Vector-Borne Diseases & Treatment

Chapter 6

Malaria Eradication: A War How To Win?

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Abstract

Since Nobel research of late 19th century by Laveran and Ross, now ample of data is available about malaria but no sign of its eradication. Today science is accelerating with an unforeseen pace resulting into a burst (an explosion) of data and analyses, still fall short to resolve the problem. What's the reason behind it? In our view the major issue behind failure is defining the problem. Here we discussed the various aspects of malaria required for malaria eradication.

Keywords: Plasmodium; Drugs; Vaccine; Malaria Eradication

1. Background

The relationship of human and plasmodium is supposed to be of 50000 years and this parasitic organism has learnt to survive during a long history of co-evolution with their hosts [1,2]. As a result there exists a fine balance between the survival tactics of parasites and immune response posed by the hosts. With the development of human race and inventions of drugs posed additional selection pressure on the parasite but not on the human host. This artificial selection led to more evolved parasites [3]. Therefore, it is must to ensure that the direction in which we are trying to move for malaria eradication is right or not because it is the right strategy which only will give the right outcome. Here we tried to discuss the available data and strategies in context to resolve and eradicate malaria.

2. Mosquito as Target

If we see the map of malaria spread out, it is the tropical countries which are predominantly affected whereas temperate zones successfully eradicated the malaria. The eradication from temperate zones is not only because of good economic ground but also the environmental conditions helped them [4]. The disease remained endemic in hotter countries; South America, Africa and South Asia and the burden is so high that claims death always more than a world war. This is only because tropics support the vector host Anopheles. In supportive environment vector control even become disastrous when they attain resistance against insecticides [5].

Keeping in mind the resistance developing nature of vectors, studies majorly focused insecticides development will be helpful in long run is a big question? Secondly no insecticides is specific to only one type insects and may also affect human friend insects that may lead to extinction of our friend without much effect on enemy.

In our view Mosquitos are not at all a problem and direct targeting them is not possible as they belongs to Arthropoda which have amazing powers of adaptations which made them unique and diverse [6,7]. Further they are not the host but vector. We should work on how to break parasite transmission from human the host to mosquito. Like all mosquitoes, anophelines go through four stages in their life cycle: egg, larva, pupa, and imago. The first three stages are aquatic and the adult stage is when the female Anopheles mosquito acts as malaria vector. The adult females can live up to a month but most probably do not live more than 1-2 weeks in nature. There is no parasite storage mechanism in them and human host is the only store house which time to time supply parasite to circulate. We should learn from chimp's behaviour of changing their habitat during monsoon to prevent mosquito bite. Such an educated mind and behaviour is expected to cope with malaria and vector borne diseases. This is the best way which could help in eradicating malaria as if we could be able to cut transmission for 1-3 year will lead to definite eradication of falciparum malaria.

3. Parasite as Target

In post Koch era of modern science, parasites become the prime focus of disease management and also lead to control and eradication of many diseases *viz* small pox, polio etc. But one of big questions 'malaria parasite' is still a big problem. Since the discovery of malaria parasite many milestones have been achieved but none led to its eradication which was the final objective. Where are we missing? What remain unnoticed? And what was over looked? Before aiming big we must look in to such issues.

The prime mode of tackling parasites is killing them. Being multifaceted life cycle of malaria parasite while attempting strategies we need to note how to kill it and in which way we should do it. This could only be achieved by thorough and serious review rather than just start-

ing by taking one aspect of its life cycle. Hence it is necessary to discuss the utility of target weather focusing on it is worthy or not and also in which context one should focus whether for drug or for vaccine.

Sporozoites and liver stages of malaria never remain prime focus even it is the first step of encounter between host and parasite [8]. Asymptotic nature of this stage made it highly unfavourable target for a drug and also if targeted for drugs, this stage may be useful only for a small class of people of non-tropics, travelling to epidemic zones. Getting drugs against hepatic stages could be much useful if these are against latent liver stage of malaria or if we establish relation with fresh infection through vector during already established septicity. In such cases they could be used in combinations otherwise it never will be of first line of choice for drug discovery.

Seeking vaccine against these stages have emerged with great potential [9] which invigorated researchers to work in this field and also provided hope to malaria victims. Vaccine against these stages also hold potential because of the blockage of door step and providing least chance to parasite to come in action for combating against human host. But in current scenario parasite entry to host liver is incessant and uninterrupted to blood to show its real macabre face.

If there are symptoms like shaking chills, high fever, profuse sweating and headache i.e. malaria with blood stage of parasite as their presence is also visible in blood smears and in true sense we call, disease. Most of studies and discoveries in field of malaria belong to this stage further most of drugs available belong to this stage.Whatever success being claimed in malaria control and decreasing death toll is because of targeting blood stage of parasite. But the major drawback in targeting this stage for combating is that it made parasite stronger and stronger [10] by insisting parasite to search alternate routes to bypass the encounter of drug bullets *viz* dormant stages and sexual stages.

