Addition By Subtraction: Exterminating Mosquito-Borne Diseases Spurred on by Climate Change.

In 2018 mosquitoes killed over 830, 000 people while we ourselves in our warring tribes murdered 580, 000 of our fellow Homo sapiens which was above our 475, 000 average for each single year of this new millennium. The crocodile killed one-thousand people, the hippopotamus five hundred, elephants and lions killed about one-hundred each, and the shark and wolf each caused ten deaths that same year. There are 110 trillion mosquitoes that swarm and maraud over our globe except for Iceland, Antarctica, the Seychelles, and several micro-sized islands in French Polynesia isolated by the vastness of the Pacific Ocean. The biting females of the deadliest species carry a minimum of fifteen biological weapons that are debilitating or fatal to humans. Males do not bite for their lives revolve around nectar and breeding. She needs your blood for its protein to grow and develop her eggs. The female mosquito warriors have killed more people than any other cause of death since our beginnings. In 200, 000 years the mosquito has decimated fifty-two billion people out of the calculated 108 billion who have ever walked this Earth. She does not directly injure anyone but is a vector for sinister pathogens and their highly evolved diseases that she transmits causing sickness and death. She has played a greater role in shaping our destiny than most historians reflect, they preferring to focus on inspirational leaders, pivotal wars and conquest, politics, religion, and economics. Before the 20th century the prevalent medical knowledge of the role of mosquitoes and their pathogens was not fully recognized, and no one grasped the full impact that they played in spreading malaria and yellow fever. The vampiric mosquito has been a prolific battlefield killer and her pathogens have helped forge events to create our present reality. Conquering armies, explorers seeking fame and treasure, homestead seeking settlers, mass migrations and the transport of slaves brought new diseases to and from distant lands. In the Americas, such diseases played further havoc destroying the would-be indigenous labor force and reinforcing the need for more slaves to be shipped from Africa to provide for the burgeoning plantation economy. Our domestication of plants through agricultural advancements have altered habitats and our livestock animals often serve as reservoirs of disease. Deforestation, high urban densities, trade, travel, and our enduring propensity towards global war have nurtured many mosquito-borne illnesses. Our immune systems are attuned to our local environs and home habitats. Microorganisms in the foreign lands brought debilitation and death to the unwitting conquerors too; from our migrations from our ancestral African homeland to our present-day global diaspora, the not-so-simple mosquito has been the destroyer of our hominid world.

Given our common origins, twenty percent of our diseases are shared by apes through various vectors including mosquitoes. Many of the mosquito-borne and other insect illnesses that affect animals including reptiles, amphibians, birds, and mammals including humans date back before, during and after the reign of the dinosaurs which ended over sixty-five million years ago. The two oldest mosquitoes on record are fossilized in petrified amber and despite being 105 million years old are identical to their modern-day counterparts. Millions of years ago, biting insects were the top predators and sought out the dinosaurs as prey. Jurassic mosquitoes and sand flies, fleas, mites, gnats, and ticks provided safe havens for viruses, bacteria and parasites functioning as vectors to transmit diseases produced by their procreation. They like us are just in an evolutionary struggle to survive, and we and other animals like them have adapted strategies to survive their infestations. The reptiles of today despite being infected by mosquitoes with twenty-nine different forms of malaria are usually asymptomatic because they have developed over time an acquired tolerance. But for the dinosaurs no such immunity existed because then the arthropod-borne malaria was a relative newcomer among diseases. Dinosaur populations were already in serious decline when the meteorite impacted the Yucatan Peninsula in Mexico over sixty-five million years ago. In the wet, tropical conditions that dominated much of the terrestrial Earth during their astounding 165-million-year reign, mosquito swarms were endemic resembling the ferocious summer feeding frenzies in today' s Arctic where the youngest caribou are bled to death by an onslaught of 9,000 bites per minute. Reindeer and caribou populations devote so much time fleeing such insidious insect attacks that they often fail to thrive suffering population decline. While the dinosaurs perished, the insects that aided their cataclysmic end remain the most prolific and diverse living creatures on Earth representing over three-quarters of all animal life. Insect numbers and variety offered parasitic micro-organisms an asylum as hosts to ensure their continued existence. Many of the older viruses like the deadly yellow fever virus and newer ones like Zika and West Nile are transmitted from animals to humans by an insect vector, in particular the mosquito. Currently *zoonosis* or 'spillover from animal sickness', account for 75% of all human diseases and is rising. When humans embraced livestock domestication first by employing beasts of burden such as yaks, oxen, water buffalos and asses to expand agriculture because their upkeep did not require much intimate contact, so the zoonotic disease burden was low. Soon other animals like fowl, sheep, goats, swine, and cattle that became barnyard livestock that were raised and nurtured within the human environment also functioned as reservoirs of disease that us as hunters and gatherers had never experienced. Horses conveyed the common cold virus, hogs and ducks contributed the influenza virus, chickens caused chickenpox, shingles, and the avian flu and from cattle arose smallpox, measles, and tuberculosis. While agriculture led to a bounty of advancements, cultivation led to an expansion of mosquito habitat and their increased breeding. While farming flourished in central and southern Americas at least 10,000 years ago, livestock domestication did not occur extensively, and the pastoral practices were limited and did not cause zoonosis to the indigenous people especially those vectored by mosquitoes despite housing the largest mosquito populations on the planet. Throughout the rest of the pre-

