



Retroviral epidemics in Guinea-Bissau: HIV-1, HIV-2, and HTLV

Background

Studies of HIV in Guinea-Bissau began in 1987 estimating an HIV-2 prevalence of 9% in adults above 14 years in urban Bissau. No HIV-1 infection was found at that time. The first case of HIV-1 infection was identified in 1989, when one case of dual infection of HIV-1+HIV-2 was detected.

Over the last 20 years the two viruses have shown a different pattern of spread in the country; the prevalence of HIV-2 seems to be stabilising or decreasing, while HIV-1 prevalence has been increasing gradually [208]. In contrast to neighbouring countries, Senegal and Guinea-Conakry, with a low HIV-1 prevalence (<1 and 1.5%, respectively), Guinea-Bissau has a prevalence comparable to the levels of the most affected countries in the sub-region (Côte d'Ivoire, Nigeria and Mali) with an HIV-1 prevalence higher than 4%.

Results

Two long-term epidemiological studies of retrovirus infections have been conducted in Guinea-Bissau since the late 1980s and a new study with a clinical approach was initiated in 2007.

Serological surveys of HIV infection in the urban study area of BHP.

Three adjacent urban districts in the capital, Bandim 1, Bandim 2 and Belém, have been followed with epidemiological sero-surveys of HIV infection since 1987. The cohort comprises individuals over 15 years of age living in randomly selected houses in these three districts. Children were included in the first survey in 1987, but due to the very low prevalence it was decided to restrict the following sero-surveys to adults. Over the years, the same methodology has been maintained, covering a 10% sample of houses in the three districts. The number of

houses included in the study has therefore been gradually enlarged from 100 to 399 with 2548 participants tested in the last sero-survey in 2006 [208].

HIV-1. The overall prevalence of HIV-1 in this population has increased from 2.3% (54/2301) in 1996 to 4.6% (118/2548) in 2006 (Table 1). Single HIV-1 infections increased three-fold, whereas the prevalence of dual infections declined (prevalence ratio 0.46 (0.23–0.93)).

HIV-2 infection has shown the opposite trend. The overall HIV-2 prevalence among adults has declined from 8.9% in 1987 to 7.4% in 1996 and 4.4% in 2006 (Table 2). The prevalence is declining in both sexes whereas this decline was initially only in men. The HIV-2 incidence rate between 1996 and 2006 was half the incidence in the preceding 10-year period. Hence, the decrease in the HIV-2 risk is genuine and not due merely to mortality or migration from a previously established cohort. Nevertheless, it should be noted that the prevalence of HIV-2 is not declining among older people. This may indicate a cohort effect, previously infected young adults coming of age due to the longer survival of HIV-2-infected individuals. However, older women continue to become infected. Hence, HIV-2 may continue as an independent infection among the oldest for some time, especially in women. An increased susceptibility to HIV and human T cell lymphotropic virus (HTLV) infections in older women possibly due to changes in vaginal mucosal immunity has

previously been suggested to be the cause of this pattern.

HTLV. Like HIV-2, HTLV has also declined. The prevalence of HTLV was 3.6% in 1996, 2.2% for men and 4.6% for women. In the latest sero-survey, the prevalence had declined to 2.3%, 1.5% for men and 2.9% for women.

Since HIV-1 is increasing, the declines in HIV-2 and HTLV are unlikely to be due to the introduction of safe sexual practices. It seems more likely that they are both relatively inefficient sexually transmitted infections. They may both have been dependent on blood transfusions to maintain the previous high levels found around 1990. Once transfusions became controlled for HIV infection they would both have declined as the two infections were often linked.

Sero-surveys in a rural population. Sero-surveys among adults were also performed in 1989, 1996-1998 and in 2006 in a rural community in Caió, in the northwestern part of Guinea-Bissau by the Medical Research Council (The Gambia) in collaboration with BHP. These surveys indicate that the HIV-2 prevalence had remained stable at around 7.8%, whilst the HIV-1 prevalence has increased (2.7%). Studies from both Bissau and Caio have found an association between having a vaccinia scar and being HIV-2 infected, suggesting that HIV-2 may have been spread initially with the smallpox vaccination eradication campaigns conducted in the 1960s [135,151].





The West African Retrovirus and Acquired Immune Deficiency cohort study (The WARAIID cohort study). In 2007 the PSB started a new project to create a clinical database and a plasma/blood repository biobank with HIV-infected individuals from Bissau and with an extensive follow-up in all patients living in the BHP study Area. This study is used for gaining insights in the overall effect of introducing ART in a treatment naïve population. The main objectives are to focus on the host/viral determinants of failure of first line ARV treatment in this unique population with concomitant infections of 3 retroviruses (HIV-1, HIV-2 & HTLV) and to study the effect of multiple infections on immune response and ART outcome. PSB has established close relationships with the National HIV Programme helping to develop new forms for the HIV care, the national codification system for the patients and opening the HIV clinic at the National Simão Mendes Hospital. This clinic has become the major HIV centre in the country following around 1000 patients and the training centre for doctors and nurses willing to work with HIV in their country.

