New Paradigms in Vaccine Evaluation and Promotion: a View from a Developing Country

Audiovisual presentation on the Mérieux Foundation Meeting on:

«Beyond Efficacy: The Full Public Health Impact of Vaccines in Addition to Efficacy measured in Trials»

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Introduction

- The era of vaccines almost 100% effective is over!
- For several reasons we have vaccines, already introduced in the market or in the vaccine pipeline, with a much lower efficacy.
- Main reasons for this lower efficacy:
  - The vaccine doesn't have the antigenic power enough to protect everybody. It protects only a certain percentage of people (Best example is the malaria vaccine, but it can occur with others)
  - The disease is provoked by a large number of strains and the vaccine doesn't contain all (a few examples: the pneumococcal, the HPV vaccines, among others.)

Confusing element

- **The same disease or clinical syndrome can be provoked by several pathogenic agents;**
- **Sometimes the differential diagnosis is not easy to make and require sophisticated laboratorial methods, not always available, particularly in peripheral Health Units in developing countries.**

Therefore:

As the immunogenic power of the vaccines is specific, the vaccine didn't protect against the disease, but only against the cases resulting from that specific pathogenic agent or strain! Un example, is the case of pneumococcal and Hib diseases! The same with diarrhea and the rotavirus!

Let's analyze a few paradigmatic cases:

- **Pneumococcal disease and vaccines;**
- **Cervical cancer and HPV vaccines;**
- **Rotavirus disease and vaccines;**
- **Malaria disease and vaccine.**

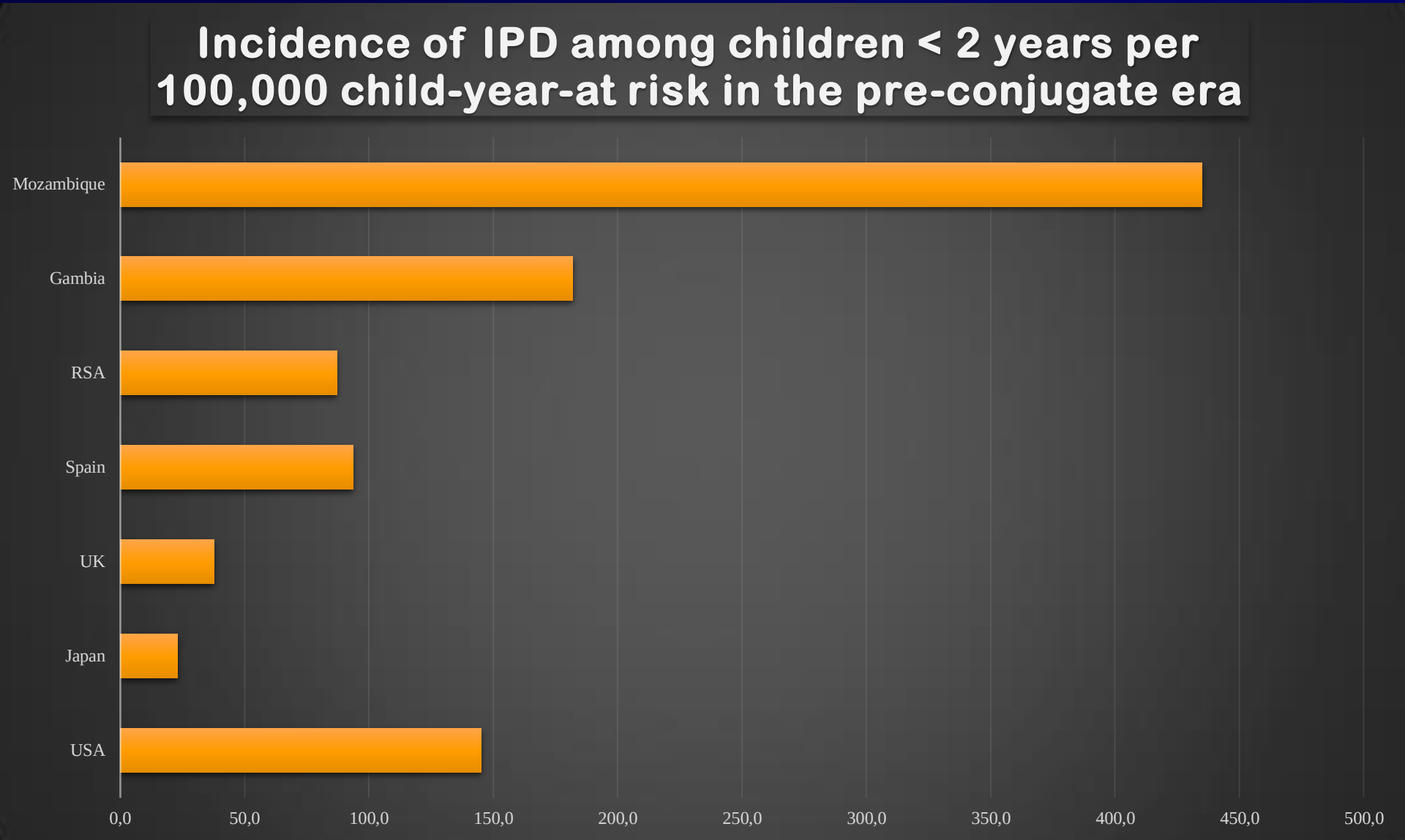
Pneumococcal disease and vaccines

- One month ago, there were known 94 strains of pneumococcus (1, 2). Eventually to-day there are more (A collaborative project to monitor new genotypes is being led by University of Emory) (1);
- Pneumovax polysaccharide vaccine (not immunogenic for young children) contains only 23 serotypes;
- The first Pneumococcal conjugated vaccine (useful for children) contained only 7 serotypes, most frequent on the Northern hemisphere;
- Incidence of the different strains have geographical variations (1);