Columbian world, malaria was the only mosquito-vectored disease that had yet to expand out of deepest Africa. Between 12,000 to 6,000 years ago, there were at least eleven independent farming areas and by 4,000 BCE, intense agronomy was practiced in the Middle East, China, India, Africa, and Egypt. The rise of agriculture and the domestication of plants and animals accelerated the mosquitoes spread but malaria emerged as a truly chronic infection only after farmers settled along the banks of the Nile, the Tigris-Euphrates, the Indus, and the Yellow, rivers.

On the eve of the Columbian Exchange only one-half of one percent of the land east of the Mississippi River was cleared of old-growth forests for cultivation by Indians compared to a rate up to 50% in European countries. Indigenous people cleared the land by burning to farm the 'three sisters' of corn, beans, and squash as well as other crops but their small plots did not disrupt the local ecosystems. The few domesticated animals that were kept like iguanas, turkeys and ducks required low upkeep and were left to their own devices until harvested. It was not until 1494, during his second voyage, that Christopher Columbus introduced many Old-World zoonotic hosts to the New World and the planet was forever rearranged biologically. Horses, pigs, cattle, chickens, goats, and sheep served as animal hosts for disease while apples, wheat, sugarcane, coffee, and a variety of greens were uprooted to the Americas. Potatoes, tobacco, corn, tomatoes, cotton, cocoa were transplanted to fertile fields in Europe and beyond. The emigration from Europe and the shipment of captured African slaves to the Americas marked the largest transfer of people and this relocation and its results had profound effects on the demographics, culture, and economics of the whole world. It is estimated now that the indigenous population before the Columbian Exchange just in the United States approached fifteen million with sixty million American bison roaming the grassy plains. For the Americas in toto, the Indian population decline in the next two centuries exceeded that of previous 'Black Death' plagues in Europe decimating their populations by as much as 95%---leaving ninety-five million dead. The exchange of disease, except for syphilis, which was brought back to Europe by Columbus, was one-directional—from the Old World to New World. The mosquito's involvement as a vector in spreading its diseases was critical and coupled with other diseases such as smallpox produced genocidal extermination. Entomologists extrapolate that within a century of colonization, indigenous and imported mosquito populations grew by fifteen times. The early American colonies were teeming with mosquitoes in numbers that were immutable, but it was not until the *Anopheles* and *Aedes* breeds reached the colonial eastern ports as stowaways onboard European ships that malaria and yellow fever became rooted in colonial America. These foreign 'angels of death' thrived in their new homes where European settlers by their agronomy and dam building had unwittingly established first-rate mosquito-breeding habitat. Foreign species thrived and at times pushed out local mosquito populations while the colonial settlers' quest for new land drove out or destroyed the native populations. With their blood carrying mosquito-borne diseases with each new colonial expansion, malaria was introduced deeper into the interior of the continent and south into Central and South

America. Researchers now estimate that by the 1520s and 1530s, malaria, smallpox and other epidemics from Europeans brought sickness and death to the native people from the Great Lakes region of Canada to the tip of Cape Horn in South America. Honeybees also were introduced by English settlers and besides pollinating their orchards and planted crops they soon became feral pollinating indigenous plants at a prolific rate. The natives soon recognized the new 'Anglo flies' as harbingers of colonial intrusion into their territories. The globe became singular and immeasurably smaller and with globalization the spread of mosquito-borne diseases became a stark reality.

