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Epidemics & Pandemics: A Global Responsibility

It’s that time of year again in the Northern Hemisphere: barbecue smoke laces the air, cold beverages run with sweat and the kids beg for a trip to the pool or beach. Hot fun in the summertime indeed—except for the mosquitoes. For us they’re a nuisance, but for others, they’re deadly.

Mosquito-borne illnesses such as dengue and malaria infect millions annually and are full-blown epidemics in many developing countries. Dengue alone—the world’s most prevalent arbovirus—inflicts 50 million a year, and dengue hemorrhagic fever (DHF) is the leading killer of children in many countries. Meanwhile, malaria kills over a million worldwide, mostly children under five. These are frightening numbers, especially since most of these are preventable deaths.

Not so with many (re)emerging infectious diseases, which are so powerful, public health systems could collapse in the face of them. Take the specter of an avian flu pandemic for example: according to the World Health Organization’s (WHO) influenza program, if this super flu takes hold, the death toll could top 7.4 million people (with up to 30% of the global population becoming ill). Cases have already appeared in South Korea, China, Vietnam and Indonesia. The strain known as ‘highly pathogenic avian influenza,’ (or H5N1), can have a mortality rate of almost 100%, infinitely more deadly than another recent epidemic, SARS (Severe Acute Respiratory Syndrome).

Direct economic effects of such a pandemic—tens of billions of dollars—would be crippling. Public health systems in the developing world, many of which are already overburdened by tuberculosis and HIV/AIDS epidemics, would be incapable of confronting such a scenario. Even in industrialized countries, inequalities mean limited flu vaccines would be available only to a minority. With such alarming rates and paths of transmission (some diseases jump directly from animals to humans), it’s no wonder epidemiologists talk in military terms regarding infectious and emerging diseases: a global war against epidemics for which everybody must be recruited.

However, the main battle remains political, as many governments lack the will to develop sustainable epidemiological surveillance and vaccination programs, essential to curtailing the spread of disease. Not only have the UN Millennium Development Goals (MDGs), designed to reverse the incidence of HIV/AIDS, malaria and other diseases by 2015, failed to hit five-year targets, but the Roll Back Malaria initiative is also in a tailspin. To reach the goal of halving worldwide malaria incidence by 2010, it recommends US$3.2 billion annually to fight malaria, but the Global Fund to Fight AIDS, Tuberculosis and Malaria, for instance, only allocates US$450 million for malaria control.[1] Among the least developed countries (LDC) receiving this funding is Gambia, (disbursements as of April 2005 were just over US$3 million).[2] where Cuban cooperation in research and the field has boosted capabilities for confronting the disease (Dusk to Dawn: Fighting Malaria in Gambia).

Yet, even with limited resources, disease can be thwarted. Through several epidemics including neuropathy, dengue and meningococcal disease, the Cuban model (Cuba’s Epidemic-Fighting Model) has proven adept at both containing and preventing disease even in a resource-scarce setting, prompting the focus of this month’s MEDICC Review.

The sudden emergence in Cuba of a national neuropathy epidemic during the economic free-fall of the early 1990s (International Workshop on Neuropathy Epidemic in Cuba: Report Summary) underscored the need for a better coordinated surveillance system that integrated knowledge and information-gathering both across disciplines and between all sectors of society (Training an Eye on Epidemics: Cuba’s National Health Surveillance System). Since its founding, that system has played a critical role in monitoring and controlling a variety of epidemics from dengue and malaria to HIV/AIDS (Approaches to the Management of HIV/AIDS in Cuba: Case Study, and Malaria Surveillance of International Travelers Living in Havana City, 2000–2001).

Since Cuba’s tropical climate provides the ideal environment for the Aedes aegypti vector, dengue is a perennial concern (Beefed Up Measures Aim to Prevent Dengue and Dengue IgM Detection UltramicroELISA Test with Ready-to-Use Reagents). Indeed, dengue and infectious disease research and clinical trials for flu, cholera and other vaccines (Cuban Cholera Vaccine Headed for Clinical Trials) are central to the work at Cuba’s Pedro Kourí Institute of Tropical Medicine. As such, we are pleased to present to MEDICC Review readers the director of that 68-year old institute in MR Interview: Gustavo Kourí, MD, PhD.

Our news coverage this month explores some new initiatives (UN Proposes Havana-Based Disaster Prevention Network) and Beefed-Up Measures Aim to Prevent Dengue. Meanwhile, heavy weather combines with political will to bring some relief from Cuba’s water woes, this month’s Top Story (Rain & New Initiatives Ease Drought). The combination of international travel and trade, overcrowded cities and overburdened public health systems led the WHO to observe that “the occurrence of the next pandemic is just a matter of time.” It’s about time then, that cooperative, global solutions are forged for this complex, global problem.

The Editors

References
SPOTLIGHT

Cuba’s Epidemic-Fighting Model

By Francisco Rojas Ochoa, MD, PhD

INTRODUCTION

Designing a model to fight an epidemic involves identifying the basic components of that fight and how to apply them. There are three essential principles: the scientific data that determines how to confront and eliminate epidemics; political (governmental) support, and mass participation in the anti-epidemic program.

Additionally, a methodology of working in sequential phases must be added to such an anti-epidemic model. First, a national surveillance system must be established that covers the entire population and provides suitable technical facilities. Second, when the surveillance system identifies the presence of a pathogen, the government, and all levels of the health system, must be alerted. Third, the effort must be directed at the highest levels of government and, without fail, involve all specialties and sectors. Although the public health system must maintain technical and logistical support in the event of an epidemic, epidemics are not its exclusive responsibility. Rather, resolute coordination is required across all sectors, coupled with an increase in resources so as to cut short the epidemic and achieve sustainable results. Fourth, the media must be fully involved so it can provide the public with practical instructions. Fifth, the lessons from each epidemic must be folded into the model.

Cuba has used these steps to fight the most important epidemics to affect the country in recent years: meningitis, dengue and neuropathy.

MENINGITIS

Until 1975, meningitis B had never been a public health problem in Cuba. The disease appeared with increasing frequency in 1976 with 72 cases, a number never before seen in Cuba, resulting in an incidence of 0.8 per 100,000.[1]

The surveillance system identified the problem and the public health system sent out an alert. That was the beginning of the fight against the epidemic that was confirmed over the next two years: in 1978, 175 cases were reported, and another 553 in 1979. The respective incidences were 1.8 and 5.6 per 100,000.

In 1981, this situation led to a very important decision: research began on finding an effective vaccine against meningitis B. Cuban scientists were convinced that the only way to contain the epidemic was through mass vaccination against the bacteria. Since no vaccine existed at that time, work to develop one was authorized. Many attempts by highly prestigious institutions outside of Cuba with plentiful resources had all failed. The scientists had complete support from the public health authorities and at the highest levels of government. The vaccine was finally developed following arduous experimental work and field tests. Thus, the first of the three fundamental principles in the model in the struggle against epidemics was applied.

Field tests confirmed the vaccine’s effectiveness. Its industrial patent was registered in 19 countries. Trials among boarding school students (52,966 received the vaccine and 53,285 in the control group received a placebo), produced no serious negative reactions. Difference in incidence of meningitis between those receiving the vaccine and those receiving the placebo was statistically significant. Eighty-six percent of those who received the vaccine showed seroconversion, exhibited by only 14% in the control group. Overall efficacy of the vaccine was 69.3%.[2]

Based on those results, the pilot plant was replaced with a larger unit that produces 110,000 doses weekly.

Later, based on the originality of the product and the practical results achieved, the Cuban Academy of Sciences
handed its Diploma for Best Scientific Work on the group of researchers who developed the vaccine. The World Intellectual Property Organization (WIPO) awarded its Gold Medal to the two principal authors of the patent and a diploma to the other eight authors.

Since 1991, the Va-mengoc-bc vaccine has been included in the Ministry of Public Health’s national immunization program, with two doses of the vaccine administered (at three and five months). According to reports from the Pan American Health Organization and the World Health Organization, no other developing or First World country has achieved success similar to Cuba’s amplified immunization program.

Following massive application in Cuba, the vaccine has been used in Brazil, Colombia, Argentina, Uruguay, the Dominican Republic, Syria, Guatemala, Chile, Nicaragua, and El Salvador. The vaccine’s subsequent successes include a joint collaboration with the prestigious St. Mary’s Hospital in London, and an agreement with SmithKline Beecham (now Glaxo SmithKline).[3]

Since 2000, the incidence of this illness in Cuba has been registered at 0.5 or fewer per 100,000.

