

# ROTAVIRUS



## Background

There is currently a global effort to accelerate the introduction of new vaccines against rotavirus, one of the most severe diarrhoeal diseases. These attempts, which are supported by major health organisations including WHO and GAVI, are explained by the fact that infants and young children worldwide are heavily affected by rotavirus disease; unlike other diarrhoeas, the common hygienic measures appear to be ineffective in preventing this infection and no specific treatment is available for rotavirus disease. Thus, vaccination is the cornerstone strategy to control rotavirus infection. Recent estimates suggest that diarrhoea accounts for 13% to 21% of all under-five deaths. Globally, it is estimated that 20-70% of all hospitalisations due to diarrhea in young children and 20% of diarrheal deaths are caused by rotavirus. Although high-income as well as low-income countries are affected by

rotavirus disease, the death-toll is substantially higher in developing countries, and in Sub-Saharan Africa alone, approximately 110,000 to 210,000 children die each year from rotavirus infection.

## Results

***Rotavirus hospital surveillance:*** In Guinea-Bissau, rotavirus infections exhibit a seasonal pattern with annual epidemics occurring during the relatively dry and cooler months, from January to April, with few cases registered from May to December. In the hospital setting rotavirus accounts for a high case-fatality ratio (8%) and a high rate of nosocomial transmission: during the rotavirus season 23% of all children admitted for non-rotavirus diarrheal disease acquired rotavirus infection during admission (>48 hours upon admission). These results cor-

roborate the idea that rotavirus is one of the most contagious pathogens within the paediatric wards and underscore the need for prevention of disease prior to hospital admission (168,204)

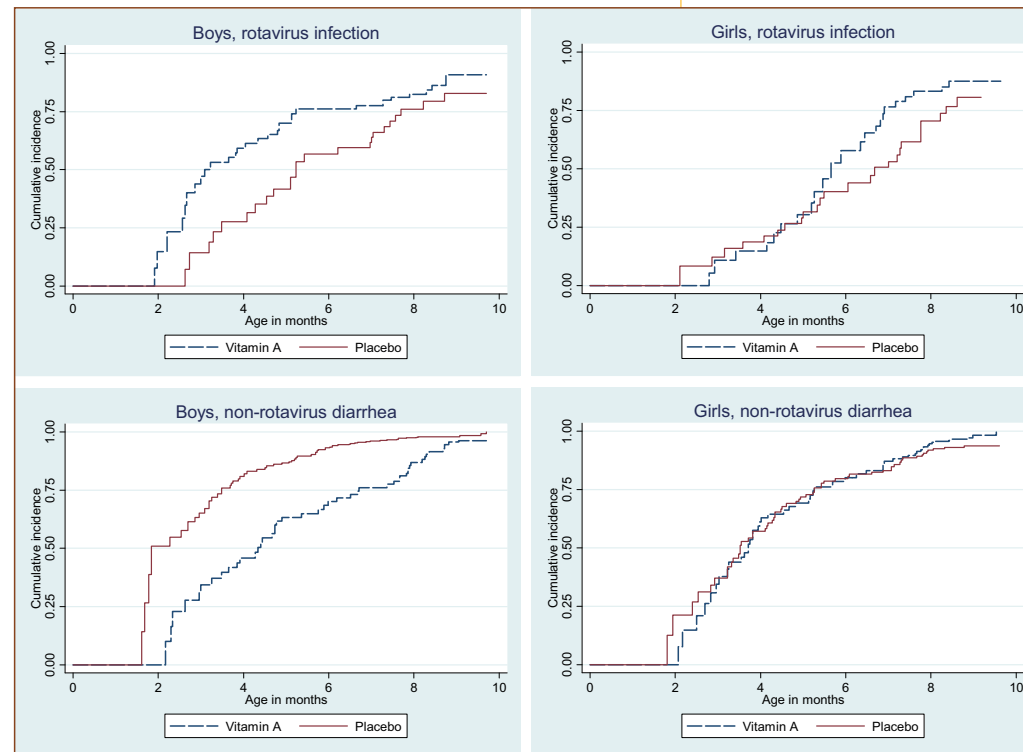
**Prophylactic vitamin A supplementation (VAS) and rotavirus morbidity:** VAS administered to children above 6 months of age in low-income countries has been associated with reduction in mortality from diarrhoea. However, studies of the prophylactic effect of VAS on diarrhoea morbidity have provided diverging results. During the rotavirus season 2005, we examined the effect of VAS on diarrhea disease in infancy in a randomised trial and in particular whether VAS would alter rotavirus colonization and morbidity. Contrary to expected, VAS did not reduce rotavirus colonization and rotavirus diarrhoea; VAS was associated with a significantly higher incidence of rotavirus colonization and diarrhea in the youngest children (Figure). There was no overall effect of VAS on non-rotavirus diarrhoea but the effect differed significantly by sex, being beneficial in boys but not in girls (205).

