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REVIEW

Mosquito vectors and the spread of cancer: an overlooked connection?

Giovanni Benelli[1] · **Annalisa Lo Iacono**[2] · **Angelo Canale**[1] · **Heinz Mehlhorn**[3]

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Abstract Mosquitoes (Diptera: Culicidae) represent a key threat for millions of humans and animals worldwide, vectoring important pathogens and parasites, including malaria, dengue, filariasis, and Zika virus. Besides mosquito-borne diseases, cancers figure among the leading causes of mortality worldwide. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 million within the next two decades. Notably, there are few contrasting evidences of the relationship between cancer and mosquito-borne diseases, with special reference to malaria. However, analogies at the cellular level for the two diseases were reported. Recently, a significant association of malaria incidence with all cancer mortality in 50 USA states was highlighted and may be explained by the ability of *Plasmodium* to induce suppression of the immune system. However, it was hypothesized that *Anopheles* vectors may transmit obscure viruses linked with cancer development. The possible activation of cancer pathways by mosquito feeding events is not rare. For instance, the hamster reticulum cell sarcoma can be transmitted through the bites of *Aedes aegypti* by a transfer of tumor cells. Furthermore, mosquito bites may influence human metabolic pathways following different mechanisms, leading to other viral infections and/or oncogenesis. Hypersensitivity to mosquito bites is routed by a unique pathogenic mechanism linking Epstein–Barr virus infection, allergy, and oncogenesis. During dengue virus infection, high viral titers, macrophage infiltration, and tumor necrosis factor alpha production in the local tissues are the three key important events that lead to hemorrhage. Overall, basic epidemiological knowledge on the relationships occurring between mosquito vector activity and the spread of cancer is urgently needed, as well as detailed information about the ability of Culicidae to transfer viruses or tumor cells among hosts over time. Current evidences on nanodrugs with multipotency against mosquito-borne diseases and cancers are reviewed, with peculiar attention to their mechanisms of action.

Keywords *Aedes* · *Anopheles* · Arbovirus · Artesunate · Dengue · Epstein–Barr virus · Malaria · Nanosynthesis · Tumor biology · Zika virus

Introduction

Mosquitoes (Diptera: Culicidae) represent a key threat for millions of humans and animals worldwide, since they act as vectors for important pathogens and parasites, including agents of malaria, yellow fever, dengue, West Nile fever, chikungunya, filariasis, and Zika virus (Jensen and Mehlhorn 2009; Dobler and Aspöck 2010; Mehlhorn et al. 2012; Liang et al. 2015; Benelli and Mehlhorn 2016; Li et al. 2016; Pastula et al. 2016; Saxena et al. 2016). Therefore, the development of effective and eco-friendly control tools against Culicidae populations is a challenge of huge public health importance (Benelli 2015a, b). Malaria killed an estimated 306,000 under-fives globally, including 292,000 children in the African region. Between 2000 and 2015, the mortality rate among children fewer than five fell by 65 % worldwide and by 71 % in

✉ Giovanni Benelli
g.benelli@sssup.it; benelli.giovanni@gmail.com

[1] Insect Behaviour Group, Department of Agriculture, Food and Environment, University of Pisa, via del Borghetto 80, 56124 Pisa, Italy

[2] Sant'Anna School of Advanced Studies, Piazza Martiri della Libertà 33, 56127 Pisa, Italy

[3] Department of Parasitology, Heinrich Heine University, Düsseldorf, Germany

Africa (White 2015; WHO 2015a). Furthermore, 390 million dengue infections per year (95 % credible interval 284–528 million) have been calculated, of which 96 million (67–136 million) manifest clinically (with any severity of disease) (Bhatt et al. 2013). An additional research on the prevalence of dengue estimates that 3900 million people, in 128 countries, are at risk of infection with dengue viruses (Brady et al. 2012).

