

A brief history of selected malaria vaccine and medical interventions pursued by the Swiss Tropical and Public Health Institute and partners, 1943-2021

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ABSTRACT

In order to be successful in global health today, all the long-established European tropical research institutes had to undergo a transition which can be described as “hunter-gatherer” and descriptive approaches during colonial and postcolonial times to a deeper understanding of infection biology and finally to public health interventions from which populations at large can benefit. During the 1980s and 1990s, the Swiss Tropical Institute (today: Swiss Tropical and Public Health Institute, Swiss TPH) based in Basel too has changed its focus from individual medicine to a public health context. This article does not present new scientific data but takes a historical perspective. Its aim is to highlight the above-mentioned transformation by focusing on selected malaria research-cum-action interventions during the crucial period of the 1990s, which were tailored to the social-ecological settings where the disease was endemic. In order for this transformation to be successful, we intend to emphasise the importance of (i) having a fundamental understanding of local transmission; (ii) building and nurturing relationships with partner institutions; and (iii) developing a coherent research portfolio as key elements for researching and applying evidence in malaria control and elimination as part of national malaria control programmes.

1. Early years of malaria research

For many years, the single most researched disease at the Swiss Tropical and Public Health Institute (Swiss TPH) has been – and continues to be – malaria. However, when the institute was founded by Rudolf Geigy in 1943, the initial research focus was directed on other diseases such as sleeping sickness and tick-borne relapsing fever. The few instances of malaria-related research and services in the early history of Swiss TPH dealt with *Plasmodium vivax* infections of Italian and Yugoslavian soldiers. Many of them were prisoners of war under Mussolini in Sardinia where they contracted the disease. Towards the end of the Second World War they were able to escape and cross the border to Switzerland where they underwent treatment in the “tropical clinic” of the Swiss Tropical Institute (Perret-Gentil, 1945; Meier, 2007).

A second early peak of malaria research and publications dates back to the mid-1950s (Fig. 1). On a research station on Jungfrauoch in the

Bernese alps at an altitude above 3,500 m, Swiss TPH researchers analysed the influence on high altitudes on the course of malaria in chicken. Later, the same experiments have been repeated in the Kilombero valley in Tanzania, replacing chicken with monkeys (Freyvogel, 1955, 1956). But as Thierry A. Freyvogel, the second director of the institute from 1972 to 1987, recalls in an interview: “At the time, we thought we couldn’t keep up with the international competition in broad malaria research (Meier et al., 2021).

2. The Global Malaria Eradication Programme (GMEP, 1955-1969)

Without explicitly naming it, Freyvogel was referring to the World Health Organization (WHO) and its Global Malaria Eradication Programme (GMEP, 1955-1969). During the WHO’s 8th World Health Assembly in Mexico City in 1955, the representatives of the member states

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decided to eliminate the deadly disease. A new tool gave them confidence in the feasibility of this ambitious undertaking: Dichlorodiphenyltrichloroethane (DDT for short) (Packard, 2007). The insecticide, produced by R. Geigy AG in Basel in 1939, raised justified hopes. Countries such as Italy, Venezuela and Greece proved that the elimination of malaria by vector control was financially and technically possible. However, it was uncertain whether the poorer countries of Africa would be able to pull off the same coup against the disease. With the *Anopheles gambiae* group and the long underestimated *Anopheles funestus* group, African countries were not only home to the most efficient disease vectors. The infrastructure was often miserable, the health systems ailing. Five years earlier - during the Kampala Conference in Uganda - people were already at loggerheads over the question of how to eliminate malaria in Africa. Numerous physicians with a respectable track record in the African colonies argued that the people of Africa would lose their natural immunity if the disease were eradicated. If an eradication programme had to be halted early, the disease would fight back relentlessly. Not surprisingly, the GMEP failed on the African continent and produced mixed results elsewhere. Thanks to GMEP, 18 countries managed to eliminate the disease by 1970. Another eight nations managed malaria elimination a few years after GMEP ended. In many other places around the world, disease and mortality rates were drastically reduced. It is striking that it was mainly the economically privileged countries in Europe, Eastern Europe or the Caribbean island states that recorded the greatest successes. The latter benefited from their manageable size and the ability to control the reintroduction of infection. Of concern was the resistance of mosquitoes to DDT already observed in the 1950s as well as the traumatic resurgence of disease outbreaks in countries that were already considered malaria-free.