### Future perspectives

In order to study the impact of rotavirus vaccines on morbidity and mortality among Guinean children we attempt to administer rotavirus vaccines to infants in the near future. Assuming that the rotavirus vaccine proves to be as protective against rotavirus disease and mortality in

Guinea-Bissau as elsewhere, and therefore a likely candidate to be introduced to the childhood immunisation programme in Guinea-Bissau, it will be competing with several other effective interventions against childhood diseases. Therefore the vaccine cost effectiveness still has to be demonstrated, and upcoming plans are to conduct a rotavirus cost-effectiveness study.

**References on rotavirus:**  
21, 22, 37, 168, 204, 205



**Figure.**

Cumulative incidence curves, by sex and presence of rotavirus.

# Long-term consequences of Chickenpox in Guinea-Bissau

## Background

There are virtually no studies of chickenpox in Africa. Based on a large outbreak of chickenpox in Bandim in 2000-2001, we described how the age distribution of chickenpox cases was similar to high-income countries. As for measles infection, intensity of exposure was an important determinant of severity of chickenpox. Although overall acute mortality was low many children had pneumonia and skin infections.

In contrast to previous ideas, community studies of measles have suggested that the long-term consequences of infection may be beneficial among the children who survive the acute phase of measles infection. We therefore examined the long-term impact of chickenpox infection.



## Results


A total of 111 cases and 111 matched controls were examined in a 6-month follow-up study. There were no significant differences in background factors for these two groups. Weight, height and mid-upper-arm-circumference (MUAC) did not differ for cases and controls at the time of chickenpox infection or prior to infection. However, six months after chickenpox infection, cases had grown better than controls with respect to weight, MUAC and height. For all three anthropometric measurements, significant differences were found only for girls; there were no differences for boys (see Table).

The frequency of consultations within the last month had been high. In both groups 42% had been to a health centre or the hospital; more controls (16) than cases (6) had consulted the paediatric ward. In the month before the exami-

Anthropometry for cases and control at the time of chickenpox diagnosis and at follow-up

	Cases	Controls	Paired Analysis
<b>TIME OF CHICKENPOX</b>			
<b>Mean age at inclusion (days)</b>	334 (305-364)	332 (301-362)	P = 0.70
<b>Mean weight at inclusion (kg)</b>	8.6 (8.2-8.9)	8.5 (8.2-8.9)	P = 0.96
<b>Mean MUAC at inclusion (mm)</b>	145 (143-148)	143 (140-145)	P = 0.12
<b>FOLLOW-UP: 6 MONTHS AFTER CHICKENPOX</b>			
<b>Mean age at follow-up (days)</b>	499 (469-529)	504 (473-536)	P = 0.45
<b>Mean time of follow-up (days)</b>	165 (162-168) F: 168 (164-173) M: 161 (157-165)	173 (166-179) F: 173 (165-181) M: 172 (162-183)	P = 0.01 P = 0.21 P = 0.02
<b>Mean weight at follow-up (kg)</b>	9.5 (9.2-9.8) F: 9.5 (9.1-10.0) M: 9.5 (9.1-9.9)	9.2 (8.9-9.5) F: 8.8 (8.5-9.2) M: 9.5 (9.1-9.9)	P = 0.04 P < 0.01* P = 0.96*
<b>Mean growth (g/day)</b>	5.8 (4.8-6.7) F: 5.5 (4.0-7.0) M: 6.0 (4.8-7.2)	3.4 (2.2-4.6) F: 2.6 (0.9-4.3) M: 4.2 (2.4-6.0)	P < 0.01 P < 0.01 P = 0.07
<b>Mean MUAC at follow-up (mm)</b>	147 (145-149) F: 147 (144-151) M: 147 (144-150)	143 (141-146) F: 141 (139-144) M: 145 (141-148)	P = 0.01 P = 0.01 P = 0.27
<b>Mean growth in MUAC (100*mm/day)</b>	1.3 (0.4-2.2)	0.5 (-0.6-1.6)	P = 0.23