The recent outbreaks of Zika virus infection mainly vectored by *Aedes* mosquitoes, occurring in South America, Central America, and the Caribbean, represents the most recent public health challenge in this field (Attar 2016; Benelli and Mehlhorn 2016). Even if Zika symptoms last only a few days in adult persons and are similar to other arbovirus infections, such as dengue (i.e., fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache), the surveys conducted on the high numbers of cases of Zika virus infections in French Polynesia (2013) and Brazil (2015) highlighted potential neurological and autoimmune complications. Indeed, during the Zika virus outbreaks in French Polynesia, a concomitant epidemic of 73 cases of Guillain–Barré syndrome and other neurologic conditions was observed in a population of about 270,000 people (Oehler et al. 2014). In northeast Brazil, during 2015, the increase in Zika virus infections has been reported in close concurrence of an increase in babies born with microcephaly. However, further research is urgently needed to shed light on the relationship between these potential complications and Zika virus infections (Benelli and Mehlhorn 2016).

Besides mosquito-borne diseases, cancers figure among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012 (WHO 2015b). Among men, the five most common sites of cancer diagnosed in 2012 were lung, prostate, colorectum, stomach, and liver. Among women, the five most common diagnoses were breast, colorectum, lung, cervix, and stomach cancer. More than 60 % of world's total new annual cases occur in Africa, Asia, and Central and South America. These regions account for 70 % of the world's cancer deaths. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 million within the next two decades (WHO 2015b; Murugan et al. 2016).

Mosquito-borne diseases and cancer: what do we really know?

To the best of our knowledge, there are rather few studies concerning the relationship between some types of cancer and mosquito-borne diseases, with special reference to malaria. Suresh et al. (2005) reported analogies at the cellular level for the two diseases, while Welsh et al. (1976) observed no relationship between malaria rates and primary liver cancer. The association between malaria and cancer mortality may be explained by the well-established ability of *Plasmodium* to induce suppression of the immune system. However, a second explanation has been recently published by Lehrer (2010a, b) hypothesizing that the *Anopheles* mosquitoes, which include vectors of malaria (Fig. 1a), might represent a source of brain tumor viruses. The evidence of an association of *Anopheles* bites with brain tumors was outlined in the relationship between malaria outbreaks in USA (Skarbinski et al. 2006) and reports of brain tumor incidence (CBTRUS 2008). Indeed, a significant association between US malaria outbreaks in 2004 and the reports of brain tumor incidence 2000–2004 from 19 USA states was highlighted by Lehrer (2010a, b), which also pointed out highly significant correlations between malaria and malignant brain tumors, as well as malaria and benign brain tumors. Since the increased numbers of both malaria cases and brain tumors could be due solely to the fact that some states, such as New York, have much larger populations than other states, such as North Dakota, multiple linear regression was performed with number of brain tumors as the dependent variable and malaria and population as independent variables. The effect of malaria was significant and independent of the effect of population (Lehrer 2010a). More generally, it was found a significant association of malaria incidence with all cancer mortality in 50 US states and the District of

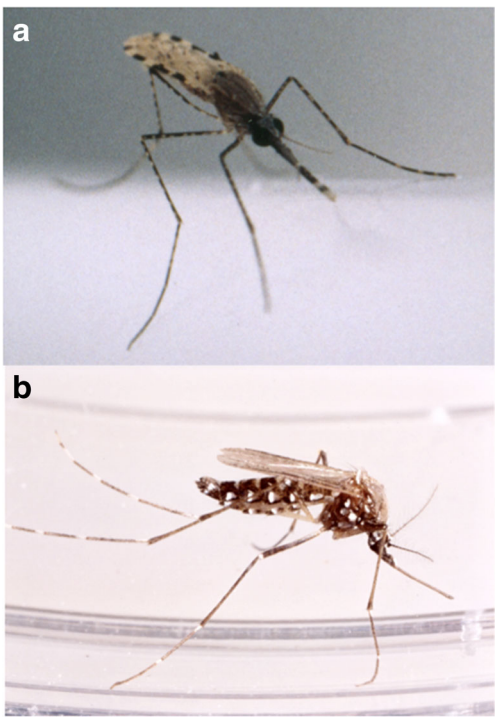

Fig. 1 Recently, a significant association of malaria incidence with all cancer mortality in USA was highlighted; it was hypothesized that Anopheles vectors (**a**) may transmit obscure viruses leading to cancer. Furthermore, Aedes feeding activity (**b**) leads to transfer of tumor cells, as well as to modification of metabolic pathways [photo credit: Heinz Mehlhorn]

Columbia. The association was independent of state population size, percentage black population by state, and median population age (Lehrer 2010b). In this scenario, it was formulated that *Anopheles* mosquito may be able to transmit an obscure virus that initially causes only a mild transitory illness but much later induces a brain tumor (Lehrer 2010a). Further research on this point is urgently needed since, if the mosquito-transmitted brain tumor viruses will be identified, the development of a brain tumor vaccine might be possible (Lehrer 2010a).

