

Presentation

Mass Drug Administration of Artemisinin-piperaquine on High Malaria Epidemic Area

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Abstract: Malaria is the one of major diseases which threatens people's life in Africa. Out of humanitarianism, Chinese scientists has contributed to research of Artemisinin and ACTS more than 30 years, China provides long-term antimalaria assistance to Africa and gain great achievements. In Moheli, the island of Comoros, the antimalaria group used a new strategy which universal medication and proactive intervention. They established not only an effective antimalaria system and reporting system but also a local antimalaria team. Furthermore, they enhanced publicity and put mass protection and treatment into effect. Finally, they achieved significant result. In order to apply those successful experience to other countries in Africa, this paper summed up those experience and inspirations.

Key words: Malaria, Elimination, Mass Drug Administration

Thank you Professor Kaneko and thank you for the opportunity to introduce our project in Comoros. I am the represent of Professor Song to introduce the mass drug administration of artemisinin-piperaquine in high malaria endemic area in Africa, Comoros.

MALARIA EPIDEMIC OF THE WORLD

You know some information about malaria transmission but I just remind the malaria is serious in Africa, this is according to the World Malaria Report 2012 [1]. We can know the information that 211 million malaria reported cases in the hospital and also the death cases are more than 616,000, but in fact because I was there in Africa a long time, in fact, more than 1 million death cases because all these cases are from the hospital report and the recent cases in the village and they are having the report (Fig. 1).

As we know, the drug resistance is widely spread in the world. Even yesterday we had some information that even artemisinin drugs will have some drug resistance and how can we affect the anti-malaria drugs to treatment of malaria. We know that quinine was already used around 200 years. Artemisinin, we just used 30 years and how can we protect artemisinin. How can we use less effect anti-malaria drugs to control malaria? We think about—that's

why we use ACT to do MDA (Fig. 2).

We considered about because now we have many kind of ACT, we use it. But, what kind of ACT we used with relate to MDA. We think about first we some advantage of these drugs. First, these drugs should give quick action, because in Africa in severe cases, short time maybe 24 hours, maybe some days, some cases will die. So this kind of ACT should be quick action and also it should have efficacy.

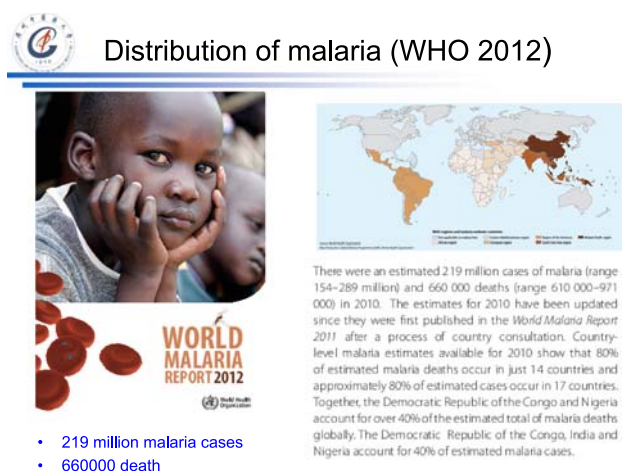


Fig. 1 Distribution of malaria

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THE ADVANTAGE OF THE ACTS FOR MDA

If we want to organize MDA, safety is the first point we think about. ACT we select must have low toxicity. For African areas because for the population, they are so poor, even one family they cannot support to buy ACT, because ACT is little bit expensive for them. For example for coartem, they have 24 tablets and continue to use 3 days, 6 times, so maybe one family may be divided to use coartem. Just they use four tablets for themselves and also four tablets for their children. They cannot finish the whole dose of ACT. So that's why we are thinking about to select one simple ACT for them to use it and learn. They can confirm high prevalence and also in the environment of Africa because it is little bit different with Asia or even in Europe.

For the medicine stocking, even issue of single block is good stability for ACTs. That's why we select this kind of ACT. This is only four tablets and 24 hours can finish the course of the treatment. Also, for the malaria transmission, how can we think about block transmission, how can we effect the gametocytes. Also, because this ACT contains artemisinin and we can know some information that artemisinin can affect gametocytes, so that can block transmission.