Note: interaction between the effect for boys and girls, p<0.04



nation, cases had used antibiotics ( $p < 0.03$ ) and chloroquine more frequently ( $p < 0.09$ ). Skin infections were more common in cases ( $p < 0.06$ ). For case children, the occurrence of skin infections or use of antibiotics could not be related to the initial severity as measured by number of pox, maximum fever response, or being a secondary case (infected at home) ( $p < 0.70$ ).

We also examined the impact on hospitalisations and mortality in the total cohort of children in the community including the 1539 children who had had chickenpox in the outbreak. The hospitalisation rate ratio (HRR) before 3 years of age was 1.16 (0.77-1.74) for previous chickenpox cases compared with children who had not had chickenpox. There was no difference in the type of diagnoses reported for previous chickenpox cases and community controls; for both groups 64% of the hospitalisations were reported to be due to malaria.

Among the 293 chickenpox cases less than 2 years of age in March 2001, 11 died before reaching 3 years of age. One of the chickenpox deaths occurred within 30 days and was consi-

dered an acute chickenpox death. If acute mortality was excluded, the mortality ratio between cases and non-cases was 0.74 (0.39-1.41) adjusting for significant background factors. The epidemic was too small to test other factors, but the effect may have been better for children who were breast-fed at the time of chickenpox infection.

## Conclusion

Weight, height, and MUAC were significantly better for female cases at follow-up. In Guinea-Bissau weight gain is undoubtedly a benefit. This growth benefit may be due to non-specific effects of chickenpox infection. We have previously documented that chickenpox have an immunostimulatory effect increasing the levels of eosinophils and in other studies we have found high eosinophils levels to be associated with better survival. Chickenpox could potentially have a beneficial impact on resistance to other infections.

Another possible explanation for the differences in growth was the use of antibiotics. If cases had

received more antibiotics after infection, it might have had a positive influence on general health in an area with a very high frequency of intestinal infections. At least for malnourished children, metronidazole has a positive influence on growth, and long-term use of antibiotics given to animals increases growth velocity.

In spite of severe infection in the acute phase, many having pneumonia, long-term mortality was slightly lower after chickenpox infection.

### **Future perspectives**

The existing vaccine against chickenpox has not been examined for possible beneficial non-specific effects. However as this vaccine is live attenuated, it may have some of the same beneficial effects which have been documented for measles vaccine. However, there are no planned studies to confirm this.

*References on chickenpox:* 5,80,85,89,117





# Measles infection and prophylactic antibiotics

## Background

The management of measles and its complications has always been a challenge for doctors worldwide. Measles is a highly contagious and severe viral infection leading to profound immunosuppression and bacterial superinfection (e.g. pneumonia, otitis media, conjunctivitis, diarrhoea).

More than 45 years of vaccination have dramatically reduced measles incidence, however there is still an estimated 30 to 40 million cases each year resulting in more than half a million deaths mostly among children in the developing world.

Since antibiotics became generally available, they have been used to treat measles and measles complications. However, it has remained controversial whether measles cases should

receive prophylactic antibiotics to prevent bacterial complications. Though it has generally been recommended not to give prophylactic antibiotics, it has been a very common practice among physicians in low-income countries often due to fear that the patient might not come back.

