Artemisia sp against Malaria: The Reality Check.

After having succeeded in halving the incidence of malaria in the world, the World Health Organisation (WHO) acknowledges in its latest report on malaria an increase (+10%) of the number of registered cases particularly in Africa.

Its current strategy based on Artemisinin-Combination Therapy (ACT), impregnated bed-nets and early diagnosis, is very expensive and its continuation depends on increasing the amounts of foreign aid far beyond what is available and reasonable. In addition, resistances to insecticides and ACTs are extending beyond Asia to Africa.

Clearly, the current strategy has reached its limits and several African authorities recognise that at this pace, the United Nations' Goals of Sustainable Development against malaria (in particular SDD N° 3.1) will not be reached by 2030.

The remedies reported so far in the international media[1] tend to be just more of the same: vaccines, genetic transformation of the vector, more complex medication, new pesticides, new diagnostics, all of which except for the last, are even more costly and hence dependent of foreign aid and hence unsustainable. Strangely, these media seem to ignore that Africans, the main victims of malaria – traditionally use plants to fight infectious diseases and that world-wide, people rely more and more on plants to fight diseases.

A number of articles in African journals discuss the alternative of medicinal plants, especially *Artemisia annua* and *afra* whose efficacy against malaria justify their growing popularity.

Based on its field experience, its regular contacts with WHO and exchanges with African and international researchers, IDAY considers that several of those declarations deserve to be clarified. Below are IDAY's views submitted to the appreciation of the media on the occasion of the World Malaria Day (April 25).

The current treatments against malaria are sustainable:

FALSE

The official strategy based only on pharmaceutical products (ACTs a bi-therapy medication) and bed nets encounter several problems, in particular their high cost. WHO considers that USD 7,5 billion are needed per year to free the world of malaria while only USD 2,7 billion are available. These costs make them inaccessible in the long term to the most deprived populations.

Moreover, this solution is based on foreign charity making it difficult for a majority of the local population to take ownership of them. Once the foreign funding stops, the situation get worse as for example in Mozambique and Burundi where malaria cases rose dramatically.

Already in February 2011, Richard Horton, the Chief Editor of the prestigious medical paper "The Lancet" in his article, "*Stopping Malaria: The Wrong Road",* showed that the current approach was not sustainable.

Artemisia annua appears to be an effective repellent against mosquitoes, is used both to prevent and cure several tropical infectious diseases including malaria. It is inexpensive, enhancing the skills of local populations by placing them as the main actors in the struggle

[1] See for instance articles in several issues of Le Monde and those in the Financial Times of April 17th.

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against the scourge that affects them and freeing them from foreign aid that too often deprives them of responsibility.

The treatment based on *Artemisia annua* is a monotherapy:

FALSE

The plant is clearly a polytherapy. Pharmaceutical companies extract the artemisinin from the plant and the trade tends to ignore the other components contained in it that fight malaria. The famous US researcher, Professor Pamela Weathers of the Worcester Polytechnic Institute, cites about 10 ingredients of the plant that could be effective against malaria. *Artemisia annua* contains anti-oxidants, essential oils, flavonoids, zinc, all known to be effective against infections. *Artemisia annua* is of the Asteracea family that contains several species known for their medicinal effects. *Artemisia afra,* for instance, is known to be also effective against malaria although it contains no artemisinin suggesting that in *Artemisia annua,* this molecule is the only active principle. Finally, *Artemisia annua* knows no resistances so far and has been used for 2000 years in Asia (mainly in China) against malaria, a feature known to be characteristic of polytherapies. In fact, *Artemisia annua* may well be the only genuine polytherapy available against malaria.

Artemisia afra should be preferred to *Artemisia annua* because it is easier to elicite WHO's approval:

FALSE

Protagonist of the use of medicinal plants against malaria have proposed to promote *Artemisia afra* against malaria instead of *Artemisia annua* assuming that this choice would avoid opposition by WHO at least in Africa where *afra* is endemic. Hence, it is easier to be considered as a traditional medicine. Since it does not contain artemisinin, it does not carry the risk of creating resistances to the ACTs.