Since May 2008 the PSB is supporting the National HIV Programme in implementing a mother-to-child transmission (MTCT) preventi-

on strategy at the maternity of the Simão Mendes Hospital. HIV testing and counseling is offered to all the women giving birth in the facility. This is an important entry-point for women to interventions to prevent MTCT, including ARV prophylaxis for the infant, and other HIV-related treatment and care services. The follow-up of the HIV-exposed children is carried out in collaboration with the NGO Ceu e Terras in Bissau.

Other studies. In 2007 the PSB carried out a prevalence study of sexual transmitted infections in 190 commercial sex workers in five regions of the country; 20% were HIV-1 infected and 7% had only HIV-2. Bissau was the region with the highest HIV prevalence (67%) among these women.

Public health implications and future perspectives

Since the beginning of the epidemic, the BHP has been actively involved in understanding the epidemics of retroviruses. The studies have generated valuable information for the National HIV Programme in order to plan public health interventions. The HIV epidemic in Guinea-

Bissau is still evolving and further studies are needed to monitor the trends in these infections.

Given that antiretroviral treatment (ART) has recently been implemented in the country monitoring the clinical response to the treatment and the viral resistance patterns is essential. These studies will contribute to develop appropriate guidelines for implementing ART regimens in populations where HIV-2 is endemic or when multiple infections with retroviruses are common. It will also be a challenge to develop collaboration between the national programmes so that patients benefit from both HIV and TB treatment. In the future BHP may also get involved in testing new vaccines against both infections.

References on retrovirus infections: 4,19, 23, 38, 56, 100, 101,135,151,182,183,191,208,212

Table 1. HIV-1 prevalence in 1996 and 2006 with dual infections included in the Bissau urban community study (208)

Sex	1996 %	2006 %	2006 vs 1996 Risk ratio (95% CI)
Men	2.1	3.6	1.7 (1.0-2.8)
Women	2.5	5.3	2.1 (1.4-3.2)
Overall	2.3	4.6	1.9 (1.4-2.6)
Single HIV-1	1.4	4.2	2.9 (1.9-4.3)
Dual infection	0.9	0.5	0.5 (0.2-0.9)

Table 2. HIV-2 prevalence in 1996 and 2006 with dual infection included in the Bissau urban community study (208)

Sex	1996 %	2006 %	2006 vs 1996 Risk ratio (95% CI)
Men	5.4	2.7	0.5 (0.3-0.8)
Women	9.0	5.5	0.6 (0.5-0.8)
Overall	7.4	4.4	0.6 (0.5-0.7)
Single HIV-2	6.4	3.9	0.6 (0.5-0.8)
Dual infection	0.9	0.5	0.5 (0.2-0.9)



HIV-1, HIV-2, AND HTLV-I: DUAL INFECTIONS

Background

The three human retroviruses, HIV-1, HIV-2, and HTLV-I circulate in the general populations both in urban and rural areas of Guinea-Bissau. While HIV-1 is responsible for the global HIV pandemic, HIV-2 is limited in its spread and mainly confined to West Africa. Guinea-Bissau has constituted the epidemiological focus of HIV-2, with the world's highest prevalence. HTLV-I is also highly prevalent in the area. The major form of transmission for all three viruses in Guinea-Bissau is by heterosexual contacts. Hence different combinations of dual and even triple infections with these viruses occur. In 1989 the first dual HIV-1/HIV-2 infection was identified (0.2%) (Table 1). In the 1996 screening, the prevalence of dual HIV-1/HIV-2 infections had increased to 1.0% (N=22/2301). In Caio, a rural area of the country, the prevalence of dual HIV-2/HTLV-I infection was 1.0%, the great majority of them being in women.

Both HIV and HTLV-I replicate through reverse transcription and both viruses infect CD4+ T-cells with different pathogenic outcome. HIV-2 is more closely related by nucleotide sequence to simian immunodeficiency virus of sooty mangabey origin (SIVsm) than to HIV-1. The time to onset of symptomatic HIV-2 infection is estimated to be at least 10 years longer than for HIV-1 infection, and HIV-2 is less transmissible. This lower pathogenic feature of HIV-2 makes it a suitable model for comparative studies of HIV-1 pathogenesis. In contrast, 95% of infected individuals remain asymptomatic carriers of HTLV-I.

Results

Dual infections and the epidemiological features
In 1998-2000 a screening of HIV and HTLV-I in adults above 35 years of age was performed in Bandim (4). One of the main objectives with the

study was to examine the epidemiological dynamics of retroviral infections around 45 years of age, since previous studies from the area had demonstrated an increased prevalence of retroviral infections particularly in women above 45 years. The prevalence of dual HIV-1/HIV-2 was 0.6%. For dual HIV-1/HTLV-I it was 0.2% and for HIV-2/HTLV-I it was 2.2%. The evolution of the prevalence of various combinations of dual infections is shown in Table 1. The observed prevalence of dual infections was generally higher than expected in women, while this pattern was not observed for men. Adjusting for age group, the female-to-male odds ratio (OR) for any combination of dual retroviral infection was 7.8 (3.1-19.9).