Although *Anopheles* mosquitoes are mainly known as the vectors of malaria parasites, they may also spread arboviruses, including those of the West Nile fever and Japanese encephalitis, while *Aedes* mosquitoes act as vectors of a wider range of arboviruses, such as dengue, chikungunya, and Zika virus (Attar 2016; Fauci and Morens 2016; Li et al. 2016; Pastula et al. 2016; Rodriguez-Morales et al. 2016). Concerning *Aedes* mosquitoes and cancer, the hamster reticulum cell sarcoma, TM, can be transmitted through the mosquito vector *Aedes aegypti* (Fig. 1b) by a transfer of tumor cells (Banfield et al. 1965, 1966). Tumor cells of TM remained viable up to 8 h after the ingestion by *Ae. aegypti* adults. Feeding on or off the tumor did not influence the rate of transmission (i.e., 10 % in a series of experiments and 5 % in another) (Banfield et al. 1966). Tumor cells were transmitted by 1 to 2 % of the mosquitoes. Notably, an attempt to transmit the Rauscher virus leukemia by *Ae. aegypti* failed, and there is no evidence of immunity to the Rauscher virus conferred by a subclinical infection. In addition, there is no evidence of multiplication in *Ae. aegypti* of an agent from TM or of the Rauscher virus (Banfield et al. 1966, but see also Kilham 1955).

However, mosquito bites may influence human metabolic pathways following different mechanisms and leading to other viral infections and/or oncogenesis. For instance, the Epstein–Barr virus-related Burkitt's lymphoma is believed to require cofactors, such as components occurring during malaria infections, for tumor development (Usherwood et al. 1996). Later on, a further example has been elucidated by Tokura et al. (2001) and Asada (2007), which reviewed the hypersensitivity to mosquito bites as a unique pathogenic mechanism linking Epstein–Barr virus infection, allergy, and oncogenesis. Hypersensitivity to mosquito bites is a disorder reported to occur in Japanese patients (being proven in 58 patients by Tokura et al. 2001 in the first two decades of life). The skin lesion at bite sites is typically a bulla that develops into necrosis. Patients simultaneously exhibit high temperatures and general malaise and subsequently may develop lymphadenopathy and hepatosplenomegaly (Tokura et al. 2001). Half of the patients reported died as a consequence of a hemophagocytic syndrome or due to lymphocyte proliferative disorders. Clinical and laboratory studies showed that the hypersensitivity to mosquito bites occurs in association with natural killer (NK) cell lymphocytosis related to chronic Epstein–Barr virus infection (Tsuge et al. 1999; Kawa et al. 2001; Tokura et al. 2001; Asada 2007). Recent studies investigated the unique pathogenic mechanism of this mysterious disease and demonstrated the close relationship between the hypersensitivity to mosquito bites and Epstein–Barr virus-carrying NK cell lymphocytosis, i.e., $CD4^+$ T cells from the patients markedly responded to mosquito salivary gland extracts, and the $CD4^+$ T cells stimulated by mosquito bites may play a crucial role in the development of hypersensitivity to mosquito bites and NK cell oncogenesis. This occurs apparently via the induction of Epstein–Barr virus reactivation and Epstein–Barr virus-oncogene expression, respectively (Asada 2007).

With respect to dengue virus infections, Espina et al. (2003) observed an increased number of apoptotic cells and increased production of tumor necrosis factor alpha in dengue (serotype DEN-2)-infected human monocyte cultures, with no increase in production of nitric oxide. These findings were related to early primary dengue viral infection, during which the dengue virus could induce apoptosis in monocytes, but monocytes may contribute to host defense mechanisms against viruses by viral phagocytosis, phagocytosis of infected apoptotic cells, and the release of proinflammatory cytokines (Espina et al. 2003). Later on, Chen et al. (2007) shed further light on this issue, observing that high viral DEN-2 titer, macrophage infiltration, and tumor necrosis factor alpha production in the local tissues are three important events that lead to hemorrhages. In vitro assays highlighted that mouse primary microvascular endothelial cells were susceptible to dengue viruses but that tumor necrosis factor alpha enhanced dengue virus-induced apoptosis. Therefore, intra-dermal inoculation of high titers of dengue virus predisposes endothelial cells to be susceptible to tumor necrosis factor alpha-induced cell death, which leads to endothelium damage and hemorrhage development (Chen et al. 2007; Yen et al. 2008).