3. Setting the scene: malaria research and partnership

The reason why malaria research at the Swiss Tropical Institute nevertheless began to play an increasingly important role was to be found in Tanzania, more precisely in Ifakara, a small town far from the metropolis of Dar es Salaam. It was in Ifakara, located in the Kilombero district in the south-eastern part of Tanzania, where Swiss TPH initiated its field laboratory in 1949. The name of the town of Ifakara means “the place where one dies” in the local language. Malaria was responsible in large part for this grim state of affairs. At the time, the Kilombero valley

was one of the worst malaria transmission areas in the world. At least 50% of all hospital admissions in the district were due to malaria. On average, residents were bitten by one infectious mosquito per day (Freyvogel and Kihale, 1968). It was only possible to improve their living conditions through intense research and smoothly running partner institutions. No one understands this better than Marcel Tanner, an epidemiologist and public health specialist who directed and developed the field laboratory at Ifakara from 1981 to 1984 and later served as Director of Swiss TPH from 1997 to 2015 (Meier et al., 2021). In 1988, he launched the Kilombero Malaria Project (KMP) to help in the urgent fight against this public health scourge. One of his stated goals was to coherently address the malaria problem in Africa through research-cum-action by setting the basis within the region for future malaria intervention studies and the subsequent translation of generated evidence for the benefit of the population and similar African settings. “For a long time, researchers conducted small malaria projects without understanding demographic, social and cultural relationships and how much the disease burdened the local population,” says Tanner. But it is precisely these factors that are critical for later clinical trials as well as for tailoring control and elimination efforts to the local settings. This is why entomologists such as Derek Charlwood (Liverpool School of Tropical Medicine) and Willem Takken (Wageningen University) in the 1980s extensively studied the extent, dynamics and conditions of disease transmission in the district (Smith et al., 1993, 1995; Charlwood et al., 1995a, 1995b, 1997). Understanding exposure served as a backbone for future immunological studies, for a better knowledge of protection and clinical trials with malaria candidates. After all, it was not enough just to know that people were infected; rather, an understanding of the entire impact of the disease was needed. In addition to expanding the body of entomological knowledge, the KMP was dedicated to strengthen the relationship to local health authorities and researchers, as well as building up partner institutions which would facilitate the translation of research results into public health action. From the early 1980s onwards, the former Swiss Tropical Institute Field Laboratory (STIFL) was transformed to a Tanzanian trust and international non-governmental organisation (NGO) under Tanzanian leadership working under the umbrella of the Tanzanian health policies, but also maintaining the strong national and international partnership. At times, over 700 Tanzanian scientists worked at what is now the Ifakara Health Institute (IHI). “Only by having functioning partner institutions and partnerships