The Columbian Exchange not only brought more deadly mosquitoes that carried malaria to the Americas, but it also put Europeans in contact to malaria's antidotal cure. Quinine from Peru was an inexplicable cure for malarial fevers. 'Fever bark' or *cinchona* was the first effective treatment and preventative prophylaxis for malaria. It was a therapy discovered in the New-World for an Old-World scourge that originated in Africa. The isolated South American cure for an African disease that developed from distinct evolutionary pathways were united by the discoveries initiated by Columbus. Quinine allowed for the European establishment of footholds in the more tropical outposts of India, the East Indies and Africa. Great Britain's control of the Indian subcontinent depended on its success in curbing endemic malaria. By the 1840s, British soldiers and settlers were yearly consuming seven hundred tons of cinchona bark powder dissolved in the form of Indian tonic water and many of them craftily added distilled gin to offset its bitter taste as well as for its intoxicating effect. It allowed a small but stable British presence to effectively rule and administer over millions of Indian subjects despite the hazard of living in a tropical colony with extensive low-lying and wet regions that were prime mosquito habitat. It was not until the end of World War-II that humans gained the upper hand in its conflict with the mosquito. Combating the mosquito was critical to victory over the Nazis and the Japanese and there were watershed improvements in technology on all war fronts including our armamentarium for combating pernicious insects. Atabrine and chloroquine---new, synthetic, effective malarial fighting compounds---and the inexpensive soon to be ubiquitous pesticide---Dichloro-Diphenyl-Trichloroethane---DDT, forced the mosquito into global retreat. Despite DDT first being synthesized by German and Austrian chemists in 1874 it was not until 1939 that Paul Hermann Muller, a German Swiss scientist studying plant dyes and outdoor enthusiast, discovered its efficiency as a contact poison against insects while causing no harm for vegetation and warm-blooded animals. Despite DDT's Teutonic origin, Hitler, on advice of his own medical practitioner, judged it useless and perhaps dangerous. DDT pesticide was not used by German forces until necessity forced its selective employment in 1944. Despite advances, there were still 725,000 reported cases of mosquito-borne illnesses among American soldiers during WW-II with 60% of all American combatants in the Pacific theatre suffering from malaria at least once. Mosquito-borne illnesses that included 575,000 cases of malaria, 122,000 cases of dengue and 14,000 cases of filariasis for American soldiers across all theatres of WW-II, accounted for over 3.3 million sick days. The Axis powers numbers

although not as reliable as the medical statistics tallied by the Americans are similar or exceeded that suffered by the Allied forces.

Between 1947 and 1970, DDT production manufactured primarily in the United States rose 900%. Wherever DDT was freely used the incidence of malaria declined sharply. By 1948 there were no malarial deaths in Italy. In South America, malaria cases fell by over one-third from 1942 to 1946. In 1951, the United States declared itself malaria free while India diagnosed seventy-five million cases but with DDT use there were less than 500,000 cases reported just ten years later. By 1975, Europe was malaria free and the global rate of mosquito-borne illnesses by 1975 worldwide was decreased by 90% from 1930 despite a doubling of the human population. With synthetic antimalarials especially chloroquine, a newly developed yellow fever virus vaccine and the quasi-Kryptonite DDT insecticide, by 1955 it appeared that we had finally overpowered our deadliest enemy. In 1945, DDT was made commercially available to US farmers, and it coupled with cheap chloroquine were both being implemented internationally to vigorously campaign against malaria. Chloroquine is less toxic and more efficacious than quinine and until recently, was the most widely administered antimalarial; chloroquine is a strong anti-pyretic and anti-inflammatory agent and is the original prototype from which most more modern treatments are derived. The first resistance to chloroquine was acknowledged in 1957 in Thailand. Researchers often blame drug resistant parasites to explain malaria treatment failures but there are a host of other problems that mitigate drug effectiveness including non-compliance often accentuated by the medical need for complicated combination regimens, inaccurate dosing, misdiagnosis, storage issues that deteriorate drug quality, drug interactions and poor absorption that can cause inadequate parasite eradication. The generation of drug resistance to antimalarials is complicated and varies among *Plasmodium* species. Many antimalarial drugs repeatedly elicit resistance in the malarial parasites—including for the most potent combinations featuring artemisinin, a drug with a novel structure isolated from the Chinese herb *qinghaosu* that has been used to reduce fevers for a millennium; this drug of last resort is always given in combination with other antimalarials. Resistant cases are observed by physicians in Southeast Asia nowadays despite the usually positive outcomes from many modern treatments. The parasites have continued to develop resistance to new frontline malarial drugs circumventing or mitigating at least partially our chemical attacks on them. Quinine, chloroquine, mefloquine and other agents fierce 'bark and bite' have been 'muzzled' by the survival instincts of the recalcitrant malarial parasites.

