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Review Article

Emerging Vector-borne Diseases in a Changing Environment

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Abstract: Vector-borne infectious diseases are emerging or resurging as a result of changes in public health policy, demographic and societal changes, insecticide and drug resistance, shift in emphasis from prevention to emergency response, genetic changes in pathogens in the last two decades of the twentieth century. Climate changes also can influence the emergence and reemergence of these diseases which are malaria, dengue, yellow fever, plague, filariasis, louse-borne typhus, lyme disease, trypanosomiasis, leishmaniasis and viral diseases. West Nile virus is just the latest example of this type of invasion by exotic virus. This paper will provide an overview of the distribution, reasons of emergence or reemergence of the important vector-borne diseases throughout the world.

Key Words: Vector-borne Diseases, Malaria, Yellow fever, Dengue, Plague, Lyme disease, Typhus, Arboviruses, West Nile virus

Çevre Değişiklikleri ile Ortaya Çıkan Vektör-Kökenli Hastalıklar

Özet: Vektör kökenli infeksiyon hastalıkları, 20. yüzyılın son yıllarında halk sağlığı politikalarındaki değişiklikler, demografik ve sosyal değişiklikler, insektisit ve ilaç direnci, koruma yöntemlerinden acil tedavi yöntemlerine kayış ve patojendeki genetik değişiklikler nedeniyle yeniden önem kazanmaya başlamıştır. İklimsel değişiklikler de, malaria, deng, sarı humma, veba, filariasis, bit ile bulaşan tifus, lyme hastalığı, trypanosomiyasis, leişmaniyasis ve viral hastalıklar gibi vektör kökenli hastalıkların yeniden ortaya çıkışında etkili olabilir. Batı Nil virusu, ekzotik virusların yayılımına ait son örnektir. Bu makalede, önemli vektör kökenli hastalıkların dağılımı, yeniden ortaya çıkışlarının nedenleri global olarak özetlenmeye çalışılmıştır.

Anahtar Sözcükler: Vektör-Kökenli hastalıklar, Malarya, Sarı humma, Deng humması, Veba, Lyme hastalığı, Tifus, Arboviruslar, Batı Nil virusu

During the history of human cultural evolution, population dispersal around the world and subsequent inter-population contact and conflict there have been several distinct transitions in the relationships of *Homo sapiens* with the natural world. Each of these transitions in human ecology and in inter-population interaction has profoundly changed the patterns of infectious disease. In the first transition, human settlements allowed countless novel strains of bacteria and viruses to make the jump from domesticated herds of naturally gregarious animals to humans (1).

Anthropological research in Africa has shown that malaria-protective sickle-cell trait arose when iron tools and slash-and-burn agriculture were introduced, presumably by creating new breeding sites for *Anopheles gambiae*, the major mosquito vector for falciparum malaria (1, 2).

The second great transition occurred from around 2500 to 1000 years BC with travel and military movements between the contiguous land masses of Europe, northern Africa and Asia. And the third great transition began around five centuries ago and entailed the trans-oceanic spread of disease.

These three great historical transitions were processes of equilibration between first humans and animal species and later, among regional human populations. As new ecological niches were created by changes in human cultural practices, microbes exploited those niches. As new contacts were made between previously isolated civilizations, infectious diseases were shared. In today's globalizing world, populations everywhere are becoming interconnected economically, culturally and physically, enhancing the mixing of people, animals, and microbes from all geographical areas

McMichael asks "Are we experiencing history's fourth transition? "at this moment (1).

In today's world, no country is safe from infectious diseases (3). Human mobility has escalated dramatically in volume and speed between and within countries. Long-distance trade facilitates the geographical redistribution of pests and pathogens. In this review article, changing social, cultural and environmental conditions have been related to the new distribution pattern of the diseases, emphasizing vectorial-diseases, to clarify the above question.

