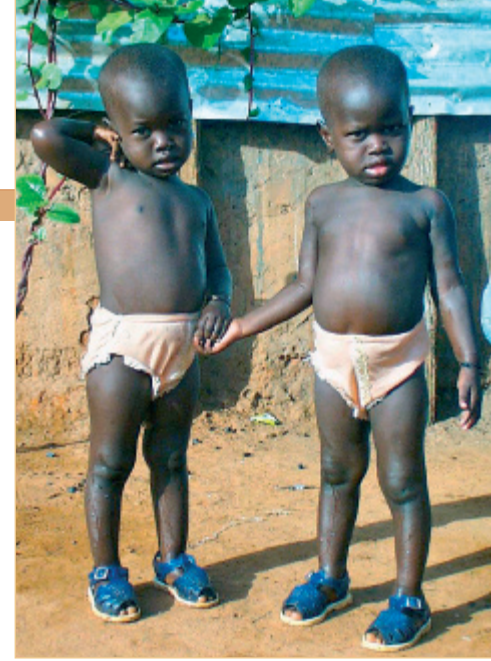
Worldwide, acute lower respiratory tract infection (LRI) is the leading cause of under-five mortality, RSV being one of the most important pathogens. The RSV study in Bissau has examined both methological issues and risk factors for severe disease as preludes to future studies of RSV vaccination.

Results

RSV-specific secretory antibodies. We assessed the duration of RSV-specific secretory IgM and IgA antibody responses in nasopharyngeal aspirates (NPA). IgM responses are short-lived among infants and may therefore be used as a marker of recent RSV infection among infants with LRI (233).

NPA vs. nasal swap
We compared detection of RSV-antigen using NPA and nasal swab (NS). Compared with the sensitivity of the NPA specimens, using NS samples was associated with a 27% to 31% reduction in sensitivity (292) but might make it possible to cover much larger population because the collection of nasal swaps is much simpler than obtaining NPA samples.

Cross-sex transmission
Opposite sex transmission may increase severity of certain viral infections. Among 1143 children from Guinea-Bissau, we tested whether mothers with recent RSV exposure (antigen or IgM positives) were more likely to have male than female children with RSV antigen-positive LRI. Equally many boys and girls had LRI, but boys were slightly more likely to have RSV detected (RR=1.36 (1.01-1.81)). With recent RSV exposure of the mother, boys were two-fold



more likely to have respiratory syncytial virus detected (RR=2.07(1.20-3.57)) (364).

BCG, LRI, and RSV

Bacille Calmette Guerin (BCG) vaccination may have a non-targeted protective effect on childhood morbidity and mortality. We examined whether BCG protected against LRI; specifically severe RSV infection. Among LRI case children, the odds ratio (OR) of being BCG-unvaccinated was 2.38 (1.32-4.26), the difference being most marked in girls. In LRI case infants with RSV detected, the OR of being BCG-unvaccinated was 3.40 (1.25-9.22). Again, the difference was more marked in girls (365).

Public Health implications

No vaccine or treatment against RSV is yet available. Passive immunisation is too expensive to be considered in developing countries. Since BCG is inexpensive and already routinely used in many countries, the protective effect of BCG on LRI caused by RSV and other pathogenes should be considered in vaccination policies.

Future perspectives

Risk factors for severe RSV infection are being identified in Guinea-Bissau and Denmark. The association between severe RSV infection and atopic disorders is also being examined in Danish children. The immunologic mechanisms that may underlie the non-targeted effects of BCG are being explored in a bovine RSV model in Denmark. The association between vaccines and severe RSV infection is being further examined in both Guinea-Bissau and Denmark (293).

References on RSV:

233, 292, 293, 294, 304, 319, 364, 365

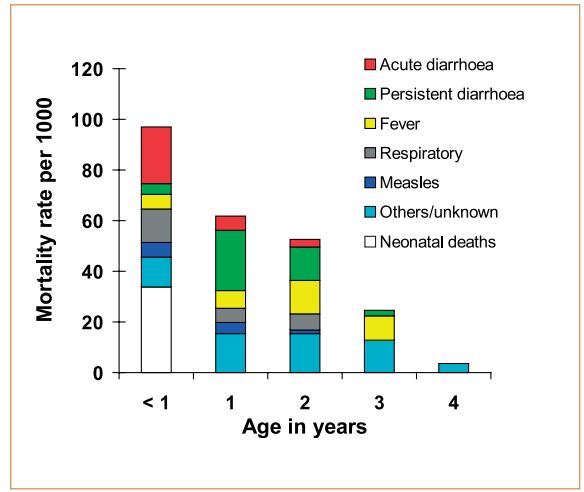
Diarrhoeal diseases research

Background

Diarrhoeal diseases are leading causes of child mortality and morbidity in Guinea-Bissau. To determine the epidemiology of diarrhoea in early childhood, we launched a series of longitudinal studies from 1987. The studies addressed morbidity, mortality, aetiology, risk factors, and the interaction between nutritional status and diarrhoea. A particular aim was to study the epidemiology of persistent diarrhoea, defined as diarrhoea with a duration ≥ 2 weeks.

Results

The under-five mortality in the study area, Bandim 2, was 243 per 1000, and diarrhoea was the cause of 31% of these deaths. Among the diarrhoeal deaths, 53% was due to persistent diarrhoea (82). The average child experienced 9 episodes of diarrhoea per year (175). Diarrhoeal episodes had a negative impact on ponderal and linear growth, and this impact could be seen beyond the acute phase (249).



Breastfeeding protected against diarrhoea well into the third year of life without any detrimental effect on weight or height (117,142,172). Indeed, mothers decided to breastfeed children with low weight longer than children with better nutritional status, and weaning was associated with a relative mortality of 3.5, independent of age (117). Other risk factors for diarrhoea included gender (boys had higher risk), diarrhoea in the previous fortnight, and being cared for by someone else than the mother. Hygienic and environmental factors such as type and ownership of water supply and storage of prepared food for later consumption were significantly associated with diarrhoeal rates. Finally, maternal education, age of family head, and ethnic group were determinants for diarrhoea (175).

Public health consequences

Management of persistent diarrhoea is an important part of a clinical strategy for the reduction of diarrhoea-related mortality and improvement in nutritional status. Programmes for diarrhoeal disease controls focused until recently on the promotion of oral rehydration salts for acute diarrhoea. The community studies from Guinea-Bissau showed that the problems are more complex, and that it is necessary to develop strategies for the prevention and differentiated management of children with acute and persistent diarrhoea. The studies also suggest that environmental interventions may reduce morbidity and mortality from diarrhoea.

Future perspectives

These investigations opened up for several focused studies on pathogens such as Cryptosporidium, rotavirus, V. cholerae and enterotoxigenic Escherichia coli, improved management of acute and persistent diarrhoea, breastfeeding, the health care seeking behaviour, and health care systems (refer to the specific sections for further information)

References on diarrhoea:
36, 63, 82, 100, 101, 110, 113, 115, 117, 142, 148, 151, 155-7, 162, 166, 167, 172, 175, 187, 206, 208, 215, 219, 221, 226, 228, 240, 242, 247-9, 251, 257, 265, 295, 306, 309, 311, 327, 329, 331, 335, 353, 354, 367, 368, 375

Cryptosporidium spp.

Background

In Guinea-Bissau, major pathogens causing diarrhoea comprise rotavirus, different types of diarrrhoeagenic E. coli, Shigella spp. and the parasite Cryptosporidium spp. (110, 331). In a series of studies we examined the epidemiology of cryptosporidiosis. The longitudinal design enabled us to address features such as long-term impact on nutritional status and survival, which were largely unknown from most other reports.

Results

The prevalence of cryptosporidiosis was 15% in cases of persistent diarrhoea, compared with 6% in diarrhoea lasting less than two weeks (100,110). Approximately one third of symptomatic cases of cryptosporidiosis progressed to persistent diarrhoea (110), and prior cryptosporidium-infection was found to be a risk factor for persistent diarrhoea in another study (219). The data from Guinea-Bissau did not suggest that children who experienced cryptosporidiosis had lower weight or height prior to infection. Cryptosporidiosis in infancy, however, had a marked and lasting effect on ponderal and linear growth when the infection was acquired during infancy (162). The data from Bissau corroborate the notion that cryptosporidiosis is a cause of malnutrition rather than the idea that malnutrition is an important risk factor for infection with Cryptosporidium. Infants who had cryptosporidiosis had a three times higher mortality than non-infected infants (100). In a nested case-control study (113) the following risk factors were identified: keeping of pigs and dogs in the household, storage of cooked food for later consumption, and being a boy. Breast-feeding was protective.

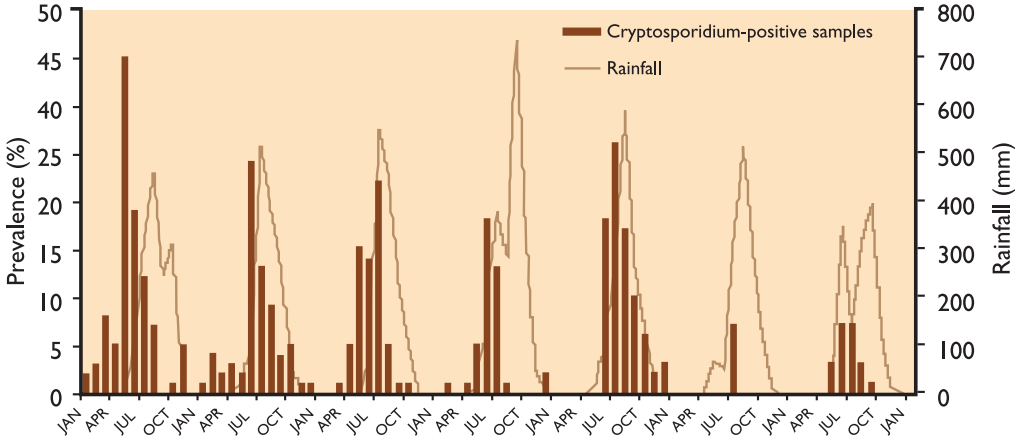


Figure
Monthly prevalence of Cryptosporidum vs monthly rainfall from January 1991 to December 1997 (from ref. 265).

Public health consequences

The acute and long-term excess mortality following cryptosporidiosis in infancy underlines the severity of cryptosporidiosis in otherwise healthy children. This excess mortality was not related to immunological deficiencies (115), and there was no other evidence of severe pre-infectious morbidity. Cryptosporidium is an agent that warrants much more attention.

Future perspectives

The concept of Cryptosporidium has changed from that of a biomedical curiosity to a major cause of diarrhoea in humans, including severe and persistent childhood diarrhoea. Unfortunately, control of cryptosporidiosis remains difficult. The infectious dose is small and the oocyst is resistant to most commonly used disinfectants, including chlorine. Hence, effective control of cryptosporidiosis by hygienic and environmental measures is difficult to achieve. Waterborne transmission is likely to be important, and animals as well as humans may serve as a reservoir. Until an effective chemotherapy has been identified, children with cryptosporidiosis will have to be managed as other children with diarrhoea. It has to be determined whether improved case-management of diarrhoeic children, particularly nutritional support for those with persistent diarrhoea, may to any significant degree reduce acute and delayed mortality from cryptosporidiosis and decrease nutritional insult.

References on Cryptosporidium:
63, 100, 110, 113, 115, 162, 219, 249, 265, 331

Case-management of acute and persistent diarrhoea

Background

In the search of an ORS formulation that would reduce the duration of diarrhoeal episodes, hospital and laboratory studies have suggested that low osmolarity ORS is beneficial compared to WHO ORS. Persistent diarrhoea, i.e. diarrhoea that lasts at least 14 days, has been recognized as a distinct type of diarrhoeal disease which is associated with increased mortality risk, increased diarrhoea-burden, and an increased risk of nutritional insult. With current standards for treatment, persistent episodes are frustrating, expensive and difficult to manage. Recent hospital-based studies from developing countries indicate that simple dietary regimes might be effective.

Results

In a double-blind randomized controlled trial, nested in a prospective cohort study of diarrhoeal disease, it was examined whether the use of low osmolarity ORS in comparison with WHO ORS was advantageous in the case-management of acute diarrhoea in the community. There was no difference in the efficacy of low osmolarity ORS and WHO ORS assessed by duration of diarrhoeal episode. However, the mothers tended to prefer the low osmolarity ORS and a reduced duration of diarrhoeal episodes was seen among non-breastfed toddlers (i.e. children aged 12-30 months) [221].

An algorithm for the hospital-based management of persistent diarrhoea was modified for use in the community. A traditional weaning food, a millet gruel, was identified from a cross-sectional survey [228]. The gruel was modified

to fit the dietary requirements for catch-up growth. We conducted a controlled population-based community study examining the short- and long-term effect on growth of dietary treatment of persistent diarrhoea. There was a short-term and a long-term weight gain and a long-term improvement in linear growth due to dietary treatment and multi-micronutrient supplementation (including Zinc) in children with persistent diarrhoea [251].

Public Health Implications

Reduced osmolarity ORS is safe and efficacious to use in the community. Following recommendations from an expert meeting in New York in 2001, WHO decided to encourage the use of low osmolarity ORS. The treatment algorithm reduces the nutritional insult associated with persistent episodes. The treatment algorithm may well be used in health centre settings. It was effective for nutritional rehabilitation of malnourished children during the war in Guinea-Bissau 1998-1999.

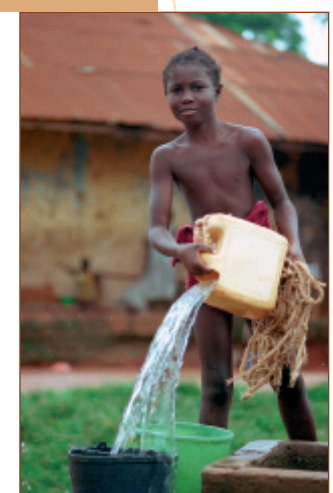
Future perspectives

It should be monitored if the recommendation to use low osmolarity ORS, as anticipated, will be associated with increased user rate, decreased mortality from diarrhoeal disease and decreased need for hospitalization and intravenous rehydration. We are currently doing a long-term follow-up of children with persistent diarrhoea to see whether the beneficial effects on growth are sustained.