This pattern could not be explained by behavioural factors so we proceeded with mortality analyses to assess whether differential HIV and HTLV associated mortality could explain the differences in dual infections for men and women. However, the higher prevalence of dual retroviral infections in women could not be explained by sex-differential mortality patterns. The objective was also to assess the mortality patterns of various combinations of dual retroviral infections as little is known on the subject. As observed in previous studies, HIV-1- associated mortality was higher than HIV-2 associated mortality (Table 2). The mortality rate ratio (MRR) for HIV-1/HIV-2 dual infections was 5.9 (95%CI 2.4, 14.3), resembling the MRR found for HIV-1. No significant differences were found in mortality between HIV-2 single, HTLV-1 single and HIV-2/HTLV-1 dual infections (191).

Table 1. Prevalence (%) of dual retroviral infections 1987-2006

Year of screening	HIV-1/HIV-2	HIV-2/HTLV-I	HIV-1/HTLV-I	Age
1987	0	.*	.*	>15 years of age
1989	0.2			>15 years of age
1990 [□]	.*	2.3	0	>50 years of age
1992	0.6			>15 years of age
1996	1.0	1.0	0.1	>15 years of age
1998	0.6	2.2	0.2	>35 years of age
2006	0.5	0.4	0.2	>15 years of age

* Not examined

Table 1. Prevalence (%) of dual retroviral infections 1987-2006

	MRR* (95% CI)
HIV-1	4.9 [§] (2.3, 10.4)
HIV-2	1.8 [§] (1.5, 2.3)
HIV-1/2 dual	5.9 [§] (2.4, 14.3)
HTLV-I all	1.7 [#] (1.1, 2.7)
HTLV I positive/ HIV- negative	2.3 ^{&} (1.3, 3.8)
HTLV-I/HIV-2 dual infections	1.7 ^{&} (0.7, 4.3)

* MRR= Mortality rate ratio; § Comparing with HIV-negative; # Comparing with HTLV-I-negative; & Comparing with HIV and HTLV-I-negative



Comparison of HIV-1, HIV-2 and HIV-1/HIV-2 dual infections. From the latest screening performed in Bandim 2004-2006 (208), 56 dually and 5 triply infected individuals were identified and enrolled along with 73 singly infected and 34 uninfected controls in an immunological case-control study. Plasma from HIV singly or dually infected individuals were tested for their ability to neutralise HIV isolates of different subgroups in a checkerboard fashion. Preliminary results from this heterologous neutralisation test show that the neutralisation ability of plasma from dually HIV-1/HIV-2 infected may differ as compared with plasma from singly HIV-1-infected. Plasma from dually HIV-1/HIV-2 infected displayed significantly lower neutralising capacity against HIV-1 isolates than plasma from singly infected HIV-1-infected; no such difference could be observed comparing neutralising capacity against HIV-2 isolates for plasma from dually HIV-1/HIV-2-infected and HIV-2 singly infected individuals. Further analyses are ongoing.

Public health implications

The pattern of the HIV-epidemic in Guinea-Bissau differs from that of South and East Africa as the epidemic started with the less virulent HIV-2. This population is also afflicted by a third retrovirus, HTLV-I, which can lead to disease. We have seen from the mortality data that HTLV-I infection is independently associated with higher mortality. Why HTLV-I-infected die to a higher extent than non-HTLV-I-infected remains to be clarified. Studies are underway

that hopefully will elucidate this. The country has recently started with anti-retroviral treatment (ART) on a national basis to assess the effects of ART on a population level in a context with three different retroviruses.

There is still no vaccine available against HIV. It is not completely known what type and quantity of immune responses should be induced by vaccination to protect against HIV/AIDS. It is therefore of special interest to study immunity such as neutralising antibodies in a population where several human retroviruses HIV-1, HIV-2 and HTLV-I coexist. In particular, HIV-2 infections that have a lower pathogenic outcome than HIV-1 may provide important information on the type of antibody response needed.

Future perspectives

Continuation of the epidemiological studies along with studies on the biology and immunology of the virus are essential for the future monitoring of the HIV epidemic. We will assess possible implications of neutralisation and innate immunity studies from a vaccine perspective. Furthermore, we will study the effects of HTLV-I single and dual HIV/HTLV-I infections on an individual and public health level, analysing which diseases are associated with HTLV-1 in this community. This will include assessment of auto-antibodies in HTLV-I infected individuals and relating HTLV proviral load to HIV and clinical symptoms.