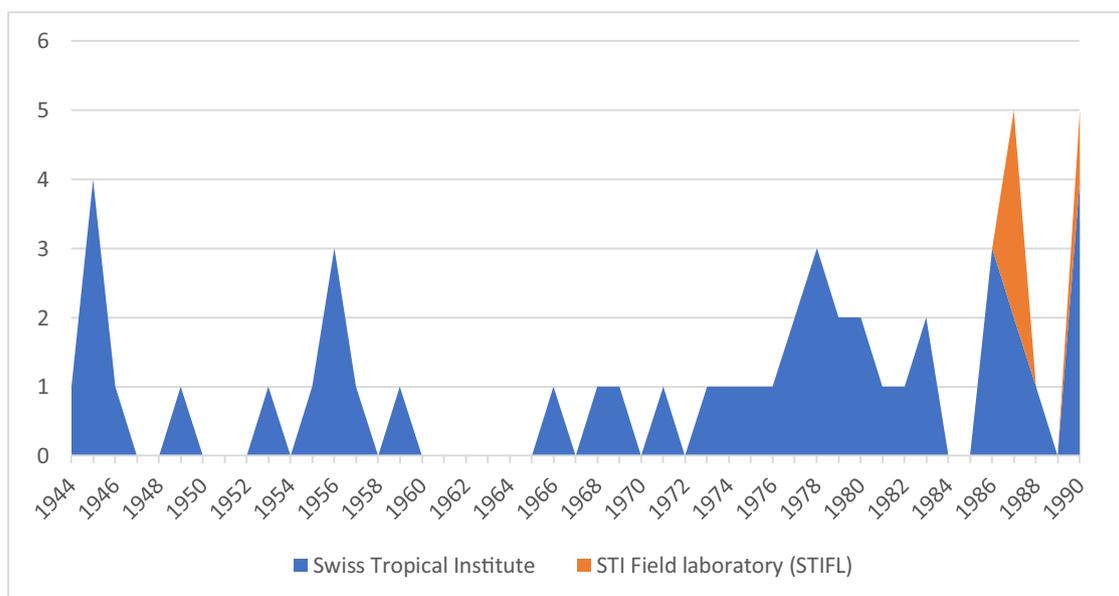


Fig. 1. Malaria-related publications between 1944 and 1990 stratified by “Swiss Tropical Institute” and “Swiss Tropical Institute Field laboratory STIFL”. Source 1 (1944-1980): Swiss TPH Database, searched on May 27, 2021. Timespan=1944-1980. Source 2 (1981-1990): Web of Science (Core collection), searched on 27 May, 2021.

can we validate health interventions such as new medicines or vaccines,” says Tanner.

4. SPf66: the first malaria vaccine attempt in Africa

Through the KMP in Tanzania, Swiss TPH and IHI had become internationally known for their ability to mount large scale trials with insecticide-treated nets or vaccines. This was something that Pedro Alonso, the current Director of the WHO Global Malaria Programme, also understood. Alonso and Brian Greenwood (London School of Hygiene and Tropical Medicine) studied the impact of insecticide-treated nets in the West African country of Gambia (Alonso et al., 1993). Alonso was also part of the phase I-II trials of the SPf66 malaria vaccine, developed by Colombian researcher Manuel Patarroyo (Patarroyo et al., 1988). The peptides that the vaccines were based on made waves around the world (Meier, 2014; Meier and Lengwiler, 2019). There was not much doubt about the safety and efficacy of the molecule, but rather about the conduct of the clinical trials in Ecuador, Venezuela and Colombia, as they did not conform to good clinical practice (GCP) standards. This led WHO to call for independent (from Patarroyo’s team) tests of SPf66 to be conducted in other countries. Alonso’s request to Tanner about whether Swiss TPH – in partnership with IHI and the Spanish team – could conduct the trial did not come out of the blue. Alonso and his team at ISGlobal in Barcelona, Spain had long been following the developments in Tanzania. “We will do it!” – was Tanner’s reply to Alonso. The Idete trial including 586 children aged 1-5 years was the first phase III trial of a malaria vaccine conducted on African soil. The trial found a vaccine efficacy of 31% in children with a confidence interval of 0% to 52% (Alonso et al., 1994). The subsequent phase III trial among infants, however, did not show any efficacy and the researchers concluded: “This vaccine in its current formulation is not of public health use” and thus SPf66 could never be implemented within health systems beyond trials (Acosta et al., 1999).

5. Laboratory-field relations

The Idete trial had considerable repercussions for the malaria research being conducted at Swiss TPH in Basel. “It wasn’t about travelling to Tanzania to collect a few blood samples,” says Tanner. “But rather, it boosted malaria research at the institute in Basel insofar as we ensured that we are reliable partners for countries in the Southern hemisphere.” In the 1990s, Swiss TPH strengthened its expertise in fundamental research, particularly in clinical immunology. Some individual projects were abandoned in favour of creating a coherent research portfolio.

This created the foundation for a series of health interventions that continue to date. For example, Swiss TPH worked together with IHI on a series of iron supplementation studies (Menendez et al., 1997) and particularly on the world’s first trial for intermittent preventive treatment in infants (IPTi) in Ifakara (Armstrong Schellenberg et al., 2010). The phase III trial of IPTi in Ifakara (Schellenberg et al., 2001a, Aponte et al., 2009), followed by the phase IV implementation in the Mtwara region in southern Tanzania with a population base of more than 1.5 million people. The safety, efficacy and community effectiveness of interventions were not the only issues taking centre stage. Increasingly, the emphasis was also on how to evaluate new technologies combined with new approaches like social marketing, particularly mosquito nets treated with insecticides – and make them accessible to people who need them. The Kilombero Treated Net Project (KINET) is a good example: it linked research with a social marketing approach with the goal of raising awareness about malaria prevention (Schellenberg et al., 1999). In the end, more than half a million Tanzanians acquired these insecticide-treated nets, and the effect on the health of the population was considerable. Thanks to KINET, infant mortality in the Kilombero and Ulanga districts dropped by 27% (Schellenberg et al., 2001b). During the same period, public health data were collected within a new

framework: the health and demographic surveillance system (HDSS), which longitudinally collects health and demographic data from the country’s inhabitants in a well-defined area (Geubbels et al., 2015). Only by having this kind of data as a point of comparison could the success or failure of projects like KINET be properly evaluated.