THE MALARIA CONTROL HISTORY

Here, I will just review the malaria control history in China. Before in 1975 China, there were many malaria cases, there were millions of cases per year. But, after 1975s, because Chinese government also focused on malaria control project and also artemisinin has been already invented at that time, already three kinds of meth-

ods for malaria-controlled project. First is mass drug administration and the second method is positive treatment. In China, we have many cases with *P. vivax*. Right now, in small areas, they have *P. vivax* relapse and until now every year Chinese government they are continuing to organize some small projects as anti-malaria, anti-relapse treatment (Fig. 3) [2].

We can get some data from 2011. Maybe someone will ask why there was less cases in 2000, because at that time the Chinese CDC they haven't build the report system, so at that time they could not get some information. But, after that we have the report system and we can know the malaria cases decreased around 2002 more than 13,000 cases per year and last year even 2011, they just had 3000 cases and most of the cases are from Africa and some cases are *P. vivax* (Fig. 4) [1].

Candidate anti-malaria medicine for MDA

- Quick acting
- High Efficacy
- Low toxicity
- High compliance
- Good Stability
- Affordable.

•1800 malaria cases in Phase II and III
•1.3 million doses used in MDA



- eliminating asexual in the blood
- Gametocyte lose infectivity to mosquito.

MDA

Fig. 2 Candidate anti-malaria medicine for MDA

The experience of malaria control in China

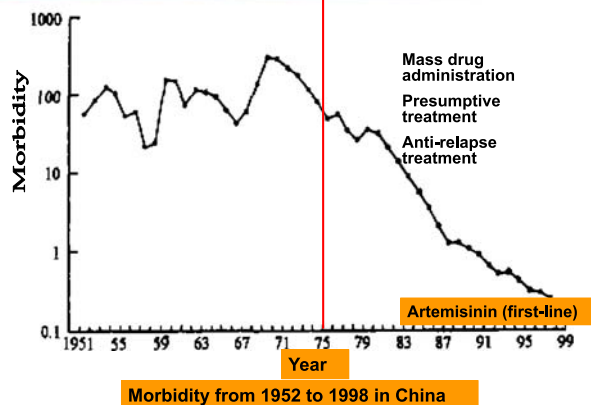


Fig. 3 The experience of malaria control in China

Malaria cases reported in China(2000-2011) 中国的疟疾病例报告

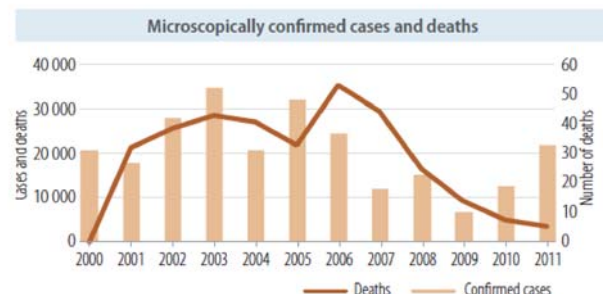


Fig. 4 Malaria cases reported in China (2000–2011)

THE RESEARCH HISTORY OF ARTEMISININ

For the artemisinin research for the Chinese scientists, how can they find these drugs and some books, just special to introduce history about this artemisinin research and later according to the complicated history reasons at that time because of the Vietnam War 1960s and at that time the relationship between China and Vietnam is good relationship and that's why the leadership of Chairman Mao and Premier Zhou just organized a special team to find out some anti-malarial drugs and they organized more than 200 scientists and this team just looked for drugs from the herbal medicine and the herbal medicine is more than 3000 of herbal medicine, they go to look for it and go to find which kind of drugs can effect malaria. Why they select—they can find artemisinin because even 1060 years ago there is one book the Chinese had Zhou Hou Bei Ji Fang and it had one sentence in the record that artemisinin annua is herbal medicine that is qinghaosu and can treat malaria fever (Fig. 5).

One scientist, she collected this information and learned. She went to do some test and checked artemisinin annua and after that artemisinin founded from artemisinin annua. This artemisinin also has some characteristics (Fig. 6).