HEMORRHAGIC DENGUE (HDF), 1981

Martínez’ Dengue y dengue hemorrágico (Dengue and dengue hemorrhagic fever) offers a brief description of the epidemic:

In 1981, the hemisphere’s first dengue hemorrhagic fever epidemic appeared in Cuba, caused by the DEN-2 strain. In May of that year, some cases were notified in the Boyeros Municipality of Havana City, involving fever and compatible with a dengue diagnosis. Retrospectively, similar cases were identified in the same place in previous months. The illness was confirmed simultaneously in Havana City, Cienfuegos and Camagüey provinces. Later it spread to the other provinces.

In all, 344,203 cases were diagnosed. The three provinces listed above, plus Holguín, had the highest morbidity. The epidemic peaked in early July, 1981. As a result of the health and hygiene measures, as well intensive vector control, the epidemic subsided, and finally was declared over on October 10 the same year.[4]

Of the total of those affected, 116,143 (33.7%) were hospitalized. Of these, 8.8% were considered serious or critical, including both adults and children. This percentage would be much higher if we considered only cases of those under 15. There were 158 deaths. Of these, 99 (60.3%) were under the age of 15, with an average age of 4. The death rate among those hospitalized was 0.13%. In terms of clinical aspects, 24,000 presented with hemorrhage; of which over 10,000 suffered dengue shock syndrome (DSS). In Cuba, the mortality rate caused by HDF/DSS was 0.46 per 1,000 cases.

The DEN-2 viral strain isolated in Cuba was genetically related to a Southeast Asian strain that had never before been seen in the region, and that stopped circulating after taking its toll in Cuba, thanks to efficient quarantine measures adopted by the public health authorities for all Cubans traveling to countries in the region. This strain has not been seen again in the Americas (Kourí, G., “La emergencia del dengue en las Américas.” International Dengue Course, Pedro Kourí Institute of Tropical Medicine, Havana, 1997).

This account reveals some unusual circumstances. The surveillance system did not discover the first cases as early as in other epidemics; and confirmed cases appeared simultaneously in three areas quite distant from one another. During the second month of the epidemic, morbidity was very high, registering 11,400 cases in a single day.

Among the 33.7% hospitalized, the death rate was very low. The low death rate can be attributed to early hospitalization, correct diagnosis and adequate rehydration therapy.[5]

Due to the high number of those hospitalized, large schools were converted into hospitals, as the outbreak occurred during school vacation. Medical and auxiliary personnel as well as equipment were dispatched to the schools, and a transportation network set up to take each patient to the most appropriate site, with the most seriously ill taken to facilities with intensive care units.

As soon as the epidemic was discovered, an intense campaign against the vector began. Human, material and financial resources were allocated to the campaign. Civil Defense authorities took charge of this aspect of the fight. In the end, the Aedes aegypti mosquito was eradicated in 13 of the nation’s 14 provinces. Approximately 10,000 public health personnel worked full-time in the campaign. An even greater number of volunteers worked in various capacities to eliminate the vector. Public participation was notable.[5]

The lessons from this epidemic were substantial and useful applications have emerged. Individual risk factors were identified among the gravely ill and those that died, including:
Prior antibodies to the dengue virus
Age (children were more seriously affected)
Sex (greater frequency among adult women)
Race (greater frequency among whites)
More serious cases associated with chronic illness (asthma, sickle cell anemia and diabetes mellitus)

Furthermore, some important observations have been made by Dr. Kourí and collaborators regarding the illness’s intra-epidemic virulence, seriousness, morbidity and mortality. Among these, it should be noted that more serious and fatal cases appeared as the epidemic advanced.[5]

The epidemic was controlled and halted in four months. Determining factors in these results were:

- Rapid diagnosis: 24 hours suspected cases, confirmation within four days.
- Early hospitalization and appropriate treatment.
- The fight against the vector, the decisive factor in eliminating the epidemic.
- The importance of centralized leadership at each governmental level.
- Political will in providing resources, coordination between sectors (anti-vector fumigation measures by the Ministry of Agriculture and the Armed Forces), urban sanitation (construction, municipal services), sites for hospitalization/isolation (Ministry of Education), education and orientation of the populace (via radio, TV and newspapers).

The short time it took to end the epidemic, combined with the aforementioned low mortality rate and elimination of the vector in nearly the entire country, confirms the model's capacity to resolve the problem, and the organizational strength offered by a centralized approach.

EPIDEMIC NEUROPATHY

The uniqueness of the neuropathy epidemic presented the national scientific community with its greatest challenge. Its cause, how it was spread, and its treatment were relatively unknown and therefore new to Cubans at the time.[6]

In early 1992, ophthalmologists in Pinar del Río Province reported an unusual number of people suffering from a progressive loss of visual acuity, with central or ceco-central scotoma; loss of color perception and scant change in pupil reflexes and ocular fundus. Some cases were accompanied by peripheral neuropathy.[7]

At that time there was talk of retrobulbar optic neuritis. In retrospect, the earliest cases appeared toward the end of 1991. The first patients were men from rural areas. Shortly thereafter, a number of cases began appearing of peripheral neuropathy, which includes all non-visual neurological symptoms of the condition, characterized by a feeling of pins and needles, a tickling sensation, numbness, cramping and a burning sensation in the extremities. Less frequently, these symptoms affect other parts of the body. They can be constant or intermittent and tend to increase at night, causing insomnia.

Other manifestations may present, thus exhibiting a polymorphic clinical picture.[8] Moreover, cases presenting mixed symptoms appeared with significant frequency. They were patients with the dual symptomatology of optic and peripheral neuropathy.

Distribution by gender showed a greater predominance among women (336.8 per 100,000 vs. 287.4 among men). Far fewer cases appeared among those younger than 15 or older than 65.

Ramírez et al. offer a synthesis of the epidemic:

Analysis of the epidemic identified five distinct phases. The initial phase showed a significant presence in the province of Pinar del Río, unequally distributed among its municipalities. The second phase, occurring between January 1 and March 27, 1993, was characterized by a moderate rise in the optical form in Havana City and Pinar del Río, amounting to 66.1% of the national total.

The third phase spanned March 28 through April 10, 1993, with a marked increase in cases and notable incidence of optic neuropathy throughout the other provinces. Of the total number of cases reported, 40.5% were in this two-week period, with an increase in reporting of peripheral neuropathy. Between April 11 and May 28, the fourth phase exhibited an irregular pattern during which the cases of optic neuropathy decreased, while peripheral neuropathy increased, thus reversing the earlier pattern. The fifth phase, from May 29, saw a drop in optic neuropathy and a marked reduction in the peripheral form. By November 1993, the epidemic was virtually halted, with only sporadic cases of both types of clinical presentations.[9]
To summarize, the model requires:

1. **Political will.**
   Perhaps the best example of this is the personal attention President Fidel Castro gave to all aspects of the epidemic; the intense mobilization of resources, coordinated among sectors by the Civil Defense; government funding of all efforts; and ample participation and cooperation from the international scientific community.

2. **Scientific evidence base.**
   The scope of scientific research supporting the struggle against the epidemic was carried out by 57 Cuban institutions and 14 from abroad, which analyzed the causal, physiopathological, diagnostic, epidemiological and therapeutic aspects of the phenomenon.

3. **Public participation.**
   Broad dissemination of information and educational material formed the basis for public awareness and cooperation. This provided valuable support for fieldwork carried out by clinicians and epidemiologists, and ensured that preventive orientations were followed, particularly use of multivitamin supplements provided free of change to the whole population. The absence of public alarm or panic, and people’s confidence in the measures being taken, are results linked to this aspect of the campaign.

4. **Epidemiological Surveillance.**
   This first programmatic component - early recognition of an outbreak or epidemic - was fulfilled by ophthalmologists who noted the rise in a very rare or unusual affliction in the area first affected (Pinar del Río). Although there was no orientation to report such cases to the existing data retrieval systems, they did notify the cases to local authorities. Official notification was not put into effect until the 13th week of 1993—that is, very late.

5. **Alerting the public health system and government.**
   The most qualified judgment comes from President Fidel Castro who said: “Unfortunately, at first, when the epidemiology department of the public health system learned of the disease, they worked on their own, didn’t tell anyone, didn’t warn anyone else, until the moment we realized the disease existed.

   "And some time passed, because nearly all of 1992 went by with isolated cases and there was no official information concerning the problem, not until the first trimester of 1993. Otherwise, we would have done what we did much sooner—coordinating all the research centers and organizing an authoritative group to confront and investigate the problem.”[10] The programmatic element of alerting the health system was fulfilled, but action wasn’t taken in accordance with the magnitude of the phenomenon and the appropriate warning wasn’t given to government—which would have prompted the government to “organize an authoritative group”, as the President said, which was the next step in the program.