6. Productive publication activity

One important (but by far not the only) indicator of excellence in research are publications in the peer-reviewed literature. Between 1981 and 2020 Swiss TPH has published 1,529 articles related to malaria (2.2% of all the 68,261 matches provided by the Web of Science Core Collection; accessed on 3 June 2021). The malaria articles of IHI during the same period amounts to 617 (0.9% of all the 68,261 malaria publications between 1981 and 2020) while there were 305 joint publications.

Fig. 2 not only shows the steady increase of malaria publications during the 1990s and 2000s but also the increasing number of joint publications and stand-alone publications by researchers of IHI. Fig. 3 in turn gives a snapshot on the publication activities in Tanzania. It elucidates the rising number of stand-alone IHI publications since 1981 and the large amount of Swiss TPH-IHI joint publications compared to publications with other Tanzanian research institutions and university (which, of course, says nothing about the quality of these institutions but rather about the historically grown and close research partnership between Swiss TPH and IHI).

7. The globalisation of malaria research

The 1990s saw not just the expansion of publications on and health intervention methods against malaria, but also the broader globalisation of research on the tropical disease. The island state of Papua New Guinea joined Eastern Africa as the focus of research at Swiss TPH. For a long time, it was believed that the pathogen *Plasmodium falciparum* was mainly responsible for all malaria cases and deaths in Papua New Guinea. This assumption was shattered by the work of Blaise Genton and Ivo Müller at Swiss TPH. Their enlightening evaluation of old epidemiological studies revealed that the *P. vivax* pathogen is also responsible for severe cases of malaria in the country (Genton et al., 2008). “This triggered a paradigm shift in malaria research in Papua New Guinea,” says Genton. “Suddenly, everyone started working on *P. vivax*.” Although this was indeed an important finding, it dampened the hopes of those who had believed in the rapid elimination of the disease in the country. Unlike *P. falciparum* – the deadliest of all malaria parasites –, *P. vivax* can survive in a dormant state in the liver of an infected individual for months or even years (Müller et al., 2003). Then, from one day to the next, the parasite invades the bloodstream and triggers the symptoms that are typical for malaria. Once it has reached human blood, the pathogen is also infectious for mosquitoes. These so-called relapses play a major role in the spread of malaria in Papua New Guinea. “Elimination of the disease is difficult at the present time,” comments Genton – for that same reason. In order to get an infection with *P. vivax* under control, you would have to target the hypnozoites, the liver-stage parasites, in all those affected. Unfortunately, this is impossible to do with the only effective medication currently available, as it has to be taken over a 14-day course and may trigger rather severe adverse events in some cases.

8. Constant investments in infrastructure

In 2004, a new clinical research facility was constructed by IHI in Bagamoyo on the coast of Tanzania. The city of Ifakara, located in the interior of the country, was no longer suitable for this undertaking: malaria transmission had been drastically reduced thanks to the success of the KINET project and other integrated interventions (Finda et al., 2018). The Bagamoyo research branch of IHI served as a venue for a