Pneumococcal disease and vaccines

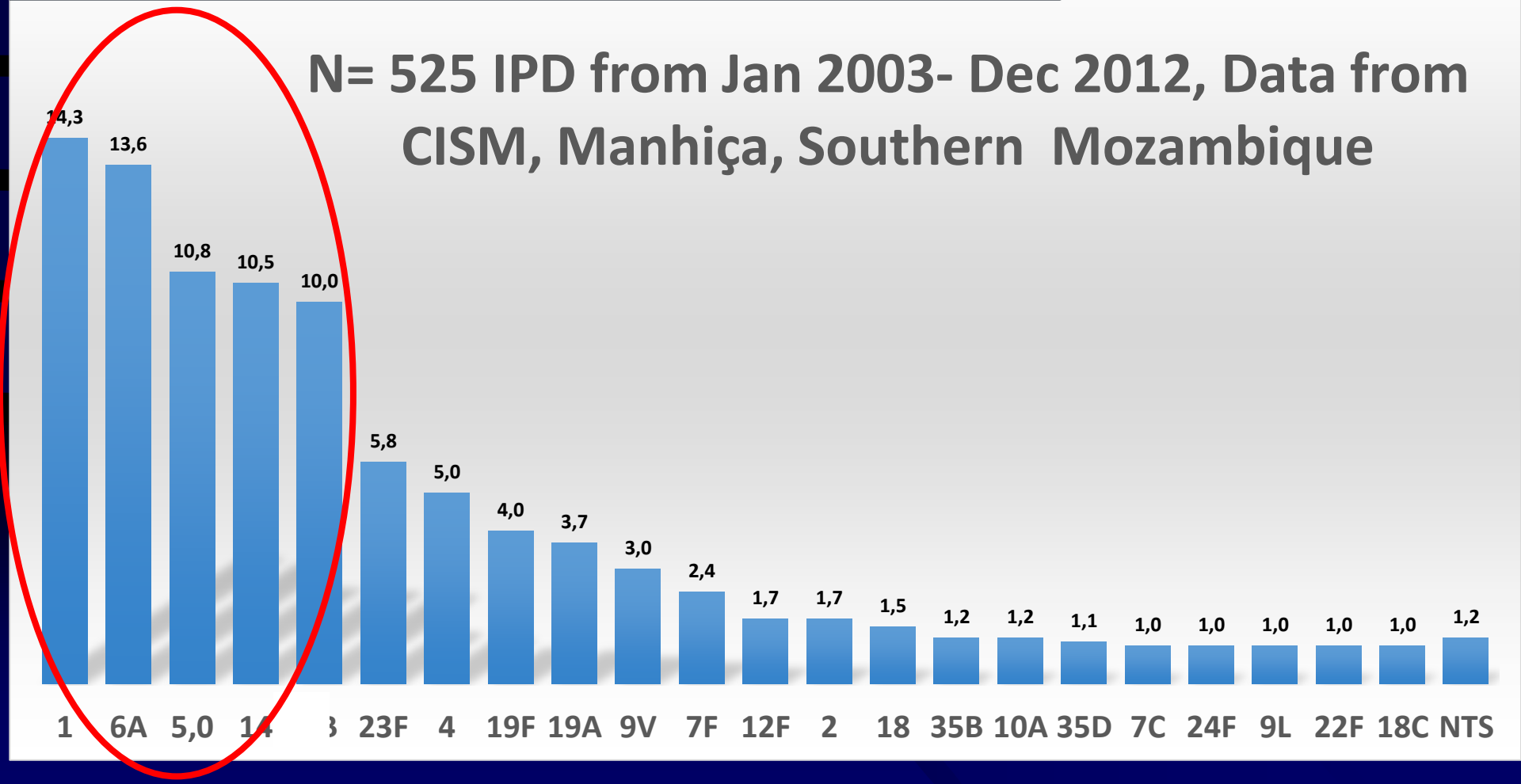
- **Serotypes replacement following PCV7 introduction in developed world, contributed to the introduction of new PCVs, with the aim of preventing serotypes in Africa:**
  - **PCV10 which also protects against non capsulated hemophilus influenza (responsible for otitis);**
  - **PCV13 with the advantage of more pneumococcal serotype coverage compared to PCV10;**
- **Crossed immunity exists but not for all strains** (1);
- **Studies in Manhiça Health Research Center show that mortality by IPD is high (13%)** (3)**. Incidence is very high** (see next slide) (4) **and the lethality only for meningitis is 29% for children <5 years old and 35% for children <2 years old** (3)**.**
- **Lethality rate for pneumococcal pneumonia is 11%** (3).

Studies in Manhiça showed an incidence higher than in other parts of the Africa and the World (4)



The most prevalent Invasive Pneumococcal Disease (IPD) serotypes

(5) SIGAÚQUE, Betuel: 2011, Based on CISM data



PCV coverage estimation

Vaccine Serotypes	N. serotypes	Estimated coverage
PCV-7	111	**32%**
PCV-10	246	**70%**
PCV- 13	291	**83%**
Other serotypes	60	

Vaccine serotypes

PCV-7: **4, 6B, 9V, 14, 18C, 19F e 23F**

PCV10: **PCV-7 + (1, 5, 7F)**

PCV13: **PCV10 + (3, 6A, 19A)**

(6) SIGAÚQUE, Betuel: 2011, Based on CISM data

Pneumococcal disease and vaccines

Conclusions:

- We are in the presence of a vaccine which is, far from being 100% effective, but that has a high potential to reduce considerably the number of cases of pneumococcal invasive disease, which cause a high burden to the NHS in terms of out and in patients (consequently with high costs) and have a high lethality rate (3, 4);
- Efforts shall be made to include more pathogenic strains in the vaccine, but the high burden of the disease, both in terms of incidence and mortality, has to be taken in account on the evaluation of the vaccine, apart from its efficacy.

