The Role of Disease-Specific Research: A Developing-Country Perspective

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Over a decade ago, the Commission on Health Research for Development published a pioneering study on the gross imbalance between the world's research funding priorities and global disease burden distribution. This study reported that less than 10% of world resources for health research were being applied to the health problems of developing countries, where 90% of the avoidable burden of ill-health was to be found. What became known as the "10/90 gap" has captured the attention and imagination of those committed to global health equity everywhere, searching for ways to incline the research agenda towards "diseases of the poor".

Such examination has inevitably led to recommendations for research capacity strengthening (RCS) in low- and middle-income countries. And that, in turn, has landed us squarely in the often acrimonious debate between the primacy of "disease-specific" research and initiatives, and those that address broader "health systems and infrastructure" needs.

We believe that Cuba's experience with dengue upholds the notion that RCS in developing countries can lead to important advances in population health when disease-specific agendas inform national health programs and action, and when, at the same time, disease-oriented initiatives are embedded in sound health systems that facilitate introduction of new discoveries and involvement by communities as well as health professionals. In short, these two approaches need not be poles apart but should reinforce each other.

Dengue, caused by a virus transmitted primarily by the *Aedes aegypti* mosquito, puts 3 billion people worldwide at risk, resulting in some 50 million cases and over 20,000 deaths annually. More than 100 countries in Southeast Asia, the Western Pacific, the Americas, Africa, and the Mediterranean report the disease, and climate change is moving its vectors further north in countries like the USA.

Cuba itself reported epidemics in 1977–1978 (Dengue serotype 1); 1981 and 1997 (Dengue 2); 2001–2002 (Dengue 3); and 2006 (Dengue 3 & 4). Still, the country has managed to control the disease and avert endemic dengue, despite the fact that the island is surrounded by dengue-endemic countries.

How have research priorities and outcomes contributed to this result? Cuba's dengue control program rests on studies in several key areas: diagnostics, epidemiology, clinical management, vaccines, and vector entomology; as well as dengue's social, economic, and environmental context.

Diagnostics research has coupled with engineering to develop and produce advanced domestic technology such as the UMELISA system for detecting IgM dengue antibodies as indicators of recent infection. The system is used in active screening programs throughout the country. Diagnosis is confirmed at the Pedro Kourí Institute of Tropical Medicine (national reference center for dengue) with enzyme-linked immunosorbent assays (ELISA) to detect IgM and IgG. We have also introduced virological and molecular surveillance with RT/PCRs and Realtime PCRs, among other methods.

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Risk-factor studies for dengue hemorrhagic fever (DHF) have led to important conclusions: a) secondary infection by a another dengue serotype is a leading risk factor in developing DHF; b) DHF can appear during a second dengue infection up to 20 years after initial infection; c) DHF risk is significantly higher the longer the interval between infections; d) children are at greater risk of DHF than adults during a secondary infection; and e) different viral sequencing of infections is associated with greater or lesser risk of subsequent dengue or DHF infection.

Our studies also reveal significant association of DHF development with white skin color and chronic diseases such as bronchial asthma, diabetes, and sickle-cell anemia—results that influence prevention strategies. Recent Cuban research also shows that certain immune-response genes are associated with severity of or protection against dengue illness.

Cuban clinical studies have characterized the clinical picture of adult DHF, establishing warning signs and measures to adequately manage patients to prevent dengue shock syndrome and fatalities. It is worth noting that the new clinical classification of DHF proposed by the WHO Special Programme for Research and Training in Tropical Diseases is based on the one used in Cuba during the country's 1981 epidemic.

Given the importance of discovering a vaccine, especially for dengue-endemic countries, Cuban research has identified two candidates based on recombinant proteins, both with satisfactory results in preclinical studies.

Entomological studies are ongoing regarding the biology of the *Aedes aegypti* mosquito and its resistance to insecticides. This has helped us develop accurate infestation indices and design better national mosquito control strategies. Social science research has been key to broadening all-important community participation in controlling the mosquito and its larvae, helping achieve greater awareness and sustainable behavior changes. We continue to seek ways to improve such "ownership" and participation.

In summary, we believe Cuba's successes thus far in addressing such a complex disease as dengue derive from research findings applied to inform national strategies, better prepare health professionals and institutions, and achieve greater multi-sector and public participation. Such a necessary, integrated approach becomes possible when population health is a priority.