Multipotent nanodrugs in the fight against cancer and mosquito-borne diseases

To combat mosquito-borne diseases and cancer outbreaks, a growing number of nanodrugs, including those synthesized using natural products, have been investigated separately against the cancer cells, mosquito vectors, and mosquito-borne diseases (i.e., mainly against *Plasmodium* parasites and dengue DEN-2 serotypes) (Majumder 2006; Barik et al. 2008; Benelli 2016a, b). However, to the best of our knowledge, limited information is available about nanoformulates synthesized using natural products showing multipotency against both public health concerns (Jaganathan et al. 2016).

Concerning plant-borne molecules, a noteworthy study case is represented by artesunate, a semi-synthetic derivative of artemisinin (the active principle of *Artemisia annua*), which has remarkable activity against multidrug-resistant strains of

Plasmodium falciparum and *Plasmodium vivax*. Efferth et al. (2001) studied artesunate for its anticancer activity against 55 cell lines of the Developmental Therapeutics Program of the National Cancer Institute, USA. Notably, artesunate was the most active against leukemia and colon cancer cell lines (mean GI_{50} values 1.11 ± 0.56 and 2.13 ± 0.74 μM, respectively). Non-small cell lung cancer cell lines showed the highest mean GI_{50} value (25.62 ± 14.95 μM) indicating the lowest sensitivity toward artesunate in this test panel. Intermediate GI_{50} values were obtained for melanomas, breast, ovarian, prostate, CNS, and renal cancer cell lines (Efferth et al. 2001; Efferth 2006; Chaturvedi et al. 2010).

As regards to nanodrugs, Rajasekharreddy and Rani (2014) proposed an eco-friendly process for the synthesis of silver-(protein-lipid) nanoparticles (Ag-PL NPs) (core shell) using the seed extract from wild Indian almond tree, *Sterculia foetida*. MTT assays testing the *S. foetida*-synthesized Ag-PL NPs on cervical cancer cell lines (HeLa) showed that HeLa cell proliferation was significantly inhibited (N90%) by Ag-PL NPs at the dose of 16 μg/ml at 24 h for nanoparticles synthesized at the temperature of 80 °C. Post-exposure to 1, 2, and 4 mg/ml of Ag-PL NPs, HeLa cell toxicity was ~15, 35, and 55 %. Post-exposure to 8 and 16 mg/ml of Ag-PL NPs, key morphological changes such as cell shrinking, rounding, and partial detachment, which may be due to the Ag-PL NP penetration through the ion channels, have been observed (Rajasekharreddy and Rani 2014). Furthermore, these Ag-PL NPs showed LC_{50} values lower than 4.5 ppm against larvae of *Anopheles stephensi*, *Ae. aegypti*, and *Culex quinquefasciatus* (Rajasekharreddy and Rani 2014).