Cervical cancer and HPV vaccines

- **According with WHO and the International Agency for Research on Cancer (IARC) cervix cancer is the 4th most frequent cancer in the world** (7);
- **In 2012 were registered 528.000 new cases (85% of them in developing countries, where it represents 12% of all cancers in women) and 266.000 deaths** (7);
- **In Mozambique it represents 31,2% of all cancers in women, one of the highest burden in the world** (7);
- **There are more than 120 serotypes of HPV known, but the 16 and 18 represent the highest risk to induce cancer in all countries, with slight geographical variations** (7, 8) **(in Mozambique: 72%)** (9), **but the next in importance are 51, 52, 45, 35, 33, 31 and 58** (7, 9);

Cervical cancer and HPV vaccines

- 6 other serotypes can also cause cancer (total of 15) (8)
- In all cases of cervix cancer an HPV ADN was always found (9);
- Multiple infections are very common: between 40 (7) and 81 % (9);
- Some serotypes are linked to more benign diseases like condiloma (7, 8);
- Studies in Mozambique show that HIV status doesn't influence the incidence of cervix cancer nor the efficacy of the vaccines (8, 10, 11);
- Secondary prevention, through systematic screening by cervical cytology of all women over 35 years (better 25 years) is very effective in preventing cervix cancer but is very expensive. Developing countries can not afford it;

Cervical cancer and HPV vaccines

- **Screening of all women by visual inspection with acetic acid is reasonably effective** (7) **and much less costly, but still at a cost unaffordable for developing countries and impracticable in large scale, because of the logistics involved;**
- **There are 2 vaccines on the market both including the serotypes 16 and 18, but one contains also serotypes 6 and 11. They are very effective, but they have only the potential to prevent 70% of the cancers because they didn't contain all serotypes** (7, 8). **Data from Mozambique show that this percentage could be between 72** (9) **and 78 %** (7);
- **Crossed immunity exists , but in limited extent, not for all strains** (7, 8);

Cervical cancer and HPV vaccines

- A new 9-Valent HPV Vaccine was very recently reported. It seems to be as effective as the previous vaccines for the initial 4 serotypes but it covers also the other 5 serotypes (31, 33, 45, 52, and 58) (12). There are no studies yet to evaluate the actual impact in cancer prevention, but it will not cover serotypes 35 and 51, which are also important in Mozambique;
- As HPV is a sexual transmitted disease, the introduction in EPI of immunization of female adolescents will have a certain impact on future generations, but all women that have not been vaccinated will not be covered. Therefore other prophylactic measures (secondary prevention) have to be continued for several decades. Only very rich countries can afford it!

Cervical cancer and HPV vaccines

Conclusion:

In developing countries, where secondary prevention is not affordable and where the burden of disease is very high (as is the case of Mozambique), there is a strong justification to introduce the vaccine in the regular EPI, even if the available vaccines did not cover all serotypes and therefore are only able to prevent around 72 to 78 % of cases of cervix cancer!