Between the years from 1950 to 1972 the United States spent $1.2 billion to sponsor malarial control programs but the mainstay of such activities depended upon DDT. Its initial success was so resounding that subsequent research on new malarial drugs and pesticides waned. In 1972, a decade after the publication of *Silent Spring* by Rachel Carson the United States banned the pesticide for domestic agricultural uses because of its undisputed toxic environmental ramifications, it also admitted the reality that the pesticide had become

ineffective against DDT-resistant mosquitoes. Resistance varied among species but ranged from two to no more than twenty years while averaging seven years.

The Earth is on a catastrophic pathway because of the climate change from fossil fuels and the mosquito is set to forcefully ponce once again. Mosquitoes cannot survive in temperatures below fifty degrees Fahrenheit [F] and the scorching daytime temperatures of our great deserts that rise above 105 degrees F boil them to death. They thrive in temperature above 75 degrees F meaning in the temperate zones they are seasonal creatures, but the tropical warmer climates can sustain year-round populations promoting the endemic transmittance of their diseases. Global warming allows the mosquito to enlarge their geographical range. As global temperatures rise, they can intrude into what were not long-ago colder zones at higher latitudes or at greater topographical elevations. Currently, four billion people in 108 nations are at risk from mosquito-borne disease. By 2050, if climate trends continue, another 600 million people will augment this total. By genetic editing, however, we can now intrude and influence natural selection to impose extinction on any undesirable species. The revolutionary gene altering innovation—CRISPR---first demonstrated in 2013 is a procedure that snips out a section of DNA from a hereditary gene and replaces it with another preferable sequence, can permanently rearrange a species' genome. It is a quick, precise 'cutting and pasting' technique that inexpensively can reduce or incapacitate disease-carrying mosquitoes. CRISPR stands for: clustered-regularly-interspaced-short-palindromic repeats. The gene-splicing technique was discovered at the University of California Berkeley by a team headed by biochemist Dr. Jennifer Doudna. Part of the DNA added encodes CRISPR itself forming a 'gene-drive' that self-replicate itself or other desirable DNA sequences like autonomously copying pathogen-resistant genes into new chromosomes. In 2016, the Gates Foundation donated $75 million to back CRISPR mosquito research to eradicate mosquito-borne diseases. Of the 3500 mosquito species, only several hundred vector disease and the stated goal is to genetically modify mosquitoes to make them incapable of harboring the parasite, not to bring the mosquito hereditary line to extinction. With CRISPR, though, we can intentionally 'with forethought and malice' cause the extinction of any undesirable species we choose or render them harmless. The only human disease that has been 100% eliminated is smallpox where the last natural case was stamped out in 1977 in Somalia. During the 20th century, before the causative variola virus was exterminated, three hundred million people died from smallpox. The lethal virus could not survive outside of humans, its only host, for more than a few hours. With CRISPR, the Anopheles mosquito can be made harmless by eliminating the parasite as they are processed through the mosquito's salivary gland. With the Aedes breed the only feasible choice is to engineer its gene drive to ensure universal sterility because it transmits a plethora of diseases from yellow fever, Zika, Mayaro, dengue, chikungunya, and West Nile viruses. As one entomologist stated, "If we eradicated them tomorrow, the ecosystems where they are active will hiccup and then get on with life." Even in insectivorous bat species mosquitoes make up no more than one to two percent of their diet. Many scientists do not seem overly concerned with ridding the Earth of

these winged pests that have inhabited the Earth for over one hundred million years. Can we justify not taking the risk? The mosquito has caused more suffering to both humans and animals than any other creature on Earth. Neutering or destroying the mosquito as a scourge might be fantastically constructive unleashing for us remaining species on Earth a brighter, new, healthier beginning. Or it may release a Pandora's Box of unanticipated dire consequences? CRISPR has enormous potential to improve our natural world and those species that we share it with, but we must be judicious when tinkering with the global ecosystem. Climate change is forcing our hand, we must decide soon if the deadliest mosquitoes like William Shakespeare's Hamlet are 'to be or not to be.'

By R. Anthony Saritelli Autumnal Equinox 2021

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