References on case-management:
221, 228, 251, 355

Additional growth in treatment group	Intervention period	Follow-up
	Estimate 95% CI	Estimate 95% CI
Weight (gram/week)	61.5 (49.2, 73.8)	12.5 (7.7, 17.3)
Knee-heel length(mm/year)	2.7 (-4.6, 10.0)	7.5 (4.8, 10.2)
Height (cm/year)	Combined for the intervention period and follow-up	0.65 (0.11, 1.19)

Table
Growth in the treatment group (n=70) exceeding that of the control group (n=71), in the intervention period(median 17 days) and during follow-up (median 6.6 months). The estimates are shown combined for nutritional status and age and are controlled for age, sex, nutritional status (assessed by weight-for-age or height-for-age) at inclusion



Infections with enterotoxigenic Escherichia coli (ETEC)

Background

We undertook an epidemiological study of enteric infections and diarrhoea among young children living in Bissau. One of the goals of this study was to describe the natural history of enterotoxigenic Escherichia coli (ETEC) infections (309) and to estimate the protection that natural ETEC infections induce against new infections to create an evidence base against which ETEC vaccine trials could be assessed (329). Infections with ETEC are common causes of diarrhoeal morbidity and mortality among young children living in developing countries. In the present longitudinal cohort study, we followed 200 children from birth until 2 years of age with weekly stool specimen collection. The specimens were collected irrespectively of whether the children had diarrhoea. In total, we analysed 11,987 stool specimens for enteric bacteria, parasites, and rotavirus. Identification and characterisation of pathogenic E. coli, including ETEC (327), was performed by DNA-DNA colony hybridisation.

Results

We identified several small ETEC epidemics (figure). These epidemics occurred mainly during the rainy season, and to a large extent with strains that were positive for the human heat-stable toxin (STh) (309). We also found that infections with STh-positive ETEC, but not with strains positive for the porcine heat-stable toxin (STp), were associated with diarrhoea. ETEC that were only positive for heat-labile toxin (LT), on the other hand, seemed to represent a mixture of both pathogenic and non-pathogenic ETEC (309). We found that exposure to LT induced a 45% (95% CI -1 to 70) protection against subsequent symptomatic infections with LT-positive

ETEC, and that infections induced a 47% (95% CI 12 to 69) protection against new infections with ETEC that were positive for the same toxins and colonisation factors (CFs). CFs are protein surface structures that anchor ETEC to the intestinal wall. Exposure to CFs, however, did not induce a protective immunity against new infections with strains that carried the same CFs.

Public health consequences

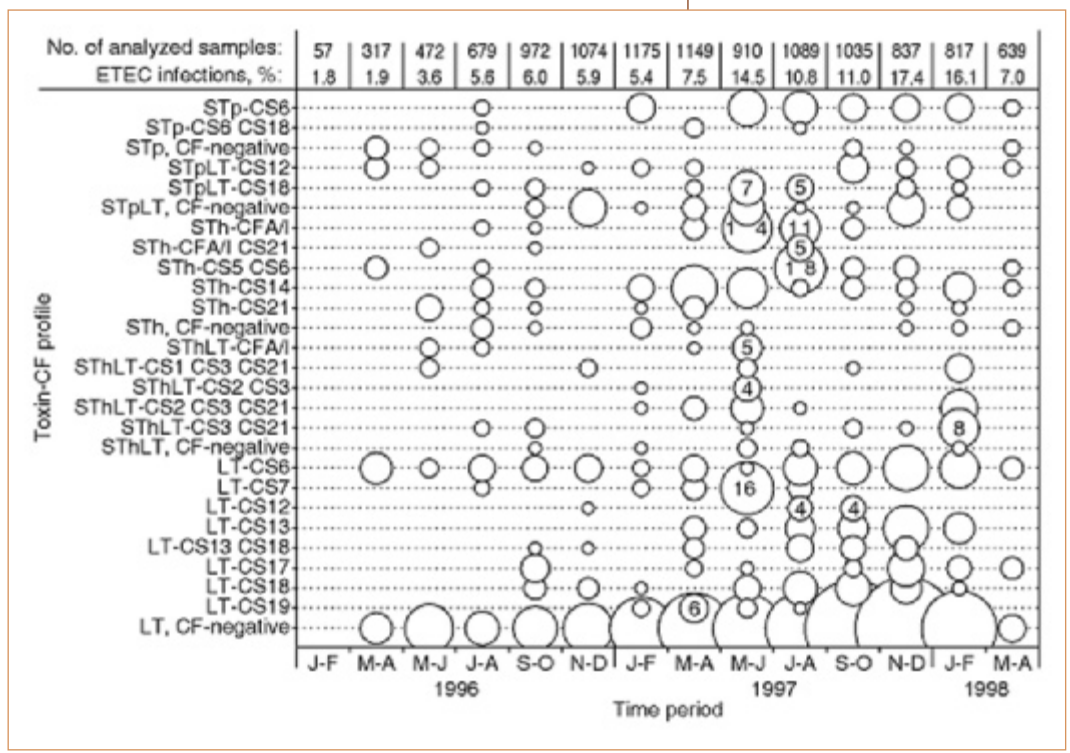
The ETEC population seems to include some strains (mainly STh-positive) that are substantially more pathogenic than others. Vaccine development, treatment regimes, and efforts to reduce transmission should primarily focus on these ETEC to reduce ETEC morbidity and mortality. The ETEC vaccine development has largely focused on inducing protective immunity against ETEC diarrhoea by immunising with CF antigens. Results from our study indicate that CF-based vaccines might not provide an adequate protection against ETEC diarrhoea for breastfed children living in developing countries.

Future perspectives

We recently described the natural history of infections with other enteropathogenic microorganisms, including other types of E. coli that these cohort children experienced (331). Apart from studying the clonal relatedness of the different types of ETEC(353) and studying the risk factors for stunting and weight-loss caused by infections with different micro-organisms (354), we plan to describe the aetiology of persistent diarrhoea, and to do in-depth molecular epidemiological studies of other microorganisms that we isolated during our study, including other types of pathogenic E. coli.

References on enterotoxigenic coli (ETEC): 309, 327, 329, 331, 353, 354

ETEC infections observed between Jan. 1996 and April 1998.
The area of each circle is proportional to the number of infections divided by the number of analysed specimens. Numbers of infections are depicted inside a bubble to indicate that the infections were observed during an epidemic.



Rotavirus

Background

Rotavirus is the most common cause of severe diarrhoea in young children worldwide. Almost all children are infected by the age of two years. Like any other pathogen transmitted primarily by the faecal-oral route, rotavirus spreads most efficiently under conditions of overcrowding and poor hygiene. Although rotavirus affects rich and poor alike, the death toll is substantially higher in low-income countries, especially among socially deprived populations with suboptimal access to adequate health care.

The strategy for rotavirus vaccine development is to mimic the immunity provided by natural rotavirus infection. However, existing protection estimates range widely. Rotavirus vaccines are designed to provide specific immunity against the most prevalent viral surface proteins. As there is a substantial geographical and temporal variation in the distribution of the different rotavirus serotypes, extensive rotavirus strain surveillance is required to guide the incorporation of relevant antigens in future vaccines. To address these issues, data on rotavirus pathogenicity, morbidity, mortality, strain diversity and on naturally acquired immunity were generated during extensive epidemiological studies in Guinea-Bissau, one of the world's poorest countries.

Results

Rotavirus diarrhoeal burden: Although rotavirus infections were confined to four epidemic months in the dry season, at least 74% of all children experienced such infections before their second birthday (see Figure). Of all diarrhoeal agents identified, rotavirus was the most important contributor to the diarrhoeal burden among 0-2-year-old children. Rotavirus had the highest pathogenicity and highest population-attributa-

ble risk of all diarrhoeal pathogens. From hospital-surveillance of rotavirus disease during a one-year period from 2001 to 2002, we found that rotavirus was associated with a case fatality rate of 7%. During the two and a half month epidemic period, 32% of diarrhoeal cases were due to rotavirus infection, and the rate of intra-hospital acquired disease was 0.19 (95% confidence interval [CI]= 0.10-0.36). Children less than two years of age constituted almost all the admitted cases of rotavirus (92%), with only one case identified in a child less than two months old (366).
Estimates of the yearly rotavirus death rates in Guinea-Bissau based on studies in the late 1980s found the rotavirus death rate to be 3.4 per 1000 in infants and 0.8 per 1000 in children aged 1-4 years. These estimates were applied to the approximated Sub-Saharan child population, and a total of 145,000 deaths due to rotavirus were estimated to occur yearly in this region (247).

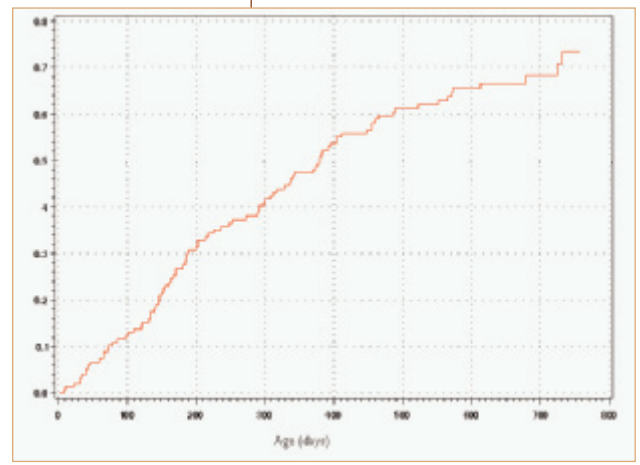
Molecular epidemiology:
Characterization of the strains revealed a wide range of different VP7 (G) and VP4 (P) genotype combinations and a substantial year-to-year shift in predominating genotypes. The globally most common strains were underrepresented whereas G2P[6] was frequently identified. G8 and G9 strains were also commonly identified, often in combination with several different genotypes. Infections with more than one strain were frequent, suggesting a considerable potential for reassortance of gene segments within this population. Sequencing of non-typeable strains revealed silent single point mutations at the primer-binding sites and use of sequencing as well as uncommon and/or degenerate primers dramatically reduced the fraction of non-typeable strains.

Immunity:
Rotavirus infection conferred a 70% and 52% protection against rotavirus diarrhoea and re-infection, respectively, supporting current vaccine development strategies. Analyses of immunity in a time-dependent model suggested that the immunity conferred by a primary infection declined substantially from one season to the next (295). These findings underscore the need for follow-up for a minimum of two seasons subsequent to the evaluation of a vaccine candidate, in order to estimate any such loss of protection.

Public health implications
Our studies corroborate the idea that rotavirus is an important cause of diarrhoeal disease in children less than two years of age, even in areas where the incidence of infections with other enteropathogens is high. Immunisation with an effective vaccine, which mimics the protection conferred by natural infection, is probably the best approach to reduce rotavirus morbidity and mortality and is likely to have a substantial public health impact in developing countries.

References to Rotavirus:
110, 240, 247, 295, 306, 311, 335, 366, 367, 368

Estimated cumulative incidence of primary rotavirus infections in a birth cohort of 200 children followed for a maximum of 2 years in Guinea-Bissau, 1996 to 1998.



Cholera

Since 1970, when the most recent cholera pandemic stroke West Africa, epidemics have been registered cyclically. In Guinea-Bissau, the first cholera epidemic was reported in 1986 and 1987, followed by more widespread and longer lasting epidemics in 1994, 1996, and 2003. The capital was the most affected area. During these epidemics case-referent studies were performed to etermine risk factors for cholera disease. These studies showed an association between limejuice and protection against cholera disease

Since limejuice is widely available and cheap, we envisaged the possibility of its use in public health prevention programmes. Thus, laboratory experiments with limejuice were carried out to determine its effect on V. cholerae in water and food taking into account the sources of water used, storage, and handling.

Results

Risk factors for cholera: In two epidemics, the risk of cholera disease was associated with storage of drinking water in open containers (OR = 4.4, 95%CI = 2.21–8.74), while drinking water from standpipe was associated with protection (166,242). A paradoxical observation was that boiled water increased the risk of cholera in our setting (OR=3.40, 95% CI = 1.50-7.68). Boiled water is likely to be re-contaminated. Some sauces, such as tomato sauce and curdled milk, eaten with rice were protective. Eating with the hand from the same bowl increased the risk of cholera, while washing hands before the meal was protective (166). The pattern of cholera morbidity varied between ethnic groups, and socioeconomic status (house and household conditions, and ownership of electrical appliances) was inversely associated with cholera disease (257).
The effect of limejuice on V. cholerae: In both

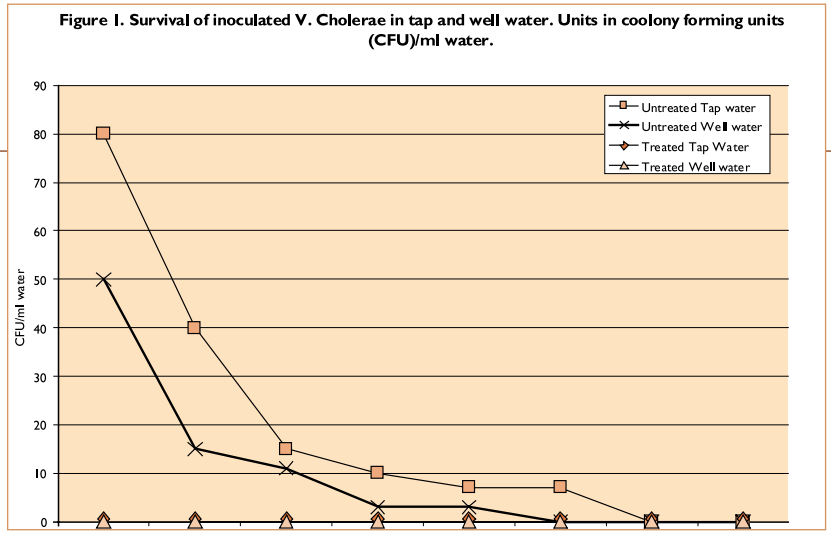


Figure 1
Survival of inoculated V. Cholerae in tap and well water. Units in coolony forming units (CFU)/ml water

epidemiological studies, limejuice was associated with protection (OR= 0.31, 95%CI=0.17-0.52) (242) and later in laboratory experiments (187,257). V. cholerae could not survive in water and food treated with limejuice, but survived well for at least 24 hours in water and food not treated with lime (257).

Public health implications and future perspectives

Cholera disease seems to depend not only on social and economic conditions, but also on biological factors. These factors should always be taken into account when designing the interventions. For example, boiling water is widely recommended, but in poor settings, as in Guinea-Bissau, where a major part of the population store water in clay pot, this apparently effective measure would be of no use, and the risk of infection remains due to re-contamination of the water through introduction of the hand into the water. In this situation, limejuice might be a better option since it kills the pathogenic agent and its action is maintained at least for the length of time water is usually stored in the home. Furthermore, limejuice is not expensive and well accepted in the communities, being a common ingredient in cooking among most ethnic groups. Although limejuice is already recommended during epidemics of cholera, its real impact in practice should be determined in future studies.