First is rapid effect to the lifecycle of the parasite even the ringform and gametocyte. All the parasite cycles artemisinin can effect and there is more effect than the others, anti-malaria drugs now we have many kinds of ACTs. For artemisinin has better stability than the other drugs and right now maybe some place because like in Thai and Cambodia border, maybe, there is some evidence that artemisinin has little bit drug resistance but we are not sure is it or not (Fig. 7).

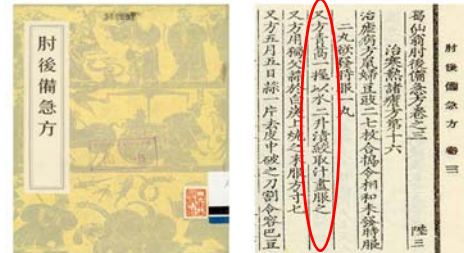
THE MALARIA CONTROL PROJECT IN COMOROS

This is model of malaria elimination project we conducted in Comoros by MDA. I think we know the transmission of the malaria. There are two reservoirs. First is mosquitoes and human. How can we block transmission, how can we eliminate the source? (Fig. 8)

Because if we wanted to kill the parasite in the mosquito, I think it is a little bit difficult for us. Even in Europe and America now, I think we will have many kinds of mosquitoes. How can we eliminate the parasite, because it is easier to kill the parasite in the human body? So that's why we think because also the lifetime of the mosquito is around 13 days and we can think about least period of the lifetime of mosquito, we can think about organizing MDA [4]. So that's why we conduct three rounds of MDA with artemisinin-piperazine in Cambodia and also in Comoros,

 Refer to <Handbook of Precriptions for Emergency Treatments>

by Ge Hong (283-343) during the Jin Dynasty



- "Take one bunch of qinghao, Soak in two sheng(~0.4 L) of water, wring it out to obtain the juice and ingest it in its entirety"

Fig. 6 Handbook of prescriptions for emergency treatments

 Artemisinin rooted in Chinese medicine-
A Detailed Chronological Record of Project 523

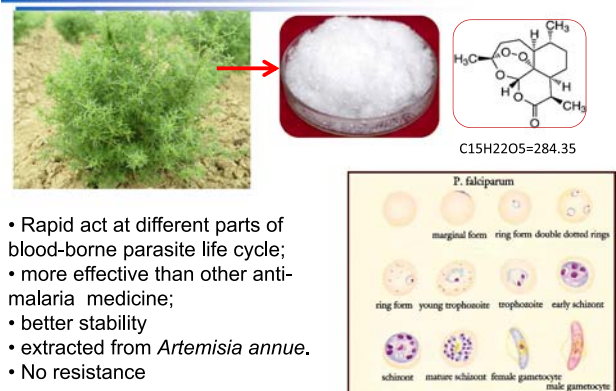
- The Vietnam War in 1960'
- North Vietnamese suffering heavy losses of soldiers due to malaria;
- Chairman Mao and Premier Zhou called for an urgent effort to find solutions.



◆ A meeting discussing action plans was held on 23 May 1967 (thus named 'Project 523')

Fig. 5 Artemisinin rooted in Chinese medicine

 Artemisinin



- Rapid act at different parts of blood-borne parasite life cycle;
- more effective than other anti-malaria medicine;
- better stability
- extracted from Artemisia annue.
- No resistance

Fig. 7 Artemisinin

Africa, and learn from the result that effect the parasite. So that's why block transmission from the human body to mosquito and then can block this transmission. This is just a model of elimination of malaria (Fig. 9) [3].