At the Bandim Health Project (BHP), there is a long-standing tradition to perform measles research, and in collaboration with IDR in Senegal we conducted an observational study in rural Senegal suggesting that children who received antibiotics in the early phase of infection had less risk of being seen with severe measles later on. Therefore, in 1996, we took up the challenge to perform a randomised double-blind placebo-controlled trial on prophylactic treatment with antibiotics in measles.

## Results

The study enrolled 84 measles cases in 1998. When war broke out in early June 1998, the study had to be stopped. Sulfamethoxazole-trimethoprim was used as active drug as it had been the recommended first-line drug against community-acquired pneumonia by the WHO when the study was planned. The main outcomes were pneumonia and admission to hospital.

As can be seen from the table 1/46 (2%) of the cases in the active group developed pneumonia, and 6/38 (16%) in the placebo group. Furthermore, the group that received prophylactic antibiotics had less conjunctivitis and significantly higher weight gains in the month after inclusion than the placebo-group.

## Public health implications

A recent Cochrane review has incorporated our results. Thus it is now recommended to administer antibiotics to children with active measles in geographical areas with a high case fatality rate or with a high incidence of post-measles pneumonia.

*Publications on prophylactic antibiotics:*  
132,157,158,162





**Table.** Intention to treat analyses of outcome measures

	Co-trimoxazole (n=46)	Placebo (n=38)	OR <sup>§</sup> (95% CI)	Adjusted OR <sup>⊠</sup> (95% CI)	Adjusted OR <sup>⊠</sup> (95% CI) Laboratory confirmed cases
<b>Main outcome measures</b>					
<b>Pneumonia after inclusion</b>	1 (2%)	6 (16%)	0.08 (0.00-0.56)#	0.14 (0.01-1.50)#	0.11 (0.00-1.22)#
<b>Hospitalised with measles after inclusion</b>	0 (0%)	3 (8%)	0 (0-1.03)§	-	-
<b>Other outcome measures</b>					
<b>Diarrhoea after inclusion</b>	3 (7%)	5 (13%)	0.27 (0.04-1.39)#	0.17 (0.01-1.55)#	0.10 (0.00-1.04)#
<b>Severe fever after inclusion</b>	6 (13%)	11 (29%)	0.32 (0.10-1.07)	0.36 (0.09-1.43)	0.34 (0.08-1.53)
<b>Oral thrush after inclusion</b>	0 (0%)	3 (8%)	0 (0-1.03)§	-	-
<b>Stomatitis after inclusion</b>	4 (9%)	7 (18%)	0.37 (0.09-1.50)	0.43 (0.08-2.26)	0.35 (0.06-2.12)
<b>Conjunctivitis after inclusion</b>	12 (26%)	17 (45%)	0.36 (0.14-0.96)*	0.31 (0.10-1.03)	0.25 (0.06-0.96)*
<b>Otitis media after inclusion</b>	1 (2%)	2 (5%)	0.38 (0.02-4.42)#	0.72 (0.05-10.6)#	0.44 (0.01-6.93)#

\* p<0.05, # Profile-likelihood confidence interval, § Exact test, <sup>§</sup> Controlled for age group, <sup>⊠</sup> Adjusted for age group, weight-for-age z-score at inclusion, time since rash and measles vaccination status

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# Malaria treatment and development of resistance

## Background

During the last 15 years the Bandim Health Project has studied the efficacy of different treatment schedules for malaria, focusing on the antimalarials available and/or recommended by the National Malaria Programme. Quinine continues to be a good and efficient choice for third-line treatment, however, the effectiveness when used as second-line treatment is more questionable (195).

Sulphadoxine-pyrimethamine (S/P), which proved to be an efficient antimalarial, was until recently recommended as second-line treatment. However, a high frequency of mutations coding for S/P resistance was found in Bissau (53), stressing the importance of monitoring the efficacy.

We have previously shown that while treating with chloroquine in the recommended dose of 25 mg/kg bodyweight had a high treatment

failure rate, increasing the dose to 50 mg/kg turned chloroquine into an efficient antimalarial.