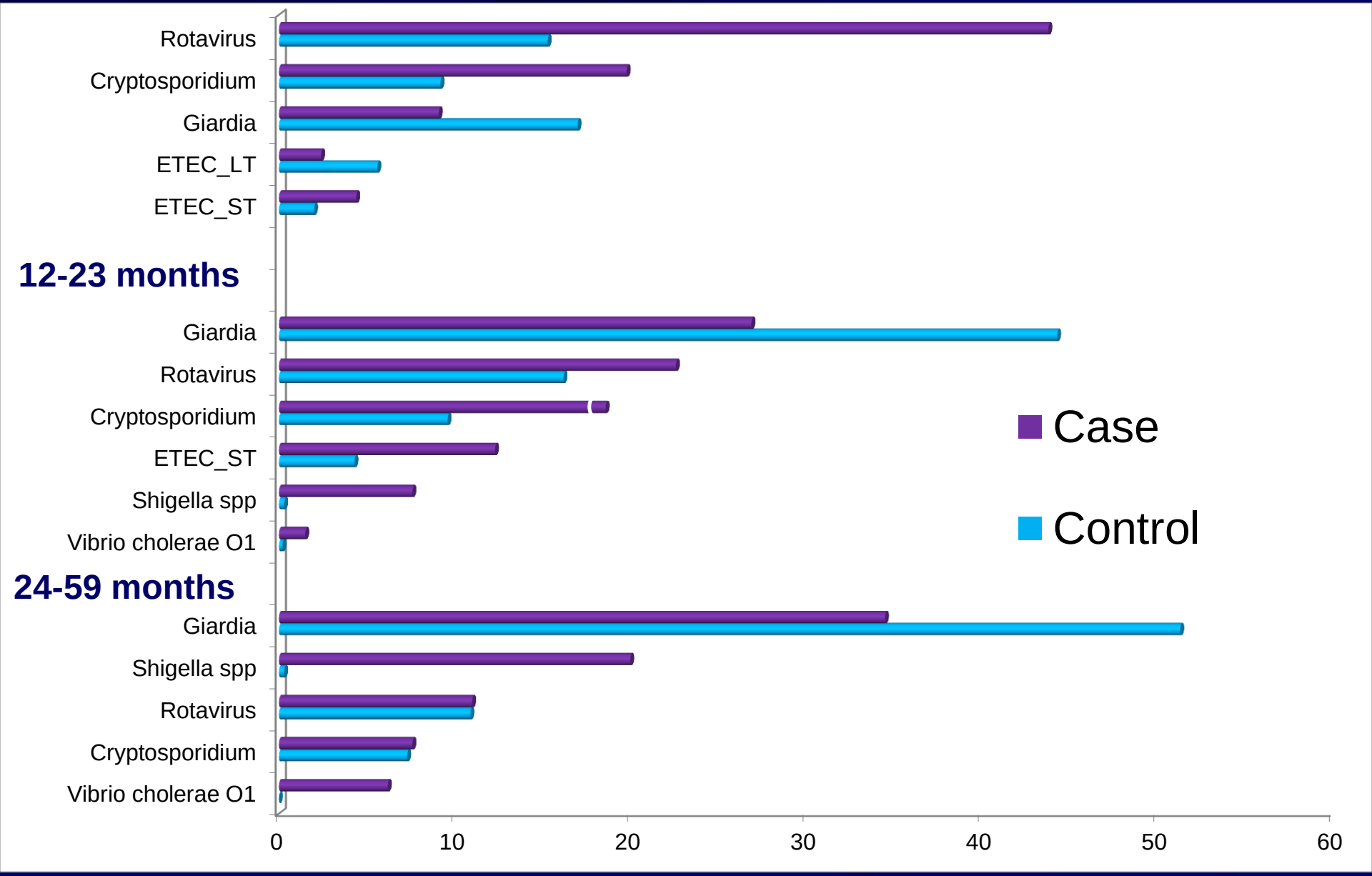
Rotavirus disease and vaccines

- **In a multi-centric controlled study (in which Manhiça Research Center takes part) to estimate the burden, etiology and sequelae of moderate to severe diarrhea among children 0-59 months, in Sub-Saharan Africa and Asia, several etiological agents were found** (13)**:**
  - **Bacteria:** Salmonella, Shigella, Vibrio, Campylobacter, Aeromonas, Diarrhoeagenic E. coli (ETEC, EPEC, EAEC, EHEC)**,**
  - **Virus:** Rotavirus, Adenovirus, Sapovirus, Astrovirus and Norovirus I & II
  - **Protozoa:** Cryptosporidium spp, Giardia lamblia & Entamoeba histolytica.

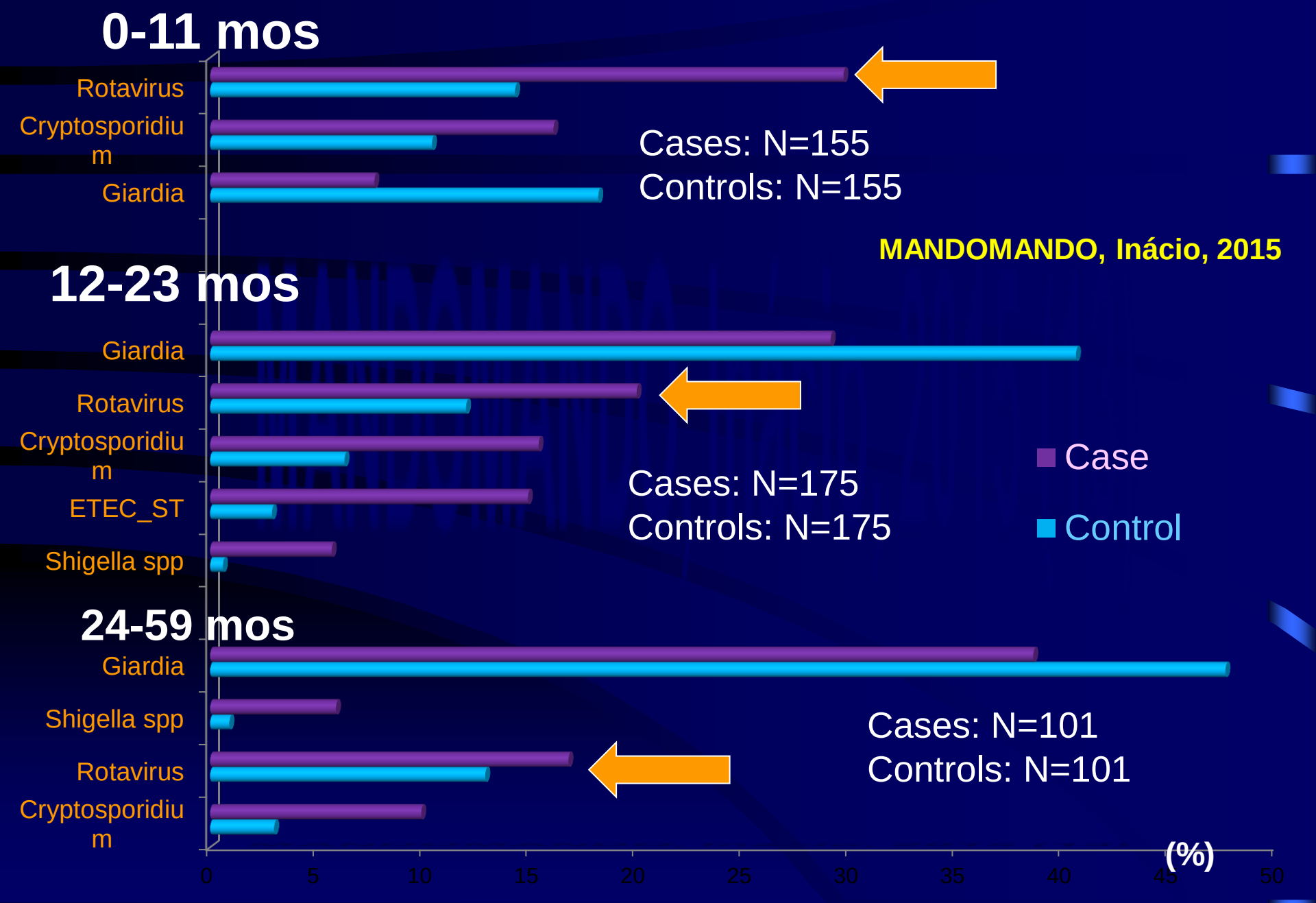
Isolation rate of enteric pathogens in MSD study

0-11 months

MANDOMANDO, Inácio, 2015 (13)