References on Cholera:
151, 166, 181, 187, 242, 245, 257

Breast-feeding practices

Background

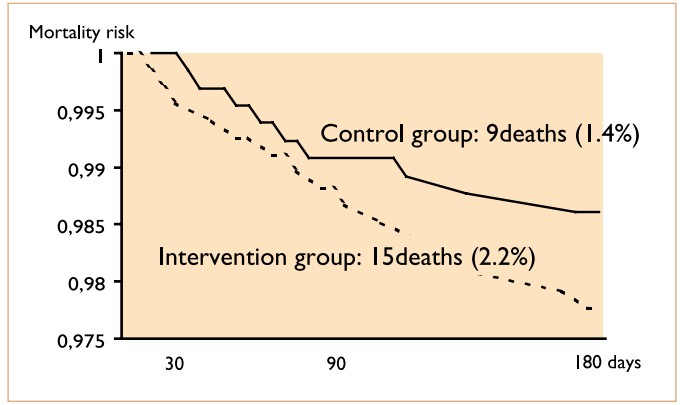
In environments with a high pressure of infectious diseases, breast-feeding is crucial for preventing morbidity and mortality among infants and children. WHO promotes breast-feeding by recommending all infants to be breastfed exclusively for the first 6 months of life and to continue breast-feeding for at least two years. Breast-feeding is promoted uniformly throughout the world despite a great variation in breast-feeding practices in different countries. Most studies addressing the relationship between breast-feeding and infant and child health originates from countries with different breast-feeding patterns and with different mortality risk than in Africa. It has also been debated to what degree breast-feeding protects beyond infancy. In Guinea-Bissau we have studied the impact of breast-feeding and related it to the recommendations given by WHO.

Results

Almost 100% of mothers in Guinea-Bissau initiate breast-feeding after delivery and the high infant mortality cannot be described to early cessation of breast-feeding (5,208). Water, milk and solids are introduced very early and the median length of breast-feeding is almost 22 months. In follow-up studies we have demonstrated that the length of the breast-feeding period is independently associated with the mother's reason for weaning as well as with the subsequent mortality risk (142, 315). Prolonged breast-feeding was shown to be of benefit for infants in Guinea-Bissau. Compared with breastfed children, diarrhoea incidence was higher among weaned children both in 1 year olds (RR 1.41 (1.23-2.15)) and in two years olds (1.67 (1.29-2.15)) and children aged 12-35 months had a 3.5 (1.4-8.3) times higher mortality than breast-fed children (117). During the civil war in

Guinea-Bissau, we demonstrated that mortality in weaned compared with breastfed children aged 9-21 months was five times higher (MR = 4.96 (1.4-16.6)), indicating the effect of prolonged breast-feeding to be particularly strong in an emergency situation with increased risk of infections (341).

In a follow-up study of 1,331 infants, we did not find any difference in morbidity and mortality between exclusively breastfed babies and infants who were introduced early to water and weaning food. On the contrary, there was a tendency towards a higher mortality among infants who were introduced late to water (157). This same tendency was observed in a study including 1,154 infants followed from birth to 6 months of age who were randomised to encouragement of exclusive breast-feeding or normal practice (figure 1).



Public Health implications

International recommendations on breast-feeding are generally believed to be beneficial for all infants. However, our results indicate that promotion of exclusive breast-feeding may not have the expected beneficial effect on infant morbidity and mortality in Guinea-Bissau. Health interventions should be evaluated in the settings where they are going to be implemented. The focus of breast-feeding promotion should be to avoid premature weaning due to the mother becoming pregnant or due to mother or child becoming ill, to maintain breast-feeding for at least 2 years and to avoid introduction of bottle feeding. This is especially important in emergency situations.

Future perspectives

Further studies should examine the impact on both growth and susceptibility of introducing weaning food and liquids when breast milk still constitutes the major part of the infant's diet.

References on breast-feeding practices:
3, 5, 80, 92, 117, 119, 128, 142, 157, 172, 175, 181, 208, 221, 249, 315, 341

Health-seeking behaviour and quality of care

Background

Behavioural studies preceding a diarrhoeal disease intervention study revealed a wide range of weaknesses in the way the health sector managed severely ill children. Initial studies focussed on knowledge, attitude and practices in terms of home treatment of diarrhoeal diseases.

Results

Care seeking and severe illness:
The care-seeking behaviour of mothers of 125 children who died at age 1-30 months in Bandim was investigated by verbal autopsy. Overall 93% of the children had been seen at a health centre or hospital during the 2 weeks before death. Time from disease onset to first consultation was shorter for children who died than for matched controls who survived. Only 56 of the 125 terminally ill children were hospitalised; 20 children died on the way to the hospital or in the outpatient clinic and 15 were refused hospitalisation due to lack of hospital beds. Forty-two percent of the hospitalised children were discharged as improved or recovered during the 30 days preceding death (167).

Use of oral rehydration salt (ORS):
Mothers with no knowledge of ORS did not use it during diarrhoea regardless of contact with a health centre; maternal knowledge is an important determinant of whether health personnel provide ORS. Diarrhoea considered to be due to teething was less likely to be treated with ORS (risk ratio = 0.6, 95% CI = 0.5-0.9). The use of ORS was related to number of reported symptoms, the mother being the caretaker, consultations, previous use of ORS, good knowledge of ORS, and having ORS sachets at home (206).

Maternal perception of severity:
The probability of taking the child for consultation increased with the number of symptoms reported by the mother. The appearance of the eyes and how the child breastfed were early warnings recognized best by the mothers. In contrast, there was an 80% reduction in the likelihood of seeking consultation when the mother perceived the diarrhoea to be caused by teeth eruption (n = 96). Children with "teething diarrhoea", however, were just as likely to develop signs of dehydration (148).

Risk for progression to persistent diarrhoea (PD):
Children who still had diarrhoea after 14 days (n = 40, 12.5% of episodes) were regarded as suffering from PD. Tired and rapid breathing (OR = 6.52 (95% CI 1.69-25.1)), mother having to force breast-feeding (OR = 8.01 (2.99-21.5)) and current infection with Cryptosporidium (OR = 5.53 (2.10-14.6)) were the most important independent risk factors for the development of PD (219).

Public Health implications

There is a clear need to improve hospital admission criteria, the recognition of the symptoms of serious illness, and discharge criteria, as well as the implementation of quality assurance systems for health services. Improved health education should focus more on the quantity of ORS needed, early signs of dehydration, treatment of teething diarrhoea, and breast feeding, and address mothers who have no prior knowledge of ORS. Management of diarrhoea may be improved by a more liberal distribution of ORS sachets. The concept of "teething" diarrhoea should be discouraged.

Future perspectives

These studies led to hospital intervention studies. An observational study on the quality of care in the paediatric emergency ward has just been finished together with a study of behavioural and socio-cultural risk factors for child death. A larger scale hospital intervention study involving medical supplies and training of emergency staff is warranted.

References on health-seeking behaviour:
103, 148, 155, 167, 206, 215, 219

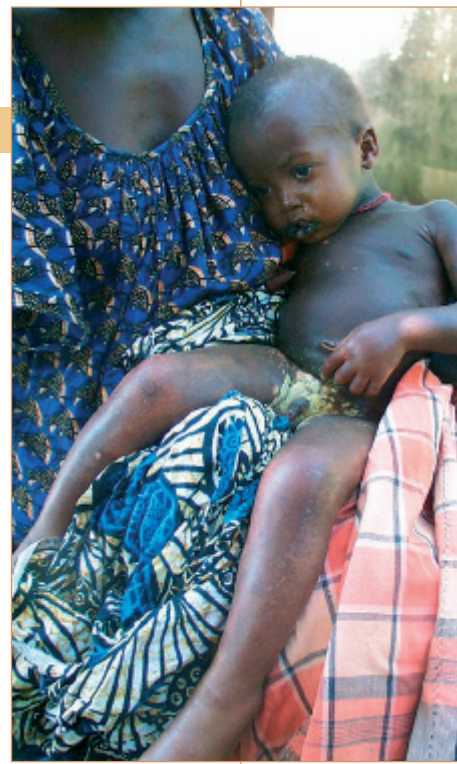
Treatment of Malaria

Background

Malaria remains one of the most important causes of morbidity and mortality in children in most sub-Saharan African countries. Due to the development of resistance, different treatment schedules have been recommended. Therefore it is important to evaluate the usefulness of the "old", cheap anti-malarials and to evaluate the efficacy of treatment schedules used locally.

Results:

Quinine: The importance of the length of treatment giving quinine 10 mg/kg twice a day was evaluated. Significantly fewer children were found to have parasitaemia during the follow-up period following 7 days treatment than following 3 or 5 days (171). A study treating children with 10, 15, or 20 mg quinine per kg bodyweight per day for 7 days showed that 15 mg and 20 mg were equally efficient, whereas 10 mg was too low a dose (223). No difference was found when evaluating the number of daily doses needed for treating children either with 15 mg or 7.5 mg/kg twice a day, or with 15 mg/kg once a day (275).
Chloroquine: treatment with chloroquine in a total dose of 50 mg per kg was compared to the treatment with the standard dose of 25 mg/kg or treatment with sulphadoxine-pyrimethamine. Treatment with 25 mg turned out to be insufficient, whereas 50 mg was as efficient as sulphadoxine-pyrimethamine (299, 301).
Sulfadoxine-pyrimethamine: Treatment with sulphadoxine-pyrimethamine has shown a high cure-rate (299). However, in parasites isolated from children suffering from acute malaria PCR analyses have shown that 45% of the parasites had mutations associated with resistance to pyrimethamine, and 24% had mutations associated with resistance to sulphadoxine (383).



Treatment combining drugs: In a group of children treated for three days with quinine followed by chloroquine the rate of recrudescence was significantly higher than in children treated with chloroquine 50 mg/kg or children treated with sulphadoxine-pyrimethamine (299). The outcome of treatment with chloroquine in a total dose of 25 mg/kg was compared with the treatment with artesunate in combinations with chloroquine. No benefit from combining the two drugs was found (336).

Public Health implications

If the resistance to chloroquine increases further a higher dose of chloroquine could be an attractive possibility as first line treatment of malaria. Sulfadoxine-pyrimethamine should be spared as second drug of choice, as the analyses of the genes in the parasites have shown that a considerable percentage of the parasites already have mutations associated with resistance to the drug. Quinine has to be given for at least 7 days, making it most appropriate as the third line drug. However, if needed it can be given in one daily dose for 7 days for treatment of uncomplicated malaria if resistance to sulphadoxine-pyrimethamine increases even further.
The combination therapies examined have no justification for treatment of malaria in children.

Future perspectives

It is important to continuously evaluate the development of resistance to the treatment recommended by the National Malaria Programme, which at present is chloroquine in a total dose of 25 mg/kg as first line treatment and sulphadoxine-pyrimethamine for treatment failures. If the rate of recrudescence following the initial treatment with chloroquine increases, a different treatment schedule should be considered. The newer anti-malarial drugs are expensive and would at present not be realistic alternatives in a poor country like Guinea-Bissau. An alternative to high-dose chloroquine could be amodiaquine, which is being evaluated at present. Furthermore, a study evaluating rectal artesunate as initial treatment is being prepared.

References on malaria:
171, 200, 223, 275, 299, 301, 324, 336, 382, 383

A national hospital without resources:

Provision of care, case fatality and post-discharge mortality

Background

Few studies from low-income countries have examined the relationship between childhood hospitalisations and community mortality. Linking longitudinal community data to prospectively registered hospital information, we have examined the use of hospital services, the role of hospitals in diseases transmission, risk factors for case fatality, hospital mortality and post-discharge mortality both prior to and during a civil war in Guinea Bissau. Furthermore, we examined the effects of routine vaccinations on in-hospital mortality and post-discharge survival.

Results

Hospitalisation and in-hospital mortality:
Almost 45% of all children in the area were hospitalised at least once before the age of 5 years and every fourth death occurred at the hospital. Overall in-hospital mortality was 12.2 % with differences between age groups and diagnostic groups. Community mortality rates for infants and children under 3 years of age were 110 and 207 per 1000, respectively, during 1991 to 1996 (326).

Post-discharge mortality:
The overall in-hospital and 12-month post-discharge mortality was 20%, and compared with community mortality, the mortality risk was 12 times higher during the first 2 weeks after discharge and remained still significantly higher in the period 3-6 months after hospitalisation (RR = 2.5 (CI95% 1.6-3.8)) (326) (see Table).

Risk factor analyses:
Risk factor analyses were performed for hospitalisation, for community and hospital mortality as well as for post-discharge mortality. The risk factors for hospitalisation did not reflect the risk factors for the hospital case fatality rate, whereas good consistency was found between risk factors for community and hospital-related mortality.

Reduced hospital case fatality during a war:
During the 12-month war period, the hospital CFR and post-hospital mortality were significantly reduced (0.68 and 0.57, respectively). The decline could not be explained by changes in recruitment, discharge policy or general changes in mortality and may have been due to better availability of drugs and more prompt treatment due to humanitarian aid during the war (374).

Routine vaccinations and hospital mortality:
Immunisations had effects on in-hospital mortality which cannot be explained by the expected disease specific effects of particular vaccines; a strong protective effect of measles vaccine on overall in-hospital mortality (MR = 0.51 (CI95% 0.27-0.98)), being strongest for girls, and a significantly higher CFR for DTP vaccinated girls than for DTP vaccinated males (MR=1.63 (CI95% 1.03-2.59)) (372). When DTP was lacking in Bissau during several months, the case fatality was markedly lower for children who had received only OPV than for children who had received both DTP and OPV (342).

Public health implications

An improved ability to deal with severe childhood illness might have a considerable effect on the overall child mortality in poor communities close to a hospital. Main targets for interventions should be a prioritised management of severely ill child at arrival and of high-risk children at discharge, as well as improvements in staff dedication and morale. Emergency treatment should be kept free of charge to avoid further in-equity by increased mortality among children of poor families.

Excess mortality during time after discharge compared to community mortality.

Time after discharge	All children Mortality Rate ratio; 95 % CI		Excluding those who fled Mortality Rate ratio; 95 % CI	
183 – 365 days	1.17	(0.68 - 1.20)	1.18	(0.69 - 2.01)
91 – 182 days	2.50	(1.63 - 3.84)	2.53	(1.65 - 3.88)
31 – 90 days	3.70	(2.51 - 5.45)	3.34	(2.22 - 5.03)
15 – 30 days	6.52	(3.91 - 10.90)	6.20	(3.65 - 10.54)
=14 days	11.67	(8.10 - 16.83)	7.59	(4.81 - 11.98)
*0-365 days	3.36	(2.72 - 4.16)	2.91	(1.33 - 3.64)
Community	1.00		1.00	

Pediatric Department, Hospital Nacional Simao Mendes, Bissau, Guinea Bissau. Children from Bandim and Belem 1991-96 Poisson regression model. * Overall estimate. Controlled for age, sex, suburb, ethnic group, year, season, mothers education, type of house and twinning status.