When parasite feels its job in one host is over it reprogram itself and turn some of the blood-stage parasites to differentiate into male and female gametocytes as asexual stage parasite cannot be transmitted naturally from one human host to another. Targeting these stages could provide great help in malaria control as it could cut down source of transmittable parasite.

4. Rescue Mechanisms as Target

Keeping themselves alive and maintaining through generations is a unique phenomenon of living organisms and it had played a great role in evolution of life. Survival of fittest is always considered as major factor which substantiate the selection of favoured races in the struggle for existence. Parasitic organisms learnt to survive during a long history of co-

evolution with their hosts. As a result there exists a fine balance between the survival tactics of parasites and immune restrictions posed by the hosts. With the development of human race and inventions of drugs further posed additional selection pressure on the parasite but not on the human host. This artificial selection led to more evolved parasites. Therefore, it would be interesting to study pathways of parasites which the rescue it from host immunity, drug pressure and nutrition deficiency in a host-parasite relationship.

Malaria parasite undergoes complex life cycle which involve two host and about six transition states. The transitions are also accompanied by decision to switch to multiplication or to enter dormant stage or to transform into sexual stages or to give polymorphic expression. This decision of commitment may very well affect development of resistance under selection pressure.

It seems that it is quite important to study survival tactics of malaria parasite for that we need to understand features of death and signalling in malaria parasite. Death of malaria parasite occurs under the stress of nutrition or drug inhibitors. However, exact mechanism is still unclear. One school of thought believes that it occur in a programmed way i.e. it is apoptotic [11] where as, the other believes it is by dis-functioning of some pathways [12]. Apoptosis in malaria is highly debatable whether it exist or not and if it is there why a single cell organism would like to die by itself where unlike to multicellular organism death of a cell is death of an organism. However in malaria parasite semi-multi-cellularity seems to occur when it shows rosseting or cytoadherence [13]. If we consider the existence of apoptosis in plasmodium then it should definitely be a communication mechanism similar to the quorum sensing in bacteria [14] which regulate gene expression in response to fluctuations in cell population density and is mediated by signaling molecules released into the environment. However in plasmodium quorum sensing an under appreciated phenomenon and very little is known about it [15].

Both quorum sensing and apoptosis seems to be survival tactics to let other parasites escape to continue future life. Recently, some transcriptional switches [16,17] which seem to play critical role in commitment toward sexual developments were also reported. However, detailed signalling mechanism and factors that regulate these switches are unknown and need to be explored. It is well known that drug pressure leads to up and down regulation of transcription and expression. However it is not known that how they determine the fate for future. Recent studies reported that in plasmodium cell to cell communication occur via exosome like vesicle [18] but it is not known that how this communication is regulated and it meant for what?

It would be quite interesting to study how various death symptoms have some protective role under various stress or and how quorum sensing like signalling aware the parasite about the threat of survival via commitment towards rescue mechanism.

5. Human as Target

Human the true victim of malaria in true sense is missing from discussions those researchers made and making about malaria. They mention threat to human but empowerment is missing. What is the meaning of this empowerment here? If we ask, who is ill with malaria? Definitely answer will be human. But the malaria eradication strategies least bothers the human as prime target. In any combat one cannot remain just dependent on the weaknesses of other but also have to make himself strong so opponent dare to attack.

How can we make ourselves strong without giving a chance to parasite for evolving? Obviously first answer will be an effective vaccine but unfortunately even after long struggle we remained failed and are vaccine less. Then what we can have or what we should to do.

Slight modified approach of Behet *et al.* [19] can be used in broad perspective. Drawback of Behet`s CQ based approach is that here purified drug is being used and it also impractical to force infected mosquito bite.

Alternatively if we search a plant product which have antimalarial and immune booster properties and have ability to become the part of daily diet e.g. *Phyllanthus, Curcuma, Syzygium* etc. It will help by two ways (a) as we know that native sporozoites are best source for developing long lasting and sterile immune protection. If we maintain safe drug bullets always at a certain basal level in blood stream to tackle the parasite, it will help in peak season or in monsoon when mosquito will definitely bite but then they will be a native source of sporozoites for immune response not for disease as bullets are already present to tackle them. b) Secondly it has been established that these plant products have immune booster properties e.g. Chwanprash an ancient formulation that is being recommended during winter to take care of common flu and other associated disease.

6. Conclusions

With above discussion we would like to suggest that we need to rethink and reprogram ourselves to deign malaria eradication strategies. Further we alsowould like invite discussion for development of ideas to achieve our goal of malaria free world.

7. Declaration

Authors have no competing Interests and manuscript can be published as part of publisher's Data Support Services.

8. References

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