That 25 mg/kg is insufficient has been observed in all of Africa. Therefore chloroquine has almost been completely abandoned and the much more expensive artemisinin combination therapies have been recommended and introduced in most sub-Saharan countries, including in Guinea-Bissau in the summer of 2008. Since we found chloroquine to be still efficient in the higher dose of 50 mg/kg and the drug is cheap and well-known, we monitored the genetic background for resistance in Guinea-Bissau.



## Results

Both amodiaquine and chloroquine have been suggested to be combined with artemisinin. We therefore examined the efficacy of different doses of these two drugs. Amodiaquine was very efficient both in the dose of 15 mg/kg and the dose of 30 mg/kg. As previously found chloroquine 25 mg/kg had a high failure rate, whereas 50 mg/kg proved to be efficient (138). In several studies using chloroquine between 2004 and 2008, we did not find any decrease in

efficacy; hence, chloroquine resistance as measured by in-vivo tests has not increased during the last 15 years. The WHO in-vitro micro test to assess chloroquine resistance has been used almost annually since 1990. A slight decrease in resistance was found during this period confirming the in-vivo results (194).

Our analyses of parasites indicate that the genetic basis of chloroquine resistance is the same in

Guinea-Bissau as in the rest of Africa (193). The prevalence of the mutation *pfcr1* 76T was found to vary between 13% and 38%, which is low compared to most other African countries. Furthermore, we have found that the prevalence

of single nucleotide polymorphisms (SNP) at *pfcr1* positions 76, 271, 326 and *pfmdr1* position 86 did not change between 1992 and 2005, indicating that the prevalence of mutations coding for chloroquine resistance did not increase during this period (194).

To study the efficacy of treating with chloroquine 50 mg/kg compared to 25 mg/kg we genotyped the parasites on the day of inclusion and in case of re-parasitaemia following treatment and found that the efficacy of the higher dose was 78% as compared to 34% for the standard dose when treating parasites carrying the mutation indicating resistance (*pfcr1* 76T) (193). An argument against using higher doses has been that the risk of re-infections with resistant parasites would increase significantly. However, the risk of re-infection with a parasite carrying the 76T mutation was only 9% for both the two groups treated with 25 mg/kg or 50 mg/kg.

Between 1994 and 2003, we monitored the malaria treatment given at a health centre in Bissau 4 to 8 weeks per year. We found that a median chloroquine dose of 63 mg/kg was prescribed, in spite of the official recommendation being only 25 mg/kg (194). Also we monitored chloroquine prescriptions and reported intake of chloroquine in 102 children. The median total chloroquine dose prescribed and reportedly taken was 81 and 77 mg/kg, respectively. No severe adverse events were reported and no adverse events were associated with higher chloroquine concentrations. Interestingly, only 3 of the 102 children had *P. falciparum* in the blood



indicating that diagnostics are poor leading to massive over-prescription (224).

As many parasites have one or more mutations coding for resistance to S/P we compared the efficacy when using S/P for children with treatment failures to the first line drug. S/P remained efficient with no difference in treatment success rates from 1995/1996 to 2002/2004 (145).

### Public health implications

During a period of approximately 15 years the resistance to chloroquine has not increased in Bissau, if anything it has decreased slightly. Treating with 25 mg/kg is insufficient, but increasing the dose to 50 mg/kg turns chloroquine into an efficient antimalarial also for treating parasites harbouring the mutation coding for chloroquine resistance. Recent studies suggest that chloroquine resistance is mediated by an energy-dependent saturable chloroquine efflux carrier, alternatively mediated by a channel. In Guinea-Bissau high doses of CQ are commonly taken and well tolerated suggesting that chloroquine resistance can be overcome by the higher doses probably due to a loss of fitness of the parasites (194,197). That loss of fitness plays a role is supported by the fact that chloroquine resistance has disappeared from Malawi 7 years after abandoning the drug. If and when chloroquine is reintroduced, alone or in combination with artemisinin, this should be done with the higher dose of 50 mg/kg to limit the spread of chloroquine-resistant parasites (159).