Isolation rate of enteric pathogens in LSD study



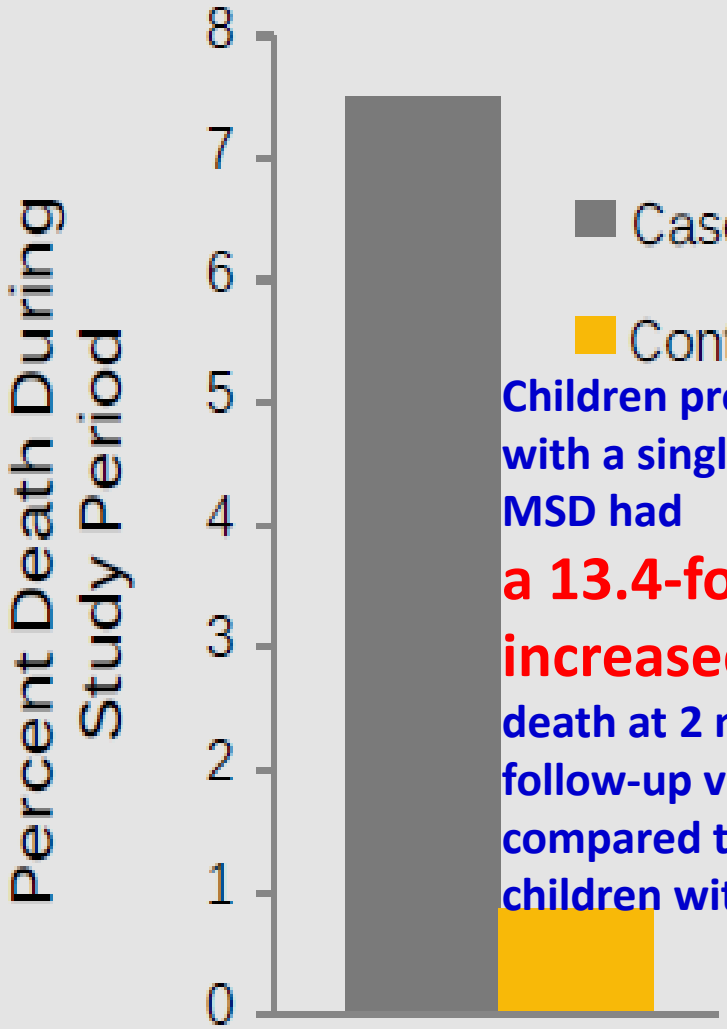
Attributable fraction & incidence of specific pathogens among MSD cases

	Unadjusted		Adjusted		
MANDOMANDO, Inácio, 2015 (13)	OR (95% CI)	AF (95% CI)	OR (95% CI)	AF (95% CI)	Incidence rate / 100
0-11 months - Total MSD (n=431)					
Rotavirus	**5.35** (3.87-7.38)	**33.27** (30.80-35.74)	**6.00** (3.65-9.87)	**34.75** (31.30-38.20)	**3.42** (2.82-4.03)
Cryptospor.	**2.62** (1.83-3.74)	**12.78** (9.96-15.60)	**3.67** (2.06-6.54)	**15.26** (11.96-18.56)	**1.56** (1.15-1.97)

High mortality among children with MSD

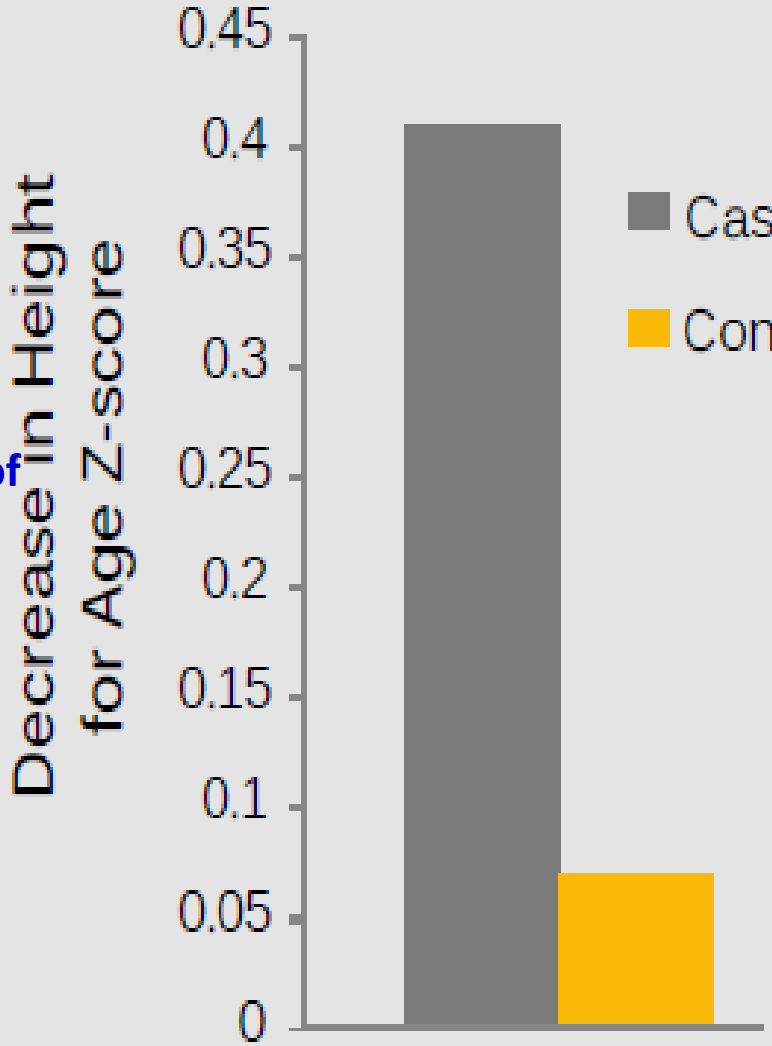
MANDOMANDO, Inácio, 2015 (13)

Increased Death from a Single Episode of MSD



Children presenting with a single episode of MSD had **a 13.4-fold increased risk** of death at 2 month follow-up visit compared to control children without MSD.

