

Parasites, Immunity, Resistance, Microbiome and Alternatives to Tackle Diseases and Prevent Health

Ivana Haluskova Balter*

Department of Medical and scientific consultant for partnership, French society of immunology, France

*Corresponding author: Balter IH, Department of Medical and scientific consultant for partnership, French society of immunology, France; E-Mail: ivankahaluskova@gmail.com

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Editorial

Bacteria, viruses, BUT parasites and fungi that are resistant to drug cause 700,000 death each year. By 2050 superbugs inured to treatments could cause up to 10 million deaths annually and costs the global economy US\$100 trillion.

Resistance is regarded nowadays as a major threat to global public health. The issue is receiving high-level political and global attention (G7 and G20 but WHO or GAVI and many other economic forums). Pandemics, drug resistance to antiparasitic, antivirals, antimicrobials, TB drugs, antifungals and neglected diseases framing health as a “global security issue”.

Today is a unprecedented sanitary and humanitarian crisis with Covid 19, previously Ebola, MERS and SRAS etc . Climate changes and our rapport with animals and environment, rapid urbanisation, interconnected world highlight need to pay attention to this area.

Problem of resistance including resistance to antimalarials (artemisia of herbal origin with spread of resistance in Asia but separately seen in French Guyenne)

It get worsened due declining number of treatment, absence of 100 % safe and effective adaptive vaccine and over proliferation of vector like seen in other vector borne diseases – dengue, chikungunya.

Multifaceted strategy to promote and prioritize highly potential alternatives to tackle resistance including better understanding of correlates of protection and enhance host immune response in adapted fashion along with targeting vector (see Wolbachia program for dengue) is required together with treating emergency of Climate issue.

Vaccines like diphtheria and tetanus did not prompt resistance. In 1980 the smallpox vaccine had eradicated the naturally circulating virus worldwide without generating resistance. Recent development of LATV for pertussis shows positive off target effect where not only antibody but innate and cellular immunity plays role. Vaccine with identified correlates of protection avoiding parasite triggered consequences on host immune response and its complicated lifecycle is a path many researchers are looking into.

Introduction of live vaccines like measles and BCG has been associated with much larger reduction of mortality than can be explained by the prevention of the targeted infections- cross protection based on immune host capacity boosting and off target effects.

Additionally, many researchers looked into link between microbiome (nutrition is a factor especially in younger age) and links with capacity to train innate cells to “block” harmful immune response once individual get infected considering genetic and immune differences.

Thoughtful and innovative vaccines development considering host microbiota “superorganism” and immune crosstalk - Immune system training linked with several inflammatory/ autoimmune diseases open large avenue for future development including tackling parasitic diseases like malaria given role of cellular protection.

Microbiota under 3 years old fluctuates substantially and is more impressionable to environmental factors than the adult microbiota. Lifestyle, sanitization, caesarean sections, antibiotic usage, immunizations. There are several diseases associated with alterations of the intestinal microbiota and consequences on host immune capacities and later development of many diseases in later age.

Accurate diagnostic and surveillance with better understanding of genetic and immunologic background of host specific response and pathogen evolution drives successful country adapted vaccine research.

BUT, importantly, vaccines, as highly potent tool and valuable alternative from long term perspective being clearly recognized as a major tool for public health already.

Malaria as VBD is of crucial medical importance within context of raising resistance and lack of new alternatives

As previously noted, the changes in the health debate can be viewed as steps towards recognizing health as collective global and economic challenge (Davos 2017) where role of climate change and preparedness for any pathogen X escaping control was underlined. (CEPI was created this time)

The nation’s most at risk for climate-triggered health crises are primarily in South Asia and are already afflicted by the highest rates of disease burden globally.

Climate change and rising global temperatures play a major role in spreading of infectious diseases and affecting global ecosystems including marine, water (stagnating or “unproper” water is a factor favorizing proliferation of vector and infectious diseases where hygiene plays role as well).

This in turn leads to more tropical diseases expanding into temperate regions with health and economic consequences one may anticipate.

Asia is currently going through a series of major transitions including globalization, urbanization, and climate change, which will present future challenges for disease control.

It is estimated that by 2020, nearly 400 million business travelers and tourists will flock the region annually, compared to 100 million in 2000. This rapid increase in travel and tourism is a major reason for promotion of disease transmission and spread.

Also, by 2050, Asia's urban population is expected to increase by 20-25 percent, which means that 1.5 billion people will live in urban areas. This rapid urbanization and over-crowding in big cities such as Hong Kong, Beijing, Shanghai, Tokyo, Mumbai, and Jakarta, could increase the risk of infectious disease transmission.

In addition, climate change and rising global temperatures also play a major role in spreading of infectious diseases and affecting global ecosystems and breaking natural chains and biodiversity. This in turn leads to more tropical diseases such as malaria and dengue fever expanding into temperate regions.

The interconnected world makes it easy for pathogens resistant to anti-infectives to travel across continents. This puts all major countries in the world at jeopardy and Asia region is no exception.