References on dual infections: 4, 191, 2008

Tuberculosis studies:

Clinical tuberculosis studies

Background

The set-up for enrolling TB patients in clinical studies was strengthened in 2003 in order to conduct randomised trials. The previously collected data were used to develop a clinical score for characterisation of severity of TB disease and to assess outcome in trials. A systematic collection of blood samples from TB patients and healthy controls from the study area was used to describe vitamin D status and to study genetic risk factors. Finally this set-up was used to conduct the first major randomised trial of the effect of vitamin D supplementation for TB patients.

In the pre-antibiotic era, vitamin D was used for treatment of tuberculosis (TB). In recent years researchers have reported evidence for an important role of vitamin D in the immune response towards TB and increased risk of TB in individuals with vitamin D deficiency. We therefore

aimed to assess whether vitamin D levels in the blood and vitamin D receptor polymorphisms were associated with TB risk in this high-burden setting, and whether supplementation would affect disease outcome (172).

Results

We developed a clinical severity score for TB based on the WHO manual for TB and HIV and applied the score to an existing dataset of 698 TB patients in the study area (180). The TBscore showed a high degree of sensitivity to change and we found that 93% of the patients had high scores at the beginning of treatment and 79% had a low score at the end of treatment. Being in the highest severity class predicted subsequent mortality with high accuracy.



Vitamin D status was examined in 362 TB patients and 494 healthy adults (185). We found female sex, old age, certain ethnic groups and Moslem faith to be risk factors for low vitamin D

status, whereas having no formal schooling was protective. Controls with vitamin D deficiency were also at higher risk of having latent TB infection determined as a positive Mantoux test > 10mm. Controlling for background factors, we found overall lower 25 hydroxy-vitamin D (25(OH)D3) concentrations among TB patients, but severe vitamin D

deficiency (25(OH)D3 < 25nmol/l) was surprisingly rare among TB patients, although this was seen in 5% of healthy controls. The data suggest a role of vitamin D in TB but it may just be a symptom.

In a genetic case control study, we investigated the role of DC-SIGN (CD209), long pentraxin 3 (PTX3) and vitamin D receptor (VDR) gene single nucleotide polymorphisms (SNPs) in susceptibility to pulmonary tuberculosis (TB) in

321 TB cases and 347 healthy controls from the study area(175). We found that two polymorphisms, one in DC-SIGN and one in VDR, were associated in a non-additive model with disease risk when analysed in combination with ethnicity (P=0.03 for DC-SIGN and P=0.003 for VDR). In addition, PTX3 haplotype frequencies significantly differed in cases compared to controls and a protective effect was found in association with a specific haplotype (OR 0.78 (0.63–0.98)). Our findings support previous data showing that VDR and DC-SIGN modulate the risk of TB in West Africans (66,199) and suggest that variation within DC-SIGN and PTX3 also affects the disease outcome.

Finally, we included 365 TB patients in a randomised double-blind placebo-controlled trial (218). Patients were given 100,000 IU cholecalciferol/placebo together with directly-observed antituberculous treatment. Cholecalciferol/placebo was repeated after 5 and 8 months of treatment. No serious adverse effects were reported, mild hypercalcemia was a rare event and present in both treatment arms. The clinical score showed a similar decrease in severity among vitamin D and placebo recipients (Figure 1). There was no difference in weight gain or time to sputum conversion. Overall mortality was 54/365 (15%) at one-year follow up and did not differ significantly among the two groups (Figure 2) but a subgroup analysis stratified for HIV infection raised the possibility that vitamin D treated HIV-1 infected TB patients had higher mortality.



Public health implications

We have developed the first clinical score for assessing severity of TB disease which can be used in low-resource settings. With this tool a physician with a stethoscope, a scale and a measuring tape may be able to have important prognostic information on which patients should achieve increased attention or hospitalisation. When grouped in severity classes the signs and symptoms in the TBscore construct a robust index usable in settings where advanced laboratory measurements are not available.

The vitamin D studies did not confirm the hypothesis that vitamin D plays an important role in development or treatment of TB, but associations were found which merits further investigation.

Future perspectives

We are currently further assessing the TBscore for inter-observer variation, and the TBscore may be used in trials to select high-risk patients including smear negative TB patients. The set up for clinical TB trials is an important resource which may be used to answer urgent research questions about the effect of micronutrient/diet supplementation of TB patients (206) and the efficacy of promising TB vaccine candidates.

References on TB: 25,28,51,66,103,105,144,160,164,165,171,172,175,180,185,199,206,218