Later on, titanium dioxide nanoparticles produced via hydrothermal synthesis exhibited dose-dependent cytotoxicity against human breast cancer cells (MCF-7) and normal breast epithelial cells (HBL-100). After 24-h incubation, the inhibitory concentrations (IC_{50}) were 60 and 80 μg/ml, for MCF-7 and normal HBL-100 cells, respectively (Murugan et al. 2016). Morphological changes were observed in nanoparticle-treated MCF-7 cells when compared with untreated cells. The most relevant morphological changes of titanium dioxide nanoparticle-treated cells observed in this study were the cytoplasmic condensation, cell shrinkage, production of numerous cell surface protuberances at the plasma membrane, and the aggregation of the nuclear chromatin into dense masses beneath the nuclear membrane (Murugan et al. 2016). Induction of apoptosis was evidenced by acridine orange (AO)/ethidium bromide (EtBr) and 4′,6-diamidino-2-phenylindole dihydrochloride (DAPI) staining. Acridine orange penetrated the normal cell membrane, and the cells were observed as green fluorescence. Apoptotic cells and apoptotic bodies were formed because of nuclear shrinkage and blebbing and were observed as orange-colored bodies, whereas necrotic cells were observed as red color fluorescence due to their loss of membrane integrity when viewed under a fluorescence microscope (Murugan et al. 2016). The nanoparticle-induced nuclear fragmentation can be observed when DAPI staining. The untreated cells showed normal nuclei, whereas after treatment of MCF-7 cells with titanium dioxide nanoparticles, the apoptotic nuclei (condensed or fragmented chromatin) were observed. Nuclear morphology analysis showed characteristic apoptotic changes, such as chromatin condensation, fragmentation of the nucleus, and formation of apoptotic bodies in the MCF-7 cells (Murugan et al. 2016). Similarly, Sanpui et al. (2011) also showed that silver nanoparticles could induce DNA damage and apoptosis in cancer cells. In a recent study by Murugan et al. (2016), increasing the concentration of titanium dioxide nanoparticles, the number of apoptotic cells increased, suggesting that these nanoparticles induce cell apoptosis. Cell death via apoptosis is an important event in a number of immunological processes, as most of the anticancer drugs are believed to trigger apoptosis via a mitochondria-mediated pathway (Shanthi et al. 2015). Therefore, it has been proposed that, as a new hybrid system, titanium dioxide nanoparticles might also initiate the apoptosis via mitochondria-mediated pathway. This may be linked to the changes of the levels of mitochondrial-dependent apoptotic protein cytochrome c and β-actin. Western blot was used to confirm cell apoptosis, analyzing the expression profiles of cytochrome c and β-actin. Western blot revealed the activation of cytochrome c expression profiles of these proteins in MCF-7 cells treated with titanium dioxide nanoparticles. The expression of the cytochrome c proteins was significantly upregulated in cells cultured with titanium dioxide nanoparticles for 24 h when compared to untreated control β-actin (Murugan et al. 2016). In agreement with these data, the expression of both mRNA and protein levels of cell cycle checkpoint gene p53 and proapoptotic gene (Bax and caspase-3) upregulated and Bcl-2 downregulated in HepG2 cell due to silica nanoparticle exposure (Gopinath et al. 2010).

Concerning the antivectorial potential of the abovementioned titanium dioxide nanoparticles, which was tested in larvicidal and pupicidal experiments conducted against the primary dengue mosquito *Ae. aegypti*, TiO_2 nanoparticles were highly effective against young instars, showing LC_{50} values of 4.02 ppm (larva I), 4.962 ppm (larva II), 5.671 ppm (larva III), 6.485 ppm (larva IV), and 7.527 ppm (pupa). These findings highlighted that titanium dioxide nanoparticles may be considered as a novel tool to build safer and highly effective mosquito larvicides and pupicides, as well as chemotherapeutic agents with little systemic toxicity (Murugan et al. 2016).

Notably, earthworm-based silver nanoparticles have been recently synthesized using *Eudrilus eugeniae* and tested against HepG2 cells (Jaganathan et al. 2016), a highly differentiated human hepatoma cell line that retains many of the cellular functions often lost by cells in culture (Knowles et al. 1980), including some of the xenobiotic metabolizing capacity of normal hepatocytes (Bao et al. 2012). Earthworm-synthesized silver nanoparticles achieved an IC_{50} value of 25.96 μg/ml against HepG2 cells. This value falls within the standard limit of activity established by the American National Cancer Institute guidelines (i.e., 30 mg/ml after an exposure time of 24 h) (Suffness and Pezzuto 1990). Analysis of DNA content revealed that earthworm-synthesized silver nanoparticles could induce apoptosis of HepG2 cells and showed a dose-dependent response when compared to control. The difference in apoptotic rates was significantly increased with increasing concentration (Jaganathan et al. 2016; Murugan et al. 2016). Since nuclear fragmentation is a hallmark of apoptosis, the nuclear DNA staining is a measure of cells treated with sample and serves as an indicator of cell apoptosis (Bao et al. 2012). Jaganathan et al. (2016) showed that, owing to the reduced DNA content, apoptotic cells were separated from normal cells by flow cytometry at 488 nm. The apoptosis in HepG2 cell lines was induced by nanoparticle treatment. At doses from 1.88 to 30 μg/ml, the apoptotic percentage among tested cells increased significantly from 1.6 to 7.8 %. Therefore, it was hypothesized that earthworm-synthesized silver nanoparticles may lead to a decline in cell proliferation by enhancing the apoptosis by initiating Bax/Bcl-2/cytochrome c/caspase-3 signaling pathway of hepatocellular carcinoma cell lines (Jaganathan et al. 2016). However, further studies using in vivo mice models are ongoing to establish these nanocomposites as safe and effective agents for hepatocarcinoma therapy.