From 2004, we conduct MDA project in Cambodia, two pilots, and the population is around 4000 and we can

know the results beyond 3 years and further parasite carriage rate is 56% and decreased by just around 1% [3-5]. But, after that, because all this work is done by our university, but after that the local government they took responsibility for this project, so after 2006, we haven't collected some more information. So, maybe, at this time, they have

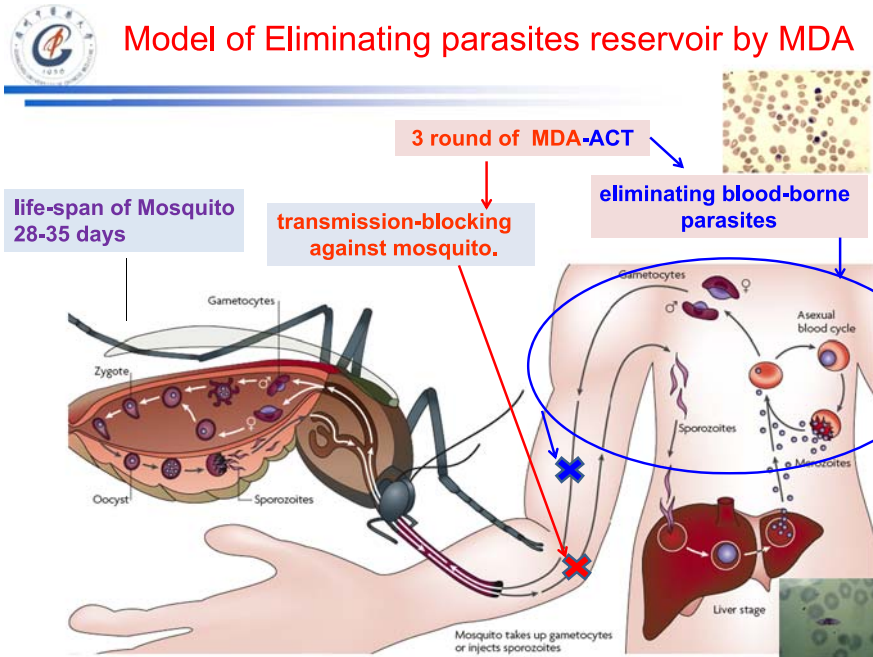
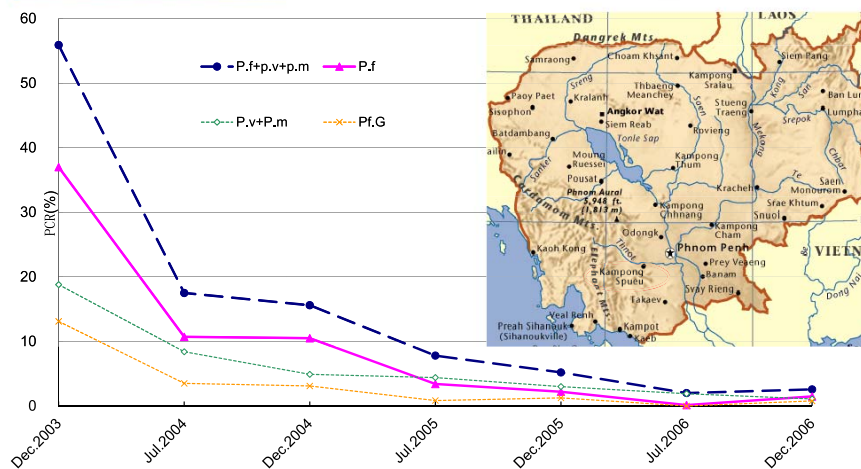


Fig. 8 Model of eliminating parasites reservoir by MDA

Rapid and effective malaria control Cambodia through mass administration of artemisinin-piperaquine



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Fig. 9 Malaria control by MDA in Cambodia

some recruiters. We can compare after the project in Comoros (Fig. 10).

Where is Comoros? Comoros is a small country. I think it is one of the smallest countries in the world. Even you cannot get it from the map. It is located in the Indian Ocean and is located between Kenya and Madagascar. They have four islands in this country. In this island, Mayotte is controlled by France and the Comoros government just controls three islands. This is the smallest island. Their population is around 14,000 and we conducted the MDA project in this island in 2007 [6, 7]. This is the second island. The population is around 320,000 and it is around 320 square kilometers.

Also, we launched the MDA project last year and we can know we have got some information that these two islands, Moheli Island just have two or three cases per month [6]. This second island, Anjouan Island, we just have five to six positive cases per month. I think these two islands are already under control of malaria. This year we launched the MDA project in this biggest island. The population is around 315,000. In this island, we now have one Chinese team and also the local team, they cooperate to carry out this project. This island they have some little bit difference with the other island. That's why we spend more time to carry out the MDA project in this island.