Historically, vector-borne diseases such as malaria, dengue, yellow fever, plague, filariasis, louse-borne typhus, trypanosomiasis, and leishmaniasis were responsible for more human disease and death in the 17th through the early 20th centuries than all other causes combined (4). After successful control programs by the 1960s, vector-borne diseases were no longer considered major public health problems outside Africa. However, the benefits of vector-borne disease control programs were short-lived, and in the last thirty years, there has been a dramatic global resurgence of infectious diseases. Some important diseases were recognized for the first time, including HIV/AIDS, hantavirus pulmonary syndrome, Ebola, Lyme disease and ehrlichiosis. Equally important was the rising incidence of many recognized diseases that had been effectively controlled since 1960s (1,4-6). New combinations of diseases have also been noted, such as the appearance and spread of co-infections of HIV virus and leishmaniasis (7). By 2004, vector-borne diseases like malaria and dengue hemorrhagic fever are among the most serious public health problems in countries where there are no properly-trained vector biologists in the Ministries of Health (5,7,8).

Although the reasons behind this dramatic resurgence of arboviral diseases are complex, Gubler (2002) listed the following factors:

Demographic changes including global population growth, population movements, and unplanned and uncontrolled urbanization;

Societal changes such as human encroachment on natural disease foci, modern transportation, containerized shipping;

Agricultural changes including changes in land use, irrigation systems, deforestation;

Changes in pathogens due to increased movement in humans and animals and genetic changes leading to increased epidemic potential;

Changes in public health including lack of effective vector control, deterioration of public health infrastructure to deal with vector-borne diseases, disease surveillance and prevention programs and possible climate change (9).

It is clear that certain demographic and societal changes in the past 30 years have had a major impact on the ecology of vectorial diseases. Modern transportation ensures faster and increased movement of humans, animals, and commodities and their pathogens between regions and population centers of the world. For example, in the past twenty years, four exotic mosquito species have been introduced and established in the United States; three of these are potential vectors of local diseases (5,10). *Aedes albopictus* (Asian tiger mosquito) of Asian origin, first spread to the America and African continents, and is now established in North and South America, Africa, Oceania and Europe. It was first detected in Europe in 1979 in Albania, after which it has been reported from many different countries (7,11-19). By late 2001, *Ae. albopictus* had rapidly become the most important pest species in northern Italy. In 1996, another introduced mosquito species *Aedes atropalpus* was discovered the Ventao region of northern Italy. More recently, *Ochlerotatus japonicus*, an Asian mosquito, has been reported from Normandy, France where it was found breeding in tires, like the above *Aedes* species (12). The establishment of exotic mosquitoes in Australia and New Zeland was viewed as a serious concern by health authorities of both countries (10).

To consider other vector species, the tick, Dipteran larva, cockroach species have been recorded as introduced species as well. There is an increasing trend of Tick-borne encephalitis cases in Europe, partly due to changes in human behaviour that bring more people into contact with infected ticks. Increasing trends in mean temperature values also effects the distribution of many tick species in Northern Europe. Dipteran larvae, a cause of myiasis, are often found or travelers returning from tropical countries. Cockroaches are ubiquitous pest aboard ships and aircraft, and exotic species are quite often transferred from one country to another (7). The high rates of transmission by different vectors to different vertebrate hosts in new geographic areas can

result in selective pressures that lead to genetic changes in the pathogen. These new strains of virus may have greater epidemic potential and virulence. For example, the unique susceptibility of young domestic geese in Israel in 1997-2000 to West Nile virus and the isolation of similar strains from migrating White storks in Israel and Egypt suggest that the recent isolates are more pathogenic for certain avian species (20).

Deforestation provides new ecological niches and conditions for proliferation of newly arriving and/or adaptive vectors and their parasites. The replacement of forests with crop farming, ranching and raising small animals can create a supportive habitat for parasites and their host vectors. New settlers to a deforested area are particularly vulnerable as they lack immunity to the zoonotic parasites endemic to the area. In adapting to changed environmental conditions, including reduction of non-human population and increased human population, some vectors display a conversion from a primarily zoophyllic (bites to animal) to primarily anthrophophilic (bites to human) orientation. Water control projects can create new breeding habitats for mosquitoes, snails, their larvae and their parasites. The construction of new roads provides access for new human, livestock, vector and parasite populations (21).

Let us see how climate can be effective on vector-borne diseases. The International Council of Scientific Unions Intergovernmental Panel of Climate change, established by the World Meteorological Organization and the United Nations Environmental Program, have estimated that by the year 2100, average global temperatures will have risen by between 1.0°C to 3.5 °C. Important ecological changes may come about in the future due to this global warming. The distribution and seasonality of diseases that are transmitted by cold-blooded insects or ticks are likely to be affected by climate change (7,21-23). Even if there are no certain data that confirm that changes in climate have been responsible for the recent resurgence of vector-borne diseases, there are many studies on this subject.

