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Malaria: an old vector-borne disease going to eradication? a short note

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Introduction

Malaria is caused by protozoans of the genus *Plasmodium* – *P. vivax*, *P. ovale*, *P. malariae*, *P. falciparum* and, more recently, *P. knowlesi*.[1] Considering the medical, economic and social importance of this parasitic disease in the world, where it is present as indigenous or imported, we have as objectives in this manuscript to contribute:

a. To the divulgation of the knowledge about human malaria in a general context.

b. To emphasize the present situation concerning malaria eradication in the world.

Thus, we present:

1. History of malaria.
2. Symptoms.
3. Who is at risk?
4. Disease burden.
5. Transmission.
6. Prevention.
7. Insecticide-treated mosquito nets.
8. Indoor spraying with residual insecticides.
9. Antimalarial drugs.
10. Insecticide resistance.
11. Diagnosis and treatment.
12. Antimalarial drug resistance.
13. Surveillance.
14. Elimination.
15. Vaccines against malaria.
16. WHO response:
    - I. WHO global technical strategy for malaria 2016-2030.
    - II. The global malaria programme (GMP).
    - III. High burden high impact approach.

History of malaria

The first evidence of malaria parasites was found in mosquitoes preserved in amber from the Palaeogene period that are approximately 30 million years old.[2] Human malaria likely originated in Africa and coevolved with its hosts, mosquitoes and non-human primates. In[3] we found, in our opinion, a good history of malaria accessible to the public in general.

From it we emphasize:

a. In 1898–1899, Bastianelli, Bignami and Grassi were the first to observe the complete transmission cycle of *P. falciparum*, *P. vivax* and *P. malaria* from mosquito to human and back in *Anopheles claviger*;

b. The attribution to Ross of the 1902 Nobel Prize for Physiology and Medicine for "his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it".

Effectivelly, Britain's Sir Ronald Ross, an army surgeon working in Secunderabad India, proved in 1897 that malaria is transmitted by mosquitoes, an event now commemorated via World Mosquito Day. He was able to find pigmented malaria parasites in a mosquito that he artificially fed on a malaria patient who had crescents in his blood.

In the nineteenth century, the first drugs were developed to treat malaria and parasites were first identified as its source. The antimalarial drugs developed were:

I. Quinine.

II. Warburg's Tincture (which was considered by many eminent medical professionals to be a more efficacious antimalarial than quinine, and it was also more economical).

III. Methylene blue; genus *Cinchona* tree.

For mosquito control was used DDT, after the link to mosquitoes and their parasites had been identified in the early twentieth century.

Today, artemisinin is present in every remedy applied in treatment of malaria. After introducing artemisinin as a cure administered together with other remedies, the mortality in Africa went down by a half.

At the close of the 20th century, malaria remained endemic in more than 100 countries throughout the tropical and subtropical zones, including large areas of Central and South America (Haiti and the Dominican Repubic), Africa, the Middle East, the Indian subcontinent, Southeast Asia, and Oceania.

The resistance of *Plasmodium* to anti-malaria drugs, as well as resistance of mosquitos to insecticides and the discovery of zoonotic species of the parasite have complicated control measures.

In the 21st century, on World Malaria Day (25/4/2019), World Health Organization (WHO), has indicated: "urgent action is needed to get the global response to malaria back on track-and ownership of the challenge lies in the hands of countries most affected by malaria".

In[4] we found, in our opinion, a good basis of information for our points below, accessible to the public in general. From it, we emphasize:

Symptoms

"The first symptoms–fever, headache, and chills–may be mild and difficult to recognize as malaria, and usually appear 10-15 days after the infective mosquito bite". Severe anaemia or cerebral malaria is frequently developed in children with severe malaria. In adults, multi-organ failure is also frequent.

Who is at risk?

In 2017, 87 countries and areas had ongoing malaria transmission, with nearly half of the world's population at risk of malaria. "Most malaria cases and deaths occur in sub-Saharan Africa. However, the WHO regions of South-East Asia, Eastern Mediterranean, Western Pacific, and the Americas are also at risk".