6. **Unified, high-level management team.**
   Applying this aforementioned measure marked the beginning of controlling the epidemic.

7. **Information to the public.**
   As explained in point 3, above. Intensive use of the media was used throughout.

**CONCLUSIONS**

These epidemics taught many lessons historically, clinically, and in terms of epidemiology, toxicology, and therapeutics. The meningitis outbreak taught us how to develop a vaccine for our specific problem, while hemorrhagic dengue allowed us to increase and strengthen our intensive care units. The neuropathy epidemic led us to strengthen our epidemiological surveillance system, the driving force behind creation and development of the municipal, provincial and national network called the Health Tendencies Analysis Unit (UATS).

**REFERENCES**

2. Ibid., p. 387.

**THE AUTHOR**

Training an Eye on Epidemics: Cuba’s National Health Surveillance System

By Conner Gorry

According to estimates by the Centers for Disease Control and Prevention, the next influenza pandemic could cause 2 to 7.4 million deaths worldwide, mostly in developing countries. Findings in *The Lancet*, meanwhile, peg global deaths in 2004 due to malaria, HIV/AIDS and tuberculosis at around 6 million.[1] Given these dire realities and prognoses, it’s no wonder Dr. Daniel Rodríguez Milord classifies surveillance of health threats as “part of our national security.”[2]

As director of Cuba’s Health Tendencies Analysis Unit, (UATS according to it’s acronym in Spanish), Dr. Rodríguez Milord is responsible for overseeing the nationwide system of surveillance coordination, analysis and strategy designed to protect public health. The system directed by Rodríguez Milord forms a part of the Ministry of Public Health. He sat down with MEDICC Review recently to discuss his work in relation to epidemics, pandemics and the history of UATS.

UATS was founded in the middle of the neuropathy epidemic that blindsided Cuba between 1992 and 1993 (see *International Workshop on Neuropathy Epidemic in Cuba: Report Summary and Cuba’s Epidemic-Fighting Model*, this issue). As the crisis worsened – more than 50,000 Cubans were eventually stricken with the disease – it became evident that the country needed a better integrated, multi-sector surveillance system that could predict, analyze and respond to health threats in a coordinated, sustainable way. Dr. Rodríguez Milord was part of the specialist team in 1993 that conceptualized how that system could work.

“What was so interesting about this was that we had to work inside of the epidemic, while it was happening, to track its progress and fight against it to protect the population’s health. But at the same time, we had to analyze how to design and implement a methodology and surveillance system,” Rodríguez Milord told MEDICC Review.

In those early planning and response stages, the designers of UATS agreed that an efficient, effective surveillance system required:

- a scientific foundation;
- systematic collection and analysis of health threats and risks;
- annual projections to anticipate possible health risks;
- systematic follow-up of threats and risks to be used in the planning, implementation and evaluation of health programs;
- efficient and timely information sharing among the actors and institutions responsible for safeguarding public health; and
- a methodology for promoting disease prevention and containing health risks.

Based on the experts’ collective experience, consensus was also reached on one of the guiding principles of the Cuban surveillance model, namely that the system be integrated both horizontally among vested health institutions and mass organizations, and vertically between those institutions and the people they serve. All of this was to be coordinated on a national, provincial and municipal level by a network of centers located throughout the country. UNICEF and PAHO were important initial supporters of this work.

With the guiding principles in place, Cuba looked internationally for knowledge-sharing opportunities that could provide insight into how to structure such a system. “From the inception of UATS we worked with a diverse group of international agencies and specialists from Paris, Liverpool, Panama, Mexico and elsewhere,” explained Dr. Rodríguez Milord. “We also worked with the CDC in Atlanta, looking at how they designed their surveillance system and analyzing how to design and improve ours.”

Not surprisingly, this international cooperation continues today in scientific exchanges like the one between Harvard’s School of Public Health and Cuba’s Pedro Kourí Institute of Tropical Medicine, which has US and Cuban researchers collaborating on epidemiology research of dengue, acute respiratory infections, hepatitis and others. In this age of facile plane travel, increased international trade, porous borders and globalization of everything - including emerging diseases like West Nile, hanta and Ebola viruses to name a few - international cooperation and vigilance of emerging threats are key to any public health system. Indeed, a cornerstone of the epidemiological surveillance work coordinated by UATS is surveillance beyond Cuba’s borders, emphasized Dr. Rodríguez Milord.

“At every turn, our surveillance system has to be a national model with more international relevance; a more global system that works within our context and needs, but responds to global developments as well. In this sense, surveillance becomes part of our national defense system,” he said.

The key to that surveillance is a three-pronged model divided into tactical, strategic and evaluation (Figure 1) modules. The purpose of the Action Alert System is to provide continuous, timely information on acute health events both nationally and internationally in order to identify, control and...
form solutions to health risks. Using a methodology of active and intensive surveillance, this system allows for rapid response when faced with unusual or unexpected threats or those requiring priority or ongoing monitoring.

The strategic aspect of the system is critical for designing effective, targeted health interventions. Along with projections, the key to this is the stratification of epidemiological data, which renders a clearer picture of how health risks behave within a population. Collecting and analyzing that data requires an extraordinary level of coordination between national, provincial and municipal specialists, which isn’t always easy given the country’s limited resources.

Cuban specialists in each province generate annual predictions based on historical antecedents, the expected behavior of a health risk and the current situation on the ground. In turn, these findings are prioritized and synthesized into a national prognosis. “Of course, certain factors can and will change,” says Rodríguez Milord, “but the statistical information, analyzed and interpreted by experts, and the history of a disease, are key to the scientific basis of any prognosis, which is a process, by the way, not a document.”

Measuring the impact of that process through evaluation and affecting changes to improve the process and outcomes is the final link in the surveillance cycle. This is crucial for constructing a sustainable public health surveillance system, emphasizes Rodríguez Milord, especially as Cuba institutes system-wide changes to health care delivery including moving services closer to patients, retrofitting and upgrading hospitals and clinics, and consolidating prescription medicine programs.

From the first alert to evaluation, the entire system relies not only on public health institutions, but also on every institution and its specialists that may lend expertise to the health risk in question - geographers, meteorologists, veterinarians, ecologists, etc. Moreover, the active participation of the population is integral to the success of the Cuban system. Says Rodríguez Milord, “Our model is based on integration, cooperation and participation between all disciplines and institutions in the function of public health…and there is no public health without political will on the part of the government.”

But it doesn’t end there: each epidemic is a learning experience that presents an opportunity to improve the system, said Rodríguez Milord. During the hemorrhagic dengue epidemic of 1981 for instance, when 116,143 people were hospitalized countrywide, it became evident that Cuba needed more intensive care units (especially for infants), to provide the expected standard of care during an epidemic. Consequently, a plan to increase services and beds available in intensive care units and train the necessary staff, in pediatric hospitals particularly, was immediately implemented.

In October, specialists from the world over will come to Havana to broaden that learning base, observing the Cuban model firsthand and imparting knowledge from their own experiences at the ‘Health Surveillance 2005’ conference, convened by the Pedro Kourí Institute of Tropical Medicine and UATS.

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Notes & References:
2. Indeed, global health security is becoming of critical importance, with individual states increasingly being held responsible for contributing to its furtherance. The WHO’s revised International Health Regulations released on May 23, 2005 mandate nations to collaborate on epidemic alert and response by “develop[ing], strengthen[ing], and maintain[ing]...the capacity to detect, access, notify and report events...as specified in Annex 1 ‘Core Capacity Requirements for Surveillance & Response.’” World Health Organization, May 23, 2005; http://www.who.int/csr/ihr/en/.
**MR INTERVIEW**

**Gustavo Kourí, MD, PhD**  
Director, Pedro Kourí Institute of Tropical Medicine (IPK)

By Michele Frank, MD

Professor Gustavo Kourí recently welcomed MEDICC Review into his office at the Pedro Kourí Institute of Tropical Medicine (IPK; www.ipk.sld.cu). In addition to its own work as a national and international center for the study and treatment of Tropical Medicine and Infectious Disease, the Institute is also home to four important PAHO/WHO Collaborating Centers: the Center for the Study of Viral Diseases; the Center for Training and Research on Medical Malacology and Biological Vector Control and Intermediate Hosts; the Center for Tuberculosis and Micro-bacteria; and the new Center for the Study of Dengue and Its Control.

Continuing the work of his father, the late Dr. Pedro Kourí, Gustavo Kourí has transformed the IPK complex into one of the field’s top institutes, research centers and treatment facilities. A world-renowned hub of scientific activity, IPK has a record of continuous outstanding achievements and plays a key role in the training of the Cuba’s future scientific and medical professionals.

