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Title

Cancer and mosquitoes – an unsuspected close connection

Authors

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Introduction

Cancer is a major public health problem, with an estimated 18.1 million new cases and 9.6 million deaths in 2018 (Bray et al., 2018). Moreover, high population growth, aging, and increased exposure to pollutants are causing a rapid worldwide increase in cancer incidence and mortality in countries with different levels of economic wealth (Bray et al., 2018; Torre et al., 2015). The predicted burden is so high that cancer is thought to be the only important obstacle to an increase of life expectancy during the 21st century (Torre et al., 2015), and it is expected to become the leading cause of death worldwide.

Meanwhile, mosquitoes represent a global public health problem because they act as vectors for viruses, bacteria and protozoa (Mehlhorn et al., 2012), including, among others, agents of malaria, filariasis, encephalitis, yellow fever, dengue, West Nile fever, chikungunya, and, more recently, Zika. Mosquito-borne infectious diseases cause significant morbidity and mortality worldwide, with more than 700 million people infected and more than a million deaths annually (Caraballo and King, 2014). They represent a growing problem, with mosquito invasions occurring throughout the world and affecting every continent but Antartica (Masterson, 2019).

Regarding the dramatic global impacts of these two concerns for humans, it is crucial to investigate whether they have a reciprocal connection. Indeed, cancers and mosquito-borne pathogens are both globally distributed, therefore affecting the same populations and can co-occur within the same individuals. Knowing whether there is a connection between cancers and mosquito-borne pathogens could also be helpful not only for forecasting the net impact of the different control strategies on human health, but also for envisioning integrative strategies targeting the two problems at the same time. Unfortunately, very few studies (Benelli et al., 2016) have examined the link between these two threats, and the existing ones have generally

focused only on the transmission of oncogenic pathogens through mosquitoes (Marcondes and Benelli, 2019; Ward et al., 2016).

In this review, we provide an overview of the possible links between mosquitoes and cancer. To do so, we focus on (i) the impact of mosquitoes on carcinogenesis in humans, (ii) the impact of cancer development in humans on mosquito behaviour, and (iii) the consequences of cancers in mosquitoes and on their disease transmission potential (see Figure). We will then discuss the most promising research avenues on this topic and the public health strategies that could be envisioned in this context.

Impact of mosquitoes on carcinogenesis

We first focus on how mosquitoes can promote the risk of developing cancer in humans. In this part, we show that this risk could result from the (i) transmission of oncogenic pathogens, (ii) inflammatory reactions following mosquito blood meals, (iii) non-inflammatory effects of indirectly oncogenic mosquito-borne pathogens, and (iv) direct transmission of cancer cells.

Oncogenic pathogen transmission.

Over the last decades, an increasing number of infections have been linked to the development of human and animal cancers (Ewald and Swain Ewald, 2015; McAloose and Newton, 2009; Parkin, 2006; Zur Hausen, 2009). The frequency of cancers with an infectious causation has certainly been underestimated because cancer symptoms generally occur after years of development, therefore making the identification of a causal link extremely challenging. Nevertheless, current estimates are that 20% of cancer cases have an infectious causality (Parkin, 2006; Zur Hausen, 2009), and it has been suggested that underlying infectious agents can only actually be strictly excluded in 5% of cancer cases (Ewald, 2009). Epidemiological studies suggest that the current increase in emerging pathogen transmission

50 (Jones et al., 2008) could have a substantial effect on the future burden of cancer worldwide
51 (currently around two million cancer cases annually are known to be caused by an infectious
52 agent) (De Martel et al., 2012).

53 An infectious agent is considered as an oncogenic pathogen when the infection is a
54 prerequisite for the occurrence and/or the development of cancer (Zur Hausen, 2009).
55 Oncogenic pathogens may make a direct contribution to cancer development, most commonly
56 through integration of their DNA into the host genome (*e.g.* Epstein-Barr virus (Moormann et
57 al., 2011)). According to Ward et al. (2016), many of the pathogens that are likely to promote
58 cancer development (Ewald and Swain Ewald, 2012; Plummer et al., 2016) could possibly be
59 transmitted through mosquitoes because they can be found in blood (Ward et al., 2016). This
60 category of pathogens includes *Plasmodium* species, Epstein–Barr virus, Kaposi sarcoma
61 herpesvirus, Hepatitis B virus and Hepatitis C virus (Ward et al., 2016). Moreover, it has also
62 been suggested that mosquitoes may be able to transmit unknown viruses that could be linked
63 with cancer (Benelli et al., 2016; Lehrer, 2010a).