The incidence of mosquito-borne diseases, including malaria, dengue, and viral encephalitis are among those diseases most sensitive to climate (21,24-27). Climate change would directly affect the transmission of the diseases by shifting the vector's geographic range and increasing reproductive and biting rates and by shortening the pathogen incubation period. Human susceptibility to infections might be further compounded by malnutrition due to crop failure caused by climate stress (21). Temperature can affect both the distribution of the vector and the effectiveness of pathogen transmission through the vector. In more detail temperature can affect survival of the vector, the rate of vector population growth, feeding behavior, susceptibility of the vector to pathogens, incubation period of the pathogen, seasonality of vector activity, and the seasonality of pathogen transmission. For example, the relation between El-Nino events and increased malaria risk is partly due to increased temperature and partly due to increased rainfall leading to increased mosquito breeding sites because of surface water collections (7,28). As another example, decreased rainfall has been shown to be associated with epidemics of SLE (St Louis encephalitis) when the vector *Culex pipien*s breeds effectively in urban drainage systems (21). Unusual abundance of some vectors, such as ticks or changed behavior of other pests, such as higher anthropophily of *Cx. pipiens* may in some areas be attributed to climate changes in Europe (29).

The northern range of the occurrences of endemic malaria has been estimated to coincide with a summer isotherm of 16°C. However, even a superficial examination shows that malaria also occurred in the northern parts of Sweden and Finland, where the summer temperature was considerably below 16 °C (30,31). Climatic factors that increase the inoculation rate of Plasmodium parasites, as well as the breeding activity of *Anopheles* mosquitoes, are considered the most important cause of epidemic outbreaks of malaria in nonendemic areas. According to malaria models under climate change scenarios, the risk of malaria epidemics would rise substantially in both tropical and temperate regions (28). In a MS thesis carried out in southern Turkey, the correlation between climatic parameters and changes in the number of malaria cases up to present was evaluated by using GIS and it was noted that these changes have a positive effect on the survival of *Anopheles sacharovi* Favre and *Plasmodium vivax* (32).

Malaria is the most important tropical diseases with more than half of the world's population living in areas of risk and with an estimated 200 million cases and two million deaths each year (3,7,33-35). It has been on the rise in many parts of Africa, with the mortality in young children almost doubling from the 1980's to the 1990s.

The disease causes some 3000 deaths each day and imposes huge losses in economic productivity (36). Widespread drug resistance in the parasites and insecticide resistance among anopheline mosquito vectors have complicated malaria control. Malaria is also the most common imported disease in the United States, where Anopheline mosquito vectors still exist (35). Until after the end of World War II, malaria was endemic throughout much of southern Europe. The Balkans, Italy, Greece and Portugal were particularly affected, although seasonal epidemics or outbreaks occurred as far north as Scandinavia, Finland, Norway and southern Sweden. The area of malaria distribution in Europe peaked at the beginning of the twentieth century. Soon after the war, intensive control measures were initiated and by 1970 the WHO declared malaria eradicated from Europe. However, populations of potential *Anopheles* vectors of malaria remain high in many countries of the continent and their presence posses the risk of renewed transmission (7,37-39). The WHO Regional Office for Europe reported a total of 15,528 cases of imported malaria in Europe in the year 2000 (7). Local transmission has also frequently occurred in Europe in the form of airport malaria. This refers to the transmission of malaria as a result of the inadvertent transport of live, malaria-infected mosquitoes aboard aircraft arriving from tropical malaria-endemic countries (6,40). The most serious problem of resurgent malaria is in the newly independent states (Azerbaijan, Tajikistan) and in Turkey; due to an influx of refugees from malaria endemic areas, the breakdown in health services, and the lack of vector control measures in most of these states, as well as in the failure to carry out adequate malaria surveillance and control measures (7). In Turkey, the mosquito species have been revised (41,42) and the malaria vectors, population dynamics and control strategies have been determined in some recent studies (43-48). According to these studies, Malaria epidemics had been seen twice in 20 years in Sanlıurfa where is in the heart of the GAP (Southeastern of Anatolian Project) project area. Earlier malaria was most frequent in Çukurova and its provinces but nowadays it is most frequent in Southeastern Anatolian region, partly because of the migration and the changing environmental conditions due to irrigation project.