The fact that S/P remained efficient for second-line treatment over a period of 10 years indicates that the drug can still be used for selected groups of patients. As it is the best antimalarial for intermittent preventive treatment of pregnant women it has been reserved for that, thus raising the question as to which antimalarial to use for second-line therapy. As an artemisinin combination therapy has been adopted as first line treatment this can not be used for treatment

failures. Therefore the National Malaria Programme has recommended quinine given three times a day for seven days – a treatment schedule which is difficult and for which one could expect a low adherence suggesting that the effectiveness should be evaluated (195).

### Future perspectives

The studies suggest that the common use of high dose chloroquine in combination with a loss of fitness associated with chloroquine resistance explains the continued efficacy of chloroquine in Guinea-Bissau. Our data are observational and cannot be taken as proof. In addition the data available on adverse events, though encouraging, does not rule out serious adverse events. Despite the flaws, the situation in Guinea-Bissau warrants further research into dosing strategies, adverse events and possible combinations of a drug that is cheap and available and which regains efficacy when it is removed from the environment.

As lumefantrine-artemether (Coartem) has now been introduced as treatment for uncomplicated malaria we are now evaluating the efficacy. As over-treatment for malaria is common (200,224) and as the treatment used now is expensive, the strategies for improving the diagnostic procedures should be followed closely, especially considering the lower incidence of malaria at present. We have shown that frequent treatment protects the children from clinical malaria (40). As the

present over-treatment can be compared to intermittent preventive therapy it will be important to study which effect improved diagnostic procedures will have on the incidence of clinical malaria.

### References on malaria:

11,40,43,53,67,136,138,145,146,193-197





# Is malaria disappearing?

## Background

Malaria has always been considered the biggest public health challenge in Guinea-Bissau, both due to the number of cases and deaths caused, but also due to socio-economic implications. Malaria transmission is present all year around, and reports from the 1980s and 1990s pointed to a prevalence of malaria parasites of 44-79% among children aged 2-9 years in rural communities. Several public health interventions and large amount of funds are available for malaria control. Environmental changes are occurring. Prioritisation of these interventions to maximise the use of resources requires better knowledge of the current situation.

## Results

Recent epidemiological studies on malaria have included community surveys and collection of

better quality data at health facilities in Bissau. The recent data have shown a decline in malaria. In a community survey carried out in Bissau in 2003, only 3% of the individuals living in the randomly selected houses had malaria parasites, contrasting with 26% in 1994. At the health facilities malaria is grossly over-diagnosed. Reports from the MOH health information system indicate that malaria is responsible for 50-70% of all consultations. In 2003/2004, malaria surveillance was established by the BHP at the national paediatric ward and three health centres in Bissau. As expected, 64% of the outpatient consultations among children < 5 years of age were clinically diagnosed as malaria, however only 13% had malaria parasites detected by microscopy. Among hospitalised children, only 44% had malaria parasites even though 73% had a clinical diagnosis (200) (Figure). The proportion of malaria-positive cases increased with increasing age. For 82% of the cases, the labora-

tory results were available to the clinicians before prescription. However, anti-malarial (96%) and antibiotic drugs (65%) were prescribed to patients with negative slides (200).



Recent figures from 2006/2008 shows that around 11% of children seen at health centres in Bissau with suspected malaria has a malaria-positive slide. Several factors may have had an impact on the decline in malaria infection. Untreated bed nets are used by around 90% of children less than 5 years of age. Since the adoption of the policy of re-impregnation of nets in 2004, the use of impregnated bed nets increased from 5% to more than 70% in 2006. Since nearly everyone consulting at a health centre has been treated with chloroquine, the health system has in fact instituted intermittent prophylactic treatment of malaria. Resistance to chloroquine has been stable, but the common use of double doses of chloroquine has been found to be effective in around 88% of the cases (138, 192, 194). The decision to change to coartem as first line drug was taken in 2007 and its implementation started in May 2008.