How about the malaria situation in Comoros? We will have some information. First is epidemic with high prevalence around the year because 33% cases of all the patients have malaria and most of the inpatient is malaria. From the data, this data is from 2007, but last year we have data, average annual cases is around 100,000 cases in the last year. But this data is 2007. Malaria is the first cause of morbidity and mortality in this country and 28% of under 5 years mortality in host-feeder is caused by malaria. But we have good opportunity for this country to control malaria

because 96% malaria is Plasmodium falciparum. That is the reason it is more easy to control with the other countries. There is low P. vivax in this country. Also, malaria is major public health problem. That's why malaria problem is the large contributor of this country for social and economic development, so that's why the President of Comoros many times he asked the Chinese government to give support and advised our university to do MDA to select this country to MDA. Also, the Chinese government requested the university to take responsibility in this malaria control project in this country (Fig. 11).

Let's show the result of the Moheli's island because the other island we are just collecting the data and after that also we can share the information. This Moheli's Island just as I told you that's just around 40,000 population and in this island [6, 7]. Before MDA, we have done two types of surveys in this island and only data is the prevalence is parasite carriage rate and we can know exactly all the village in this island is 24 villages and we have already covered all the survey in each village and we can know the result. Mostly parasite carriage rate in some village is severe and the average of the prevalence is around 23%, most of it is Plasmodium falciparum (Fig. 12).

When we conducted MDA, how can we do it? Because we should make training of the local team. Because for the Chinese team we just have few persons to go to stay in the area and do some technical support and most of the work is according to the local team to do it. So how can we select local team and how can we train them? We have just few pictures to show. All of this people they have low education. Even they don't know how to speak English but Comoros is French-speaking country and also most of them they don't speak French. Before that they don't know how to use microscope, so we should organize