Delayed Growth Below Target Height for Age in Infants



Rotavirus disease and vaccines

The author of this study Concludes(13)**:**

- **Rotavirus, Cryptosporidium, ETEC_ST, Adenovirus 40/41, Shigella are the most important causes of MSD;**
- **Preventive strategies, including accelerating the introduction of rotavirus vaccine, should be promoted on a wider scale, to reduce the current diarrheal diseases burden in Mozambique;**
- **There is a need to accelerate Shigella & ETEC vaccines, and cryptosporiodiosis control/prevention strategies.**

Personally, I put big emphasis on the need for a vaccine against Escherichia coli, because it is the causative agent of many diseases

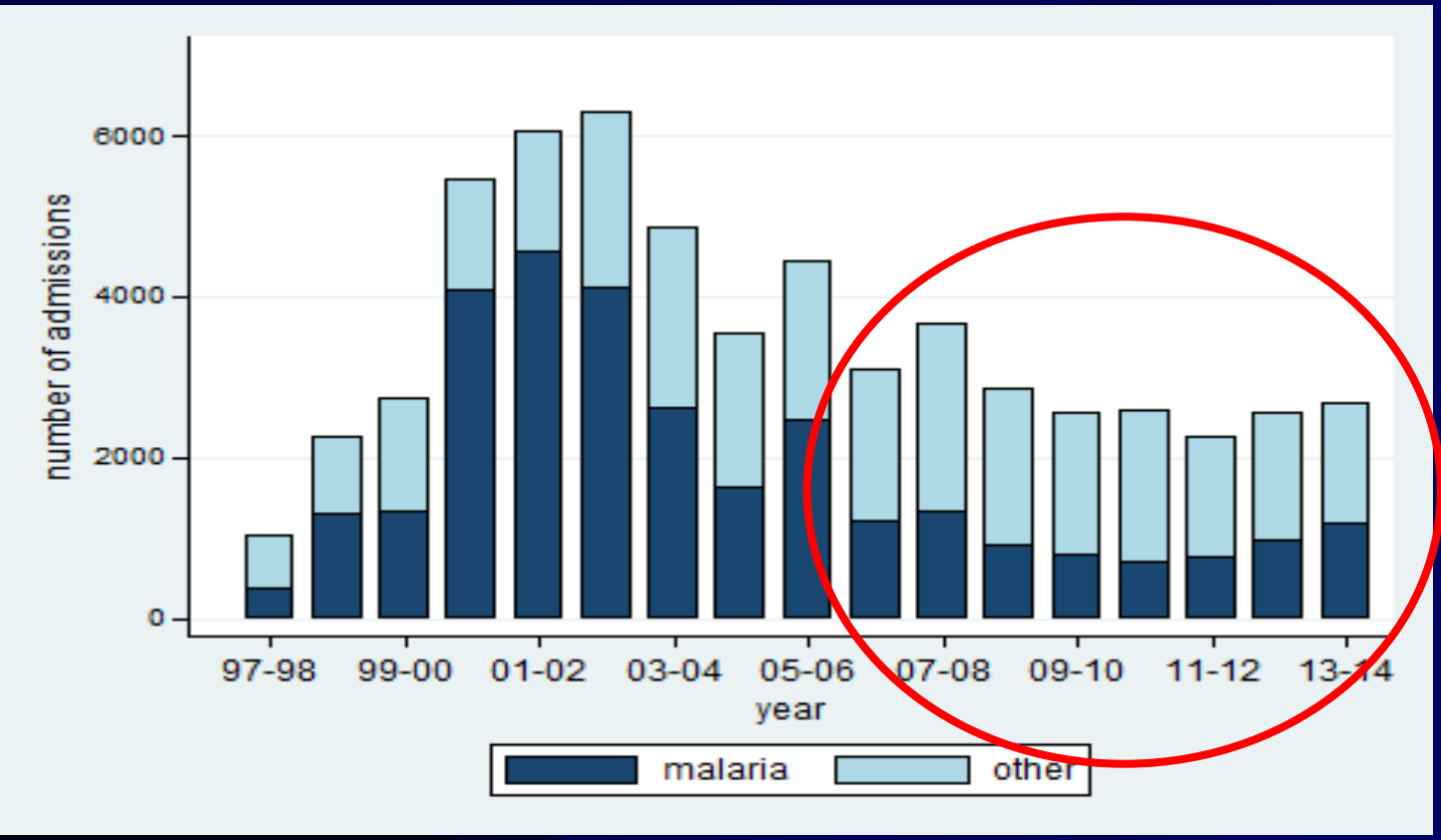
Rotavirus disease and vaccines

- **As with pneumococcus, incidence of the different genotypes have geographical variations, but this is less important with rotavirus because there is strong crossed immunity** (15)**.**
- **One of the vaccines on the market is monovalent, the other has 5 serotypes**.
- **Efficacy of those vaccines seems to be good but being the attributable fraction of MSD cases, in children <1 year old, around 35%** (13), **still it is justified to introduce this vaccine in the regular EPI because the burden of disease is high in terms of morbidity and mortality and because of the bad consequences of rotavirus infection on child growth** (13).

Malaria disease and vaccine

- **Globally, an estimated 3.3 billion people are at risk of being infected with malaria and developing disease, and 1.2 billion are at high risk** (16 – WMR 2014)**;**
- **In 2013, in the world, around 200 million cases of malaria occurred and the disease led to around 600.000 deaths** (16)**;**
- **Malaria transmission occurs in all 6 WHO regions, but the burden is heaviest in the WHO/AFRO, where 90% of all malaria deaths occur, particularly, in children aged <5 years, who account for 78% of all deaths** (16)**;**
- **In 2014, in Mozambique 5.485.327 cases and 2.927 deaths were reported** (17)**;**
- **Economic costs of malaria are also very high:**
  - **On one side, by the days of absence to work cause by the disease,**
  - **On the other side, by the NHS expenditure with treatment of the cases, particularly, in-patient treatment** (see next slide) (18)**;**
  - **In 3rd place by the deaths provoked.**