Disease burden

World malaria report, released in November 2018, indicated that have been found 219 million cases of malaria in 2017, up from 217 million cases in 2016. "The WHO African Region continues to carry a disproportionately high share of the global malaria burden. In 2017, the region was home to 92% of malaria cases and 93% of malaria deaths".

Transmission

The *Plasmodium* parasite is mainly spread through the bites of female *Anopheles* mosquitoes. which mainly bite at dusk and at night. When an infected mosquito bites a person, it passes the parasites into the bloodstream.

Malaria can also be spread through blood transfusion and the sharing of needles, but this is very rare. The long lifespan and strong human-biting habit of the African vector species is the main reason why approximately 90% of the world's malaria cases are in Africa.

Several climatic conditions may affect the number and survival of mosquitoes, in particular: temperature, humidity and rainfall patterns. So, in many places, transmission is seasonal, "with the peak during and just after the rainy season".

In areas of moderate or intense transmission conditions, immunity is another important factor principally among adults. Effectively, over years of exposure, partial immunity is developed, and although it never provides complete protection, it does reduce the risk of severe disease. So, although all age groups are at risk, most malaria deaths in Africa occur in young children, in areas with less transmission and low immunity.

Prevention

Vector control is the main way to prevent and reduce malaria transmission. If coverage of vector control interventions within a specific area is high enough, then a measure of protection will be conferred across the community.

Insecticide-treatment mosquito nets

Protection for all people at risk of malaria with effective malaria vector control is recommended by WHO. In a wide range of circumstances, two forms of vector control – insecticide-treated mosquito nets (ITN) and indoor residual spraying (IRS)–are effective.

Sleeping under an insecticide-treated net (ITN) can reduce contact between mosquitoes and humans by providing both a physical barrier and an insecticidal effect. Population-wide protection can result from the killing of mosquitoes on a large scale where there is high access and usage of such nets within a community.

In 2017, about half of all people at risk of malaria in Africa were protected by an insecticide-treated net, compared to 29% in 2010. However, ITN coverage increased only marginally in the period 2015 to 2017.

Indoor spraying with residual insecticide

Indoor residual spraying (IRS) with insecticides is another powerful way to rapidly reduce malaria transmission. It involves spraying the inside of housing structures with an insecticide, typically once or twice per year. To confer significant community protection, IRS should be implemented at a high level of coverage.

Globally, IRS protection declined from a peak of 5% in 2010 to 3% in 2017, with decreases seen across all WHO regions. The declines in IRS coverage are occurring as countries switch from pyrethroid insecticides to more expensive alternatives to mitigate mosquito resistance to pyrethroids.

Antimalarial drugs

For areas of the Sahel sub-region of Africa, WHO has recommended, since 2012, seasonal malaria chemoprevention as an additional malaria prevention strategy. This involves the administration of monthly courses of amodiaquine plus sulfadoxine-pyrimethamine to all children under 5years of age during the high transmission season.

Insecticide resistance

According to WHO, 68 countries reported mosquito resistance to at least 1 of the 5 commonly-used insecticide classes in the period 2010-2017; among these countries, 57 reported resistance to 2 or more insecticide classes. Despite the emergence and spread of mosquito resistance to pyrethroids (the only insecticide class used in ITNs), insecticide-treated nets continue to provide a substantial level of protection in most settings.

Despite the emergence and spread of mosquito resistance to pyrethroids (the only insecticide class used in ITNs), insecticide-treated nets continue to provide a substantial level of protection in most settings. This was evidenced in a large 5-country study coordinated by WHO between 2011 and 2016.

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While the findings of this study are encouraging, WHO continues to highlight the urgent need for new and improved tools in the global response to malaria. To prevent an erosion of the impact of core vector control tools, WHO also underscores the critical need for all countries with ongoing malaria transmission to develop and apply effective insecticide resistance management strategies.