**MEDICC Review:** Perhaps we could start with some history: could you speak about your background and what this institution does?

**Gustavo Kourí:** Well, I have been around for quite a long time now! I was part of the first group of doctors and scientists, after 1959, to engage in serious scientific research. We set up the first scientific research center and worked on multiple projects at the same time.

**MR:** So this institution has been responsible for confronting important challenges. How do you evaluate the progress in terms of the epidemiological situation in Cuba?

**GK:** It is my opinion – speaking about our objectives – that we have met our goals. In the first place, in today’s Cuba, epidemics are very limited. For example, we sometimes still have influenza (flu) epidemics. These are situations that need to be confronted quickly, through good epidemiological surveillance and with vaccines. I’d say that this is an important goal at the moment – dealing with flu, with acute respiratory infections (ARIs). They are prevalent here and all over the world.

**MR:** Do you mean ARI epidemics? Or do you mean outbreaks? Are there flu outbreaks that are considered important from an epidemiological point of view?

**GK:** That depends on what you consider an epidemic. The concept of an epidemic is when there’s a notable rise in cases as compared to what is “normally” the situation. But if you’re talking about a situation where the norm is that there are no cases and then one case appears, that – technically – is an epidemic. One case of a disease that has been eradicated or that doesn’t exist in the country would be considered an epidemic. We don’t call it that: we usually refer to it as an epidemic outbreak or a localized outbreak, but really it is an epidemic because it’s a “new” disease registered in the country. This is the concept, and it reflects our approach – the Cuban approach. It’s one of the things that distinguishes Cuba from other countries. Worldwide, more than 13 million people die from infectious diseases every year, and one death in three is due to infectious or communicable diseases. The main causes of these deaths are influenza and pneumonia, (ARIs) first, then HIV/AIDS, malaria, tuberculosis, and measles.

**MR:** So ARIs are the most important in terms of mortality and morbidity?

**GK:** Yes, ARIs are killing many people in the world every day. The next most important killer is HIV/AIDS. And the thing is, almost all of these deaths occur in the non-industrialized world, in the poorer countries... The difficulty with ARIs is the issue of vaccines – or rather vaccine availability, access to the vaccine, to flu shots. If we could count on an efficient vaccine, then the numbers of cases would go down.

With HIV/AIDS it’s a different story – it’s much more complex – because there is no vaccine and because it’s a disease that’s transmitted sexually or by injections; it’s a blood-borne infection generally, and an autoimmune disease, so it’s a very different and more complicated issue in terms of finding a vaccine. The situation internationally is really critical: there are entire countries - in Africa, for example - which are condemned. They are likely to just disappear, countries with infection rates of 40% of their population or more.

When you think about all of this, when you analyze this situation and see it in terms of how health inequality not only affects the way people live, but also dictates how and at what age they die, it becomes evident that economics constitute a critical component of the problem. It all boils down to the issue of willingness to do anything about this crisis. We’re talking about preventable diseases. And another thing, infectious
MR: In Cuba as well?

GK: In Cuba we have some influenza or flu, we have some pneumonia, but there is a political will to seriously confront this. Still, we have a problem and we are working towards more and more extensive vaccination campaigns. If I’m not mistaken, this year we’re going to begin to vaccinate everyone over 60 years old for flu. As soon as we can - when we can get more vaccines, when we can get financing – we’ll begin to lower this age and we will be offering this to more and more people. Influenza and pneumonia are the fourth cause of death in Cuba. Our health indicators are similar to first world countries, and our top 10 causes of death are basically the same. So number one on the list is heart disease and/or cancer – they go back and forth in terms of which is number one - followed by cerebrovascular diseases, influenza and pneumonia, then accidents. So we have a very low mortality rate from infectious diseases, with the exception of influenza and pneumonia. If you leave this out, 0.9% of all deaths are due to infectious diseases – less than 1% for all infectious diseases combined. If you include influenza and pneumonia, then the mortality rate is about 8%. This is not that high, but still it’s significant. It concerns us.

MR: How does Cuba deal with this?

GK: We have an epidemiological surveillance system, a national network, monitoring for early detection – especially an Eye on Epidemics: Cuba’s National Health Surveillance System, this issue). We are also keeping a close watch on dengue, and working very hard to control the situation to prevent an epidemic. In terms of infections, the status is very favorable. In Cuba children are immunized for 13 different illnesses. I would say that besides being favorable, this is unique, exclusive to Cuba.

MR: Could you elaborate?

GK: Because vaccinations are universal and free of charge. The other thing is that anyone who needs further protection gets it. The leptospirosis vaccine is an example of this – some people need it, because of their work or where they live. But all children get the basic 13, along with the appropriate booster shots and all that. This is unique, unusual, exclusive, as I said before. I’ve been to 45 countries and I can tell you that no other country has this degree of protection; there is no other health care system like this one.

MR: And part of this, clearly, has to do with human resources. Could you speak to this point and perhaps share your thoughts on training?

GK: Training and/or the formation of human resources is the determining factor for the development of a good health care system. I really do believe that human beings are absolutely fundamental and I think we are clear on this point here in Cuba: we have prioritized human resource development and professional training. In fact, we are even helping other countries in this respect – many other countries in a variety of ways.

At IPK, the formation of human resources has always been a top priority. My entire career has been inextricably linked to teaching and mentoring - everything I do is science and human resources development. We have fully trained close to 3,000 students and young professionals from 72 countries and five continents at this institute.

Altogether over the last 25 years, 28,000 people have received some form of training or continuing education here. We have a doctoral program, masters degree programs, and a wide variety of shorter courses of study; we even have classes and educational programs for children.

Additionally, this August, we are offering our 9th International Course on Dengue, considered the best dengue course in the world, [see www.ipk.sld.cu for more information, eds]. Moreover, the IPK is now officially a WHO Collaborating Center for dengue.

MR: Let’s talk about dengue and some of the history of dengue in Cuba.

GK: We have information about dengue in Cuba going back to the 19th century, on the epidemic of 1828, for example. In 1977, there was a serious epidemic of dengue1, a real pandemic situation in the entire hemisphere and it was demonstrated that almost half of the Cuban population had been infected. Then there was the dengue2 epidemic of 1981. At that time, dengue2 was introduced into Cuba at several different locations and a very serious hemorrhagic dengue epidemic ensued.

MR: Is it known for a fact that this was intentionally introduced into the country?

GK: There is no solid scientific proof. There is scientific data and there has been research done. In the first place, dengue2 was not circulating in the Americas at that time. And secondly, it appeared suddenly and simultaneously in three separate locations: in the Havana City, in Cienfuegos and in Florida, Camagüey.

When a disease is transmitted by vectors there is generally an initial illness focus. It’s inconceivable that in a matter of days, two other foci appear at distances of some 300 kilometers apart from one another, and practically simultaneously. More recently, we have the results of genotyping studies of the genome of the dengue2 strain. That genome had not circulated since 1947. It was generally considered to be a laboratory strain. I wouldn’t be surprised if one day documents turn up that show this to have been a deliberate biological aggression. There were 10,312 cases of hemorrhagic dengue fever (HDF). The worst epidemic of it’s kind to occur in the Americas...the 1981 epidemic breaks the epidemiological context. Before 1981 there were only 60 reported cases of HDF in the entire region. This is PAHO data. The epidemic of HDF in the Americas doesn’t really start until 1988-89. So this spike in 1981 is totally out of context, this is not natural.

MR: This seems to indicate that there is currently a serious situation in terms of dengue in the Americas.

GK: Yes, now it’s endemic to the region. Almost every country is reporting cases of hemorrhagic dengue fever, and this situation is sure to continue.

MR: Are there recent publications by Cuban authors?

GK: We have a lot of research written on dengue in Cuba. We did a review and update on the situation for The Lancet in 2000. The editors just recently sent us a letter of congratulations because this article is part of the 1% of most often cited publications on dengue in the world. We are currently preparing a CD, which compiles the hundreds of publications by Cubans for the upcoming dengue course.
 MR: And what about tuberculosis (TB)?

GK: Our projection is to eliminate TB, which according to the WHO means fewer than 5 cases per 100,000. Our indicators are around 6.2%, so we are doing quite well. We need financing to do the necessary research and achieve the complete elimination of TB in Cuba; we would be the first country of the “South” and one of the few countries in the world to achieve this. We have a lot of advantageous conditions here to make this happen. For example, TB here generally responds well to antibiotics, unlike many other countries which have a high degree of multi-drug resistance. Also, we have the infrastructure to easily apply the Direct Observation Treatment (DOTS) method.