## Public health implications

The decrease in malaria transmission will probably shift the peak of cases to higher age groups and we have started observing this trend. If further declines occur, a good surveillance system for early warning will be necessary and we will need to be prepared for possible epidemics in the future. The introduction of coartem, a more expensive drug than chloroquine, should be accompanied by attempts to improve the diagnosis of malaria by using both microscopy and rapid diagnostic tests. If implemented, it will improve the diagnosis and treatment of both malaria and other conditions that might otherwise have been ignored. Thus, several unneeded doses of coartem and the scarce money of users would be saved. However, this will reduce the intermittent prophylactic effect of chloroquine given to almost all cases seen with fever at a health facility. Hence, in a worst case scenario, treatment of individual malaria case will be improved with coartem but malaria might reappear because there is less chloroquine prophylaxis in the high risk age groups, although we recognise that coartem might also have a preventive effect as it acts also on gametocytes preventing maintenance of transmission. The decline of

malaria has occurred, but control is vulnerable and malaria might be reappearing.

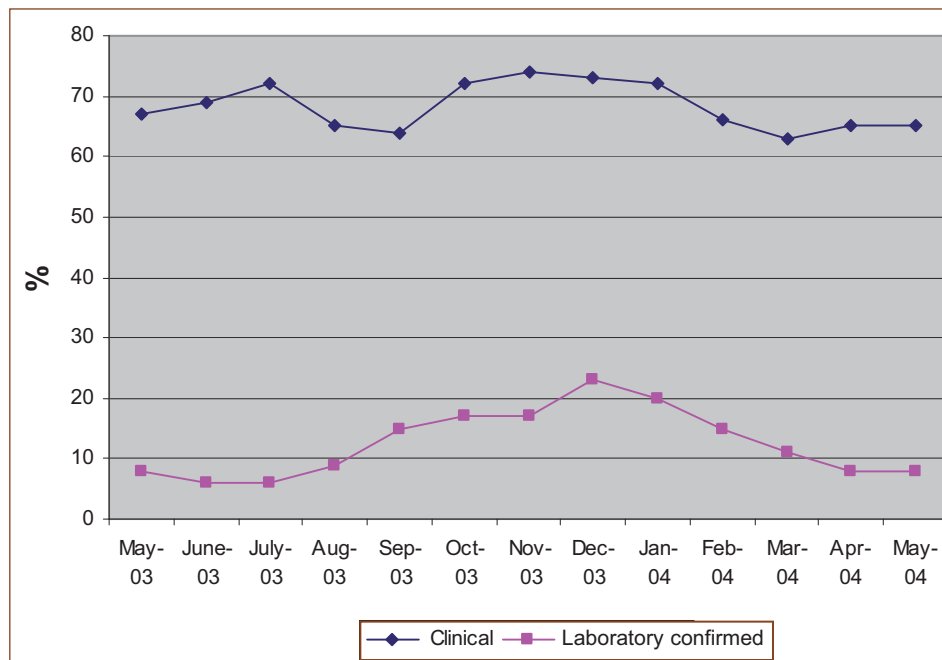
### Future Perspectives

Malaria is decreasing in several parts of the world including the neighbouring countries in West Africa. This has revived the hope for elimination and an expert meeting was convened in January 2008 by WHO to revise previous positions. In West Africa, joint collaboration on a common programme for monitoring elimination is being discussed between The Gambia, Senegal and Guinea-Bissau. This will require reinforcement of existing interventions, testing the most cost-effective combinations. It will be very important to continue monitoring the changes in the epidemiology of malaria using simple methods as well as good entomological data. For this reasons, the BHP is creating sentinel sites all over Guinea-Bissau in order to collect good quality data.

The implications of the different policies should be studied. Health personnel are resistant to use laboratory results in deciding on the use of anti-malarial drugs. We are currently studying the consequences of treating or not treating a child

with a malaria-negative slide with coartem or chloroquine for clinical outcomes and preventive effects against further attacks of malaria.

### References on the disappearance of malaria: 200



**Figure.** The prevalence of clinical and laboratory diagnosis among children less than 5 years of age at the health facilities in Bissau, 2003/04



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# Respiratory syncytial virus: Taking the observations to Denmark

## Background

Respiratory syncytial virus (RSV) infection leading to early childhood hospitalisation is still a major paediatric concern globally. The incidence of RSV hospitalisation appears to increase (6, 92). In high-income countries, the incidence of atopy has been increasing steadily for decades, and wheezing and asthma have become the most frequent chronic diseases in childhood (118). Severe RSV infection often present with wheeze and a major part of RSV-infected children wheeze months after their primary RSV infection. Therefore, an important question in RSV research has been to find out whether severe RSV infection cause wheezing and atopy.