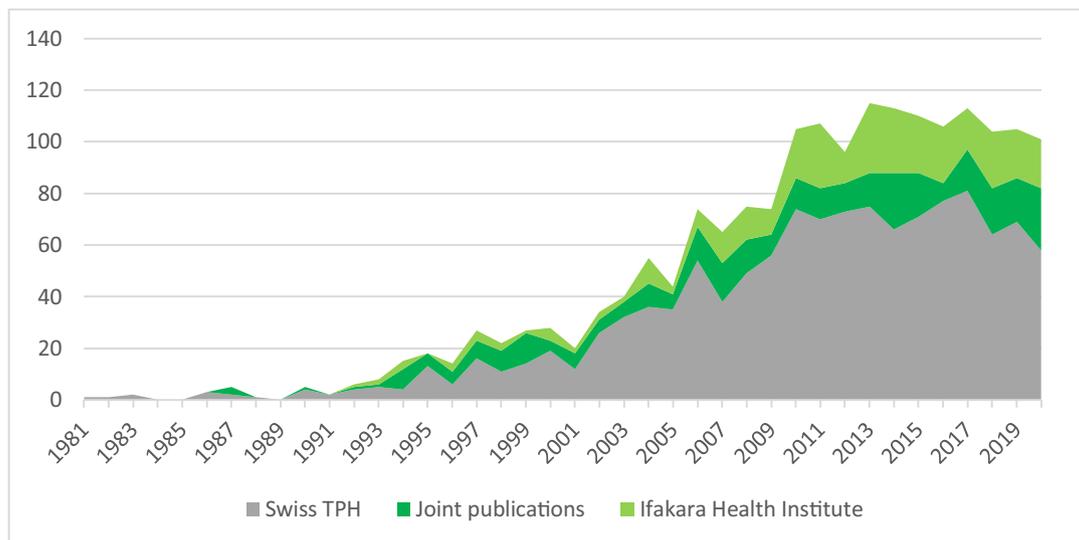


Fig. 2. Overall malaria-related publications between 1981 and 2020 by Swiss TPH, stratified by “Swiss TPH”, “Ifakara Health Institute (IHI)” and “joint publications.” Source 1: (1981-2020): Web of Science (Core Collection), searched on 27 May, 2021. Publications types: Journal articles, Reviews, Editorials, Letters, Book chapters.

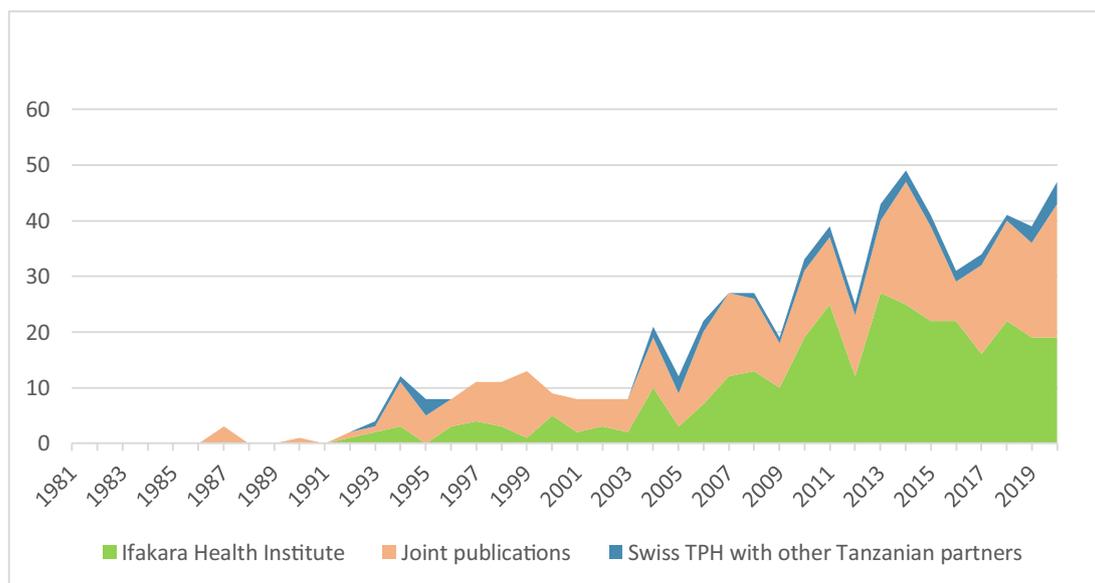


Fig. 3. Malaria-related publications between 1981 and 2020 with Tanzanian institutions (affiliations). Source: Web of Science (Core collection), searched on 7 June, 2021. Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC. Timespan=1981-2020. Publications types: Journal articles, Reviews, Editorials, Letters, Book chapters.