Figure 1. TBscore at different time points for the two treatment arms

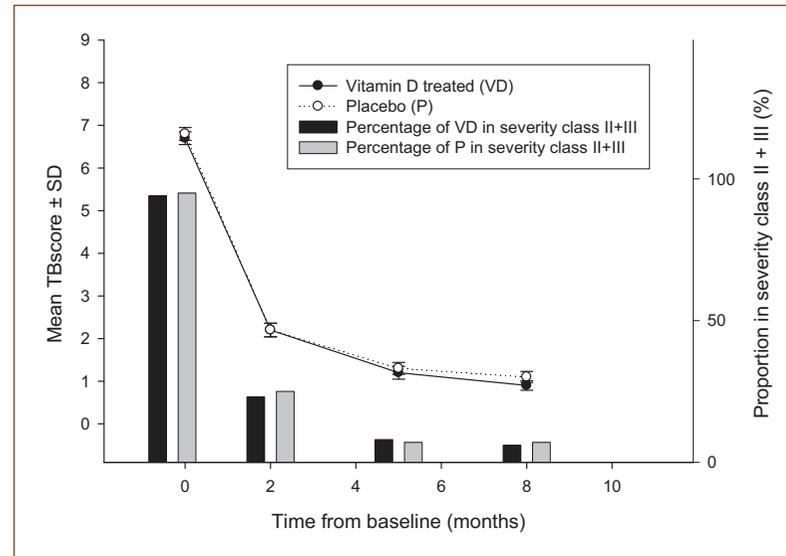
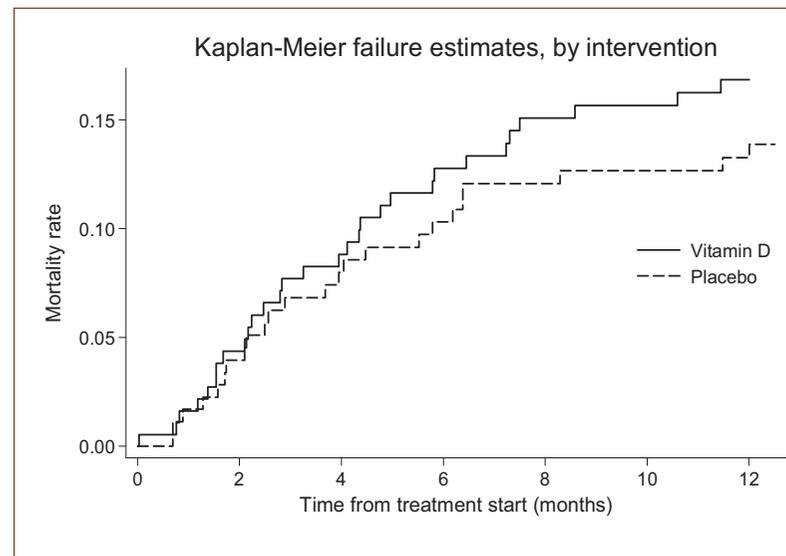
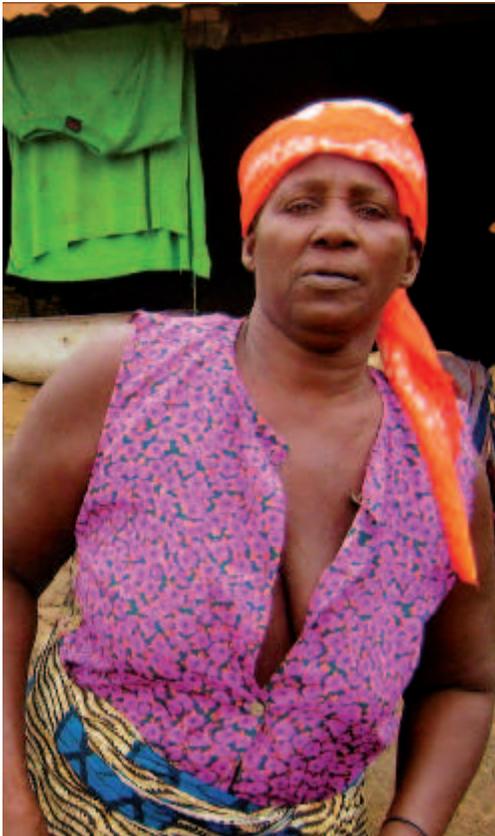


Figure 2. Kaplan-Meier plot of cumulative mortality for the two treatment groups



TB-negative individuals: Using SuPAR to identify individuals with high mortality risk



suPARnostic ELISA

Background

Tuberculosis (TB) continues to affect the lives of millions of people worldwide. In Guinea-Bissau, TB is a common cause of morbidity and mortality. In a community study the incidence TB was estimated to be 471/100,000 person-years. Of those who come to the hospitals with symptoms of TB, only one in four is diagnosed with active TB based on sputum smear and X-ray. The individuals who are negative in sputum and X-ray are called “assumed TB-negative” (aTBneg). Little is known about this group because follow-up is not routinely conducted by National Tuberculosis Programmes in sub-Saharan Africa. We have previously shown that plasma levels of soluble urokinase receptor (suPAR) were eleva-

ted in patients with active TB, carried prognostic value during the treatment period and that suPAR levels decreased in patients that responded to therapy. Since the group of assumed TB negative individuals is very large, we aimed to determine 1) mortality levels among these individuals and 2) whether suPAR can be used to determine post-consultation mortality.

Results

Mortality among aTBneg

Baseline characteristics and mortality during 3-month follow-up according to suPAR quartiles are shown in Table 1. Interestingly, there are more women than men in this group whereas there are more men than women among patients diagnosed with TB. The total mortality rate among individuals that were aTBneg was 21 per 100 person-year-observations (PYO) compared

with 0.03 per PYO among 4983 age-matched controls from the study area. Thus, mortality was 7-fold higher among aTBneg patients.