Diagnosis and treatment

Protecting the efficacy of antimalarial medicines is critical to malaria control and elimination. Regular monitoring of drug efficacy is needed to inform treatment policies in malaria-endemic countries, and to ensure early detection of, and response to, drug resistance. Early diagnosis and treatment of malaria reduces disease and prevents deaths. It also contributes to reducing malaria transmission. The best available treatment, particularly for *P. falciparum* malaria, is artemisinin-based combination therapy (ACT). WHO recommends that all cases of suspected malaria be confirmed using parasite-based diagnostic testing (either microscopy or rapid diagnostic test) before administering treatment. Results of parasitological confirmation can be available in 30minutes or less. Treatment, solely on the basis of symptoms should only be considered when a parasitological diagnosis is not possible. More detailed recommendations are available in the *"WHO Guidelines for the treatment of malaria"*, third edition, published in April 2015.

Antimalarial drug resistance

Resistance to antimalarial medicines is a recurring problem. Resistance of *P. falciparum* malaria parasites to previous generations of medicines, such as chloroquine and sulfadoxine-pyrimethamine (SP), became widespread in the 1950s and 1960s, undermining malaria control efforts and reversing gains in child survival.

Surveillance

"Surveillance entails tracking of the disease and programmatic responses, and taking action based on the data received. Currently, many countries with a high burden of malaria have weak surveillance systems and are not in a position to assess disease distribution and trends, making it difficult to optimize responses and respond to outbreaks.

Effective surveillance is required at all points on the path to malaria elimination. Stronger malaria surveillance systems are urgently needed to enable a timely and effective malaria response in endemic regions, to prevent outbreaks and resurgences, to track progress, and to hold governments and the global malaria community accountable.

In March 2018, WHO released a reference manual on malaria surveillance, monitoring and evaluation. The manual provides information on global surveillance standards and guides countries in their efforts to strengthen surveillance systems."

Elimination

In malaria it is necessary to differentiate between malaria elimination and malaria eradication. So:

I. Malaria elimination is defined as the interruption of local transmission of a specified malaria parasite species in a defined geographical area as a result of deliberate activities. Continued measures are required to prevent re-establishment of transmission.

II. Malaria eradication is defined as the permanent reduction to zero of the worldwide incidence of malaria infection caused by human malaria parasites as a result of deliberate activities. Interventions are no longer required once eradication has been achieved.

Countries that have achieved at least 3 consecutive years of 0 local cases of malaria are eligible to apply for the WHO certification of malaria elimination. In recent years, 9 countries have been certified by the WHO Director-General as having eliminated malaria: United Arab Emirates (2007), Morocco (2010), Turkmenistan (2010), Armenia (2011), Maldives (2015), Sri Lanka (2016), Kyrgyzstan (2016), Paraguay (2018) and Uzbekistan (2018). The WHO *Framework for Malaria Elimination* (2017) provides a detailed set of tools and strategies for achieving and maintaining elimination.

Vaccines against malaria

RTS,S/AS01 (RTS,S, trade name Mosquirix, is a recombinant protein-based malaria vaccine, approved for use by European regulators in July 2015).It is the first and, to date, the only vaccine to show partial protection against malaria in young children. It acts against *P. falciparum*, the most deadly malaria parasite globally and the most prevalent in Africa. Among children who received 4 doses in large-scale clinical trials, the vaccine prevented approximately 4 in 10 cases of malaria over a 4-year period.

In view of its public health potential, WHO's top advisory bodies for malaria and immunization have jointly recommended phased introduction of the vaccine in selected areas of sub-Saharan Africa. The vaccine will be introduced in 3 pilot countries – Ghana, Kenya and Malawi – in 2019."

The pilot programme will address several outstanding questions related to the use of the vaccine in real-life settings. It will be critical for understanding how best to deliver the required four doses of RTS,S; the vaccine's potential role in reducing childhood deaths; and its safety in the context of routine use.

This WHO-coordinated programme is a collaborative effort with ministries of health in Ghana, Kenya and Malawi and a range of in-country and international partners, including PATH, a non-profit organization, and GlaxoSmithkline (GSK), the vaccine developer and manufacturer.