Future perspectives

Hospital registration is an important tool for monitoring quality of care and to evaluate the impact of clinical interventions and consequences of cost recovery systems. Studies on the impact of follow-up regime after discharge and availability of emergency medicine have been implemented and are awaiting analysis. A larger scale hospital intervention study involving medical supplies, training of emergency staff and implementation of IMSC-based case-management regimes is warranted but unlikely to be funded. It is planned to examine whether administration of rectal artesunate in the waiting room may reduce the severity of malaria cases. The changes in hospital case fatality rates associated with different vaccines were consistent with community findings and warrant further research to understand and control the immune stimulatory effects of routine vaccines.

References on hospitalisations:
16, 103, 167, 326, 342, 372, 373, 374

Maternal Mortality

Background

To describe the epidemiology of maternal mortality in rural Guinea-Bissau, we conducted a prospective cohort study of 15,844 women aged 15-45 years. To examine level and causes of pregnancy-related mortality, we developed a structured interview with filter questions, which was applied to all deaths occurring during the study period. The cause of death was ascertained with a series of diagnostic algorithms for the most common causes of maternal mortality, including postpartum haemorrhage (PPH), ante partum haemorrhage, puerperal infection, obstructed labour, eclampsia, abortion, and ectopic pregnancy.

Results

Compared with a reference mortality 7-12 months after delivery, women who had given birth within 6 weeks had a 15.9 times higher mortality (95%CI = 9.8 – 27.4). From day 43 to 91 the mortality was still significantly elevated (RR= 2.8; 95% CI = 1.4 – 5.4) (see Table). Of 350 deaths of women of fertile age, 32% were maternal. The most important causes were postpartum haemorrhage (42% of 112), obstructed labour (19%), and puerperal infection (16%). Reproductive age mortality rate was 581/100,000 person-years-at-risk (95% CI: 521 – 642). The maternal mortality rate of 186 death per 100 000 pyrs (95% CI: 152 –221) constituted 32% of the reproductive age mortality. The maternal mortality ratio was 822 per 100,000 live births (95% CI: 671 – 974). The total

Interval	Person-days at risk	Deaths	Deathrate / 100,000 person-days	Rate Ratio (95%LRC)	
					Adjusted for region*
0-42 days	580 581	82	14.13	15.93 (9.80 - 27.36)	15.92 (9.8-27.35)
43-91 days	653 911	16	2.45	2.76 (1.39 - 5.42)	2.76 (1.39-5.42)
92-182 days	1 146 791	16	1.39	1.57 (0.79 - 3.09)	1.57 (0.79-3.09)
183-365 days	2 029 652	18	0.89	1	1

Table
Person-days at risk, deaths, crude death rates and rate ratios in different time intervals after termination of pregnancy

fertility rate was 6.5, implying that 1 woman in 19 suffers a pregnancy-related death.

Pregnancy with twins or triples tripled the risk of maternal death (OR=3.4 [95%CI: 1.3-7.5]). The maternal mortality ratio increased with the distance from the regional hospital (OR >25km=7.4 [1.6–132]). Delivering a stillborn foetus increased the risk of subsequent maternal death (OR=5.3 [2.8–9.4]), and women living in the Gabu region had a higher mortality than those living in Biombo (OR=2.5 [1.3–5.1]). Maternal mortality by region is shown in figure 1. No category of age or parity exhibited increased risk of maternal mortality. Positive predictive values never exceeded 3% for any of the significant risk factors.

Public health consequences

Where living conditions are harsh, pregnancy and delivery affect the health of a woman for a prolonged time after termination. Using the WHO definition of maternal deaths within deaths 42 days of delivery may underestimate the pregnancy-related reproductive age mortality. Extending the definition to include deaths within 3 months of delivery may increase current estimates of maternal mortality by 10-15%. Maternal mortality in Guinea-Bissau is among the highest in the world. Intending to reduce maternal mortality, the screening approach of antenatal care is of limited value. Age and parity should not be used as selection criteria for transfer of otherwise healthy pregnant women to higher-level health institutions. Twin pregnancy seems to be the only operational risk factor. Stillbirth should be recognized as a serious sign of maternal illness. Availability of obstetric care plays a central role in the efforts to reduce maternal mortality. Regional differences must be studied further.

The verbal autopsy (VA) used in the present study left 30% of the deaths unclassified without a specific diagnosis, but in contrast to methods using a panel of physicians to establish cause of death, the present VA is feasible in areas where health workers have only minimal training.

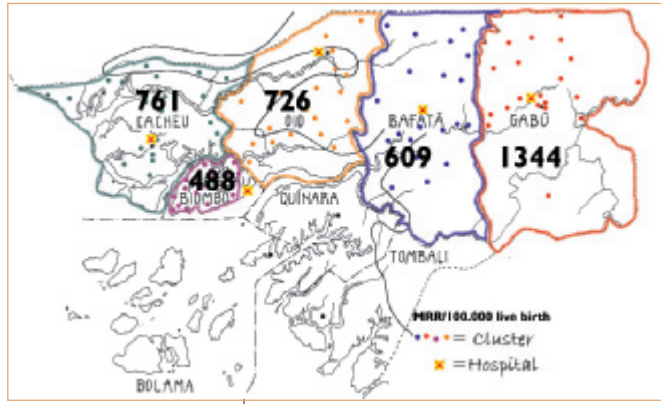


Fig. 1. Maternal mortality by region.

Future perspectives

Postpartum haemorrhage was the most frequent pathology behind the high mortality. As other studies from low-income settings have found atony of the uterus to be the most important underlying condition behind PPH, we have initiated an intervention study of an uterotonicum, Misoprostol. This prostaglandin E1 analogue can be administered orally or rectally and stored at room temperature for years, an obvious advantage compared to the traditional forms of intravenously administered oxytocics in a low-income setting.

References on maternal mortality:
203, 207, 277, 300, 344, 350, 352

Motherless children in rural and urban areas of Guinea-Bissau

Background

In developing countries, the high incidence of maternal mortality has rendered numerous infants and children motherless. The numbers of motherless children will continue to increase, particularly as a consequence of the increase in prevalence of HIV-1 and tuberculosis among women in African countries. The number of children who are orphaned will more than double by 2010. In parts of Africa 20 to 37 percent of children under 15 years will have lost one or both parents, in most cases as a result of the AIDS epidemic. African children have been hardest hit by the AIDS epidemic. This study investigated the mortality, breastfeeding and social situation among motherless children in urban and rural areas of Guinea-Bissau.

Results

A historical cohort study was set up in urban and rural areas in Guinea-Bissau. Motherless children were selected from two study cohorts followed by demographic surveillance since 1990. We examined and interviewed the relatives of 192 motherless children from the urban cohort and 128 from the rural areas as well as a total of 807 controls. Controlling for significant background factors, motherless children had a markedly higher mortality than controls in both urban (mortality rate ratio (MR) 2.32 (1.11-4.84)) and rural areas (MR=4.16 (2.79-6.22)). All excess deaths occurred among children under two years of age when their mother died (Table 1). Since nearly all Guinean children are breastfed until two years of age, premature weaning may be one of the major causes of the higher mortality observed among motherless children. Few motherless children had been provided with surrogate breastfeeding.

There were few differences between surviving motherless children and control children in nutritional status, use of health care services, school attendance, quality of housing, household chores, and clothing. Motherless children were observed to have moved more often, and were more likely to live in small families, often with an older grandmother.

Public health implications

In conclusion, for orphans in Guinea-Bissau, a low-prevalence HIV community, as long as the extended family system functions, only the youngest orphans who should have been breast-fed may have increased risk of mortality. So far, in Guinea-Bissau, the extended family system appears to be capable of handling orphans in a socially non-discriminatory fashion. The system of extended families may be particularly well functioning in the West-African community compared with the rest of Sub-Saharan Africa.

But no matter how well functioning the extended family systems are, they will be stretched to the limits by catastrophes like the AIDS epidemic, war or migrations.

Future perspectives

With the expected rise in the number of orphans in coming years, the social and financial coping mechanisms within the extended family system may well be stressed. Different options in the response to the orphan crisis, such as non-familial adoption or community-based orphan visiting and healthcare programmes may have to be considered, together with saving the lives of the parents through access to antiretroviral therapies.

References on orphans: 350, 352

	Bissau			Rural areas		
Age *	Orphans deaths/pyrs	Controls deaths/pyrs	MR (95%-CI)	Orphans deaths/pyrs	Controls deaths/pyrs	MR (95%-CI)
0-30 days	1/0.6 [11]	2/1.2 [21]	0.95 (0.1-10.5)	8/1.7 [28]	3/5.5 [79]	8.90 (2.4-34)
31-182 days	3/4.8 [16]	4/8.8 [29]	1.38 (0.3-6.2)	14/11.0[41]	7/48.3 [148]	8.81 (3.6-21.8)
6-11mo	6/5.7 [18]	1/12.8 [34]	13.48 (1.6-112)	9/13.3 [37]	14/81.0 [196]	3.93 (1.7-9.1)
12-23 mo	2/15.9 [26]	2/39.8 [60]	2.51 (0.4-17.8)	10/29.6 [45]	9/196.0 [247]	7.36 (3.0-18.1)
24-35 mo	1/27.1 [40]	1/55.8 [81]	2.06 (0.1-33)	0/38.7 [48]	13/224.0 [281]	-
36-59 mo	1/87.9 [70]	1/163.2 [122]	1.86 (0.1-29.7)	5/109.7 [80]	10/560.8 [390]	2.56 (0.9-7.5)
60 mo-18 years	4/622.0 [156]	4/964.1 [246]	1.55 (0.4-6.2)	0/68.0 [58]	3/321.5 [265]	-
Total	18/764.0	15/1245.7	2.37(1.2-4.8)**	46/271.9	59/1437.2	4.16(2.8-6.2)**

Pyrs = Person-years of observation; MR = Mortality rate ratio ; CI = Confidence interval; mo = months; [ ] = Number of children contributing to the age interval – a child can contribute to more than one interval; *) Age during follow-up;
**) Corrected for age, sex, and residence in a Cox proportional hazards model

Table
Mortality rate ratios between orphans and controls in Bissau and rural areas

Immunological markers, susceptibility and resistance

Background

The observation on the strong effect of measles vaccination had suggested that measles infection was associated with long-term immunosuppression producing delayed excess mortality. To document this process we needed a simple test for T-cell subsets, which could be used under conditions where there was no laboratory infrastructure. As a result the immuno-alkaline phosphatase staining method was adapted to tropical conditions (58).

Results

Compared with the T-cell staining methods in use in the mid-1980s, the immuno-alkaline phosphatase method was much cheaper and could be used under conditions where there was virtually no laboratory infrastructure and most importantly, samples could be stored for long to be analysed when convenient, whereas the flow-cytometry samples had to be analysed with very short delay (58). The immuno-alkaline method produced results were very strongly associated with flow-cytometry (136,176). Since the method only needed a small amount of capillary blood it was usable under field conditions. Hence, it became possible to use the method in relation to many different infections, including HIV-2, malaria, diarrhoea, and measles, but also to describe general patterns of T-cell subsets among children according to age, sex and season (169). The original purpose had been to document immunosuppression and delayed excess mortality among previous measles cases. We therefore started a case control study during small epidemics in Bissau in 1988 and in Senegal in 1992 (144, 197). Contrary to expectation there was no immune suppression beyond 2 months after infection and, if anything, convalescent cases had increased CD4

levels (197). The measles cases that had survived the acute phase actually had lower mortality than children who had not been infected. At the same time it was possible to document that there was no significant immune suppression after high-titre measles vaccination (112). T-cell subsets vary strongly during the acute phase of infection (197), but there is no indication that T-cell levels in general are correlated with survival. However, we continued the attempt to identify immunological methods and markers, which are sufficiently simple to be used under field conditions such that they can be used for a large number of individuals and therefore can be related to mortality. Thymus scanning had been used in Denmark to document that breastfed children had larger thymus (190). We were able to document that thymus size at birth is strongly associated with survival in infancy, in fact better associated with survival than birth weight (289). Thymus size during infancy is also associated with survival.

Interestingly, it turned out that both BCG-scar and positive tuberculin reactions are strongly associated with better child survival (267, 320).

Public health implications and future perspective

The insistence on simple markers has already produced surprising results, which may change our perception of susceptibility to child mortality. Contrary to the overwhelming clinical emphasis on immune suppression, some infections and vaccinations may in fact be enhancing the immune system. We need such simple markers to be able to assess the immunological impact of vaccines, infections, seasons and environmental exposures and their possible contribution to child mortality. With the development in technology it will soon be possible to assess more detailed markers of the immune system including cytokine levels for large numbers of children. Using these more detailed methods, future research should continue to examine which of the many human and environmental exposures that infants experience are really important for increasing or reducing child mortality.

References on immunological markers:
58, 64, 93, 94, 112, 115, 118, 136, 144, 149, 152, 154, 156, 169, 176, 180, 190, 197, 234, 246, 255, 256, 267, 289, 290, 320, 358

Prenatal multi-micronutrient supplementation

Background

The international recommendations for prenatal iron and folic acid supplementation are under revision, and UNICEF promotes a daily multi-micronutrient supplement with one recommended dietary allowance (RDA) of five minerals and ten vitamins. We compared the effects of three different prenatal supplements on birth weight and mortality in a double-masked randomized controlled trial among 2100 women, 22.0±6.8 weeks pregnant at inclusion. The three supplements contained either one (MN-1) or two RDA's (MN-2) of five minerals including iron and 10 vitamins including folic acid, or iron and folic acid only.

Results

The overall mean birth weight was 3050±498 g with 11.9% being low birth weight (LBW, birth weight < 2500 g). Perinatal mortality was 82 per 1000 deliveries, and neonatal mortality 45 per 1000 live births. Mean birth weight in MN-1 and MN-2 groups were 63 [-9; 134] and 99 [28; 170] g higher than controls (Figure 1). The proportion of LBW was 13.6 % in control, and 12.0 % and 10.1 % in the MN-1 and MN-2 groups, respectively (P=0.33). The effect was seen particularly among anaemic women (30%), where MN-2 increased birth weight by 218 g [81; 354] compared to controls, with a corresponding decreased risk of LBW of 69 [27; 87] %. There were no differences in peri- and neonatal mortality between groups.