HIV and mortality

Both HIV-1 and HIV-2 was common among aTBneg individuals with 185 HIV-1-positive and 85 HIV-2- positive out of the 947 aTBneg individuals tested. The mortality rate was much higher for HIV infected subjects compared to HIV-negative subjects, especially HIV-1 compared with HIV-negative subjects. Higher suPAR levels were found among HIV-1 compared with HIV-2 infected and HIV negative individuals.

suPAR as a predictor of mortality

suPAR was included as a linear predictor in a survival analysis that included HIV status and gender. Mortality increased with suPAR levels regardless of HIV status as shown in the Figure 1. A 1ng/ml increase in suPAR was associated with a 46% (95% CI 34-59%) increase in the mortality rate.

Public health implications

Our study suggests that the National Tuberculosis Control Programme should develop guidelines for the management of aTBneg individuals to reduce the high mortality of this group. The problem is to identify individuals in need of further testing among this large group of patients. We found that the suPARnostic® assay can identify individuals with high post-consul-

tation risk of mortality. An increased suPAR level is likely to reflect an elevated inflammatory and ongoing progressive disease state. Hence, an increased suPAR level should lead to further diagnostic testing to identify the cause of increased risk of mortality. This could include testing for HIV, further TB diagnostic testing with culture or PCR methods, sepsis, malaria, bacterial pneumonia, bronchiectasis, bronchial carcinoma, pneumocystis carinii, lung abscess, empyema and chronic obstructive pulmonary diseases.

Future perspectives

Our data provides a solid ground for future development of guidelines for the management of individuals that are TB-negative in order to reduce the high mortality of this group. Further cost-effective studies are needed to determine how suPAR can be included in a clinical decision tree for the management of aTBneg individuals. Thus, we hope in future to conduct a randomised study including suPAR as a decision marker in one arm of the trial.

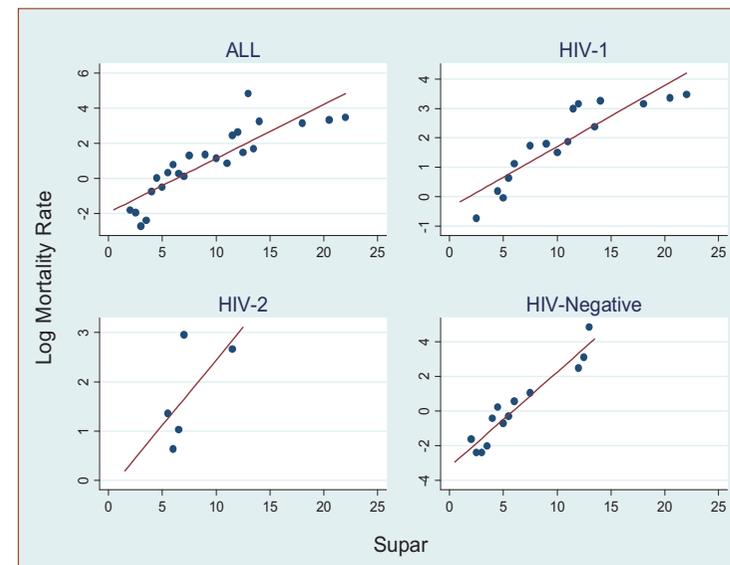
References on TB negative individuals and suPAR: 229



Characteristic	1st suPAR Quartile (0.9–2.6)	2nd suPAR Quartile (2.6–3.3)	3rd suPAR Quartile (3.3–4.4)	4th suPAR Quartile (4.4–45)	Total Range (0.9–45)	P-value
No. of subjects	239	240	239	240	958	
Median age years	32 (17-66)	38 (18-70)	44 (19-71)	41 (21-69)	38 (18-69)	<0.01
Male	113 (47%)	91 (38%)	113 (47%)	100 (42%)	417 (44%)	0.11
Female	126 (53%)	149 (62%)	126 (53%)	140 (58%)	541 (56%)	
HIV-1*	24 (10%)	42 (18%)	36 (15%)	80 (33%)	182 (19%)	<0.01
HIV-2	9 (4%)	20 (8%)	25 (10%)	31 (13%)	85 (9%)	
HIV negatives	203 (85%)	177 (74%)	174 (73%)	124 (52%)	678 (71%)	
No HIV status	3 (1%)	1 (0%)	4 (2%)	5 (2%)	13 (1%)	
Died	2 (1%)	3 (1%)	3 (1%)	38 (16%)	46 (5%)	<0.01

Table 1 Characteristics of aTBneg individuals according to quartiles of suPAR in ng/ml

Figure. Log-mortality rates are plotted against plasma suPAR concentrations according to HIV status. Mortality increased with increasing suPAR independent of HIV status.