64 The International Agency for Research on Cancer has recently mentioned malaria, which is
65 caused by the mosquito-borne protozoan *Plasmodium* and produces 228 millions new
66 infections every year, as a probable oncogenic pathogen (WHO, 2019). This parasite can have
67 a direct action on carcinogenesis because analogies at the cellular level have been reported for
68 malaria and gastrointestinal tumours (Suresh et al., 2005). The association between malaria
69 and the risk of developing cancer could be explained by the ability of *Plasmodium* parasites to
70 induce the immune response towards the destruction of plasmodium-infected cells (Degarege
71 et al., 2009), which could decrease the immune system's ability to target cancer cells. This
72 action could also be indirect, especially through reactivation of oncogenic viruses. For
73 instance, endemic Burkitt lymphoma occurs at higher incidences in areas where malaria is
74 endemic because *Plasmodium falciparum* fuels transmission of Epstein Barr virus that is

75 associated with more than 95% of cancer cases (Burkitt, 1961). Burkitt lymphoma is an
76 aggressive B-cell malignancy (Brady et al. 2007). The B-cells are the primary targets of
77 Epstein Barr virus (a known oncogenic pathogen) infection (Shannon-Lowe et al., 2017). By
78 stimulating the proliferation of B-cells, *Plasmodium falciparum* could enhance oncogenic
79 effects of the Epstein Barr virus on these target cells (Ewald and Swain Ewald 2014).
80 Knowing that mosquito-borne pathogens could stimulate antibody production (*e.g.,*
81 stimulating B-cell replication), there is good reason to think that other pathogens might
82 similarly contribute to amplified the oncogenic effect of Epstein Barr virus.
83 This connection is supported by the fact that several studies have found a significant
84 relationship between malaria cases and mortality across all cancers in all 50 states of the USA
85 (Lehrer, 2010a, 2010b). More specifically, relationships between malaria outbreaks in the
86 USA and reports of brain tumour incidence have also been observed (Lehrer, 2010a, 2010b).
87 While these results strongly suggest an association between malaria and cancer, they do not
88 provide a direct proof of causality between these two pathologies.
89 It is worth pointing out that other studies found that the stimulation of the host immune
90 system could also limit cancers development and progression. For example, malaria infection
91 can reduce the growth of lung tumours via the induction of innate and adaptive anti-tumour
92 responses in a mouse model (Chen et al., 2011; Faure, 2016). Therefore, the interaction
93 between *Plasmodium* parasites and cancer might be complex and needs much more
94 investigation.
95
96 *Immune reaction following the mosquito blood meal*.
97 Mosquito blood meals are characterised by an edema and an inflammatory influx of
98 neutrophils that yield localised innate immune reactions (Pingen et al., 2016). This
99 inflammation induces different immune responses, which are different for each mosquito

species (Donovan et al., 2007; Fontaine et al., 2011; Schneider et al., 2011, 2004), and accompanied by tissue damage, which could increase the risk of developing cancer (Coussens and Werb, 2002; Hanahan and Weinberg, 2011; Johansson and Ward, 2017). Moreover, it is now becoming clear that the tumour's microenvironment, which is largely organised by inflammatory cells, is driving the neoplastic process by fostering the proliferation, survival, and migration of cancer cells (Coussens and Werb, 2002). Therefore, in areas where humans are particularly exposed to mosquito bites, the risk of developing cancer should rise following exposure to multiple mosquito blood meals. To the best of our knowledge, this has never been investigated.

Mosquito-borne transmission of indirectly oncogenic pathogens

Each mosquito-borne pathogen can also indirectly contribute to carcinogenesis by inducing changes in the microenvironment via inflammation or the immunomodulation they produce (Dalton-Griffin and Kellam, 2009; Jacqueline et al., 2018; Zur Hausen, 2009). In this case, their diversity of action ranges from chronic inflammation (*Helicobacter pylori*, which is associated with 65% of stomach cancers (Sepulveda, 2013)) to immunosuppression (HIV (Gopal et al., 2014)). Moreover, pathogen persistence within the host induces successive genetic, epigenetic, and/or immune changes that facilitate cancerous development (Ewald and Swain Ewald, 2012; Ewald and Swain Ewald, 2013).

Direct transmission of cancer cells.