Public health implications

Daily supplementation with 2 RDA's of multi-micronutrients significantly increased birth weight even when taken late in pregnancy. The supplement can be distributed within the existing primary health care system for pregnant

women, replacing the conventional iron-folic acid supplement at a little extra cost with potential benefits for both infants and their mothers.

Future perspectives

It remains to be evaluated whether the increased birth weight is accompanied by decreased infant morbidity and mortality, or by improvement of growth or other health indicators. Yet, based on the effects on birth weight our data suggest that a future prenatal multi-micronutrient supplement should contain two rather than one RDA.

References: 285, 355

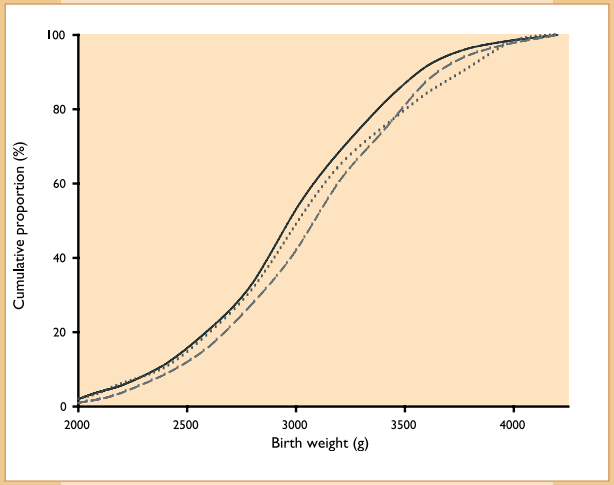


Figure 1
Cumulative distribution of birth weight in 1126 neonates, whose mothers received different prenatal micronutrient supplements. The solid line represents control (iron-folic acid), the dotted line MN-1 (one RDA of 15 micronutrients) and the dashed line MN-2 (two RDAs of 15 micronutrients), respectively.

Vitamin A supplementation

Background

In the 1980's it was discovered that children with xerophthalmia, i.e. ocular signs of vitamin A deficiency (VAD), died more frequently than children without xerophthalmia. Subsequently large intervention trials with high-dose vitamin A supplementation (VAS) were undertaken, and it became clear that VAS to children above 6 months of age could reduce overall mortality with 23-30%. Based on these observations, WHO recommended regular VAS at immunisation contacts to prevent VAD. Though vitamin A was acknowledged to affect the immune system, the potential interactions between vaccines and vitamin A were not explored.

Results

Measles-specific antibody titres:
We found that 100,000 IU vitamin A given with measles vaccine at age 6 months was safe (127) and had no effect on measles-specific antibody levels at 9 months of age (137). However, 100,000 IU vitamin A given with the recommended measles vaccine at age 9 months increased measles-specific antibody titres at age 18 months (177), and it reduced the numbers of children being unprotected against measles at age 6-8 years (273).

CD4-CD8 counts:
There was no effect of VAS given with measles vaccine on CD4/CD8 ratio at the ages of 9 and 18 months (246).

Atopy:
There was no indication that VAS given with measles vaccine was associated with increased risk of being atopic at age 6-8 years (313).

Survival in an emergency:
During the war in Bissau, we provided vitamin A to children from 6 months to 5 years of age and VAS was associated with lower mortality and reduced cultural and socio-economic inequalities in childhood mortality (359).

Dose size:
As the only two studies comparing different dosages of VAS found the smaller dose to be beneficial for morbidity or mortality, we randomised the children to the recommended or half the recommended dose of VAS with oral polio vaccine in connection with a national immunisation day. The preliminary results indicate a marked interaction between sex and dosage, the recommended dose clearly being worse for girls (see table).

Explaining the effect of VAS on childhood mortality:
It has been assumed that the beneficial effect of VAS is due to prevention of VAD. However, existing data on the impact of VAS fits poorly with the prevention-of-deficiency hypothesis (338). Most strikingly, there is an age pattern with beneficial effects of VAS when given at birth and after 6 months of age, but no such effect when given between 1 and 5 months of age. This is similar to the mortality pattern observed after routine vaccinations. We hypothesised that the mortality effect of VAS may depend not only on the prevention of VAD, but also on vitamin A amplifying the non-specific immune modulation induced by vaccinations. Most data on the impact of VAS fits better with this hypothesis (338).

Public health implications

WHO used our study to reinforce the recommendation to give VAS with measles vaccine. If the hypothesis about amplifying the effects of vaccines is true, the recent drive to combine VAS with the three DTP vaccinations in the first months of life may have no beneficial effect. However, much may be gained by optimising the timing and dosage of VAS, combining it with other vaccines observed to have beneficial effects on survival in early childhood (338).

Future perspectives

We will continue our search for the mechanisms underlying the effect of VAS, and the interactions between dosage of VAS, vaccines and sex. This will be done in epidemiological studies and, as something new, in immunological studies based on murine and human dendritic cell models.

References on vitamin A supplementation:
127, 137, 177, 246, 273, 313, 338, 359

Table
Mortality during 9 months of follow-up according to dose of vitamin A supplementation for children aged 6 months to 5 years of age. Guinea-Bissau, November 2002- September 2003

Dose of Vitamin A	Deaths/no of children supplemented 9 months of follow-up		
	Boys	Girls	All
6-11 months			
100.000 IU	3/159	3/155	6/314
50.000 IU	6/205	3/189	9/394
Mortality ratio			0.8 (0.3-2.3)
12-59 months			
200.000 IU	11/1133	18/1076	29/2220
100.000 IU	9/1033	3/1039	12/2071
Mortality ratio			2.3 (1.2-4.4)
6-59 months			
Recommended	14/1303	21/1231	35/2534
½ recommended	15/1238	6/1228	21/2466
Mortality ratio	1.0 (0.5-2.0)	3.7 (1.5-9.2)	1.7 (1.0-2.9)

Standard measles vaccine

Background

After the severe measles epidemic in 1979, we organised the first measles vaccination campaign in December when the children were re-examined. At the time there was no general vaccination programme in Guinea-Bissau. Since 80% of the children attended the re-examination, the large majority of the children received measles vaccine. This campaign had been intended not as a research project but only as a service to the community. However, it soon became clear that it was necessary to follow the effect of measles vaccination more closely.

Results

Measles vaccination had a marked effect on measles mortality not only by preventing measles cases but also by reducing crowding and, hence, the case fatality among the remaining cases by securing milder infection for those who got measles infection in spite of being vaccinated, and by mild vaccinated cases transmitting milder infection contributing to less severe community outbreaks (25, 34, 168). However, more important was the overall effect of measles vaccination on child mortality levels. As shown in Figure 1, measles vaccine was introduced in December 1979 and December 1980. The following year, mortality in the age group 6-36 months dropped three fold (13).

Such data was strong vindication that it was not merely the "weak" children who died and death could be prevented (2,13). The effect in this and several subsequent studies was in fact so marked that it could not be explained by the prevention of acute measles infection (2, 11, 13, 28, 48, 62, 104, 130, 316). The reduction in mortality has been in the order of 40-50% (129). The effect has been found in before-after comparisons (13,

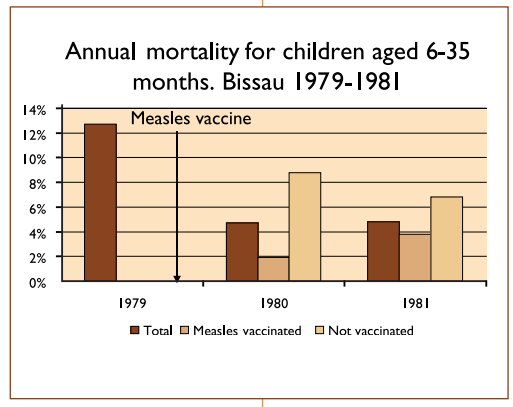
130), in comparisons of vaccinated and unvaccinated areas (2, 316), in studies controlling for individual risk factors (62), and randomised or blind studies (38, 321) making it unlikely that bias would explain much of the effect.

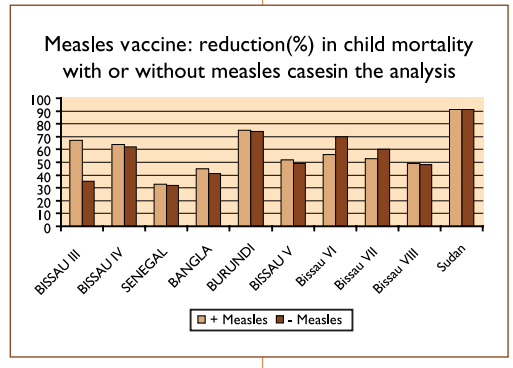
In view of the marked effect of vaccination, we suggested that measles infection was associated with long-term excess mortality, presumably due to immunosuppression, vaccines preventing such excess mortality (13,46). Studies suggested that exposure before 6 months of age had a marked negative effect on long-term survival (55). However, only several years later did we compare survival of uninfected children and measles infected children after the acute phase of infection. Once again, the result was contrary to expectation, previous measles cases, particularly mild index cases, having lower mortality than uninfected individuals (144,145,302, 316).
In an attempt to assess how much of the mortality reduction was associated with prevention of measles infection, we have estimated the vaccine efficacy against death (VED) in an analysis comparing the survival of vaccinated and unvaccinated children. Censoring for measles infection in such an analysis, and hence comparing uninfected-vaccinated and uninfected-unvaccinated children, should indicate how much of the estimated VED can be explained by the specific prevention of measles infection (129). Surprisingly, as indicated in the figure, there was virtually no difference in the estimates with and without censoring for measles. Since measles vaccine does prevent measles deaths, the pattern can only be explained if there is indeed lower mortality after measles infection.
Strangely enough the beneficial non-targeted effect of standard measles vaccine appears to be much stronger for girls than boys (102, 130, 321, 323, 326, 347). In hospital studies, the beneficial effect has been found for all the major types of diseases but most strongly for pneumonia (326).

Public health implications and future perspectives

Measles vaccination has contributed far more to reduction in child mortality in low-income countries than usually assumed. Measles vaccination and possibly also mild measles infection are associated with a beneficial immune stimulation. Stopping measles vaccination after eradication would probably increase child mortality in the poorest countries. The coverage for measles vaccine, and not DTP3, should be used as the coverage indicator by international agencies. Increasing the coverage for measles would contribute significantly to lower mortality in the poorest countries. It must be a major priority to explain the immunological basis for non-targeted beneficial immunestimulation.

References on standard measles vaccine:
2, 11, 13, 25, 28, 32, 34, 46, 48, 62, 71, 104-106, 109, 111, 122, 123, 126, 129, 130, 132, 134, 140, 143, 147, 168, 177, 195, 202, 205, 209, 211-213, 218, 227, 235, 239, 241, 244, 253, 258-262, 269, 271, 273, 279, 302, 303, 305, 312, 314, 316, 321, 326, 338-340, 347





Two-dose measles vaccination strategies

Background

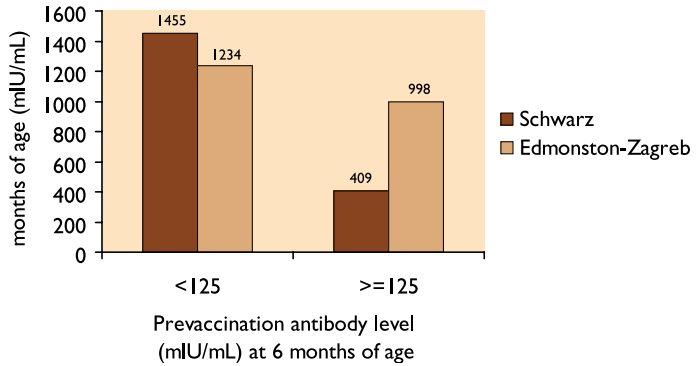
Despite a safe and effective measles vaccine, measles gives rise to an estimated 40 million cases and about 800,000 child deaths per year. Measles accounts for about half the childhood deaths due to vaccine-preventable diseases in low-income countries. Strategies to reduce the disease burden from measles are to increase vaccination coverage by providing two opportunities for vaccination, to give the first vaccination at an earlier age to reduce the pool of measles susceptible individuals and to prevent life-threatening measles infection in very young infants. From year 1995 to 2002, 8.500 children from the Bandim Health Project (BHP) area were included in a two-dose measles vaccination trial. The children were randomised to either a one-dose group receiving an inactivated polio vaccine (IPV) at 6 months of age and a measles vaccine at 9 months of age, or a two-dose group receiving two doses of measles vaccine at 6 and 9 months of age.

Results

An early two-dose schedule increased coverage considerably and provided better protection against measles among infants than the recommended one-dose schedule at 9 months of age (209, 227). The standard-titre Edmonston-Zagreb vaccine (EZ) boosted a secondary immune response better than the standard-titre Schwarz (SW) vaccine. Further, the SW vaccine was less able to induce a protective level of antibodies when used from 6 months of age than the EZ vaccine (253) (see figure).

According to studies of maternal antibodies measles-vaccinated mothers in contrast to mothers who experienced natural measles infection passed a lower level of measles antibodies on to their babies resulting in susceptibility to measles at a very early age (312, 314).

The survival benefit of getting measles vaccination versus IPV vaccination at 6 months of age



was demonstrated during the war (321). Since vaccinations were stopped during the war, 430 children did not get their 9-month vaccination as planned; these children had in fact been randomised to measles vaccine or "placebo" vaccine (IPV). Though unplanned, this is one of the few randomised comparisons of measles vaccine vs. no measles vaccine. The beneficial effect was marked and strongest for girls (303, 347).

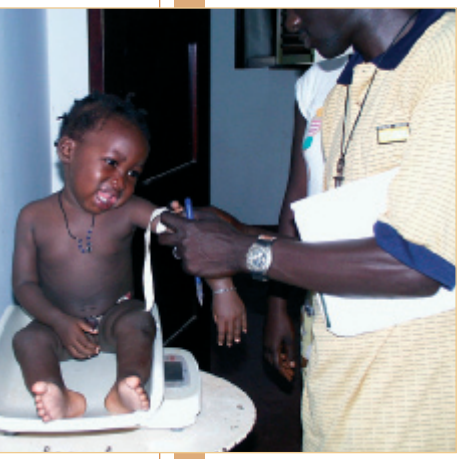
Public Health Implications

Two-dose measles vaccination schedules are a feasible way of improving measles vaccination coverage, and providing protection against measles.