Global Health perspective: Too many chefs in Africa

Child mortality fell rapidly in the 1980s concomitantly to the introduction of childhood measles vaccination and maternal tetanus vaccinations but this momentum was lost in the beginning of the 1990s and the fall in child mortality diminished. With vaccination coverage of less than 50% in some low-income countries it has not been possible to decrease child mortality through this intervention. Very little has happened in terms of mortality from pneumonia among children in low-income countries and a fall in neonatal mortality has been completely absent.

Millennium goals

By 2000 the UN agreed on eight development goals for year 2015: *The Millennium Development Goals*. Three of these goals are directly aimed at health issues: reduction in child mortality, improved maternal health and reduction in prevalence of several diseases such as HIV and

malaria. The high ambitions expressed by the goals have strengthened several large-scale global health initiatives such as *Global Fund to fight AIDS, TB and Malaria*, *Roll Back Malaria*, and *The Global Alliance for Vaccines and Immunization*.

Foresight in a small mind

There are available and well documented interventions that could prevent 6 of the 10 million deaths among children under five that occur every year. Likewise available knowledge is often deliberately not used to tackle certain health problems: increasing birth spacing to 36 months or more can reduce under-five mortality by 35%. In 2004, ten years after the introduction of impregnated bed nets only 5% of under-five-year-old children slept under a bed net in malaria areas. It took the WHO further 3 years to publicly apologize for their resistance to approve and distribute impregnated bed nets which Margaret Chan did at the Global Forum for

health research in Beijing 2007. For the past 5 years many countries in Africa have experienced a rapid and substantial decline in malaria prevalence most likely due to the distribution of bed nets. Political, religious and methodological research issues impede the process to reach at least some of the goals in some low-income countries. The goals are meant as a moral incentive and have been developed over more than a decade. Their fulfilment requires a long term commitment with overall solutions and an obligation to establish the foundation for the necessary continuous funding. The goals have put a focus on capacity building and poverty reduction as crucial for the process.

Uncertain numbers

The central parameter for child health in the 2015 goals is the reduction in under-five mortality and among the most important sources to monitor this are the repeated demographic health surveys (DHS). However, it has been argued that the number of children participating in the surveys is too small to capture the changes in child mortality that is expected by 2015. With the uncertainty of mortality figures from the DHS surveys it will not be possible to detect a fall in mortality with five year intervals.

Yet, uncertain data like these will form the basis for donations to the health sector, and low-income countries that are not able to demonstrate a reduction in child mortality will experience that donations are withheld or are blocked completely. Nevertheless, longitudinal demo-

graphic health surveillance research sites in low-income countries follow child populations that are large enough to capture even smaller changes in child mortality.

On the contrary, donors have excluded long term involvement with rapid diminishing resources for development aid, demands for short term goals and lacking support of valid mortality data. In an editorial in *The Lancet* 2004 it was concluded that biomedical research had failed to tackle the massive health problems in DC.

Increasing worries

Many low-income countries do not stand a chance of achieving the 2015 goals before 2015. The most worrying is that the countries farthest from the goals are those with the biggest likelihood of not achieving them. Many agree that the largest hindrance for achievement of the millennium goals is the health care system itself and the World Bank has pointed out that poverty and child mortality levels are increasing in some African countries. Donors are only just realising that an important bottleneck in health development is the weak and fragmented health care systems in low-income countries that have lost the confidence of the population and are unable to deliver even the simplest services with a reasonable level of quality and coverage. Hospitals in low-income countries suffered during the boost into public health campaigns in the early 1980s and now have to fight a vicious circle of low quality of care, lack of motivation and

mistrust of the population. Donors on the other hand prioritise disease oriented vertical programmes with no intention of building capacity in the existing health care system. WHO's *High Level Forum on Achieving the Health Millennium Goals* has pointed out that a major challenge is to increase donor cooperation.

The bitterest pill of them all: we don't know enough

The *Bellagio*-group on child mortality showed in a 2003 paper in *The Lancet* that there is a need for investments in how to translate rational knowledge into action but nothing has happened since then. Research in pneumonia and diarrhoea among children, two diseases that are responsible for 50% of child deaths in low-income countries, only constitute 1% of research funds in childhood diseases in low-income countries.

In spite of the fact that interventions promoting simple hand washing reduce diarrhoea incidence at virtually no cost, large-scale water supply and sewerage projects are still stealing scanty funding for low-income countries. We lack knowledge on why some good health information spreads rapidly while other (too simple?) information is left unused. Less than 3% of the funding from the National Institute of Health (NIH) and the Gates Foundation go to research in the dissemination of interventions. The past four years not a single US dollar has been given to better coverage of proven effective childhood vaccines like the measles vaccine. There are,

however, large areas of Africa where the coverage of this vaccine is less than 1%. By increasing coverage of existing interventions to 99% we would be able to reduce under-five child mortality by 30-50%.