While not observed in natural conditions, a study has shown that a hamster reticulum cell sarcoma, named TM, can be transmitted by the mosquito species *Aedes aegypti* through a direct transfer of cancer cells (Banfield et al., 1966, 1965). When passed by subcutaneous transplantation within the hamsters, cancer cells appear in their blood after five days and

increase constantly until reaching a high density just before host death (greater than 100,000 per mm^3). TM cancer cells remained viable for up to eight hours after ingestion by the adult mosquito, and only 1 to 2% of the mosquitoes tested had viable cancer cells after several days, which could be due to the digestion processes in the mosquito gut. Mosquitoes carrying cancer cells were able to implant these cells into 5 to 10% of other hamsters (Banfield et al., 1966, 1965).

Consequences of cancers in humans on mosquitoes

A variety of changes in mosquito behaviour have been reported when they are exposed to people infected with pathogens (Busula et al., 2017; Emami et al., 2017; Lacroix et al., 2005; Robinson et al., 2018). Infection induces a change in host odour, CO_2 blood concentration, and many other physiological factors (Cummins et al., 2014; Shirasu and Touhara, 2011), which could impact the attractiveness of mosquitoes for infected hosts. Since cancer can influence many aspects of host physiology, it could similarly influence attraction of mosquitoes.

Malignant cancers are often associated with a higher iron level in blood (Kwok, 2002). This surplus of iron is needed during early steps of tumour development, *i.e.*, enhanced survival (Bauckman et al., 2015) and proliferation of transformed cells (Steegmann-Olmedillas, 2011), as well as during late stages to promote the metastatic cascade (Jung et al., 2019). Moreover, iron is required for optimal egg development and viable offspring in mosquitoes (Zhou et al., 2007), suggesting that blood meal with higher iron concentration may impact mosquito behaviour and reproduction (hence vector population dynamics and infectious disease transmission intensity).

Some cancers can change human odour (Shirasu and Touhara, 2011). For example, patients with gynaecological tumours also complain of heavy vaginal discharge with an

offensive odour resulting from the production of acetic, isovaleric, and/or butyric acids (Kuge et al., 1996). Matsumura et al. have shown that the urine from mice with artificially induced cancerous lung tumours could be clearly discriminated from non-affected (control) mice by the detection of volatile biomarkersin their urine (Matsumura et al., 2010). Dogs are also able to detect these odour modifications and so can be used as potential detectors of different cancers, such as melanoma, bladder cancer, ovarian cancer, and colorectal cancer (Horvath et al., 2008; McCulloch et al., 2006; Pickel et al., 2004; Sonoda et al., 2011; Willis et al., 2004). Other study have investigated the potential of using the Drosophila's olfactory system to recognise cancer cells by their scent (Strauch et al., 2014).

Cancer can also change the CO_2 concentration in the blood (major driver of mosquito host seeking behaviour). Lung cancer is often associated with dyspnea (shortness of breath) or previous respiratory disease including chronic bronchitis, emphysema, or pneumonia, all of which can alter the CO_2 concentration in the blood (Brenner et al., 2012). Dyspnea was also observed for other cancers (e.g., breast cancer, lymphoma) but could be linked to risk factors such as a history of smoking, asthma, or chronic obstructive pulmonary disease or a history of exposure to asbestos (Dudgeon et al., 2001).

Since cancer can modify many physiological factors in humans, we would expect that their attractiveness to mosquitoes could also be altered. This suggests that individuals with cancer could be more or less actively targeted for the transmission of mosquito-borne pathogens.

Consequences of cancers in mosquitoes on humans

No study has yet detected natural cancer in mosquitoes, so the impact of cancer on mosquito life history traits is highly speculative at the moment. Nevertheless, several types of tumours occurring naturally (Robert, 2010; Salomon and Rob Jackson, 2008; Scharrer and Lochhead, 1950) or triggered by genetic engineering (Mirzoyan et al., 2019), including

neuroblastoma, ovarian, and imaginal disk tumours, have been reported in different insect species, especially in *D. melanogaster* (Mirzoyan et al., 2019; Salomon and Rob Jackson, 2008). It is therefore possible that natural cancers exist in mosquitoes and have significant effect on traits such as longevity, fecundity, or feeding-behaviour.