series of clinical studies with diverse test subjects and a broad portfolio of diseases such as malaria, tuberculosis and viral diseases. Over the past few years, Swiss TPH and IHI successfully co-spearheaded the development of GlaxoSmithKline’s RTS,S vaccine against *P. falciparum* through clinical trials supported by the Bill & Melinda Gates Foundation. Of central importance to this project was the pivotal phase II trial in 2008 that involved 340 children aged 2-4 months. The trial demonstrated vaccine efficacy of 65.2% and confirmed the safety profile of RTS,S as well as its compatibility with other childhood vaccinations (Abdulla et al., 2008). These results were a green light for the large and essential phase III studies with 16,000 infants and children in 11 centres of 7 African countries. This research showed that for clinically significant and severe malaria, RTS,S had an efficacy of 34.8% in children aged 5-17 months (RTS, Clinical Trials Partnership, 2011) and only a modest efficacy (26%) in infants aged 1.5-3 months (RTS, Clinical Trials Partnership, 2012). The European Medicines Agency (EMA) had given the

vaccine a positive evaluation, and the WHO called for further pilot implementation studies in Ghana, Kenya and Malawi before the launch of RTS,S on a broad scale in the spring of 2019 (WHO, press release, 2017; Penny et al., 2015). Vaccinations alone will not be enough to defeat malaria going forward. “We still need a complete integrated bundle of interventions with vaccines, insecticide-treated nets and effective medicines tailored to a given endemic setting,” says Tanner.

9. New drugs to fight malaria

The development of a sound pipeline of new compounds has also received a boost over the past decades. In the 1990s, many pharmaceutical companies had turned their backs on the fight against malaria and other diseases of poverty and neglected tropical diseases. In 1997, the pharmaceutical company Roche in Basel transferred its malaria research unit to Swiss TPH. Around this time, it became clear that there

was enough knowledge and medicine to efficiently fight the disease. In the same year, Swiss TPH and the Swiss government acted as a founding member of the Medicines for Malaria Venture (MMV). The overarching goal was to put new affordable antimalarial drugs on the market. MMV is a public-private partnership (PPP) that won people over with its unique organisational structure: governments or philanthropic organisations provided funding, pharmaceutical companies provided their large substance libraries, and research institutes such as Swiss TPH tested the substances for their biological activity against malaria parasites. This allowed for the expensive research and development process of antimalarial drugs to be shouldered by multiple parties instead of just one company or research group. MMV revitalised the search for antimalarial drugs as well as their development and registration (Hooft van Huijsdijnen et al., 2019). One key product of a PPP with Novartis, even before the creation of MMV, was Coartem; discovered by Chinese scientists and brought to Europe for further development. Since its introduction in 2001, more than one billion doses of this combination therapy have been distributed. Researchers at Swiss TPH assisted in the development of Coartem by conducting the first clinical trial among children. Following these clinical studies in Tanzania (Hatz et al., 1998) and by the London School of Hygiene and Tropical Medicine in Gambia, the institute provided fundamental data that allowed Coartem to be approved on fast track by Swissmedic (Tanner & Hatz, personal correspondence). “Malaria research will continue to play an important role at Swiss TPH – from basic research to support of national malaria control programmes” says current Director Jürg Utzinger. However, in order to successfully eliminate the disease one would need – apart from a sound research and development agenda and a global strategy – new transformative tools; not just a lightly better drug, but innovations that have a significant impact on the interruption of transmission.

10. Conclusion: from innovation to implementation

This briefly outlined history of the selected malaria interventions pursued by researchers at Swiss TPH together with colleagues abroad that led to crucial interventions now globally applied as part of the Global Technical Strategy of malaria control and elimination (GTS; WHO 2015) unfolded along a value chain that spanned from innovation to validation to the implementation of research results with people on site. The fascination surrounding *P. falciparum*, the malaria pathogen par excellence, is central to the story. In order to plan successful public health innovations, it is first key to develop an understanding of the biology of this single-celled organism and how it interacts with its environment and the human host, particularly also the immune system – along with a deeper understanding of people and the strategies they use to protect themselves against the deadly parasite. But that is still not enough. Insecticide-treated nets, drugs, and new vaccines all have to be scientifically validated, adapted to local conditions and integrated into health care delivery within health and social systems. And to make all of this possible, it is first fundamental to engage in a process of mutual learning, i.e. to have trust-based partnerships, to build institutions and to promote the careers of scientists – both in partner countries in the southern hemisphere and at Swiss TPH (Saric et al., 2019; Tanner and Meier, 2019). Effective malaria interventions at Swiss TPH benefited enormously from the creation of a coherent research and research-cum-action portfolio and from new governance structures at the turn of the millennium that brought sponsors, pharmaceutical companies and academic partners together under one roof. Today, we are a great deal closer to the goal of eliminating malaria. This progress becomes even more surprising considering that just 30 years ago, no one really believed in the possibility of making great strides in the fight against the disease.

Declaration of Competing Interest

No conflicts declared.

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Supplementary materials

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