MR: Let’s switch to HIV/AIDS. What’s new on this front?

GK: Our way of handling HIV/AIDS was considered very controversial, at least at first. Lately we hear that what we did was the smart thing to have done at the time. The Jorge Pérez article just published by the WHO is very important (Approaches to the Management of HIV/AIDS in Cuba: Case Study, this issue). It’s a significant recognition and acknowledgement of the Cuban health care system and our approach to HIV/AIDS. Dr. Peter Piot, the UNAIDS Executive Director, has repeatedly praised the Cuban program, especially regarding prevention. In Cuba, mortality has diminished and the quality of life for people living with HIV/AIDS keeps increasing, with treatment of course. I think we’re on the right track; we’re doing very well in that respect. The total number of people infected since 1985, when the first case was detected, has been approximately 6,000.

MR: That’s impressive!

GK: Yes, it’s incredible. There have been 1,200 deaths. IPK is the national reference center for HIV/AIDS. People living with HIV can come whenever they wish. They can get regular attention here, whether they are sick or not.

MR: I understand that the IPK is one of the institutions of the “scientific park,” which is involved in vaccine research and development – is that right?

GK: All the Cuban vaccines have gone through trials here at IPK; this Institute evaluates them all. The hepatitis B vaccine, meningitis B, leptospirosis, the synthetic haemophilus influenzae vaccine…all of them.

The vaccine for cholera has been a big challenge because cholera was eliminated in Cuba back in the 19th century and cholera is not endemic to Cuba. So to do the necessary evaluations, we had to induce cholera in people experimentally; we literally had to find volunteers and give them cholera because there is no animal model. Of course we first had to select the vaccine – this entails a long experimental research process: we had to find a Vibrio cholerae that was immunogenic, that was protective, but that was not toxigenic. This was done by scientists at the National Center for Scientific Research (CENIC) and also the Finlay Institute. I should be clear: we didn’t do this part here at IPK. We did the clinical trials. So once the immunogenic, non-toxigenic Vibrio cholerae was selected, the vaccine went to clinical trials.

Then we administered Vibrio cholerae to both the people who had been vaccinated and the people who had not. The results were excellent (see Abstracts: Construction and Characterization of a Non-proliferative El Tor Cholera Vaccine Candidate Derived from Strain 638, this issue). Cholera is an example of a disease which shouldn’t kill anyone – it responds very well to antibiotics. People die of dehydration, for lack of medical attention. It’s a disease that is directly associated with poverty. And it’s not a tropical disease either. So we did the trials and were able to demonstrate that this vaccine candidate did indeed protect against cholera in the vaccinated volunteers while all the others got sick. Now this vaccine is being produced in Cuba by CENIC and the Finlay Institute and they are ready to move on to the next phase clinical trials, which have to be carried out in a country where cholera is endemic, in Africa for example (see Cuban Cholera Vaccine Headed for Clinical Trials, this issue).

This is typical here in Cuba – we work collectively, all the institutions in the scientific park work together collaboratively. This institute’s role is research-based and clinical, we don’t produce vaccines, but we evaluate them and we have input during the production process.

MR: Why devote so much time, energy and resources to scientific research to develop a cholera vaccine when there’s no cholera in Cuba?

GK: First of all, we’re applying science. We are scientists and this is our work. It has been demonstrated for centuries now that an effective vaccine produces effective protection from infectious disease. So we produce vaccines and we have a national immunization program to protect our population. According to the World Health Organization, we have one of the best programs in the world. In the case of cholera, this will be for other Third World countries – and I’m using the term “Third World” intentionally, rather than developing world.

MR: Why?

GK: Because it’s about solidarity. Cholera is a typical case, but let’s take another example: there was an outbreak of meningitis in Uruguay back when we did not have political or diplomatic relations with that country. But we sent them our vaccine free.

Solidarity is a very important component of our system. Cuba has people working in more than 60 countries, for free…those countries, those people, are not charged anything. For us it’s a matter of principle. I don’t think there’s any other country in the world that does this. 

The ‘Little Car for Life’ is a mobile HIV/AIDS information and education center emphasizing prevention.
INTERNATIONAL COOPERATION REPORT

Dusk to Dawn:
Fighting Malaria in Gambia

By Gail A. Reed

World malaria figures are staggering: 350-500 million cases per year, one million deaths, over 80% of them in sub-Saharan Africa. That’s 3,000 deaths a day.[1] In Gambia, the homeland of Alex Haley’s forbearer Kunta Kinte, 100% of the country’s 1.4 million people are at risk, and nearly 40% of hospital deaths among children and pregnant women are due to malaria.[2] Malaria is the country’s number one health problem. The culprits are the most deadly of malaria parasites, *Plasmodium falciparum*, and its most frequent carrier, the *Anopheles gambiae* mosquito.

Gambia is not only the smallest independent nation in Africa, but also one of the poorest, ranking 155 out of 177 countries in the 2004 human development index. Thus, it faces the two main obstacles blocking effective malaria control identified in the WHO’s *World Malaria Report 2005*: shortage of global funding and in-country capacity. The WHO estimates that it will take US$3.2 billion annually to finance effective malaria control, but so far, only US$600 million is available. This shortfall further hobbles in-country health systems and personnel already pushed to the limit by multiple disease burdens and the ever-increasing brain drain.

Though the uphill climb is a steep one, Gambia shows progress can be made if government takes strong and sustained action. Under the National Malaria Control Program, headed by Malang Fofana, the health department has also made the best of an array of partners, including the WHO, UNICEF, the Global Fund to Fight AIDS, TB and Malaria, the Medical Research Council (MRC), local and international NGOs and foundations, and various governments - Cuba prominent among them.

As a result, malaria cases have registered a significant drop in the last several years: from close to 600,000 in 2002 down to some 200,000 in 2004. People are being diagnosed sooner and better; vulnerable groups are receiving more attention; deaths are fewer; and insecticide-treated bed nets (ITNs) are being used by 63% of the population - this last statistic among the best in Africa.[4] On the basis of this record and a well-crafted plan, Gambia was awarded a US$13.8 million three-year grant from the Global Fund in 2004.

Such progress also merited Gambia a special citation from the WHO. Resident Representative Dr. Nestor Shivute notes: “Gambia, and especially the government, deserves this citation. It has shown a commitment to the control of malaria, and in fact …Gambia has one of the strongest malaria control programs in the region.”[5] He notes that the program’s success relies on four main strategies: vector control, access to early diagnosis and treatment, prevention through public education and involvement, and research. Cuban physicians and experts have been involved in all four, he adds.

Gambia-Cuba Partnership

Significant malaria has not been reported in Cuba since 1967, and the WHO officially recognized malaria eradicated on the island in...
1973. But the Cubans took with them to Gambia a more recent experience in their successful campaigns against dengue, another mosquito-borne disease. In 2000, at the request of Gambia’s President Dr. Yahya A. J. J. Jammeh, a team of experts from Havana’s Pedro Kourí Institute of Tropical Medicine (MR Interview: Gustavo Kouri, this issue) arrived in the capital of Banjul to join the national malaria effort. The group included an entomologist, parasitologist, epidemiologist, clinician, and biolarvicide engineer. They were asked to review the national strategies, make recommendations, and above all, pitch in to help make them work.

The team was headed by Dr. Lázara Rojas, who said she was immediately struck by the many factors that seemed to conspire against effective malaria control in Gambia: “First, was immediately struck by the many factors that seemed to conspire against effective malaria control in Gambia: “First, was immediately struck by the many factors that seemed to conspire against effective malaria control in Gambia: “First, was immediately struck by the many factors that seemed to conspire against effective malaria control in Gambia: “First, was immediately struck by the many factors that seemed to conspire against effective malaria control in Gambia: “First, nearly 90% of the people are Muslim, and they kneel to pray devoutly several times a day, but especially at dawn and dusk, when the mosquitoes are at their peak.”

Since they first arrived, the Cuban team was charged with implementing and reinforcing key aspects of the National Malaria Control Program, specifically to:

1) Improve data collection and analysis by epidemiological mapping of malaria throughout the country, stratifying cases and identifying the most vulnerable populations.

2) Map breeding sites of mosquitoes and other harmful vectors most prevalent in Gambia, including *Culex quinquefasciatus*, which carries lymphatic filariasis.

3) Determine insecticide susceptibility of *Anopheles gambiae* to permethrin and deltamethrin insecticides used in the country, especially in ITNs.