With respect to the antiplasmodial potential, Jaganathan et al. (2016) showed that the earthworm-synthesized silver nanoparticles were toxic against CQ-resistant (CQ-r) and CQ-sensitive (CQ-s) strains of *P. falciparum*. The IC_{50} earthworm-synthesized silver nanoparticles were 49.3 μg/ml (CQ-s) and 55.5 μg/ml (CQ-r), while chloroquine IC_{50} were 81.5 μg/ml (CQ-s) and 86.5 μg/ml (CQ-r). Moreover, acute toxicity of the earthworm-synthesized silver nanoparticles was reported toward young instars of the malaria vector *An. stephensi*. LC_{50} were 4.8 ppm (larva I), 5.8 ppm (larva II), 6.9 ppm (larva III), 8.5 ppm (larva IV), and 15.5 ppm (pupa). Notably, little non-target effects of earthworm-synthesized silver nanoparticles against mosquito natural enemies were found. Indeed, the predation efficiency of the mosquitofish *Gambusia affinis* toward the II and II instar larvae of *An. stephensi* was 68.50 % (II) and 47.00 % (III), respectively, while in nanoparticle-contaminated environments, predation was boosted to 89.25 % (II) and 70.75 % (III), respectively. Taken all together, these findings show that earthworm-synthesized silver nanocomposites may be potentially helpful to develop novel drugs against hepatocellular carcinoma, *P. falciparum* parasites, and *Anopheles* vectors, with negligible detrimental effects on mosquito natural enemies (Jaganathan et al. 2016).

Conclusions and perspectives

Overall, there are few contrasting evidences of the relationship between cancer and mosquito-borne diseases, with special reference to malaria. Analogies at the cellular level for the two diseases have been reported, and a recent significant association of malaria incidence with all cancer mortality in 50 USA states was highlighted (Lehrer 2010a, b). This may be explained by the ability of *Plasmodium* stages to induce suppression of the immune system. The additional hypothesis that *Anopheles* vectors may transmit obscure viruses linked with cancer development needs further research. Furthermore, the potential activation of cancer pathways by mosquito-feeding events is not uncommon, since hamster reticulum cell sarcoma can be transmitted during bites of *Ae. aegypti* due to a transfer of tumor cells (Banfield et al. 1966). In addition, mosquito bites may influence human metabolic pathways to follow different mechanisms, leading to other viral infections and/or oncogenesis. For instance, the hypersensitivity to mosquito bites is routed by a unique pathogenic mechanism linking Epstein–Barr virus infection, allergy, and oncogenesis (Asada 2007). Even during dengue virus infection, high viral titers, macrophage infiltration, and tumor necrosis factor alpha production in the local tissues are the three important key events that may lead to hemorrhages (Chen et al. 2007). In this scenario, basic epidemiological knowledge on the relationships occurring between mosquito vector activity and the spread of cancer is urgently needed, as well as further detailed information about the ability of Culicidae to transfer viruses or tumor cells among hosts over time.

Further studies evaluating nanodrugs with multipotency against mosquito-borne diseases and cancers are required. In particular, a focus on effectiveness and non-target effects of metal nanoparticles synthesized using natural products as reducing agents (Benelli 2016a; Benelli and Mehlhorn 2016) may lead to the development of novel antiplasmodial, mosquitocidal, and anticancer tools.

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Compliance with ethical standards

Conflict of interests The authors declare no conflict of interest. Heinz Mehlhorn and Giovanni Benelli are Editor in Chief and Editorial Board Member of *Parasitology Research*, respectively. This does not alter the authors' adherence to all the *Parasitology Research* policies on sharing data and materials.

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