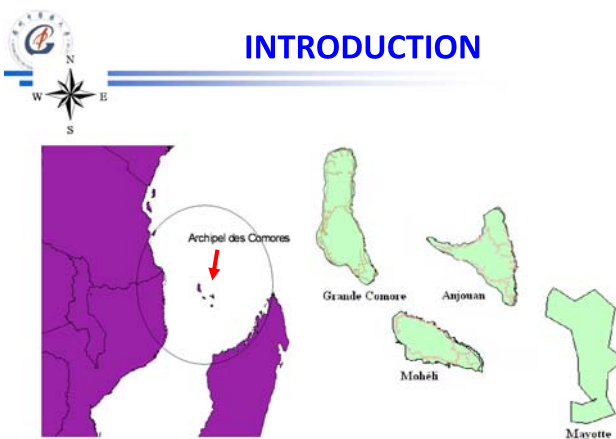


Fig. 10 Comoros

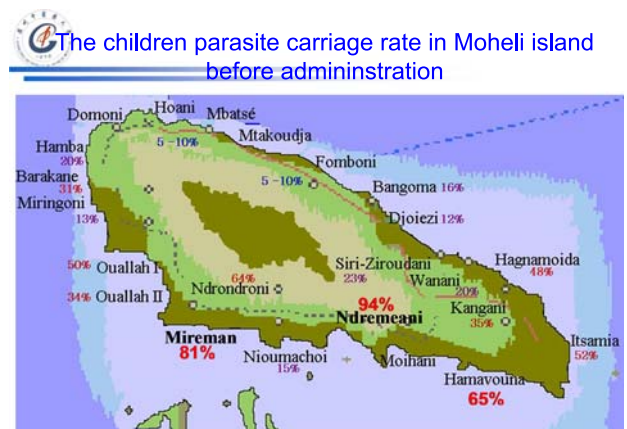



Fig. 11 Parasite carriers

 The result of blood survey in 25 villages of Moheli Island on Nov.2006

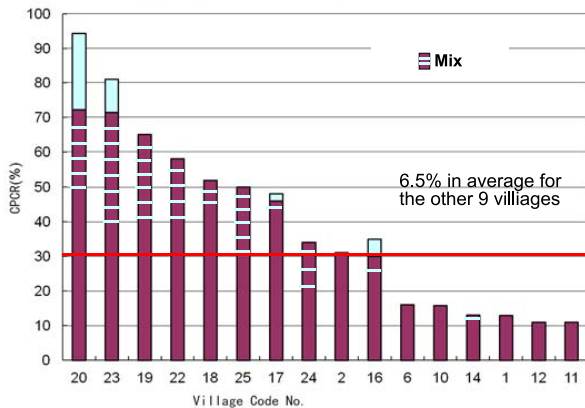


Fig. 12 Blood survey in Moheli island

this team to maintain the work, so that's why we selected this team and we trained them to use microscope and training them to do the survey, to do the blood smear and after 3 months after training all of them they know how to do the survey and even they know to check blood smear, which is positive and which is negative. This local team, they continued to work and also the local government supported this team to continue and that's why as a result Moheli maintained malaria (Fig. 13).

This is the first day of MDA in the village this is some interesting story. This is the oldest man, their chief of the village and he was the first guy to take drug and you can look all the population is looking at him and after he took the drug the other population asked this oldest man, how about the taste? Is it bitter or sweet or sour and is it poison? So after 1 hour this guy took the drug, the other population they believed this drug is for health, is not poison. That's why I speak about drugs because to organize MDA, it's difficult to ask all the population to take the drugs at the same time, but we should organize very well. We should do the relation and mobilization before MDA, so that is why we spend lot of time to do this. Every day we go to the village to give them the information, why we organize MDA, what about the malaria situation in the island, how to protect the family. That is not easy. I just say MDA—but now we have some experience and we can know the result after 3 months of MDA. We can know the parasite carriage rate decreased by 97% and this is the rapid for malaria control project (Fig. 14) [6].

Further parasite carriage rate also we can compare before MDA and after MDA. This is 23% and after MDA just around 1% and we continue to do survey and is maintained 1% right until now [6]. We also in the first year of



Fig. 13 Local team

this project we did some survey of the entomology survey and this is for human checked and we can compare with country island. Entomologist result just changed by the natural change by the seasons and the country island we can know after MDA just after some months is 0%. This is the result of the positive cases in the hospital country island and study island and we can know exactly for the country island for the positive cases just natural change and for the study island just have some few cases in the month (Fig. 15).

For the progress, also this is summary of this MDA project because also I introduced the progress of this project in Comoros and also I think someone will ask is it possible to eliminate malaria in Comoro. For myself the answer is yes, but I don't know when. We know how to eliminate but we don't know when we can eliminate malaria in this country, because most of the work should be done by the local government and also we needed international cooperation and also make sure they integrate methods to eliminate malaria. Thank you (Fig. 16).