4) Apply biolarvicides in a pilot study and then at breeding sites throughout entire divisions (provinces). This was a new experience for Gambia - where the country’s small size, its river and rice fields make an ideal combination for interrupting the *Anopheles*’ reproduction cycle. A Cuban biolarvicide was first tested in 2001, then with WHO funds, gradually applied to various divisions through 2004, with excellent results. The biolarvicide, explains entomologist Mayra Castex, is particularly safe, since it does not rely on chemicals, but rather on bacteria found in nature whose only aim is mosquito larvae.

5) Introduce quality control measures for malaria diagnosis - both clinical and laboratory. In countries with endemic malaria such as Gambia, there are not often the resources (including electricity) to make a quick and certain laboratory diagnosis. An option proposed by the Cuban team and included in the Global Fund grant was to set up a National Reference Laboratory to confirm clinical diagnosis in a patient sample and train physicians and other health professionals to improve their examination skills. WHO funding allowed the initial laboratory to be established at the Royal Victoria Teaching Hospital in Banjul.

6) Provide further training to both Gambian and Cuban personnel - including a semester of medical entomology by Cuban professors at the Medical School (for nursing and public health students as well), plus more specific training for Cuban laboratory technicians in Farafenni and Bansang cities; short courses in medical entomology and epidemiology for health department staff at national and division levels; and specific technical training for Gambians working in biolarvicide application.

7) Participate in studies on drug resistance - The Medical Research Council, notes Dr. Rojas, has carried out an important in-depth study of chloroquine resistance in Farafenni town among children under five. The goal now, she says, is to carry out five additional studies in high-morbidity regions to more broadly determine if the parasite in Gambia is resistant to traditional chloroquine treatment, as it is in most of Africa. The results will have serious implications for the Malaria Control Program, as the latest artemisinin-based combination therapies (ACTs) are more effective, but cost ten to 20 times as much as chloroquine.

8) Work with other partners to develop the Global Fund appeal based on specific projects.
9) **Implement all aspects of the National Malaria Control Program** through the over 200 Cuban physicians deployed at major and minor health centers and clinics throughout Gambia’s rural and urban areas. This is perhaps the single most significant “on-the-ground” Cuban contribution.

The doctors, who live in the villages they serve, are playing a key role with Gambian nurses and public health officials, working with local populations in public education to recognize malaria symptoms and know what to do, as well as to remove breeding habitats (the government’s “Operation Clean the Nation”). They also locally promote and participate in bednet dipping campaigns spearheaded by UNICEF and the Department of Health. These campaigns focus particular attention on children under five and pregnant women, to whom nets are provided free. The Cuban physician-Gambian nurse teams are also implementing Intermittent Preventive Treatment (IPT), recommended by the WHO, for pregnant women, which projects reaching 70% of expectant mothers over the next three years under the Global Fund grant.

Finally, the Cuban doctors themselves are akin to a human shield against malaria, since for the first time the health system can guarantee diagnosis and treatment within the first - and critical - 24 hours after onset. Heretofore, 90% of malaria deaths occurred at home or on the long walk to the hospital.

“We find doctors at a community level now, qualified doctors, who can prescribe medicine for the communities. Previously it wasn’t like that,” says Malang Fofana, Director of the National Malaria Control Program. “Before, doctors were concentrated in the growth centers, like the greater Banjul area. But now, all the country’s major districts - major villages, strategic locations - have clinics manned by Cuban doctors and Gambian nurses, working together to provide the services for needy people.”

The highest levels of the Gambian government concur. “We have permanent doctors,” says Mrs. Isatou Njie-Saidy, Gambia’s Vice President. “Communities now have access to a doctor within a reasonable distance.” She also stresses the advantages of this kind of South-South cooperation: “We have found that there’s no cultural shock for the Cuban doctors. They adjust very well in our communities. Immediately they arrive, they are at home...They relate to the people. They see themselves as equals with the people. And people really appreciate that in this country - including the government. And so, they’ve done wonders, a lot of indicators have improved since the existence of the Cuban doctors in this country. It’s commendable.”

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CUBAN MEDICAL LITERATURE

Approaches to the Management Of HIV/AIDS in Cuba: Case Study

Jorge Pérez(1); Daniel Pérez; Ida González; Manuel Díaz Jidy; Mylai Orta; Carlos Aragónés; José Joanes; Manuel Santín; María Isela Lantero; Rigoberto Torres; Ailen González; Alejandro Álvarez

Cuba is one of the few developing countries to provide comprehensive health care for people living with HIV/AIDS. Key to its success has been the political will to act and not wait for external assistance. Their HIV/AIDS programme is based on a comprehensive health care system that has facilitated good control over blood transfusion and blood products as well as prevention of mother-to-child transmission of HIV. Access to antiretroviral drugs has been possible largely through Cuban resources.

The island of Cuba has a population of 11 million inhabitants on approximately 100,000 square kilometres. The infant mortality rate is 6.5 per 1000 (2003) live births, and citizens enjoy a life expectancy of about 75 years. A well-developed epidemiological and surveillance system ensures that most infectious diseases are well under control; malaria, lymphatic filariasis, cholera and yellow fever have long been eradicated.

Cuba has the lowest HIV prevalence at 0.05% in the Americas and one of the lowest in the world. It has been reported (Castro, 2003; Pérez-Avila, Pérez-Correa, 2003) that of the 5,018 infections that have been recorded from 1986 to September 2003, 79% are among men of whom the vast majority have been infected through sex with other men. With 21% of HIV infections occurring among women, the ratio between male and female HIV-positive people is about 4:1 in Cuba.

Despite early and intensive measures to control the epidemic, there has been an increase in the number of people diagnosed with HIV since 1996 (Figure 1). This can be attributed partly to the economic problems experienced during the period 1992-1995, when Cuba lost most of its strategic economic partners from the former socialist countries. In addition, it has been reported (Hsieh et al., 2001) that the growing number of people tested, and diagnosis in people who have multiple sexual partners, mainly men who have sex with men, have also contributed to this increase. For example, due to the recommendation to test all sexual contacts of newly detected cases, Cuba now performs approximately 1.5 to 1.6 million HIV tests each year. As a result of these tests, significantly more homosexuals are being identified as HIV-AIDS positive.

In 1983, in response to the first news on AIDS, the Cuban Government established the National AIDS Commission and introduced an epidemiological surveillance system in each hospital to detect clinical manifestations of AIDS.

The main goals of the National AIDS Commission were to:

- develop a national HIV-prevention programme for the general population and for specific risk groups;
- develop a national network of sanatoriums to admit all persons detected as HIV-positive;
- conduct epidemiological surveillance and control;
- lead scientific research and biotechnology production in this area; and
- make sustainable efforts for the prevention of mother-to-child transmission of HIV, the prevention of HIV-

Figure 1. Number of HIV-infected people, by year of detection, sex and sexual behaviour, 1986-2002

* Note: no homo-bisexual transmission among females detected
related opportunistic infections; and the prevention of AIDS itself.

At the end of 1985, the first AIDS case was clinically diagnosed in a heterosexual male returning from duty travel abroad. From that time on, the Ministry of Public Health applied classic epidemiological procedures as for any other sexually transmitted infection.

Starting in 1986, sexual contacts of people diagnosed with HIV were enrolled in a Partners Notification Programme and tested for the virus every six months for a period of one year after the last sexual contact with the HIV-infected person (Hsieh et al., 2001). While the tests were performed on a voluntary basis, the results were revealed to the respective authorities.

Screening for HIV was progressively expanded from 1987 to include specific groups such as blood donors, pregnant women, and adult patients diagnosed with sexually transmitted infections. Also included in screening were prisoners, army recruits and those who had travelled to areas with high endemic infectious tropical diseases since 1975 or who had frequent contacts with foreigners. In addition, people who came forward and requested testing because of their own personal interest or following their physicians’ advice were tested in anonymous test centres, with the process of testing remaining confidential.

The AIDS Sanatoria

In April 1986, the Cuban Government announced the death from AIDS of the first Cuban citizen as well as the presence of HIV infection among people in the country. At the same time, a policy ensuring the care of the infected in AIDS sanatoria was introduced. The aim of this policy was to:

- provide the best medical care to the infected people;
- understand the natural history of the Cuban epidemic; and
- contain the spread of the epidemic.

Between 1986 and 1993, HIV-positive persons were cared for exclusively at the 14 sanatoria at various locations in the country (Schepher-Hughes, 1993; Pérez Stable, 1991; Santana, Fass, Wald, 1991; Santana, 1992). These sanatoria are like suburban communities on several acres of land with modern one- and two-storey apartment duplexes that are surrounded by lush vegetation and a small garden. Two persons, who could be friends or couples, lived in each apartment. Medical care for the residents was provided by family physicians. The patients were assessed periodically, and laboratory analysis performed either at the sanatoria, hospitals or the Pedro Kourí Institute of Tropical Medicine (IPK). During this period, a group of specialists consisting of public health officials, epidemiologists, psychologists and physicians attending the sanatoria patients, together with AIDS activists, continuously studied different strategies to improve care for people living with HIV/AIDS (PLWA).