During the past 5 years, we have studied risk factors for severe RSV infection in both Guinea-Bissau and Denmark. Furthermore, we studied the association between RSV hospitalisation,

wheezing and atopy, RSV hospitalisation in children with congenital heart disease, and the association between RSV hospitalisation and invasive pneumococcal disease in the Danish child population. Using cord-blood from newborns in the Danish National Birth Cohort ([www.bsmb.dk](http://www.bsmb.dk)), we studied the seasonal variation of maternally derived RSV-neutralising antibodies and the association to RSV hospitalisation as well the influence of maternally derived RSV-neutralising antibodies on RSV hospitalisation and on recurrent wheeze. In the Danish twin population born 1994 to 2004 we further examined the associations between RSV hospitalisation, wheezing and asthma.

## Results

In Guinea-Bissau, BCG immunisation protected against severe RSV infection (88), and we obser-

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ved that mother-to-son cross-sex transmission might be part of the explanation as to why boys are more frequently severely infected with RSV (60).

In Denmark, both recent hospitalisation for RSV infection and for non-RSV respiratory infection increased the risk of invasive pneumococcal disease among children less than 2 years of age (202). We observed a 2-fold increased risk of RSV hospitalisation in Danish children with congenital heart disease. Among the children with congenital heart disease, risk factors for admission were Down syndrome, cardiomyopathy, and haemodynamically significant heart disease. Young age and cardiac de-compensation were associated with more severe course of RSV disease (227).

In the general Danish child population, male gender, medical non-atopic risk factors, the presence of other children less than 12 years of age in the home, day care attendance, and maternal smoking were associated with an increased risk of RSV hospitalisation. Interestingly, atopic disposition and a history of wheezing increased the

risk of RSV hospitalisation; the factor associated with the largest risk increase for RSV hospitalisation was early recurrent wheeze (141).

When we then examined the associations between RSV hospitalisation, wheezing and asthma in Danish twins, we found a bi-directional association between severe RSV infection and asthma. Severe RSV infection was associated with a short-term increase in the risk of subsequent asthma suggesting RSV induce bronchial hyperresponsiveness; and asthma was associated with a long-term increased susceptibility for severe RSV disease, suggesting a host factor





being responsible for the severe response to RSV infection. This suggests that severe RSV infection and asthma may share a common genetic predisposition and/or environmental exposure (219). We observed an increased concordance of severe respiratory syncytial virus infection in identical twins, pointing to genetic factors being important for the severity of respiratory syncytial virus infection (222). Hence, RSV infection, severe enough to warrant hospitalisation, does not cause asthma but is rather an indicator of the genetic predisposition to asthma (228).

Studying maternally derived RSV-neutralising antibodies, we found a clear temporal association between the RSV antibody level in cord blood and RSV hospitalisation in infancy suggesting that RSV-neutralising antibody level plays a role in the seasonal pattern of RSV infection (220). In addition, we observed that maternally derived RSV-neutralising antibodies protect infants against RSV hospitalisation, also when the infant has recurrent wheeze. However,

to our surprise high maternally derived RSV neutralising antibody levels were associated with an increased risk of recurrent wheeze (221).

### Future perspectives

Our future studies will focus on risk of RSV hospitalisation in children with chronic diseases; on genetic markers of severe RSV infection, wheezing, asthma and eczema; and on studies on maternally derived RSV-neutralising antibodies, lung function, wheezing and asthma. To link back to the Guinean studies which generated this line of research on RSV, we also intend to explore whether vaccinations are related to the major change in the relative female-male incidence of RSV which occurs in the first year of life in Denmark (141).

*References on RSV:* 6, 60, 88, 92, 106, 118, 131, 141, 202, 219-222, 227, 228