Future perspectives

The Global Measles Strategic Plan 2001-2005 recommends a second opportunity for measles vaccination either through campaigns or routine immunisation. Campaigns are taking place on a large scale in Africa these years, and children might get two, three or even more measles vaccines in an uncontrolled and not necessarily beneficial manner. Additionally, the most commonly used monovalent measles vaccines, SW and EZ vaccines, have never been compared with child mortality as end-point. In July 2003 a new two-dose trial was initiated in Guinea-Bissau with the following objectives: To test 1) whether the SW or EZ measles vaccine will perform best in a one- or two-dose measles vaccination schedule in terms of antibody response, protection against measles, and child survival, and 2) whether the EZ vaccine can be used in a very early 4½ and 9 months two-dose vaccination schedule. Results from the two-dose trials conducted at the BHP are likely to be important for the planning of future vaccination policies in developing countries.

References on measles vaccination strategies:
104, 111, 177, 209, 227, 253, 303, 312, 314, 321, 347, 360, 361



BCG vaccination – non-specific effects and vaccination strategies

Background

Bacille Calmette-Guerin (BCG) vaccination against TB was introduced in 1921 and probably has the highest coverage among current vaccines. The estimated efficacy against TB varies from 0 to 80 percent between different settings; much effort is currently made on finding a better vaccine against TB. BCG vaccination stimulates cell-mediated immunity in humans. In several animal studies, BCG has protected against non-mycobacterial infections including malaria, salmonella, and listeria. When BCG vaccination was introduced in the 1920s, it was sometimes considered to have a non-TB-related beneficial effect on the survival of children. There has been virtually no study of the impact of BCG on child survival in low-income countries. Due to the non-specific effects of measles vaccination, we started examining the effect of BCG as well.

Results

Childhood mortality:
In a study from rural Guinea-Bissau, BCG vaccination as opposed to no BCG vaccination was associated with a 45% reduction in infant mortality (241). In three prospective studies from Bissau there was an association between BCG scar and better infant survival (320, 377, 378). In two studies, a positive tuberculin reaction showed the same association (320, 378) (See figure). Nothing similar was found for responders to diphtheria-tetanus–pertussis (DTP) vaccine (320), and the effect could not be explained by protection against tuberculosis (320, 378). BCG vaccination may induce non-specific immune-stimulation protecting against other infections. In a study of verbal autopsies on children in Bissau with known BCG scar status, no specific causes of mortality could be related to scar reaction (377). The BCG effect may thus be non-specific and affect several major infections.

Atopy:
Among children who had received BCG vaccine, 21% were atopic compared with 40% of the BCG-unvaccinated children (OR 0.19 (95% CI 0.06-0.59), adjusted for confounders), the largest risk reduction was seen in children vaccinated in the first week of life (236).

Anergy:
BCG vaccination and a positive tuberculin reaction were associated with a lower prevalence of anergy to both tuberculin and diphtheria–tetanus. Thus, again indicating that BCG vaccination may contribute to better cell-mediated immune responses among infants (267).

Immunology:
BCG vaccination at birth induces a memory Th1-type response of similar magnitude to that obtained when given later in life. Thus, human newborns can be immunised against pathogens controlled by a Th1 immune response (229).
Administration of BCG markedly increased the cellular and antibody responses to hepatitis B vaccine, and increased the antibody response to oral polio vaccine. Although BCG induced a potent Th1-type response to mycobacterial antigens, it promoted the production of both Th1- and Th2-type cytokines in response to unrelated vaccines. Thus, BCG influences the immune response to unrelated antigens in early life, possibly through its influence on the maturation of dendritic cells (288).

Specific infections: In a case control study from Bissau it was shown that BCG vaccination may have a non-specific protective effect against acute lower respiratory tract infection (ALRI), including ALRI caused by respiratory syncytial virus (RSV), the effect being most marked in girls (365).

BCG vaccination policy: The policy of not BCG-vaccinating at birth was shown to have a negative long-term impact on the vaccination coverage for low birth-weight (LBW) children. BCG vaccination of LBW children may have a beneficial effect on survival that cannot be explained by protection against TB (376). Vaccination technique and BCG strain have been shown to be of large importance for PPD reaction and scarring in response to BCG vaccination in Bissau (379).

Public Health Implications

The current BCG vaccine has been in use for more than 80 years and seems to have a profound beneficial impact on child health leading to decreased child morbidity and mortality unrelated to protection against TB. New vaccines with better efficacy against TB will soon be ready for clinical trials. A new vaccine should not only be tested against BCG with protection of tuberculosis as end-point, but also regarding general childhood morbidity and mortality. Introduction of a new vaccine lacking the non-specific beneficial effects of BCG could be disastrous.

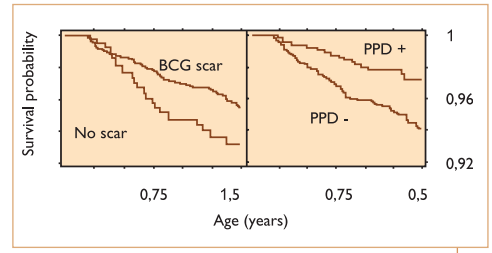
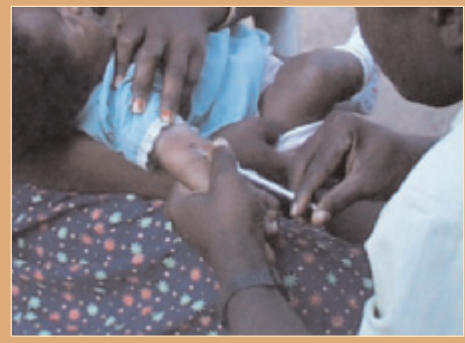


Figure
BCG scar and PPD reaction and 18-month survival.
Guinea-Bissau 2000 – 2002 (378)



PPD application

BCG scar

Future perspectives

We will further examine the implications of the beneficial effects of BCG on vaccination strategy, the impact of BCG on specific morbidity and investigate the immunologic mechanisms underlying our observations. Currently we are conducting three randomised trials in Bissau to improve vaccination policy and child survival: early revaccination at 19 months of age, early vaccination of LBW children and early supplementation of vitamin A together with BCG. Further studies may examine BCG immunology; vaccination technique; strain; and the impact on specific diseases including RSV, rotavirus and malaria.

References on BCG:
227, 229, 236, 241, 258, 262, 267, 288, 305, 320, 347, 348, 358, 365, 376, 377, 378, 379

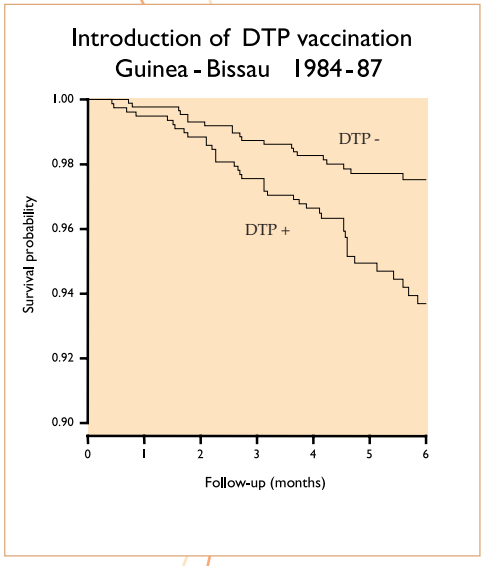
Non-targeted effects of inactivated vaccines

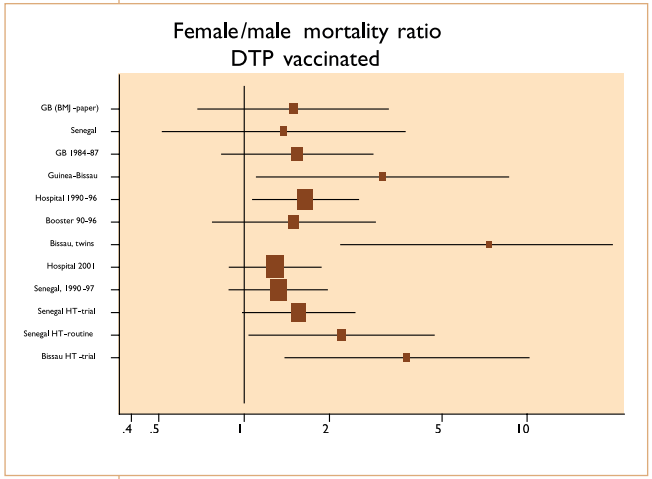
Background

None of the vaccines currently used in low-income countries were introduced after studies showing that the vaccine reduced overall mortality. It has been assumed that the effect of the vaccine would be proportional to the impact of the infection prevented. However, if measles vaccine and BCG can have such marked beneficial effects on infant survival what is the effect of the other routine vaccines, in particular diphtheria-tetanus-pertussis (DTP) vaccine. A randomised study would not be ethically acceptable. One of the advantages of having 25 years of data is that it might be possible to re-examine old data with a new question without actually having to perform a new study.

Results

Our mobile team doing nutritional surveillance in more than 20 villages in the interior of Guinea-Bissau had introduced measles vaccine in these villages already in 1980-1981. DTP was introduced in 1984 at a time when there was no functioning national vaccination programme. We obviously did not randomise children to receive DTP, but some children did not receive DTP because they were travelling on the day the village was visited, other children had fever and were therefore not vaccinated, and on certain days there had been no vaccinations due to logistic reasons. Comparing the DTP-vaccinated children with the mixed group of non-randomised controls, the DTP-vaccinated children had a two-fold higher mortality than the unvaccinated children in the following 6 months until the next visit of the team (see figure) (348).





DTP vaccine has been missing in certain periods in Bissau. We therefore compared the case fatality at the hospital for children who had received DTP and OPV, as prescribed, and children who had only received OPV because DTP was not available. The case fatality was three-fold higher for the children who had received both DTP and OPV (342).

Differences between vaccinated and unvaccinated children are usually dismissed as most likely due to selection bias. Though selection could obviously explain some differences, there are two features suggesting that more than mere chance is at play. Firstly, several studies have suggested that BCG and measles vaccines are associated with beneficial effects whereas the effect is the opposite among DTP recipients. In a rural survey, DTP was associated with 84% higher mortality whereas BCG was associated with a 45% reduction in mortality (241). Secondly, all studies have shown that the effect is worse for girls. Given that the effect of measles and BCG is better for girls, it would seem impossible that sex differential behaviour could explain both tendencies. Among female-male twins the female-male mortality ratio was significantly reduced when BCG was the last vaccine but significantly higher when DTP was the last vaccine (347). When vaccinations were stopped during the war, mortality was three-fold higher for girls than boys who had received DTP as the last vaccine just before the war, whereas girls had lower mortality if they had received measles vaccine (303). As seen in Figure 2 in all studies of DTP, girls had higher mortality than boys.

The only other inactivated vaccines that we have used are IPV and HBV.

They have both been associated with an increased female-male mortality ratio (360,361). These observations offered an unexpected explanation of the increased female mortality after high-titre measles vaccination (323,325).

Public health implications and future perspectives

To the extent non-targeted effects are true there are numerous possibilities for improving the vaccination programme and child survival in low-income countries. Our observations are obviously problematic to health authorities. WHO has decided that there is no negative effect of DTP and no interaction with gender (Global Advisory Committee on Vaccine Safety. Weekly Epidemiological Record 2002; 77:393-4) but has yet to publish any result in support of this conclusion. Hence, the immediate problems are to establish the consistency of these findings, to examine the possible immunological basis and to convince health professionals that there might be a problem.

References on inactivated vaccines:

130, 241, 258-262, 303, 305, 321, 323, 325, 326, 333, 342, 347, 348, 360, 361

Edmonston-Zagreb and high-titre measles vaccines

Background

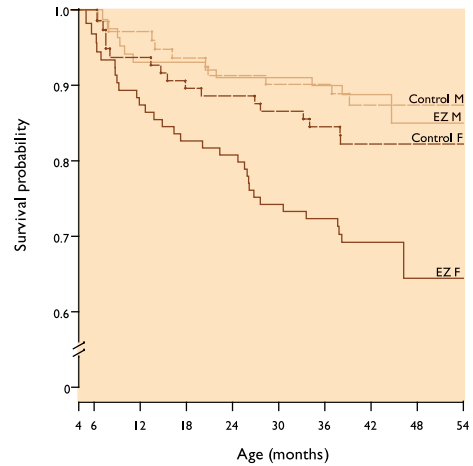
Due to the positive experiences with the first measles vaccination campaigns in Bissau, we were very interested when Sabin and Whittle published studies showing that Edmonston-Zagreb (EZ) measles vaccine could immunise infants in the presence of maternal antibodies at 4-6 months of age. In 1985, we therefore initiated trials with EZ vaccine in Bandim, hoping to be able to show an even stronger effect on survival. Subsequently in 1987, a trial was also initiated in Niakhar, Senegal, to show that EZ was also effective in a rural area. These trials randomised children at 4-5 months of age to receive EZ vaccine or IPV (in Bissau) or placebo (in Senegal). At 9-10 months, children were invited back and the control group received standard measles vaccine whereas the EZ group received IPV in Bissau and DTP-IPV in Senegal (323).

Results

Results of the first trial using a medium-titre dose of EZ were very positive. EZ provided clinical protection against measles even when given already at 4 months of age (43). There were also good antibody responses (116). To increase the number of participants we initiated a second trial in Bissau in 1986-7. This time a high-titre dose of EZ was used. This trial produced a major surprise; girls who had received EZ vaccine had a two-fold higher mortality than girls who had received standard measles vaccine at 9 months of age (99). There was no difference for boys (see Figure 1).

When this became clear by the end of 1989, WHO had just recommended EZ high-titre for general use in countries with a high incidence of measles before 9 months of age. When analyses were carried out in 1990, the considerably larger study in Senegal demonstrated a similar pattern (102,107)

Figure 1
High-titre measles vaccine trial, Guinea-Bissau



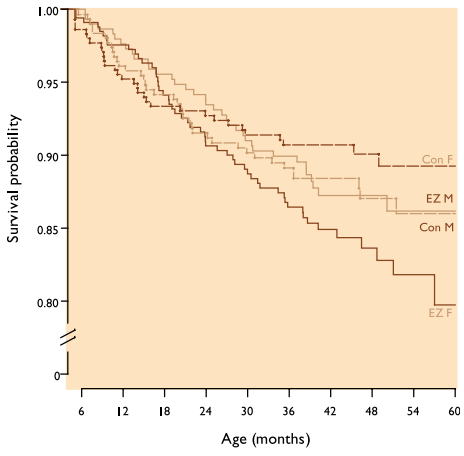


Figure 2
High-titre EZ measles vaccine trial, Senegal

(see Figure 2). EPI in Geneva convened an expert meeting to review the data in 1991. The experts decided that the results were unplanned and biologically implausible and recommended WHO to continue the use of the EZ high-titre vaccine. In 1992, a study in Haiti found a similar tendency. In the same year, a second meeting of experts decided to rescind the recommendation of high-titre measles vaccine. In a meta-analysis of the West African trials, EZ high-titre vaccine was found to be associated with a 33% increase in childhood mortality (143).