Leishmaniasis, which comes next after malaria in importance, is a protozoon disease in which clinical manifestations are dependent both on the infecting species of Leishmania and the immune response of the host. Leishmaniasis and its sandfly vectors are found in some 88 countries, mainly in tropical and sub-tropical areas, is also widespread in southern Europe (49). The overall prevalence of Leishmaniasis is 12 million cases worldwide, and the annual global incidence of all clinical forms approaches 2 million new cases. Clearly human and canine leishmaniasis is a serious problem in southern Europe, with infection showing a rising trend, especially leishmania/ HIV co-infection cases (7). A total of 14 *Phlebotomus* species have been identified from Turkey (50-55). More recent studies have insisted on the changing environmental conditions due to new water regimes and agricultural practices and the increasing numbers of the human cutaneous leishmaniasis cases have been observed (48,56-58).

Historically, African sleeping sickness transmitted by the tsetse fly, has been a major impediment to the social and economic development of Central and East Africa. In the past 20 years, major epidemics have occurred in East and Central Africa, mainly because control programs were disrupted by war (35).

Tick-borne diseases are also sensitive to climatic conditions but favor cooler temperatures (26). Lingren stated that, the distribution of tick vectors in Sweden has expanded northward between 1980 and 1994, consistent with observed changes in climate. Documented increases in the incidence of Tick-borne encephalitides over the last decades have been reported from many countries in Europe, as the result of increased densities of vector tick species (7).

Lyme Disease, transmitted by *Ixodes scapularis* or *pacificus* ticks is caused by *Borrelia burgdorferi*. Discovered in the United States in 1975, the disease has continued to increase in incidence and geographic distribution since national surveillance was initiated in 1982 (7). It is the most commonly reported vector-borne disease in Europe and North America; its incidence is clearly increasing, and new species of *Borrelia* are continuously being found. Among the reasons for this increase are ecological changes such as reforestation that favour greater densities of tick vector populations and increased exposure of persons to tick bites when visiting endemic areas (7). The Swedish study indicated that the reported northern shift in the distribution limits of ticks was related to fewer days during the winter seasons with low minimum temperatures below – 12°C (59).

Plague, is the original emerging disease, having caused major pandemics. Like many other vector-borne diseases, plague was controlled with antibiotics, insecticides and rat control in the latter half of the 20th century. In recent years, however, epidemic plague has resurged, most notably in Africa, with an average of nearly 3,000 cases reported annually (35).

Onchocerciasis or "river blindness" vector requires fast-flowing water for succesfull reproduction and the adult vector can be spread by wind. According to the increased temperature and precipitation levels, black fly populations may increase by as much as 25 % at their current breeding sites (21).

Among other vector-borne diseases affected by climate changes, Schistosomiasis has increased in prevalence in arid warm regions primarily from expansion of irrigation systems where snails serve as the intermediate host (28).

Viral diseases transmitted by blood-feeding arthropods (arboviral diseases) are among the most important of the emerging infectious diseases public health problems facing the world at the beginning of the third millennium (5,60-63). These include Dengue, Dengue haemorhagic fever, Yellow Fever, Japanese Encephalitis, West Nile Fever, Kyasanur Forest disease, Venezuelan equine encephalitis, Epidemic polyarthritis, Barmah forest and Mayaro Rift Valley Fever, Oropouche, and Crimenean-Congo hemorrhagic fever (5,35). There are currently 534 viruses registered in the International Catalogue of Arboviruses, of which 40 % are known or probable arboviruses; 25 % have caused documented illness (5). Although some arboviruses that cause human disease such as Barmah Forest disease in Australia have been newly recognized, the greatest problem is by far the viruses mentioned above. Arboviruses have a worldwide distribution. But, in the last two decades, the geographic distribution of both vectors and viruses has expanded globally. The geographic distribution of each arbovirus is restricted by the ecological parameters governing its transmission cycle. These cycles are usually silent and undetected in nature until some environmental change allows the virus to escape the primary cycle via a secondary vector or vertebrate host, or when humans invade or encroach on the nidus of infection. Mosquitoes are by far the most important vectors of arboviruses, and birds and rodents are the most important vertebrate reservoir hosts. These zoonotic viruses circulate in nature either in an Aedes-mammal, Anopheles-mammal or Culex-bird transmission cycles (64,65).