However, WHO's rules regarding the official use of medicines against a deadly disease like malaria are just as stringent for *Artemisia afra* as for *annua.* The latter having been the subject of more prolonged research is better known. Hence, even WHO representatives have declared that *Artemisia annua*, which has at least one recognised effective component against malaria, is a better bet to achieve WHO support. Both plants are of course useful and should be integrated into the strategy against malaria in Africa.

Artemisia annua can be used to prevent malaria (prophylaxis):

TRUE

The plant is indeed used to prevent malaria in several African countries while high toxicity levels of the ACTs and disagreeable side effects make the medication less recommendable for daily prevention. However, one must prove the evidence observed in the field with the plant through an international scientific study for WHO to lift its reservations. IDAY and the Kenyatta University signed a Memorandum of Understanding to conduct this research in accordance with WHO requirements. The research will be conducted by Kenyatta University (Kenya) with the support of several reputed international research centres and world-class specialists. The cost of the research is estimated at USD 12,5 million, a fraction of the research expenditures on uncertain vaccines or alternative medications.

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In Uganda, 3000 workers of a flower farm produce the plant and use it as prevention against malaria since 2006: no resistances have been reported. The same observation is reported from 50 schools in Kenya using the plant since 2010.

It appears that people who were never exposed to malaria have a lesser degree of natural immunity against the parasite. They must therefore probably be more cautious when they take the plant preventively against malaria.

WHO is opposed to the use of *Artemisia annua* against malaria:

TRUE BUT…

Considering the stringent requirements imposed by WHO to have a plant like *Artemisia annua* accepted, some have concluded that WHO's position is dictated by special interests from the pharmaceutical companies and will therefore systematically oppose the integration of *Artemisia annua* into the fight against malaria. During the years 2012 to 2015, WHO indeed opposed even *in vivo* research on the plant, while authorising field tests of vaccines that showed a lesser efficiency than the plant.

In 2017, WHO acknowledged its interest in research regarding the plant[2]. Regular contacts with WHO show that it simply applies to *Artemisia annua* the stringent rules that apply to all medication proposed against deadly diseases. It also acknowledges that it is only a normative organisation and that countries - the shareholders of WHO - can authorise any medication they consider safe. Hence, several African countries tolerate or even encourage the use of *Artemisia* plants against malaria.

This situation, however, is unsatisfactory, and WHO's approval of the plant would be welcome because it would authorise UN organisations such as FAO and World Food Programme to integrate the plant in their vast school garden and agricultural programmes hereby giving rapidly access to this lifesaving plant to a multitude of Africans and reducing the financial burden imposed by the costly current strategy. Hence the urgency of carrying out the appropriate research respecting WHO's norms.

There is a risk for *Artemisia annua* to create resistances:

TRUE BUT …

Malaria is a complex and treacherous infectious disease with a phase in its cycle when a very large number of gametocytes are liberated in the blood. This « explosion » of individuals is prone to the advent of mutations and hence of potentially resistant strains. Since mutations are a rare phenomenon and the production of cure resistant mutations even rarer, one can definitively conclude about the capacity of a cure to avoid resistances only after millions of users have experienced the cure over a long period of time.

Experience has shown that both monotherapies and bitherapies (ACTs) give rise to mutations that produce resistant plasmodium. Today, resistances to the medication reported since several years in Asia, have now also been reported in several African countries[3]. In the meantime, no resistances have been reported against *Artemisia annua*, including in instances where the plant

[2] Letter to IDAY of May 17 2017

[3] Lutgen P. Artemisinin resistances in Africa Malaria World 30 October 2016.

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has been used preventively for more than 10 years on several thousand individuals[4]. Research on rodents[5] has shown that *Artemisia annua* is very much less prone to resistances than ACTs. And, after all, the Chinese have used *Artemisia* against malaria for more that 2 000 years without the advent of resistances.

Nevertheless, if ever *Artemisia annua* was distributed on a large scale, especially as prophylaxis, the advent of resistances cannot be ruled out and will require close surveillance.