Public health implications: Non-targeted effects of vaccines

High-titre measles vaccine had been fully protective against measles infection and the differential mortality therefore had to be due to some form of non-specific immune stimulation (129,143,147). Due to production problems in Zagreb, the policy was never fully implemented but if the results from West Africa were representative – which they might not have been – implementing the policy in Africa would have meant one million additional child deaths per year. At the time the effect was ascribed to high-dose presumably having an immunosuppressive effect like natural measles infection (323) and the international health community was encouraged to search for a new vaccine which could be given safely before 9 months of age. Ten years later a new measles vaccine is not in sight. We suggested at the time that since standard measles vaccine had non-specific beneficial effects, which were particularly good for girls, the increase in mortality among high-titre recipients could be due to high-titre vaccines not having these non-specific beneficial effects – and therefore a difference was seen for girls, and only girls. However, none of these hypotheses explained all the data (323).

The most important observations were undoubtedly that the effect had been found only for girls and that girls in the high-titre group had higher mortality than boys. There is no way these effects can be explained by reference to natural immune suppression. If anything previous studies have found the standard measles vaccine to be particularly good for girls, and girls did not have higher mortality than boys in the pre-vaccination era (102,129,130,347).

Lately a number of studies have found inactivated vaccines to be associated with increased female mortality. Using this observation, we re-examined the high-titre trials. Apparently the effect was due to a change in the sequence of vaccinations. Normally, children would receive their three doses of DTP at 2-5 months of age and then standard measles vaccine at 9 months of age, which would produce a beneficial effect for girls. However, high-titre measles vaccine was given early and most children therefore got DTP or IPV after measles vaccine. The excess female mortality was only found among children who got DTP or IPV after measles vaccine (323,325,333).

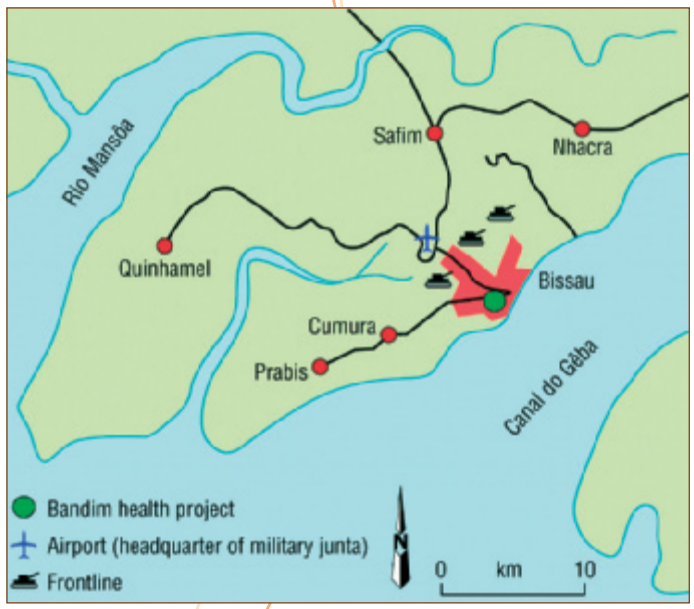
References on EZ and high-titre measles vaccine:
42, 43, 76, 99, 102, 107, 108, 112, 114, 116, 119-122, 124, 129, 139, 143, 147, 210, 211, 213, 323, 325, 333

Mortality patterns during the 1998-99 war in Guinea-Bissau

Background

In June 1998, the president Nino tried to arrest the commander-in-chief, Ansumane Mane, as responsible for selling arms to the rebels in Senegal though it was probably Nino's own men who were selling arms. When the key officers resisted arrest, Nino got the two neighbouring countries to send 5-6.000 soldiers and the conflict turned into a civil war confronting, on the one side, the president and his foreign army occupying the capital and, on the other side, the rebels controlling the airport and the road to the interior of the country (see figure). During the first 2-3 weeks of the conflict the rebels reinvented the ideology of Amilcar Cabral and the liberation struggle (1963-1974) emphasising the corruption of Nino's regime, demanding social justice. They succeeded in getting popular support and many veterans from the liberation struggle joined the rebels. The artillery fight between the foreign army and the rebels became intense already during June 1998. Bombs were falling everywhere in the capital and within 10 days virtually everybody had fled from the capital, leaving only soldiers, thieves, a few young men to defend family property and some old people who refused to leave.

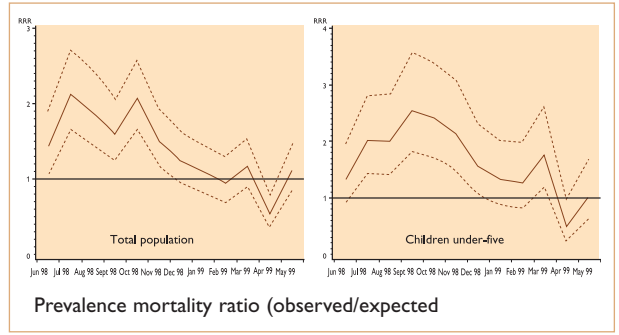
Most people fled to Prabis or continued to the interior through Prabis. The first war lasted until August and most displaced persons returned home when they started believing the ceasefire was true. However, fighting broke out again for short periods in October-November, January-February and in May 1999 when the war ended with the rebels taking the capital and the president as prisoner. Throughout all of the war, BHP assumed a role as humanitarian organisation, distributing food (from World Food Programme's (WFP) stores) and water to displaced persons, diesel for transport, bednets, vita-



min A, organising general medical consultations, treatment for TB patients, growth monitoring and feeding of malnourished children, and measles and meningitis vaccination campaigns among displaced and returning people. Finally, BHP organised the distribution of building material to the roughly 15% of the houses which had been damaged due to the conflict. A major part of routine data collection continued throughout the conflict.

Results

Crowding and mortality:
Crowding was extremely high among displaced persons, reaching an average of 104 persons per house in Prabis itself. Nutritional status declined steeply and mortality was markedly increased. As soon as the population returned to their normal area, the situation improved, nutritional status improved and mortality declined in spite of the fact that less food was available (224). Breastfeed children did considerably better during the war even though they had had worse nutritional status than the weaned children (341). The figure, which compares the expected mortality (forecast based on 3 previous years) with the observed mortality, shows that excess mortality was mainly observed in the initial 6 months when people had fled from their normal residence in Bissau.



Prevalence mortality ratio (observed/expected

High-risk groups:
Analysis of our cohort of people under TB treatment suggested a 3-fold increase in mortality for those whose treatment stopped when the war interrupted all health services (263). This effect was particularly strong for HIV-infected TB patients and in general HIV-1 and HIV-2 infected people suffered disproportionally during the conflict.

Vaccinations:
The breakdown of routine services meant that we inadvertently initiated one of the few randomised studies of measles vaccine, the non-specific beneficial effect being better for girls (321). There was a marked inversion of the female-male mortality ratios during the war, DTP being associated with increased female mortality and measles vaccine with lower female mortality (303).

Humanitarian aid organisations:
For distribution of humanitarian aid, it made no sense to distinguish between resident and displaced persons in Prabis when the home is suddenly invaded by 5-10 times as many displaced persons as the number of persons normally living in the house. Nonetheless, WFP insisted that help could only be given to displaced persons because this is "what the donors want". We were able to show that both nutritional status and mortality was worse for resident people during the war in Prabis (224). The input of the international organisations was deeply unsatisfactory (298). Their main concern was own rules and regulations and not flexibility in helping the population. For example, though imported rice was available locally for sale because trading had stopped and money had been donated by Sweden, WFP refused to buy because according to their rules they could only buy locally-produced rice, sacks had to be labelled with the WFP logo and sacks had to be fumigated, none of which was possible in Bissau.

Public Health Implications

The mortality effect of the war was clearly worse while people lived under crowded conditions in the rural areas. Hence, it ought to be the policy in an emergency situation to dissolve such concentrations as soon as possible, and an aid organisations should be able to let the aid follow the displaced people when they move for better options rather than concentrating people for the convenience of distribution.

Future perspectives

Having a population documented before an emergency, as in Bissau, is unique and provides a different possibility of assessing the total impact of an emergency. Most analyses of complex emergencies are based on camp population gathered after a disaster and this may well affect our understanding of the impact and of risk groups and priorities. Much remains to be analysed.

References on war:
202, 224, 263, 298, 303, 311, 321, 341, 359, 362, 374

Interventions during the 1998-99 war in Guinea-Bissau

Background

Humanitarian aid may be important for the survival of people in emergencies, but the evaluation of the impact of many interventions is faulty. More specific evaluations would help target and optimize humanitarian aid in future conflicts. During the conflict in Bissau, BHP implemented many interventions including vitamin A supplementation, free medical consultations, identification and follow-up of malnourished and at-risk children, distribution of bed nets to pregnant women and children less than 2 years of age, general measles vaccination campaigns, and distribution of building material. Assessment of such interventions is difficult because formal comparisons cannot be made for ethical and practical reasons. Hence, we used several different designs to evaluate the interventions and we examined whether the interventions had an impact on socio-economic differentials. Since interventions were free, one would expect they reduced socio-economic differentials.

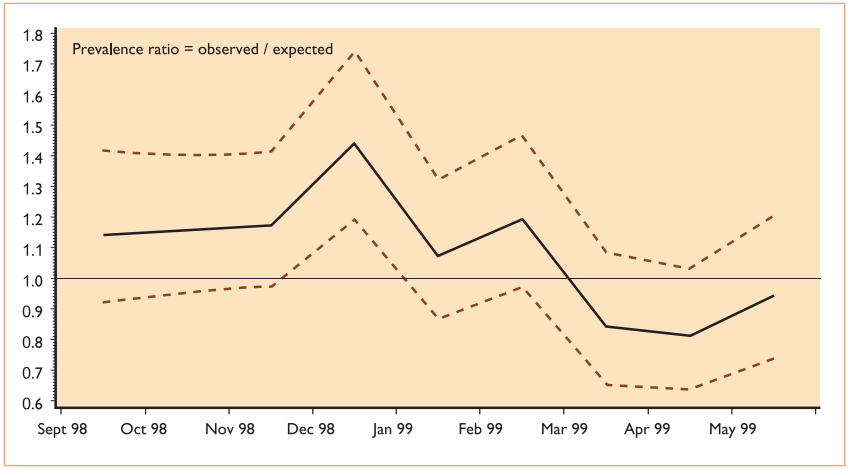
Results

Vitamin A supplementation:

Vitamin A supplementation is recommended by WHO in emergency situations but has not been evaluated. Using the variation in the time of supplementation with vitamin A comparing with children who had not yet received vitamin A, we found a 51% (MR 0.49; 95% CI 0.09-2.70) reduction in mortality for children between six months and five years of age. Comparing with a three-year period before the war, children who were offered vitamin A at home during the war had a 12% (MR 0.88; 0.41-1.87) reduction in mortality, whereas the overall impact of the war was an 89% (MR 1.89; 1.32-2.71) increase in mortality.

Vitamin A supplementation was associated with a reduction in cultural and socio-economic inequalities (362).

Supplementary feeding of malnourished children:
Supplementary feeding programmes intend to prevent deterioration of nutritional status, and the associated mortality among malnourished children. Sixty-seven percent of those who received supplementary feeding and medical treatment recovered. Compliance was 89%, better compliance being associated with shorter time to recovery. Compared with malnourished children before the war, degree of malnutrition measured as mean MUAC was the same during the intervention. Prevalence of malnutrition in the community increased initially during the war but then decreased during the intervention (Figure). As will be seen in the figure, the observed prevalence of malnutrition fell below the expected level, based on the three previous years, in the last part of the war. Mortality of malnourished children did not increase during the intervention period (381).



Supplementation of drugs at the paediatric ward.
During the war, drugs were supplied to the paediatric ward. The case fatality fell by 32%. The decline was more marked for children of poor mothers without any education (374).

Public health consequences and future perspectives

Vitamin A supplementation may have a beneficial impact on childhood mortality in an emergency situation, and the supplementary feeding programme is likely to have prevented a nutritional deterioration during the war in Guinea-Bissau. The impact of several other interventions still needs to be assessed.

References on interventions:
202, 303, 321, 341, 359, 362, 374, 381

Anthropology of war and reconciliation

Background

In media representations, folk understandings and academia alike, African warfare has become equated with anarchy, incivility and the resurgence of age-old ethnic hatred. Through in-depth anthropological research of the aftermath of the civil war in Guinea-Bissau and the following period of social and political instability, Bandim Health Project has been able to challenge this backdrop of perceived anarchic and archaic violence, and to contribute, in novel ways, to the social scientific understanding of processes of war, mobilization, demobilization and reconciliation.

Results

In her master thesis entitled: *"In search of recognition : A Study of War Veterans in Guinea-Bissau"*, Susanne Branner Jespersen studied the re-mobilization in the 1998-1999 war of the veterans or former heroes of the liberation war (369). Focusing on the social standing of the war veterans, she accounts for the differences in the influx of former 'antigo combatentes' into the different sides of the war – rebels and government troops – and thus adds to our knowledge of the processes of mobilization as well as of the political problems caused by the inopportune social position of war veterans in many parts of Africa.

In her master thesis entitled *"Experiences of war"*, Malene Flanding focuses on civilian understandings and strategies of flight and refuge (370). Locating different civilian reactions to the war within cultural conceptualisations of disorder, Flanding contributes to our understandings of how ordinary people's ways of life in peacetime determined the ways in which they met and managed the vicissitudes of wartime. The thesis forms a valuable input to our knowledge

of the patterns and the demography of population movements in times of war.

In his PhD thesis entitled *"Navigating terrains of wa: youth and soldiering in Guinea Bissau"*, Henrik Vigh focuses on the way youth seek to navigate the terrain of war as it emerges in a prolonged context of generalized decline and instability (371). The dissertation argues that youth, in Bissau, engage in warfare fighting less against an ideological enemy than for a social possibility, as acts of mobilization forge social allegiances and obligations that constitute paths through present and imagined future unstable social environment. Through researching the social and political positions and possibilities of youth, the thesis thus nuances and contributes to our understanding of youth warfare and reconciliation.

Implications and future perspectives

Taken together the described body of research forms a contribution to our knowledge and understanding of the social process and conflict dynamics emerging in and through so-called 'small wars'. However, working with such aspects as state decay, patrimonial networks and factional conflict, this research also represents a general insight into the political processes of low-income countries under stress (LICUS). Furthermore, the investigation has come to constitute a platform on which new research is being planned and undertaken.