Changes in an organism's life-history traits may be an adaptive response to a parasitic infection (Adamo, 1999; Minchella and Loverde, 1981; Polak and Starmer, 1998). One solution developed by many animal species against biotic aggressors (such as parasites) is the adjustment of life-history traits to compensate for their negative effects on fitness (Forbes, 1993; Hochberg et al., 1992; Michalakis and Hochberg, 1994; Thomas et al., 2000). An example is the work by Vezilier and colleagues, which shows that mosquitoes infected by *Plasmodium* species lay their eggs two days earlier than non-infected ones (Vézilier et al., 2015) to compensate for the rapid decrease in egg quality observed in infected mosquitoes. This type of adaptive response can have consequences on mosquito communities and indirectly on the evolution of pathogen communities.

Because malignancies usually also reduce survival, and hence potentially host fitness, a similar process could also exist in this context. Indeed, it has been shown that *Drosophila melanogaster* harbouring an early gut cancer adjust their life-history traits by having their egg-laying period peak two days earlier than normal, which would maximise their immediate reproductive effort and therefore compensate for the reduced survival (Arnal et al., 2017).

Conclusion and perspectives

Despite the significant impact of cancers and mosquito-borne diseases on human health, there is little documented evidence of a relationship between these two concerns for humans. Briefly, we know that the direct transmission of cancer cells is mechanistically possible based on a single experimental model and that mosquitoes can transmit oncogenic pathogens or

induce immune reactions, which could favour carcinogenesis. In addition, we have seen evidence that cancer in humans or in insect can alter the insect's life history traits, hence pathogen transmission dynamics. Nevertheless, the impact of these connections *in natura* needs to be quantified, especially in populations affected by these two threats.

First, we need to determine if there are more oncogenic pathogens transmitted by mosquitoes than are currently observed, especially by refining our knowledge on the oncogenic capacities of malaria. Identifying such connections between pathogens and cancer could have a strong impact on prevention strategies, as exemplified by the papillomavirus vaccine that avoids cases of cervical cancer by protecting against its infectious causation. Moreover, this interaction could be more complicated because mosquito bites can create immunosuppression, which can favor proliferation of oncogenic pathogens but also directly cancer development (so called "promoter arthropods" hypothesis (Coluzzi et al., 2003, 2002)). In the case of mosquito-borne pathogens, identifying such connections could create an unprecedented synergy between vector control programs and the prevention of numerous cancer cases, with paying much attention on using insecticides to avoid increasing cancer risk.

It is worth pointing out that the vast majority of blood feeding events will be by mosquitoes engaging in their first (*i.e.* mosquitoes are non-infectious) blood meal or by mosquitoes that do not carry infectious agents from previous blood meals. Thus, while all feeding events will cause inflammatory reactions and possibly impact cancer dynamics, only a small proportion of feeding events will involve the vectoring of infectious agents.

Regarding the huge number of people living in areas affected by mosquitoes, investigating the link between the rate of mosquito bites and the probability of developing cancer through local inflammation could also be very informative. Experimental studies are first required to evaluate the immunomodulation effect after exposure to mosquito saliva (therefore mosquito blood meal) on cancer development and to characterise interactions between the inflammatory

process involved following mosquito blood meals and the one involved in cancer initiation. Second, large-scale statistical analyses are now possible due to improved both cancer surveillance in tropical countries and mosquito surveillance in the North hemisphere (Sankaranarayanan, 2014).

Importantly, experiments on mosquito transmission of cancer cells must be repeated with different host species, different mosquito species, and different types of cancer cells. While very promising, these experiments cannot conclusively prove the existence of such transmission in the field, and most importantly to humans. Once mosquito transmission has been quantified experimentally in a more robust way, the question of the importance of this transmission route *in natura* can be addressed.

Experiments on odour modification in people affected by cancer and its correlation with mosquito attractiveness can quantify the impact of human cancer development on mosquito behaviour. The technical tools are available today (Vantaux et al., 2018) to perform such experiments, and the integration of such information to epidemiological models could provide a first estimation of the impact of human cancers on the epidemiology of mosquito-borne pathogens (Roux et al., 2015).

Finally, the potential consequences of natural cancers in mosquitoes on human health could be also important. We first need to identify natural cases of cancer in mosquitoes, even if the prevalence is low. Once this has been quantified, we can expose mosquitoes to radiation, pesticides or other xenobiotic agents. We can also use genetic engineering to create cancerous mosquitoes in order to design experiments to study the evolution of mosquito life history traits when a cancer affects them.