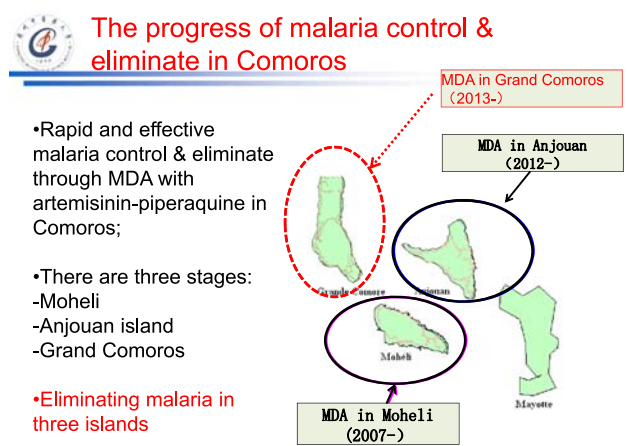
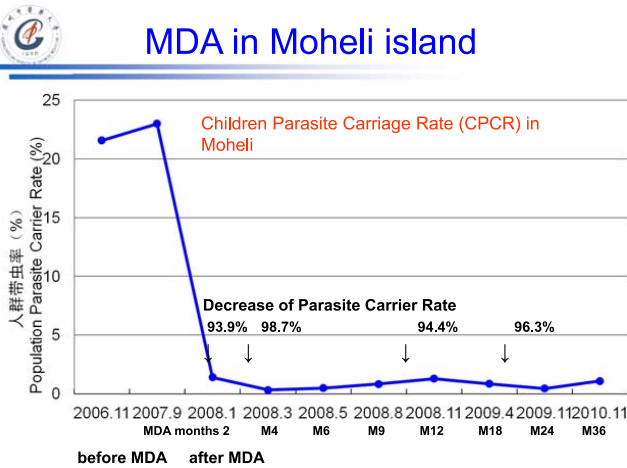
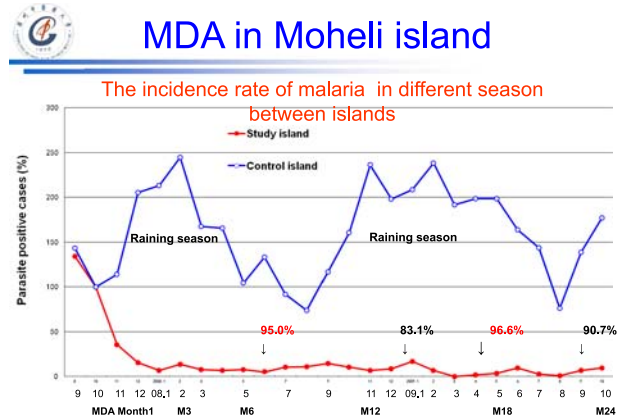
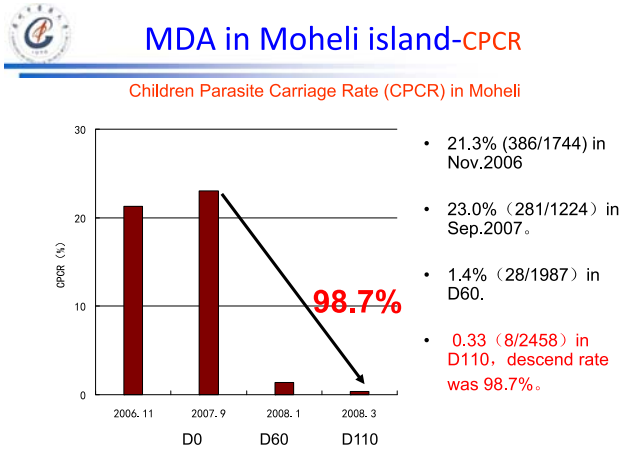


Fig. 14 Children parasite carriage rate

Fig. 16 Incidence rate of malaria

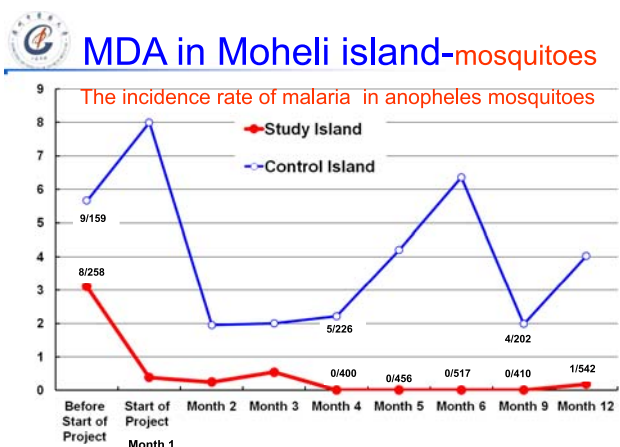


Fig. 15 Mosquitoes situation

QUESTIONS AND DISCUSSION

Akira Kaneko at the introduction

Now, we have controversial issue that is mass drug administration for malaria elimination. We have exciting guests from Guangzhou University of Chinese medicine, Professor Song and Dr. Deng. Almost 40 years ago, their group led by Professor Lee successfully developed artemisinin from Chinese traditional medicine qinghaosu.

Akira Kaneko Now open for discussion and comments. Yes please.