The existence of AIDS sanatoria generated a lively and controversial debate on whether the rights of PLWA were violated by Cuba’s Ministry of Public Health when it advanced its controversial AIDS program…”

At the end of 1993, following recommendations from the group of specialists, the ambulatory care system was opened for all those who wanted to leave the sanatorium. Currently, an in-patient and ambulatory system is offered to people diagnosed with HIV, but the number of people attending sanatoria has decreased significantly since 1994. As of September 2003, 60% of HIV-positive people were followed in the ambulatory care system, while only 40% remained in the sanatoria.

### Box 1: “How to live with HIV”

An eight-week information course tells HIV-infected people about:

- HIV/AIDS in general
- progression of the disease
- safe-sex practices
- their own rights

Those who accept referral to one of the regional sanatoria for the duration of three to six months receive in addition to the necessary medical treatment that has been determined based on the results of their health monitoring, clinical and psychological evaluation and a high-calorie diet. In addition, people attending the sanatorium participate in an eight-week information course and a physical education programme. During this time they are granted their full salary.

People diagnosed with HIV who opt to continue living at home and receive ambulatory care have to attend a day clinic every day with the same schedule as followed in the sanatoria. To ensure appropriate nutrition, they are entitled to special food rations.

After these first months of close observation either at the sanatorium or in ambulatory care, all HIV-infected people are monitored on an outpatient basis by their family physician.

### The Antiretroviral Treatment (ART) Programme

#### History

The use of products that bolster the immune system for all HIV-positive people has been recommended in Cuba since 1986. From 1987, zidovudine (ZDV) was recommended as monotherapy for all those who developed AIDS. In 1996, after the World AIDS Conference and the recommendation of Highly Active Antiretroviral Treatment (HAART) as the treatment of choice, the Ministry of Public Health bought antiretroviral treatment for all children with AIDS and their mothers. Since 1997, HIV-infected pregnant women have been receiving ZDV to prevent mother-to-child transmission of the virus as well as breast milk substitutes (Farmer, 2003; Gonzalez-Nunez, Diaz-Jidy, Perez-Avila, 2000). From 1998 to 2001, 100 AIDS patients were maintained on treatment through donations of antiretrovirals (ARVs).

During the same period, the Government, the National AIDS Commission, and the Ministry of Public Health explored...
the possibility of local production of generic antiretroviral drugs. The first drug produced was zidovudine (ZDV) which was followed by the production of lamivudine (3TC), stavudine (D4T), zalcitabine (DDC), didanosine (DDI) and indinavir (IDV). In early 2001, bio-equivalence was tested for all these drugs and they were registered with the Centro para el Control de los Medicamentos, the national regulatory authorities, before being provided to patients. Production of nevirapine (NVP), abacavir (ABC), efavirenz (EFV) and nelfinavir (NFV) is currently being assessed.

Since the introduction of locally produced antiretroviral drugs in 2001, the number of patients who benefit from ART has increased significantly (Figure 2), and 100% HAART coverage was achieved in 2003 (Box 2).

**Objectives**

The ART programme takes advantage of already existing practices, facilities and experiences, and is designed to meet the following objectives:

- to use existing medical personnel working with HIV/AIDS patients to implement and manage the antiretroviral treatment;
- to train all physicians working with HIV-positive patients in the use of antiretroviral therapy;
- to establish a national electronic registry (SIDA/TRAT) that facilitates monitoring and clinical follow-up;
- to show that generic drugs produced in Cuba are safe and effective; and
- to demonstrate that in poor countries HAART can be delivered by harnessing the capacity of the human and technical infrastructure and that barriers to treatment in such settings are not so much a lack of infrastructure but a lack of political will.

**Drugs and Regimens Used**

Based on Cuba’s production of antiretroviral drugs, first line regimens currently available are:

- ZDV, 3TC, IDV
- ZDV, DDI, IDV
- D4T, 3TC, IDV

Since the introduction of locally produced antiretroviral drugs in 2001, the number of patients who benefit from ART has increased significantly (Figure 2), and 100% HAART coverage was achieved in 2003 (Box 2).

**Figure 2:** The number of HIV-positive people receiving ART has increased steadily since the production of generic ARVs in Cuba

Source: IPK, 2004

- D4T, DDI, IDV

These triple combinations are used initially for all patients. However, those who develop tuberculosis during treatment are switched to a dual therapy scheme using two nucleoside reverse transcriptase inhibitors (NRTI), with either nevirapine or nelfinavir as options for second-line treatment. In other patients, second-line treatment possibilities are protease inhibitors, if available.

**Criteria to Initiate ART**

An HIV-infected person will be included in the HAART programme after meeting the following criteria:

- confirmed diagnosis of HIV (with 2 Elisa + 1 Western blot);

**Box 3: Checklist for patient monitoring**

**Every 3 months:** Laboratory tests, including complete blood counts, LDH*, GPT*, GOT*, glucose test, urinalysis, kidney function tests, bilirubin, and CD4 count to assess adverse side effects and the patient’s status.

**Every 6 months, or whenever a drop in the CD4 count is noticed:** Viral load determinations.

**Every 4-8 weeks:** Patients are seen by their physician and their weight measured; relevant laboratory results are registered in their clinical records. The most sophisticated analyses like viral load and CD4 counts are done at the IPK, while other tests can be performed at the provincial hospital or sanatorium.

* LDH=lactic dehydrogenase; GPT=glutamic pyruvic transaminase; GOT=glutamic oxaloacetic transaminase
CD4 count less than 350 cells per mm3; viral load higher than 55,000 copies per ml; and presence of an opportunistic infection.

Each patient is prescribed one of the four first-line regimens and receives a personal card to collect the ARV drugs at the hospital pharmacy. The physician at the outpatient services or at the sanatorium (Box 3) closely monitors the patients.

Their clinical histories including the results of continuous monitoring are entered in an electronic database (SIDA/TRAT) that is centralized at the IPK.

The clinical technical committees supporting the ARV programmes are based at the IPK and the National Technical AIDS Commission. They define guidelines and clinical selection criteria, and determine the treatment scheme for patients starting ART. The selection process is soon to be devolved out to staff at the treatment centres.

Human Resources and Capacity Building

The Cuban health care system has three levels through which it provides universal, free and easily accessible health care to all Cuban citizens. This includes primary level care with family physicians, a secondary level care consisting of sanatorium care for HIV and provincial hospitals, and the tertiary level with the research institutes.

Personnel involved in the national protocol for ART are from all levels of the health system. At least four physicians are in charge of ART in each province and they work closely with the team at the IPK. In addition, they are responsible for entering data in the computerized database (SIDA/TRAT). Physicians working at the IPK, the AIDS Sanatorium, provincial and municipal hospitals, as well as family physicians and nurses, prescribe drugs, supervise ARV treatment and follow up patients.

To support the rational use of drugs, the National AIDS Commission, the Ministry of Public Health and the IPK combined their human and financial resources in a country-wide training focusing on ARV therapy, the use of drugs for opportunistic infections as well as logistics and stock management. Training of physicians from all provinces in the country on antiretroviral treatment started at the IPK in 1998 and was conducted by cli-
nicians, epidemiologists, microbiologists, pharmacists, psychologists and nurses.

By early 2001, more than 700 health care workers, a sufficient number to care for the HIV-infected in the country, had participated in training courses on the management of HIV/AIDS.

The training team at the IPK continues to support further capacity-building of human resources involved in providing care to people living with HIV/AIDS. Likewise, faculty members of all medical institutions in Cuba have been trained to teach HIV/AIDS care in post-graduate medical courses.

The Ministry of Public Health seeks to ensure that appropriate training materials are developed and that training courses are available for all workers of the health system. Efforts in this area have been quite successful; by September 2003, health workers in each of the more than 169 municipalities in the country had been trained in HIV/AIDS.

**Impact**

At the end of 2003, a total number of 1,292 HIV-positive patients received ART; all but nine who could not tolerate three drugs because of ongoing tuberculosis treatment benefited from HAART. Since the introduction of HAART in 2001 there has been a decrease in the number of deaths from AIDS and the incidence of opportunistic infections (OIs) related to HIV/AIDS (Figure 3). Since all OIs are treated in the hospital, the reduction in the number of OIs has in turn, resulted in a countrywide drop in hospital admissions; as for the IPK, admissions for opportunistic infections have decreased by almost half (Table 1).