WHO response

a. WHO global technical strategy for malaria 2016-2030: The World Health Assembly, in May 2015, has adopted the WHO *Global Technical Strategy for Malaria 2016-2030* which provides a technical framework for all malaria-endemic countries. It is intended to guide and support regional and country programmes as they work towards malaria control and elimination.

"The Strategy sets ambitious but achievable global targets, including:

I. Reducing malaria case incidence by at least 90% by 2030.

II. Reducing malaria mortality rates by at least 90% by 2030.

III. Eliminating malaria in at least 35 countries by 2030.

IV. Preventing a resurgence of malaria in all countries that are malaria-free.

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This Strategy was the result of an extensive consultative process that spanned 2years and involved the participation of more than 400 technical experts from 70 Member States".

b. The global malaria programme (gmp): "The WHO Global Malaria Programme (GMP) coordinates WHO's global efforts to control and eliminate malaria by:

(i) Setting, communicating and promoting the adoption of evidence-based norms, standards, policies, technical strategies, and guidelines.

(ii) Keeping an independent score of global progress.

(iii) Keeping an independent score of global progress.

(iv) Developing approaches for capacity building, systems strengthening, and surveillance, and

(v) Identifying threats to malaria control and elimination as well as new areas for action.

GMP is supported and advised by the Malaria Policy Advisory Committee (MPAC), a group of global malaria experts appointed following an open nomination process. The mandate of MPAC is to provide strategic advice and technical input, and extends to all aspects of malaria control and elimination, as part of a transparent, responsive and credible policy-setting process."

"The WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, at the World Health Assembly in May 2018, called for an aggressive new approach to jump-start progress against malaria. A new country-driven response – "High burden to high impact"–was launched in Mozambique in November 2018". "The approach will be driven by the 11 countries that carry the highest burden of the disease (Burkina Faso, Cameroon, Democratic Republic of the Congo, Ghana, India, Mali, Mozambique, Niger, Nigeria, Uganda and United Republic of Tanzania). Key elements include:

I. Political will to reduce the toll of malaria.

II. Strategic information to drive impact.

III. Better guidance, policies and strategies, and

IV. A coordinated national malaria response.

Catalyzed by WHO and the RBM Partnership to End Malaria, in "High burden to high impact"[5] builds on the principle that no one should die from a disease that can be prevented and diagnosed, and that is entirely curable with available treatments".

Conclusion

Malaria epidemics can occur when climate and other conditions suddenly favour transmission in areas where people have little or no immunity to malaria. They can also occur when people with low immunity move into areas with intense malaria transmission, for instance to find work, or as refugees.

To prevent an erosion of the impact of core vector control tools, WHO also underscores the critical need for all countries with ongoing malaria transmission to develop and apply effective insecticide resistance management strategies.

Considering the medical, economic and social impact of malaria on humans, the big objective of these is to obtain malaria eradication. As contribution for the elimination of malaria in the world, the World Health Assembly,[4] in May 2015, has endorsed a new "Global Technical Strategy for Malaria 2016-2030," whose key milestone for 2020 is the elimination of malaria in at least 10 countries that had the disease in 2015.This initiative was designated as the "E- 2020 initiative."[5]

Finally:

(i) That the eradication of malaria is possible demonstrated in Argentina and Uzbekistan, countries that have reported zero indigenous cases of malaria since 2011. Uzbekistan was officially certified malaria-free by WHO in December 2018 and Argentina has obtained this certification in May 2019.[6]

(ii) Considering the results already obtained in malaria eradication, we hope that within a short period of time, the eradication of malaria is obtained, being more a victory by the human for better health in the world. Several years ago, when we were working on malaria control in Angola - Africa, using several methodologies, it was only possible to control, eradication being a dream.[7]

Now, we are happy with the progress in fight against malaria in the world.

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Conflict of interest

The authors declare that there was no conflict of interest.

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