Malaria disease and vaccine



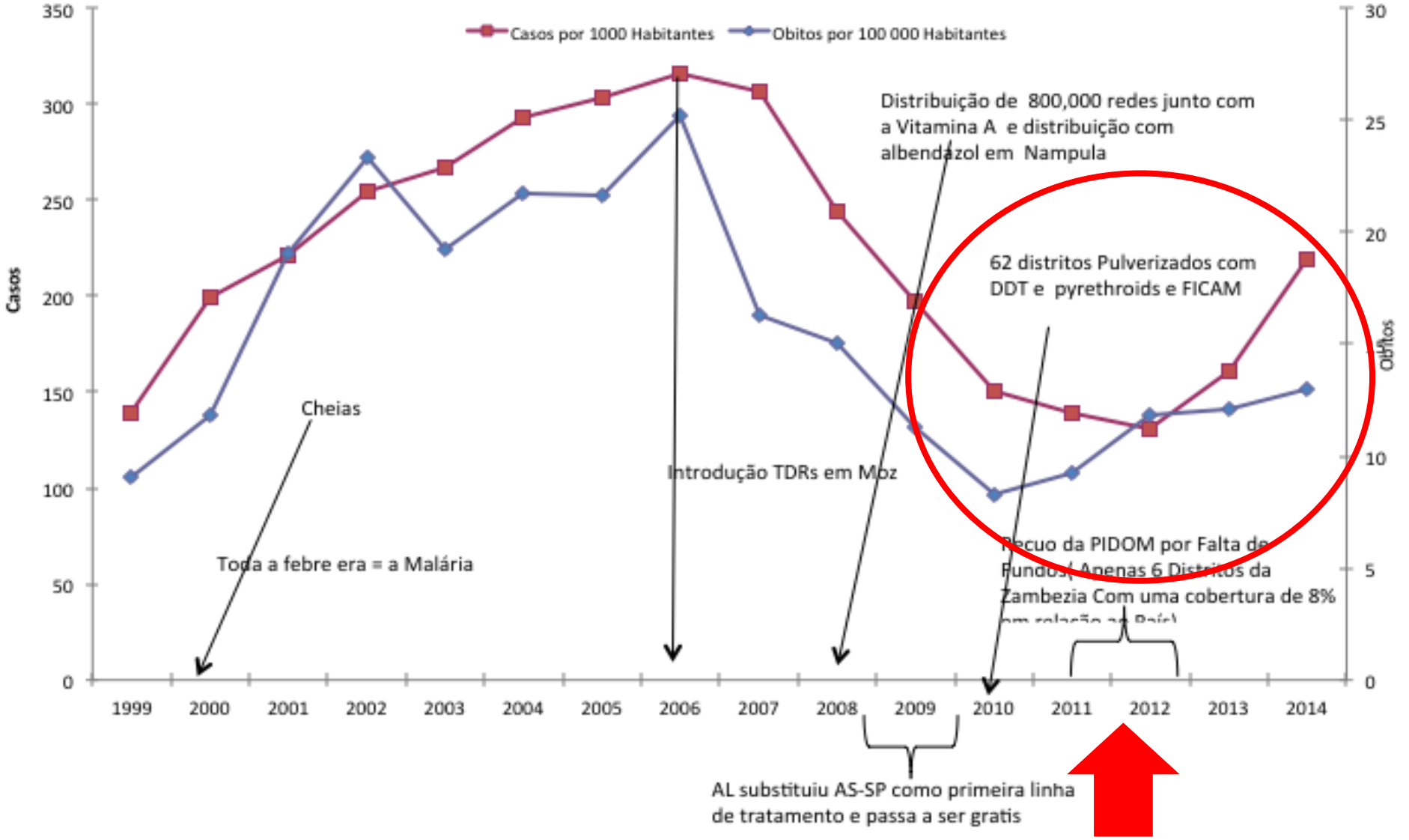
Total number of admissions due to malaria in Manhiça (1997-2014) (18)

- **In 2008, a Mozambican researcher (MABUNDA) proved that «*In Mozambique, malaria is the major cause of death, of hospital admittance and of outpatients' attendance and it also contributes to the high rate of maternal mortality*»** (19).

Malaria disease and vaccine

- **In 2008, WHO estimated that globally, malaria reduces the economic productivity of the human capital in 1 to 4%** (20)**.**
- **In 2009, I made a study on the economic consequences of malaria and, based on national and international data, I concluded that, in Mozambique, malaria damages the economic productivity in between 3 and 4% of the Gross Domestic Product (GDP)** (21)**.**
- **In Mozambique, since 2010, the number of deaths has steadily increased and since 2012 the number of cases had also increased** (22, 23, 24) (se also next slides)**.**
- **This trend of increase is occurring also in other countries of Southern Africa** (22, 25)**.**

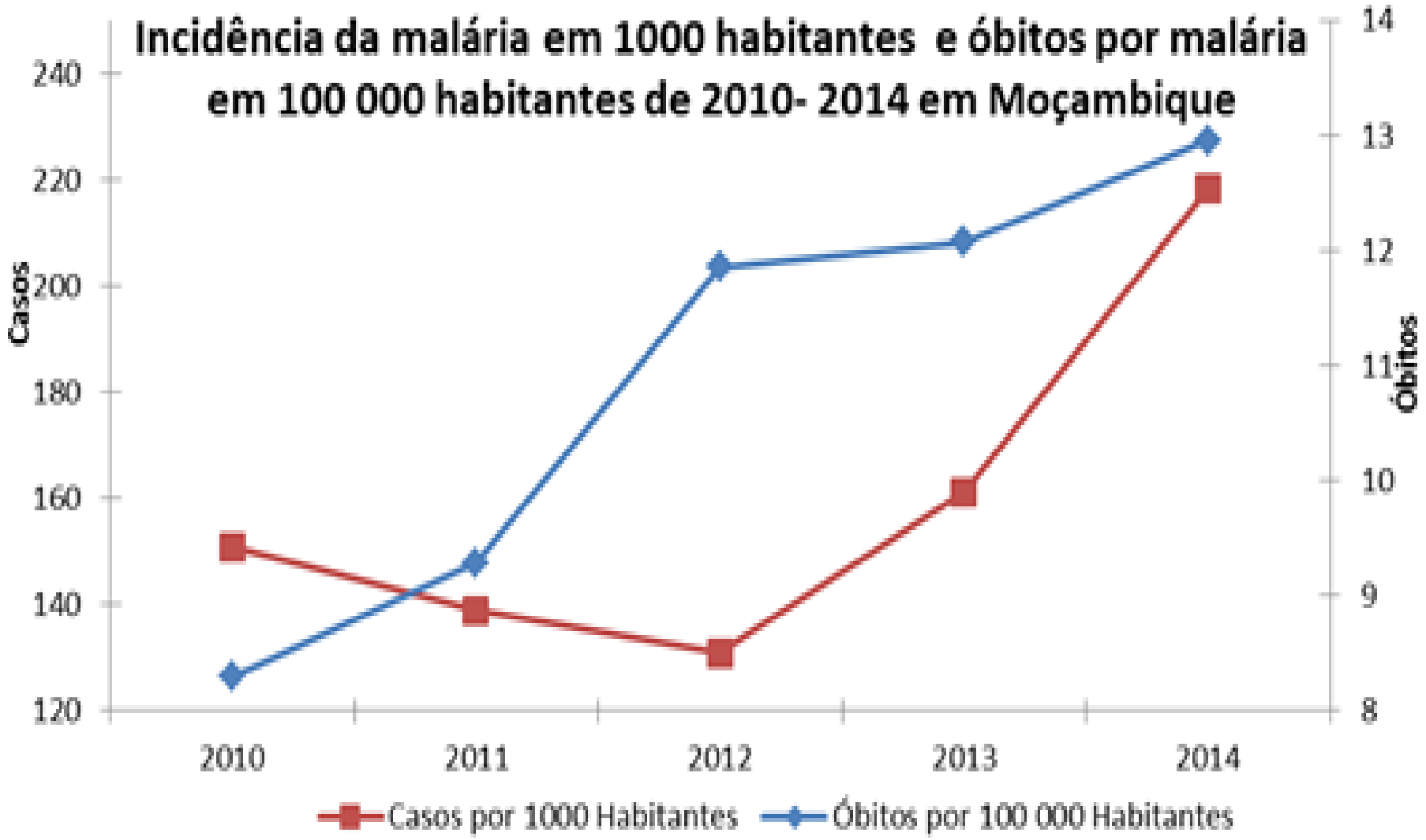
Trend of Incidence and Deaths 1999 – 2014, in Mozambique (17)