Artemisia annua is forbidden in several European countries:

TRUE

The plant is considered dangerous and its trade forbidden in Belgium and France. It is however, sold freely in Germany, Austria and Luxembourg. It is also officially authorised, for instance, in Australia and China. The plant is of course not dangerous and its infusions considered by the Chinese as a well-being tea, taken regularly preventively against numerous diseases. According to a text found in a tomb of a Chinese doctor dated 168 BC, he claimed to be treating 52 diseases with natural extracts of *Artemisia*.

A mail from the Ministry of Health of April 11 2018 explains to IDAY the procedure to be followed to authorise the introduction of *Artemisia annua* as a medicinal plant in the trade. We are far from the time when IDAY was considered a "witch doctor" by WHO and the Institute of Tropical Medicine of Antwerp for having dared to promote *Artemisia annua* to fight various infectious diseases.

Artemisia annua is from Asia and does not grow in Africa:

FALSE

Artemisia annua cultivation is demanding, needing a lot of water and technical competences to obtain high yields. Seeds are very small, need to remain on the ground because they germinate only if they receive light, and need to be irrigated three times a day. This is why most growers fail their first attempt and why they need training for cultivation and harvesting the plant. It needs to be cut and dried before seeds appear because it looses its healing capacity after seeds appear. It is an annual plant: hence it dies after having seeded and needs to be replanted every year (which is not the case of *afra* that grows as a bush). Hence, one must keep at least one *Artemisia annua* plant for the production of seed. `

Artemisia annua comes from Mongolia and is highly sensitive to photoperiodism (it grows only when day length increases and dies when they shorten). Since daylight is constant around the equator, it could be grown initially only in areas far away from the equator (Madagascar for instance). Happily a cultivar was developed to be insensitive to photoperiodism and the Agricultural Faculty of Liège (Belgium) demonstrated that the cultivar found in Kenya grew also well in Western Africa and hence over the whole continent. *Artemisia annua* is highly productive: well cured over one hectare, it can protect 150 000 persons.

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[4] Ogwang P. Unpublished document. April 2018. The author was rewarded by the President of Uganda for his extensive work on *Artemisia annua*.

[5] Elfawal MA, Towler MJ, Reich NG, Weathers PJ, Rich SM (2015) Dried whole plant *Artemisia annua* slows evolution of malaria drug resistance and overcomes resistance to artemisinin. PNAS USA 112:821-826, doi: 10.1073/pnas.1413127112.

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Artemisia annua could become invasive in Africa:

FALSE

One has to be careful when it comes to introduce new species in a delicate environment. We have all heard about examples of invasions but it exists since the beginning of international trade, thousands of years ago (Slik Road) but with globalisation and climate warming it will be a major challenge for biodiversity.

Since *Artemisia annua,* is a plant that originated in a temperate climate and does not grow easily, the *World Wide Fund for Nature* (WWF), has informed IDAY that it carries a very low and acceptable risk of endangering the native African flora.

ACTs are the last weapons to fight malaria:

FALSE

This declaration was certainly warranted a few years ago, when resistances to ACT were confined to a limited area in Asia, and the capacity to withstand resistances by *Artemisia annua* and *afra* unknown. Today, the situation could well become just the reverse since the *Artemisia* plants could become the ultimate weapons to fight malaria sustainably: it is urgent to start the international researches in order to be able to introduce the plants in the panoply of the means available in the fight against malaria.

Conclusion

Efforts in fighting malaria gave remarkable results so far but are facing new challenges.

Artemisia annua and *afra* offer cheap solutions, easily appropriated by the local population since they correspond to the traditional ways of fighting diseases. They require little foreign aid and research protocols are ready to verify their conformity with WHOs norms. Complementing the actual official means used against malaria with the plants, on could rapidly control this plague in Africa. Experiences in the field have demonstrated their efficacy. Schools and corporations that have adopted *Artemisia annua* to prevent malaria have seen their absenteeism and health costs drop significantly and productivity or school results rise spectacularly. Malaria is estimated to cost Africa 1,5% of annual GDP growth, just what is missing to reduce the number of Africans living under the poverty threshold. It is up to the media to inform our generation of what needs to be done to liberate the Africans from a major obstacle to their development.

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