References on war and reconciliation: 369-371

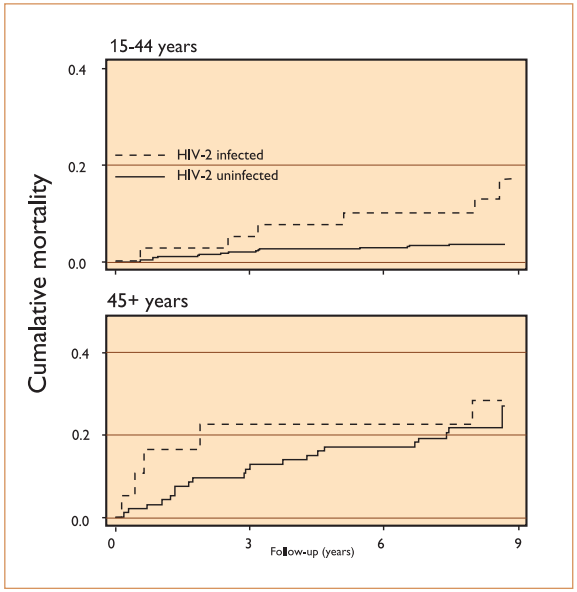
Retroviral epidemics: HIV-2, HTLV, and HIV-1

Background

When the first report of the isolation of a new retrovirus in patients from Guinea-Bissau and Cap Verde appeared in 1986, it was feared of this virus was transmitted by mosquitoes. The Ministry of Health in Bissau asked BHP to organise a survey to assess the situation. Hence, already in 1987 we conducted the first community study of HIV-2 (52). To the extent funding can still be obtained to continue this cohort, it will be the oldest cohort of HIV-2 infected individuals. In 1992, BHP was asked by MRC, The Gambia, to administer the logistic side of their HIV-2 project in a rural area of Guinea-Bissau, which is the only other community study of HIV-2. There is also close collaboration with the National Public Health Laboratory (LNSP) in Bissau and the Swedish group managing a professional cohort in Guinea-Bissau.

Results

Risk factors:
The first survey clearly showed that there was no reason to fear transmission from mosquitoes and bedbugs, and the transmission risk factors were the same as for HIV-1 related to sexual activities and blood contacts, including transfusion and scarification. We did a household survey, and there was no indication that close contact increased the risk for others except sexual partners. We found no evidence of vertical transmission in the first survey, and subsequent surveys have confirmed that there may be a 10-fold difference in the risk of vertical transmission of HIV-2 and HIV-1 (52,79). The original study also pointed to a limited excess mortality associated with HIV-2 (52), the effect being strongest among people under 45 years of age (170) (see Figure). A special feature of the HIV-2 epidemic was the high prevalence among older people. All of these features sugge-

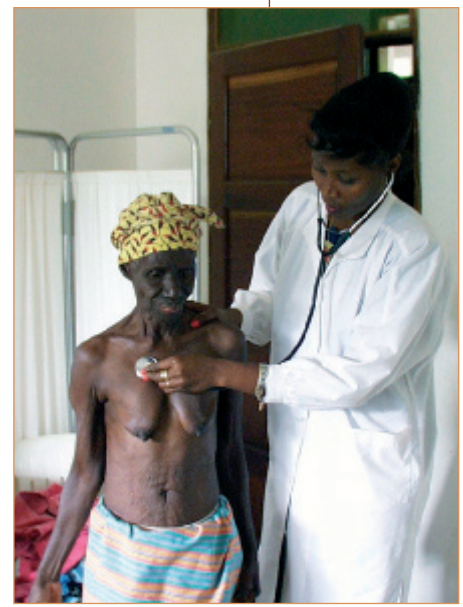


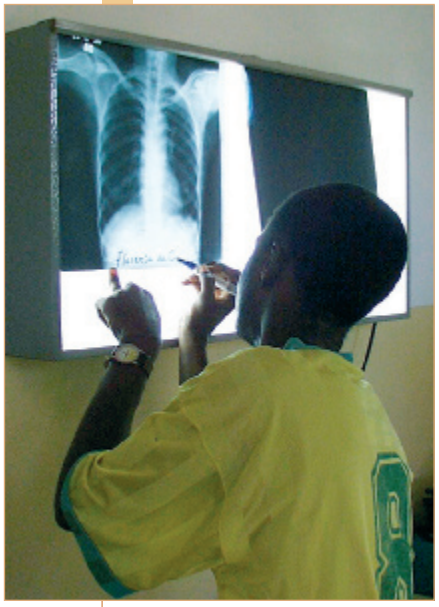
sted that HIV-2 was much less severe as a public health threat than HIV-1.

Natural history:
Subsequent studies also showed that the degree of immune suppression associated with HIV-2 was much less marked and the progression slower (64, 149). As for HIV-1, we subsequently documented that mortality was associated with both DNA and RNA viral load (146,310).

Development of the HIV-2 epidemic:
The HIV-2 epidemic has dominated in certain ethnic groups, which have a tradition of temporary migratory prostitution (231). It seems likely that the large colonial army which was established in connection with the liberation war from 1963-1974 may have been important in propagating the virus (238). Blood transfusions were clearly important since 20% of the blood donors were HIV-2-infected in 1987 when the virus was detected. Smallpox vaccination campaigns may also have been important for the propagation of the virus in the 1960s and 1970s, since we have found a smallpox scar to be a risk factor for HIV-2 positivity. The annual incidence among adults in the late 1980s was around 1%, but this has been declining and the prevalence of HIV-2 has thus been stable or declining through the 1990s (98,199) . It would seem likely that control with blood transfusions has been important in limiting the transmission of HIV-2.

An epidemic among grandmothers?
Studies of concordant and disconcordant couples indicated that age of the woman was a major risk for both partners being infected (158). Several subsequent studies have suggested that the relative risk of HIV-2 for women compared with men increased after 40-45 years of age. In the first long-term follow-up study, the incidence of HIV-2 was actually higher among women over 45 years of age than among younger women (170). We have subsequently found this pattern to apply to all three retroviruses in African community studies (230); the relative prevalence or incidence increases for women after 45 years of age, suggesting a marked change in women's susceptibility (280).





HIV-2 and HIV-1: A protective role?

In the mid-1990s, Science announced a parallel to vaccinia protecting against smallpox, HIV-2 protected against HIV-1! This observation was based on a study of the incidence of HIV-1 in a Senegalese cohort of prostitutes in which HIV-2-infected prostitutes were less likely to contract HIV-1 infection than HIV-2-uninfected prostitutes. Unfortunately, the observation was not true and is most likely due to the study not having controlled for the prevalence of retrovirus infection among the clientele of the prostitutes; in all of the Guinean and Gambia cohorts, HIV-2 was not protective (173,266). On the contrary, HIV-2 was a marked risk factor for subsequently contracting HIV-1. Until recently HIV-2 positivity has been the main risk factor for contracting HIV-1. Our studies have highlighted the observation that dual or even triple infections among HIV-1, HIV-2 and HTLV-infected individuals are relatively common (287). Emphasising the importance of increased susceptibility among older women, dual and triple infections are far more common in (older) women than in men (287,317).

HTLV:

There have been few community studies of HTLV (196,237). The importance of HTLV-infection for mortality patterns may have been underestimated. Data from Bissau suggest that HTLV-infected individuals may have a 2-3 fold higher risk of death than the uninfected population. This indicates that HTLV have more or less the same impact on mortality as HIV-2. The viral load of HTLV is also associated with subsequent mortality (337).

War and retrovirus infection:

Few people would rate the quality of health services in Bissau very high and expect them to have any major impact on the survival of HIV-infected individuals. Nonetheless, there was a marked increase in mortality of both HIV-1 and HIV-2-infected individuals during the war (263). It is unclear whether this is due to the anxiety during the war, or whether the availability of simple treatment has a preventive effect on the progression of disease.

Public Health Implications

HIV-2 turned out to be much less of a public health problem than originally feared. Unfortunately this may have introduced some complacency in the attitude towards HIV-infection that may be problematic in relation to the approaching HIV-1 epidemic. Though not a new pandemic, HIV-2 is a risk factor for adult mortality particularly among young adults, as is HTLV. Our community studies have emphasised the importance of age for the risk of infection, particularly among women. We have found no indication of major behavioural changes for women after 40 years of age that explain this pattern. Since sexual activity is decreasing with age (77), it seems most likely that the increased risk after 40 years of age is related to age-specific changes in susceptibility, presumably due to changes in vaginal immunity. If this is true, there may well be reasons to examine the consequences of improvement in treatment and longer survival

of HIV-1-infected individuals. On the African continent, this may mean that older women may be more likely to be exposed to HIV-infected men. The next epidemic may be among grandmothers. There has been a tendency to define the HIV problem as a question of youthful sexual behaviour, and the middle-aged like nothing better than telling the young what to do. However – at least in Bissau – the middle-aged have been the focus of the epidemic.

Future perspective

The likely increasing availability of retroviral drugs may well change the epidemic patterns in the coming years – it remains to be seen whether it will be for the better.

References on retrovirus infections:

23,44,49,52,58,64,77,79,93,94,98,136,146,149,158, 160,170, 173,176,178,185,186,196,199,201,204,220, 230,231,234,237,238,255,263,266,272,280,286, 287, 310,317,332,337,345

Epidemiological, clinical, immunological and genetic aspects of TB

Background

In 2000 is was estimated that 1/3 of the world's population was infected with tuberculosis (TB), 8.3 million new active cases occurred and the disease caused the death of almost 2 million persons, of which 12% were attributed to HIV. In developing countries, in which 95% of all cases occur, TB accounts for 25% of all avoidable deaths. Even though TB is a disease with a long history, the factors contributing to individual susceptibility to TB have not been fully determined. There is a lack of community-based data regarding environmental as well as personal (immunological and genetic) risk factors. In 1996 a TB surveillance study was initiated in the project area, including and investigating all adult TB-cases from the area. Comparing with the whole population or controls, we have examined several factors associated with the susceptibility and spread of TB.

Results

From May 1996, to April 2001, 811 TB-cases were included. A total of 284 cases died during a follow-up of 1983 person-years at risk. The risk factors for infection have been investigated in the general population and also among contacts of the TB-cases [358]. The prevalence of positive tuberculin reaction (>10mm) was 22% in the general population and 41% in the case contacts. Positive reactions were associated with previous exposure to TB and the intensity of exposure. Furthermore, testing during the rainy season may reduce the reaction.

Bissau has a high incidence of active TB, 471/100,000, for the adult population [356]. As during the TB epidemic in the industrialised countries, male sex, older age, adult crowding and poverty were risk factors for active disease whereas an increasing number of children in the

family appeared to be protective to adult women [356]. HIV infection increased the risk of TB considerably; HIV-1 and HIV-2 infection increased the risk 18 and 3 times, respectively [272]. The irregular treatment during the war increased the mortality risk 3-fold, an effect which was most pronounced in HIV-positive persons who had an 8-fold increase in TB-mortality [263]. The increased risk among the HIV-positive persons, however, continued also after the war [357]. The overall case fatality rate during TB-treatment was 16% over the study period. Clinical predictors easily assessed in a developing country associated with death were evaluated [357]; apart from HIV-infection, important factors were clinical signs of immunosuppression (oral candida/leukoplakia), anergy to tuberculin and malnutrition, as measured by the mid-upper-arm-circumference. Immunologic studies have been performed in order to analyse possible diagnostic tools and predictors for mortality [290], as well as further clarification of the pathogenic process of TB [291]. Several genetic studies are ongoing with the purpose of elucidating the genetic factors predisposing for TB infection and disease [351].

Public Health implications and future perspectives

The epidemiological findings have implications for TB control both in Guinea-Bissau and other developing countries. The immunological and genetic studies, of which several are ongoing, may provide a better understanding of the pathogenesis of TB and may lead to new diagnostic tools, better treatment and better vaccines.

References on TB:
250, 263, 272, 281, 282, 290, 291, 351, 356, 357, 358

SuPAR – a potential marker for HIV disease progression and TB treatment efficacy

Background

In addition to affordable HIV antiretroviral drugs, there is a need for simple and inexpensive markers for monitoring when to start antiretroviral treatment. The current markers, CD4 and particularly HIV viral load, require expensive technical equipment and the test cost is high. Previous studies have shown that the plasma level of soluble urokinase receptor, suPAR, is a strong marker for HIV disease progression among Danish individuals. Hence, we set out to determine whether suPAR carried prognostic value in TB, and whether TB would influence the prognostic value of suPAR among individuals coinfected with HIV (290).

Results

SuPAR was measured with ELISA in 262 individuals enrolled into a cohort in Guinea Bissau on suspicion of active TB and in 101 individuals after 8 months of treatment. SuPAR levels were highest in patients positive for TB in direct microscopy (N=84, median suPAR=3.2, $p<0.001$), followed by the SuPAR level in patients who were microscopy-negative but culture-positive (N=35, suPAR=2.4, $p=0.005$) and patients diagnosed on clinical grounds (N=63, suPAR=2.1 ng/ml, $p=0.06$) compared to patients found to be TB-negative. Among the 262 individuals, 41 were HIV-1-positive and 66 HIV-2-positive. SuPAR was strongly associated with survival among both HIV-1 and HIV-2 positive individuals, and suPAR was the only variable significantly associated with survival in a multivariate analysis including age, sex, TB diagnosis and CD4 count. SuPAR was also found to be associated with survival among TB-positive HIV-negative individuals during the 8-month treatment period (MR=1.14 per ng suPAR increase, 95%CI: 1.0-1.3). Eight months of TB treat-

ment lead to a significant decrease and normalization of suPAR levels (290).

A long-term survival follow-up was carried out in January 2003. Post-TB treatment suPAR levels had been measured in 33 HIV positive individuals at the end of the 8 month TB-treatment period. During follow-up, 21 of the 33 HIV-infected individuals died. Plasma suPAR levels varied from 0.13 to 6.37 ng/ml plasma. Cox regression analyses showed that suPAR was strongly prognostic for survival ($p<0.001$, RH per ng suPAR increase = 2.3). The Kaplan Meier analysis shown below of all 262 individuals followed from inclusion until 2003 showed that individuals with high suPAR (2 x median, bottom line) had decreased survival compared to individuals with low suPAR (below 3.42 ng per ml, $p=0.003$, upper line)

Public health consequences and future perspectives

Our data indicate that SuPAR could possibly be used to guide clinical decision-making in HIV management. Measurement of suPAR is technically simple and production of an inexpensive ELISA kit is in progress. Studies determining the kinetics of suPAR following TB treatment e.g. after one week or one month are needed to determine whether suPAR can be used as a marker of TB treatment efficacy.

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