To conclude, it is essential to develop integrative strategies considering both cancers and mosquito-borne pathogens. Such a research avenue will require inter-disciplinary collaborations from evolutionary biologists, entomologists, experts in chemical ecology,

oncologists, immunologist, epidemiologists, and public health experts. Considering the potentially huge impact of such connections, quantifying them to forecast the impact of different control strategies for human health should lead to promising benefits.

Figure list

Figure 1. Schematic representation of the possible connections between mosquitoes, mosquito-borne diseases, and cancer. (A) The impact of mosquitoes on carcinogenesis in humans, including the mosquito transmission of oncogenic pathogens (symbolized here by a human herpesvirus 8), the mosquito transmission of cancer cells from a cancerous person to another susceptible person, and the possible immune reactions following mosquito blood meals. All these processes could increase the risk of developing cancer in the human population. (B) The possible negative or positive impact of cancer on human attractiveness to mosquitoes, and therefore on the transmission intensity of mosquito-borne diseases, and (C) the possible negative or positive impacts that natural cancers could have on mosquito phenotype (lifespan, fecundity, feeding behaviour) and therefore on their vector capacity.

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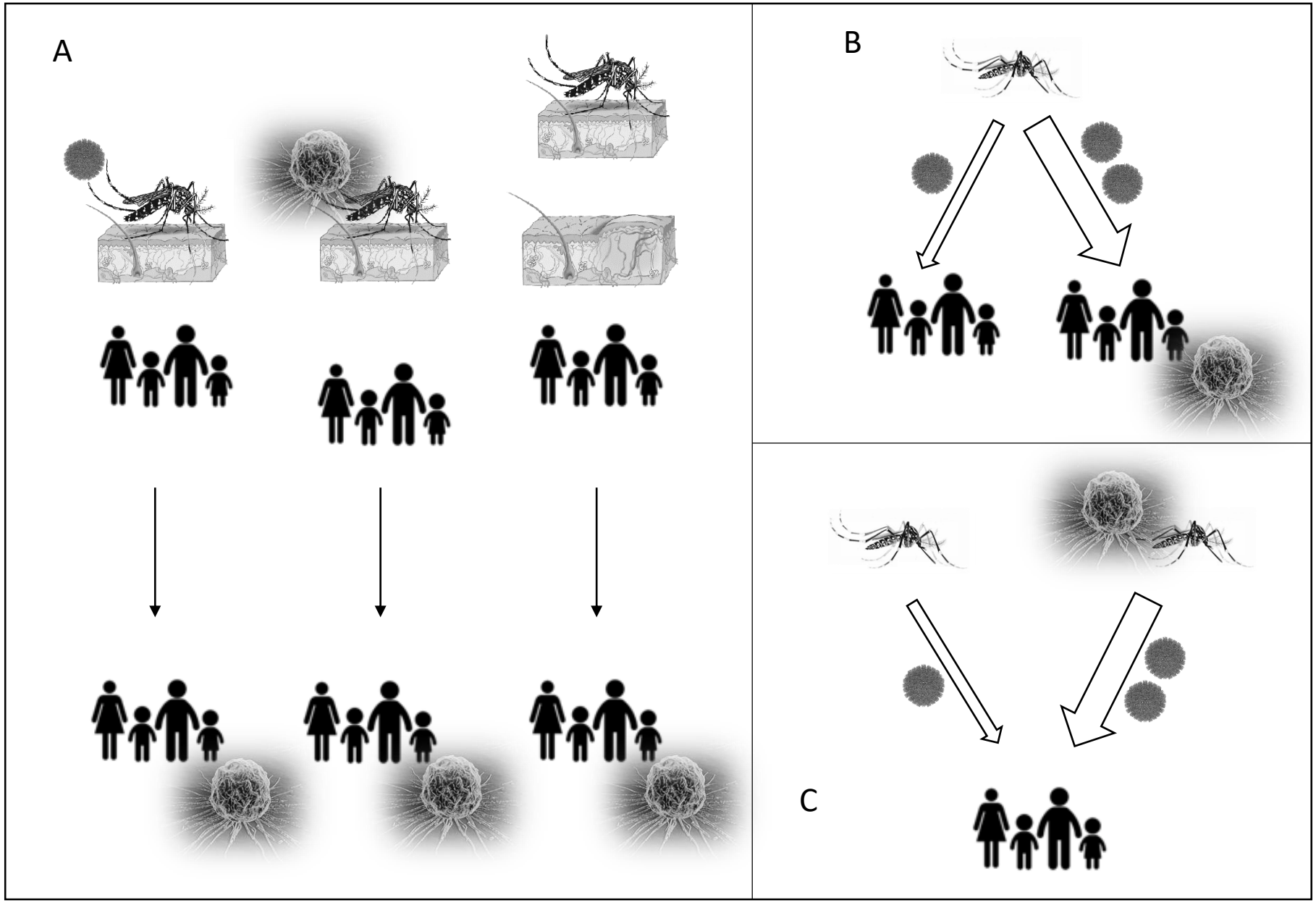
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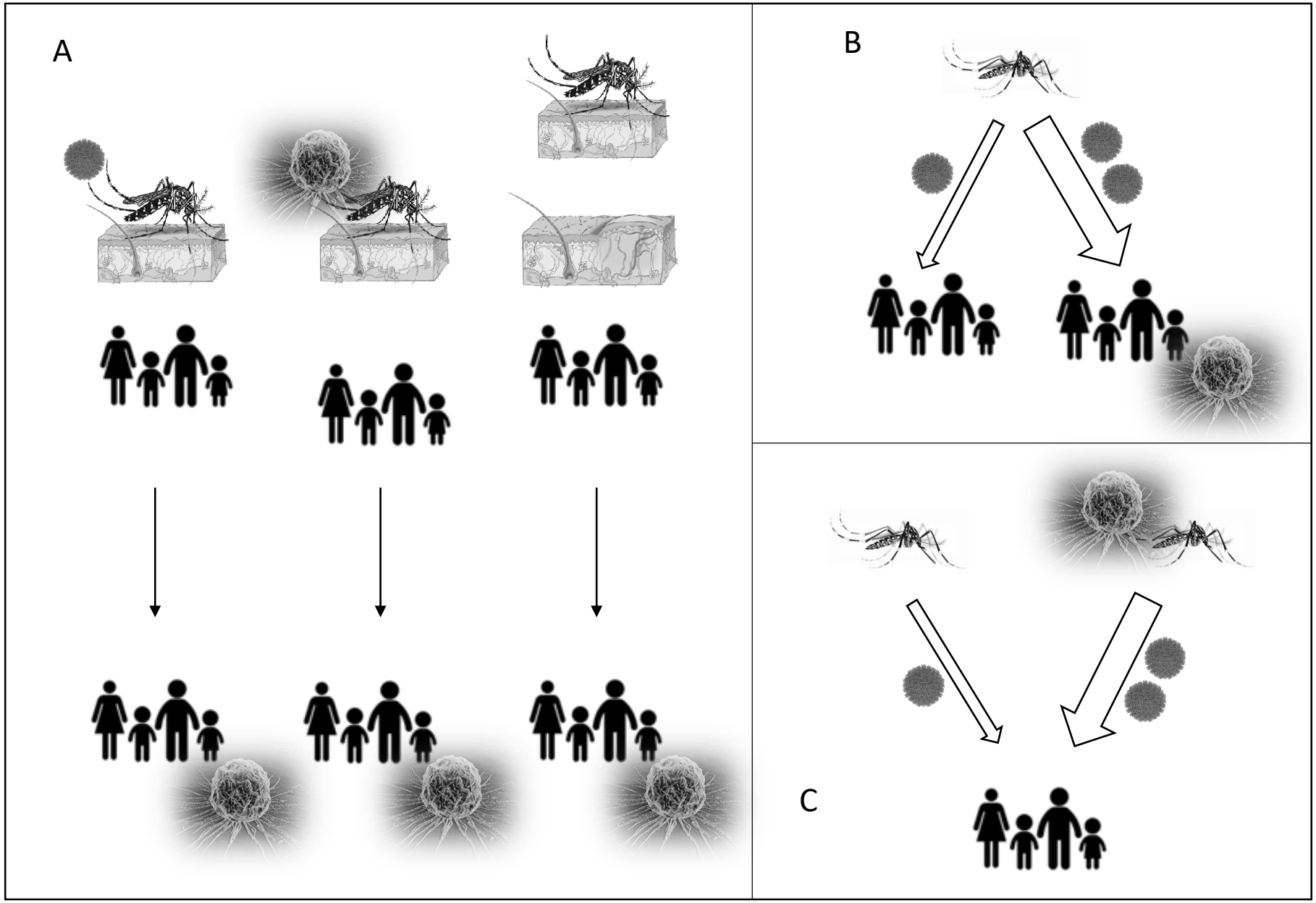
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