Malaria disease and vaccine

Trends of incidence and deaths by malaria in last 5 years

(17, 24)



Malaria disease and vaccine

Conclusions:

- **Malaria is the highest burden on the NHS in many African countries, in terms of incidence, mortality and on the economic point of view;**
- **Up to now, all known strategies for malaria control (including impregnated mosquito nets) do not give us so much encouraging signs!?!**
- **Is this recrudescence of malaria in recent years due to climatic changes??**
- **We need to have a malaria vaccine!**

Malaria disease and vaccine

- **Everybody knows that a malaria vaccine was tested in 11 research centers in 7 Sub-Saharan African countries and the coordination was in Manhiça Health Research Center. Results were published** (26, 27)**.**
- **They show that** (26, 27)**:**
  - **There are considerable differences on the vaccine efficacy (VE) in different research sites, probably in relation with differences in the levels of malaria transmission,**
  - **in the absence of a booster dose «*VE was about 28% in children and 18% in young infants*», but still «*this resulted in a substantial reduction in the number of cases of clinical malaria*»,**
  - **«*a booster dose at month 20 prolonged protection against clinical malaria in both children and young infants*»,**
  - **Vaccination significantly reduced overall hospital admissions because of malaria and severe anaemia and therefore the need for blood transfusion in children.**

Malaria disease and vaccine

- **The results also show that** (26, 27)**:**
  - «***No significant effect was noted on overall mortality and on malaria mortality, pneumonia, or sepsis***»**,**
  - «***the high standard of care provided to all trial participants might have limited the ability of the trial, to detect an effect on mortality or other severe outcomes***»**.**
  - «***Severe Adverse Effects (meningitis) were reported in about a quarter of children in the trial, with a similar incidence in all study groups, but only 0,3% were judged to be vaccine related***» **and** «***the mechanism that could have brought this about is difficult to understand***»**.**
- **These studies raised a series of questions that require further investigation** (22, 27)**.**
- **Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency have not yet given is final scientific opinion on the Vaccine** (22, 27)**.**

Malaria disease and vaccine

Conclusions:

- This vaccine requires further investigation, in many aspects, but particularly, in relation to the SAEs;
- VE is very low, but still from its use results a substantial reduction in the number of cases of clinical malaria, which in hyper-endemic countries or more restricted geographical settings could be very very important.
- So: burden of disease has also to be taken in consideration.

Relations between efficacy and promotion strategy

If a vaccine is 100% or nearly effective	It Can be stated: You take the vaccine and you will be protected (the disease will not occur)
If a vaccine has a lower level of efficacy	Total protection against the disease can not be promised ! Public Health Strategies to promote vaccines must be based on the truth!

Relations between efficacy and promotion strategy

- Regulatory Agencies for Drugs and Vaccines are very strict on what shall be stated in the information leaflet contained in the vaccine pack, as well as, in the scientific information that vaccine producers shall give to medical doctors and this shall reflect the exact level of efficacy, as observed in clinical trials, but, particularly in developing countries, nobody reads the information leaflet, even the professionals that administer the vaccine.
- Therefore, the most important is to devise appropriate and accurate messages for Public Health Strategies to promote these vaccines!

Difficulties to face

- **Even now with vaccines nearly 100% effective, there are anti-vaccine lobbies** (leading to the so called «*vaccine hesitancy*» that should be better called «*vaccine refusal*»);
- **With vaccines with lower levels of efficacy, vaccine promotion will be more difficult;**
- **But still, Public Health Strategies to promote these vaccines, based on the truth, must be devised and used with determination. For this purpose:**
  - **Mass campaigns of Health Education and Community involvement have to be implemented**

Difficulties to face

- When the same disease or clinical syndrome can be provoked by several pathogenic agents, the situation, in terms of Health Education for the promotion of the vaccines, **becomes still more difficult!**

- Mass campaigns of Health Education and Community involvement have to take in consideration all these elements!

Final Conclusion

Therefore, we have to conclude that, we are in a new era, that implies changing the paradigms of vaccine efficacy evaluation, but also of vaccine promotion!

Many Thanks for your Attention!

The End

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  - Pedro AÍDE.

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