The Dengue viruses are the most widespread geographically of the arboviruses and are found in tropical and subtropical areas where 2.5-3 billion people are at risk of infection with 50-100 million cases of Dengue fever and 500.000 cases of DHF. It is an old disease that distributed worldwide in the tropics during the 18th and 19th centuries when the shipping industry and commerce were expanding. Both the principal mosquito vector, *Aedes aegypti* and the viruses responsible for Dengue fever were spread via sailing ships. In those times because of the slow mode of transportation, epidemics were infrequent with intervals of 10-40 years. The global epidemiology and transmission dynamics of dengue viruses were changed in Southeast Asia during World War II. Today, dengue fever causes more illness and death than any other arbovirus disease of human (9,35,66-69). New dengue virus strains and serotypes will likely continue to move between areas where *A. aegypti* occurs in infected air travelers, resulting in increased frequency of epidemic activity and increased incidence of Dengue haemorhagic fever (70). Although funding for dengue vaccine development has been sparse, good progress has been made over the past ten years (9,71).

Currently, Dengue viruses are being transmitted in the tropics between 30° north and 20° south latitude, since frosts or sustained cold weather kills adult mosquitoes and overwintering eggs and larvae. Warming trends, therefore can shift vector or disease distribution to higher latitudes or altitudes as was observed in Mexico when dengue reached an altitude of 1700m during the unseasonably warm summer in 1998. Temperature also affects the transmission dynamics of dengue, because warmer temperatures reduce the size of *Ae .aegypti* individuals, smaller adults must feed more frequently to develop egg batches, resulting in double feeding (28).

West Nile virus is the latest example of invasion by exotic viruses. West Nile virus was first isolated in 1937 from the blood of a febril patient in the West Nile district of Northern Uganda. During 1994-2000, epidemics of WNV meningoencephalitis occurred at a new alarming rate in North Africa, Europe, North America and the Middle East (72,73).

Yellow fever is an old, well-known disease that caused major epidemics in the Americas and in Africa from 17th to 20th centuries. Like Dengue and DHF, these were primarily urban epidemics transmitted by *Ae. aegypti* (9).

West Nile virus was first detected in the United States in September 1999 during the investigation of an outbreak of encephalitis in humans in New York City (74-80). The dramatic appearance of epidemic meningoencephalitis in New York City in 1999 is an unsettling reminder of the ability of viruses, including arboviruses, to jump continents and hemispheres. WNV rapidly spread across the United States and invaded California during 2003 (81). The continued movement west into large population centers in California increases the urgency of continued efforts to develop intervention methods (73). WNV is mainly transmitted by *Culex* mosquitoes. Compared with most arboviruses, however, WNV has been identified from an exceptionally broad range of species. *Aedes albopictus* and *Cx. erraticus* were recorded as the vector species for the first time in New York State (79). After that, in North America only, the virus has been identified in 43 different species of mosquito. With such a broad vector range, expansion of the geographic distribution of WNV into new areas and its establishment seem inevitable (82).

There are an enormous number of studies carried out in America after the first outbreak (83-92). The first report of West Nile virus activity in Canada was in August 2001, when the virus was found in dead birds and mosquito pools in southern Ontario and the worst Canadian outbreak occurred in 2002 (93).

Except for a small outbreak in southern France in 1962, WNV has not been a public-health threat in Europe. The first major West Nile Fever epidemic in Europe occurred in Romania in 1996, with a high rate of neurological infections (94-96). Other records came from Ukraine (97), Croatia (98), Germany (99), Jourdan (100), and Czechoslovakia (101).

Mosquito-borne arboviruses are also important public health issue in Australia (102-107).

It was recorded that Israeli researchers in the 1950's were the first to characterize the clinical presentation of WN fever, but by the end of the 20 th century, WN virus infection was an almost forgotten disease in Israel. The vectors of WN virus in Israel were observed as *Culex* species, *Cx. pipiens* and *Cx. perexiguus* (91,108,109).