Unexpected observations

At the epidemiological level it is not uncommon to see that child mortality varies by up to 50% within geographically small areas and homogeneously poor populations. At the individual level it is surprising that some poor mothers can bring all of their children through childhood without losing any of them, while her equally poor neighbour has lost more than half of her 8 births. In Guinea-Bissau in the period 1998-2002, 7% of mothers who lost a child were responsible for 34% of all child deaths in the same period. Some mothers lose more children, while others never lose a child. Death is not a random event and is highly determined by socio-economic conditions, but there are other factors that can weaken or re-enforce the effect of poverty. Two such factors would be social capacity and favouritism and if these factors are not taken into account when interventions are created we run the risk that the intervention does not reach those in most need of it: the poorest population groups. Health research is also about accepting the validity of unexpected observations. Such observations often arise within longitudinal studies of population groups over longer time spans (typically more than 10-15 years). Among others the Danish-Guinean Bandim Health Project in Guinea-Bissau has come up with such results.

A poor choice

Poverty and poor health condition fix people in a helpless situation: even if one intervention prevents a child from dying of malaria, the next year the child could die from measles because there are no vaccination campaigns in the poorest and most rural areas. Discrimination by sex, ethnic belonging and religion further boost the vulnerability of the poor.

The poorest children in Indonesia have a four times higher risk of dying before they reach five years of age compared with children of the richest families in the same country. It is estimated that in 2000 99% of all under-five child deaths in the world took place in poor areas. The World Bank Reaching the Poor programme last year published a case report from 12 low-income countries on health and disease in which they demonstrated that the richest 20% of these populations receive more of public health budgets than the poorest 20%.

Some are deadlier than others

The poor are badly off, but other vulnerable groups like illiterates, rural populations, anemic or malnourished children, low birth weight children and very young mothers associated with poverty are also independent risk factors.

There are fundamental problems in the health care system in low-income countries and these problems have consequences for all population groups regardless of social status although with varying impact. The child mortality problem in low-income countries is not solved by exclusive

focus on the ultra poor. Their less poor fellow citizens are also exposed to low quality of care and violation of simple human rights in access to preventive and curative care. The richest population groups in Guinea-Bissau still have a child mortality 30 times higher than an average Scandinavian level. Quality of preventive health care and care in low-income countries is elementarily different from what should be expected from professional well trained health care workers. If we fail to acknowledge the significance of this we are definitely facing serious problems in reaching the 2015 goals.

No laboratory model

In today's Western medicine it is impossible to introduce a pink child plaster without placebo controlled double blind studies, but in Africa it is possible to turn entire health care systems upside down without the least bit of evidence or scientific background. Child vaccines produced and tested under the past reality of European and American epidemics were introduced without further testing in low-income countries with completely different patterns of disease transmission and morbidity burden with high incidences of diarrhoea and malaria as dummies in the game. Only now after 20-25 years of use the first studies on long term effects of child immunizations in DC have demonstrated that some of the vaccines in a best case scenario are useless and in a worst case scenario are detrimental to health. User fees were tested in small hierarchal Muslim societies and thereafter introduced on a large scale as a principle all over Africa. These fees have, like the decentralisation process, com-

pletely paralyzed the entire health system and only increased inequity in access to health care.

Shoot first – then ask

This absence of a scientific public health basis in low-income countries directly opposes a knowledge-based development in the field and the responsibility for this rests on the shoulders of donor organisations, WHO, NGOs and national governments. The will and power to coordinate knowledge-based development and constant learning by experience is simply not present. Decision makers should realize that every new health programme introduced kills one or more existing health programme or activity because resource allocation to health in DC is extremely limited.

One year they prioritise primary health care with free medicine, next year it is malaria prevention that is popular, and then it is control of diarrhoeal diseases with oral rehydration that is important or a cholera epidemic calls for desperate health measures, then it is polio eradication campaigns because the vaccines were donated, vitamin-A in campaigns, everybody needs impregnated bed nets, two-drug malaria treatment last year and now HIV treatment. The health care sector is forced to focus on the priorities of the donor organisations this year, while there is no national incentive to try and monitor efficacy and long-term consequences of these radical yearly changes. As a result we see a falling coverage of measles vaccination because health workers get the idea that this activity is no longer an important health activity.

Too many chefs in Africa

There are too many chefs in Africa: NGO's, WHO, UNICEF, UNDP, UNFPA, The World Bank, vertical disease programmes, relief organisations, religious health programmes and hospitals, unregulated private clinics and national health authorities.

The national authorities have no available professional counsellors to help prioritise and coordinate the many offers from donors in relation to national health plans and future needs. The result is a fragmented and anarchistic health sector where simple diseases and trivial infections turn into a catastrophic social event that forces entire families to spend most of their savings and time on a substandard health product.

A Kyoto agreement on health

The WHO is weakened economically and in terms of influence. We need a strong international professional health institution to serve as the advocate for users of health care and which is capable of generating better knowledge on how to use sound evidence. The international board of health should create and govern a Kyoto agreement on health rights ensuring the foundation on which we can reach the 2015 health goals.

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