Region and countries develop various strategies to manage and tackle the issues concerning healthcare infrastructure, huge population, spending on healthcare and fighting poverty.

To illustrate more in details, the past two decades have seen more than 30 re-emerging diseases and unexpected outbreaks of new infectious diseases.

Asia has seen unprecedented population growth. Region has been a focal point of economic development, driving unprecedented urban growth and every Asian city has a new airport through which millions of people, animals and commodities travel each year.

Many efforts seen and obstacles to overcome for effective public private partnership to invest in public health infrastructure to prevent and control infectious diseases.

While looking from economic standpoint, in an increasingly interconnected world many public goods (GPCs) generate benefits such a safer world, protection against the impacts of climate change and better health that are of vital importance to everyone and to the survival of future generation.

Since 2000, the fight against AIDS, tuberculosis BUT malaria has contributed to significant shifts in the main paradigms of the health economics literature applied to developing countries: improvements in public health of the population are now

considered a prerequisite, rather than a consequence, of economic growth; for health care financing, priority is given to promoting prepayment and health insurance mechanisms rather than “cost recovery” policies and user fees at the point of consumption.

Global health diplomacy as seen several times if well conducted results in better health security and health outcomes for each and all of the countries involved and improved health and economic situation.

Women play key role in South Asia contributing to improved relationship between states in region and commitment of all stakeholders involved in health to work together to increase health awareness, education, equity and reduce poverty.

From management standpoint and based on many lived project management examples in South Asian region (particularly in India) various stakeholders involved and strong cultural and historical diversity along with modality of gender integration could be seen as difficult challenge but for various reasons while compared to Western countries as very strong driving force.

Back to parasitic diseases where I pick malaria as an example.

Diagnostic test developed by Pasteur Institute of Cambodia shows promising path to help monitoring of parasite and early diagnostic /surveillance.

Looking into history of last drug development when chloroquine resistance spread to Africa, let look to Artemisia story.

The herb Artemisia annual has been used for many centuries in Chinese traditional medicine as a treatment for fever and malaria. In 1971, Chinese chemists isolated active substance - Artemisinin from the leafy portions of the plant responsible for its reputed medicinal action. Thus artemisinin and its derivatives offer promise as a totally new class of antimalarials. This discovery of Artemisinin for malaria is a result of scientific work based knowledge from Traditional Chinese Medicine (TCM) and presents best case for reverse pharmacology approach.

There are challenges of R&D pharma for new drugs, potential to use reverse pharmacology for new compound evaluation coming from natural sources as well to be considered as alternative

Reverse pharmacology is the science of integrating documented clinical/experiential hits, into leads by transdisciplinary exploratory studies and further developing these into drug candidates by experimental and clinical research.

Many potential compounds seem to be used empirically in traditional medicine in Asia and Africa which share many similarities and this effort seems to be confirmed by agreement between Malaysia and India to move forward this direction (only one of many examples)

The scope of reverse pharmacology is to understand the mechanisms of action at multiple levels of biological organization and to optimize safety, efficacy, and acceptability of the leads in natural products, based on relevant science.

The herbal knowledge database allows drug researchers to start from a well-tested and safe botanical material.

Trans-discipline A golden triangle consisting of Ayurveda and traditional Asian, African and South America herbariums, modern medicine and science will converge to form a real discovery engine that can result in newer, safer, cheaper and effective therapies.

The mass screening of plants in the search for new leads or drugs is vastly expensive and inefficient, but traditional knowledge offered better leads.

It is estimated that over hundred new natural product- based leads are in clinical development. • About 60% of anticancer and 75% of anti-infective drugs approved from 1981-2002 could be traced to natural origins.

It would be cheaper and perhaps more productive to re-examine plant remedies described in ancient texts.

Reverse Pharmacology can reduce three major bottlenecks of costs, time and toxicity.

Natural product drug discovery, ethnopharmacology, traditional, complementary, and alternative medicines are re-emerging as new strategic options.

The World Health Organization's Commission on Intellectual Property and Innovation in Public Health also has duly recognized the promise and role of traditional medicine in drug development for affordable health solutions.

Recently, *Nyctanthes arbor-tristis* Linn has been shown to possess antimalarial activity. The plant extracts are being standardized and studied phytochemically as exploratory studies have already shown ant plasmodial effects in vitro and disease modifying activity in patients.

Conclusion

Further strong support and partnership to promote all paths and support for accelerated clinical development opening doors to all valuable but ACCESSIBLE/AFFORDABLE alternatives accompanied by accurate accessible diagnostic, prevention, education and open data sharing (surveillance of evolution of parasite and vector) need joint endorsement including regulatory and economic stakeholders along with necessary partnership regrouping public, private sector and societies supported by strong intergovernmental regional and global cooperation and strategy with concrete rapid, effective and accountable actions .

But as noted many times, approach is multiple- targeting host immunity, parasite and its particular lifecycle and vectors (where applicable) along with tackling climate and environmental burning issue linked to Public health.

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