Male Participant Thanks for the talk. It is incredible to see the reduction and very, very optimistic and promising results. It's beautiful, well done. I suppose it is the obvious question and probably everybody is thinking about and that is the Comoros islands there. Even if you do manage to eliminate malaria if you don't eliminate the Anopheles mosquitoes you have still got the potential for malaria to come back and the

big worry of course is that you change the situation from one of stable endemic malaria to one of epidemic malaria and you sandwich between Madagascar and between Kenya where there are high rates of malaria and there is presumably transfer of people, you're going to have to monitor forever, presumably cases of malaria coming in because it will be extremely dangerous if in 10 years or 50 years' time when all the immunity in the local is gone. If an epidemic of malaria occurred in this region, it could be, well, you know, disastrous. So, the long-term commitment to the island has to be extremely long-term forever or until that beautiful day when malaria itself is eliminated from Africa. So what plans do you have to stay in Comoros and monitor after the elimination has been achieved. I think that's my main question.

Deng Changsheng Thank you for your comment and the question. Just now also I speak we can achieve elimination of malaria in Comoros and also we think about how can we maintain after MDA and so that's why we request, also we cooperate with the local government. They should have responsibility to maintenance and they should build the system, the health system to maintain this result and also how can we prevent the transmission from the other island and from the other countries. We have already built one station in the airport and also in the port and they will have some local team to continue to do this work and also we think about cooperation with other integrate project for example the [Unclear] DDT in the island. We do not think about it in a single way to eliminate malaria by MDA. We think about the other integrate methods, strategy for elimination of malaria.

Akira Kaneko Any other comments? Yes please.

Male Participant Thank you very much for your nice presentation. My question is related to the Richard's [ph] question. You have 1% prevalence in malaria after the MDA so that means 400 people still have parasite, right?

Deng Changsheng From the data of the hospital we just found...

Male Participant From the hospital, okay.

Deng Changsheng Yes, in the hospital cases.

Male Participant In that case, the 1% prevalence is continued now, but after maybe for several years if the prevalence increases, that means probably the resistance parasite produce it after MDA. In that case, the situation maybe serious so what is your idea about this?

Deng Changsheng Yes, maybe, some small area maybe recruiters in some time but that's why we have the

supervised team, supervised system to avoid this to happen and also every village we have one local team to supervise to follow up in the village. Every week they should report the cases to the Center of Malaria Control Program in the country and every week we can know the information exactly and if some cases if it is increased we can control it rapid. Is it clear?

Male Participant Okay. [Unclear] countries follow their population structure of the parasite and compare it before and after MDA.

Deng Changsheng Sorry?

Male Participant Population structure of the parasite before and after MDA.

Deng Changsheng I don't understand very well.

Akira Kaneko Parasite population before MDA and after MDA do you have a plan to compare?

Male Participant To detect the recent parasite.

Deng Changsheng For the parasite, most of it is *Plasmodium falciparum* in this island.

Male Participant Okay.

Akira Kaneko You can discuss later. I have one question. What is the inning of the malaria eradication game? How long does it take to globally eradicate malaria? Is it 50 years, 100 years, or 1000 years? Do you have any view? What is your view?

Deng Changsheng Actually, I have no idea about it. Can I invite Professor Song's comment?

Jianping Song It is a very good question, maybe most of the people are concerned, the malaria elimination date. I hope it is tomorrow, but actually malaria can be eliminated, because Japan, America, malaria is free and in many European countries, no malaria. Why Africa and other malaria epidemic countries still have so severe malaria? I think we have very good drugs, artemisinin. In the anti-malarial history, only artemisinin has the efficacy to [Unclear]. So, it is opportunities for the human to eliminate malaria in the world. So we use the mass medication of artemisinin in Comoros and Cambodia. Already, more than 400,000 people freed with malaria. Actually, no people died and the malaria problem is keeping very, very low levels. But, if we want to do global malaria elimination, it is very complicated progress. We need to correct the policies, the [Unclear] and cooperation between the countries and the different people, more people enrolled in the project. But, I think Comoros motto will lead African countries to put elimination procedure in the world. Thank you.

Akira Kaneko Thank you very much. We are going to end the session. So thank you very much for all

speakers and also all audience for your cooperation.
Arigatou gozaimasu.

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