The close genetic relationship between WN virus isolates from Israel and New York suggest that the virus was imported into North America from the Middle East (110), but the mode of introduction is unknown. There are some studies on phylogenetic analysis of WNV strains isolated from different areas (73,111,112). According to initial nucleotide sequencing studies, strains found on the eastern seaboard of USA were nearly identical in sequence to the prototype New York 1999 strain. According to some researchers there is no evidence for selection of any phenotypic differences between isolates in North America (82,113).

Birds are the natural reservoir hosts for WN virus, which has been shown to infect at least 111 bird species in North America only (73,86,114-117). In North America, WN virus seems to be particularly virulent in species belonging to the family Corvidae (eg.crows and jays) (118) and these have a central role in dead-bird based surveillance programmes for detecting and tracking the virus (73).

Bird deaths due to WN virus are unusual outside North America, with the exception of deaths of geese in Israel and pigeons in Egypt (119). Whether high avian death rates in the United States are due to higher virulence of the circulating strains or to higher susceptibility in North American birds requires further evaluation (110). Then it was recorded that the unique susceptibility of young domestic geese in Israel in 1997-2000 to WNV and the isolation of similar strains from migrating White storks in Israel and Egypt suggest that the recent isolates are more pathogenic for certain avian species. Infected birds have recently been found in the Caribbean and the infection will no doubt continue to spread through the Americas (7).

Transportation of WN virus strains between different areas by migratory viraemic birds along established flyways is probably a common occurrence. In the eastern hemisphere, WN virus is thought to be regularly introduced in Mediterranean and European countries by birds (20,120). Campbell emphasized that WN virus will almost certainly continue to spread into the contiguous western parts of the USA over the next years, primarily via the movement of viraemic birds (73).

In Africa, WN virus is principally transmitted in an enzootic cycle among *Cx. univittatus* and birds (121). Many northward migratory routes follow a flyway across

the Middle East, Turkey and the Black Sea, along which the Danube delta is a main avian refuge (95). Regarding this migration routes, Turkey is important place for potential arboviruses. Up to now, there are few seroprevalence studies showing different viruses presence. In 916 human sera collected from Southeast Anatolia, 40.06 % were positive for West Nile antibodies (122). In the Aegean region of Turkey, Sindbis, West Nile Fever, Dengue 1, CETE, Tahyna virus and Naples prototype from Phlebotomus Fever group viruses caused infections in the population (123).

A broad range of mammalian species are also susceptible to natural or experimental infection with WN virus. In the USA during 1999-2001, nine mammalian species (human beings, horses, cats, rabbits, skunks, squirrels, chipmunks and two species of bats) were found to be naturally infected with WN virus. The role, if any, that mammals play in the WN virus transmission cycle is unknown (73,87,124).

No human vaccine for WN virus is currently available. So, effective prevention of the disease depends on integrated arboviral surveillance and vector mosquito control programmes to reduce the density of vector species, including those that might serve as a "bridge" from birds to human beings (73,82). Cases were also of WNV transmission transplacentally by transfusion, by lactation, by organ transplants as new routes of transmission (82). Werner pointed that the scope of infectiology keeps widening, while the threat of bioterrorism can not be neglected (125).

In a review article by Whitehouse on Crimean-Congo hemorrhagic fever, the recent presence of this tick-borne disease in Turkey was recorded for the first time(126).

As seen in the above articles, without sustained vector control in urban areas, even the world's affluent cities are at risk for epidemic arboviral diseases. And we do not know how many potential organisms will share our planet with us that are awaiting the right conditions for their chance at stardom by becoming emerging infectious diseases. Bearing in mind this alarming fact, new FP6 project named "Emerging Diseases in a changing European Environment" have been already launched on January 2005 consisting of 98 scientist in 78 institutes in 24 countries in which we take part (127). The aim of this project, is to increase preparedness by developing and coordinate at European level a set of generic investigation methods, tools and skills within a common scientific framework (Landscapes, Vector and Parasite bionomics, Public Health, Animal Reservoirs). Some of the diseases which are already present in Europe such as West Nile, Rodent-borne, Tick-borne, Leishmaniasis, Bluetongue, some were present historically such as malaria and so may re-emerge, whilst a final group such as Plague and Rift Valley Fever will be subject of the project. It will be the first ever European large scale research project which will investigate diseases from an environmentally driven perspective. We will share the outputs of the project with the researchers, public, national and international policy making authorities in the next few years.

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