Furthermore, treatment with ARVs showed beneficial effects on survival: from the time people developed AIDS, average survival time for those who did not receive treatment*, during 2000-2003 was at 1.2 years while AIDS patients with ARV treatment survived almost four times longer (4 years; p < 0.001). Out of the 1,292 patients under treatment, only 87, about 7%, died.

* Based on the assumption that patients receiving ART would have a much shorter survival time than those not receiving it.

**Table 2:** Reported adverse reactions to generic ARVs

<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>Frequency, in %</th>
<th>Type of reaction</th>
<th>Frequency, in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertriglyceridemia</td>
<td>37</td>
<td>Anaemia</td>
<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
<td>Elevated indirect bilirubin</td>
<td>13</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>23</td>
<td>Heartburn</td>
<td>10</td>
</tr>
<tr>
<td>Abnormal addis court</td>
<td>23</td>
<td>Metallic taste</td>
<td>9</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>21</td>
<td>Epigastric pain</td>
<td>9</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>17</td>
<td>Hypocalcemia</td>
<td>8</td>
</tr>
<tr>
<td>Elevated aminotransferase</td>
<td>17</td>
<td>Headache</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16</td>
<td>Hyperglycemia</td>
<td>4</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>15</td>
<td>Diarrhea</td>
<td>4</td>
</tr>
<tr>
<td>Paronychia</td>
<td>15</td>
<td>Hair loss</td>
<td>4</td>
</tr>
<tr>
<td>Lumbar pain</td>
<td>14</td>
<td>Kidney stone</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>Thrombocytopenia</td>
<td>1</td>
</tr>
</tbody>
</table>

**Figure 4:** The immunological and virological response of 100 patients after 18 months on ARVs shows the benefits of HAART.
Adherence Support Strategies

Physicians measure adherence by monitoring viral load and CD4 counts and also by conducting surveys among patients. The results obtained after 18 months of treatment show that most patients adhere well to it. In addition, the decreased mortality, increase of survival time, and the remarkable improvement of the patients’ well-being have strongly encouraged the AIDS community to adhere to treatment.

Patients on ART exchange their experiences through privately organized meetings, conferences, or gatherings at the outpatient services or AIDS sanatoria. Workshops with HIV/AIDS activists are organized regularly not only to further encourage adherence to treatment but also to address problems affecting the HIV/AIDS community, such as rights issues, news about treatment protocols, prevention and the need for voluntary workers.

For patients with poor adherence, nurses working with the family physician at the community or from the AIDS sanatoria, monitor and support treatment through regular visits either at the community or at the AIDS sanatoria. During these visits, most appropriate ways of taking medication (e.g. with or without food or water, best time schedule, etc.) are explained to the patients, and intake of medication is checked. In addition to the nurses, community activists and HIV-infected people who are trained in prevention work and supporting others, play an important role in providing counselling and support to those being treated.

Drug Supply and Management

In 1996, when the Ministry of Public Health bought drugs (SQV, ZDV, 3TC) to treat HIV-positive children and their mothers, the cost of treatment per person per year was US$14,000. Now, with the production of generic drugs in Cuba, the price varies from $811 to 4,388 Cuban pesos (US$31 to US$169) per year (Table 3). These costs are well below that of ARVs in other developing countries, and have been made possible through the Cuban Government’s substantial subsidies to treatment.

The price for each CD4 assay is US$5 and about US$88 for the viral load determination. Given their high cost, viral load assays are only performed in patients under treatment or when CD4 counts drop below 350 cells per mm3 or both. All these expenses are borne by the Ministry of Public Health.

Cuba has recently received a grant from the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) that will permit purchase of drugs that are not yet produced locally as well as reagents for CD4 count and viral load assays.

The National AIDS Commission and the Ministry of Public Health determine which drugs should be produced. The factory (Novatec Plants) sends the drugs to the IPK, where they are kept in a specially built storage room. Since the central registry of HIV cases is at the IPK, the distribution of ARV drugs is currently determined there with input from medical specialists working with HIV patients. In the near future however, ARV drugs will be directly distributed by the factory to hospitals and pharmacies through the National Network of Drug Distribution. Distribution is expected every three months based on information on the number of patients and characteristics of individual treatment from the IPK. Drugs acquired with the money granted from the GFATM continue to be stored at and distributed by the IPK. In general, the amount of drugs stored is sufficient to guarantee treatment for 6-12 months.

While the Government and the Ministry of Public Health are in charge of acquiring ARV drugs, the Ministry of Basic Industries carries the responsibility for producing generic drugs. In several of these processes, the HIV/AIDS community, in particular people living with HIV/AIDS, are involved. For example, they participate in the National AIDS Commission where they provide ideas and criteria for implementing strategies for treating AIDS. Also, their contribution to the Ethical Commission is valuable for the approval of therapeutic protocols for ARVs.

Accreditation and Quality Assurance

Since the beginning of the epidemic, the Ministry of Public Health and the National AIDS Commission have taken steps to ensure the quality of clinical services offered in each provincial hospital, at the

Table 3: Price of antiretroviral drugs made available to health facilities in Cuba

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Presentation</th>
<th>Price per unit in Cuban pesos</th>
<th>Price per pack in Cuban pesos (in US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine 150mg (3TC)</td>
<td>Fscos x 60 tab</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Zidovudine 100mg (ZDV)</td>
<td>Fscos x 100 cap</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Stavudine 40mg (D4T)</td>
<td>Fscos x 60 cap</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Indinavir 200mg (IDV)</td>
<td>Fscos x 360 cap</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Didanosine 100mg (DDI)</td>
<td>Fscos x 150 tab</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Zalcitabine 0.75mg (DCC)</td>
<td>Fscos x 60 tab</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Nevirapine 200mg (NVP)</td>
<td>Fscos x 60 tab</td>
<td>0.45</td>
<td></td>
</tr>
</tbody>
</table>

* When ART was started, only the most severe cases could be treated because of the limited availability of ARV drugs. In addition, not all patients who qualified for treatment accepted it, and in some cases HIV status was confirmed only after the patient was already deceased.
AIDS sanatorium and the IPK. A commission from the offices of the Department of Hygiene and Epidemiology regularly visits all facilities to ensure the quality of services in the HIV Treatment Network.

The National HIV Treatment Network includes one AIDS sanatorium in each of the 14 provinces, 14 provincial and 52 municipal hospitals, the hospital at the IPK and the family physician clinics. Each family physician attends about 150-200 families from the community. Criteria have been established that qualify a health facility for participation in the network (Box 4).

Other Programme Benefits
Prevention Versus Care: A False Dichotomy

Since the beginning of the epidemic, the Cuban National HIV/AIDS Program understood the importance of preventing HIV, and prevention activities have played a key role in containing the spread of the virus and achieving current results. At the same time, the availability of adequate treatment has contributed significantly to the reinforcement of HIV prevention. For example, during the past few years, people in Cuba have become increasingly more open to discussing HIV prevention activities. This is so not only because of the wealth of prevention activities at the national and provincial level but also because of the hope for a longer and better life that has become possible through treatment with antiretrovirals.

Participation of PLWA

The participation of all key stakeholders, particularly of the PLWA community, is key in the Cuban HIV/AIDS prevention strategy (Figure 5). They support those activities that are directly related to prevention (e.g. information, education and communication). They are also involved, for example, in adherence support and drug distribution, international conferences, the telephone hotline, ethical committees and support to people at the time they receive the results of their HIV test. The HIV community, hence, has become an integral player in the Cuban fight against HIV/AIDS.

Research and Technical Development

This component’s objective is to define and develop a research plan that responds to the course and the needs of the epidemic in the country. Multi-centre research comprising areas such as sociology, psychology, social communication, epidemiology, clinical sciences, diagnostic, vaccine and pharmacological product development, is conducted through a network of research centres. These include, for example, the National Biotechnology Centre (CIGB), the National Reference Laboratory (LNR), the Immunocompound Centre (CIE), the IPK, Havana University School of Psychology, Centres for Hygiene and Epidemiology (CPHE), and others. CIGB has produced a therapeutic vaccine for AIDS, which will be evaluated in a clinical trial at the IPK. The vaccine boosts the immunologic response against the virus, and eventually destroys it when the viral load is not detectable. It is reported (Fink S, 2003; Toledo et al., 2001) that the development of a preventive vaccine against HIV is currently underway at the level of basic research.

Challenges and Sharing Lessons Learned

Cuba was faced with an economic crisis while establishing a sustainable national HIV/AIDS programme. Nevertheless, they built a programme with a strong prevention and comprehensive care component without external assistance, relying solely on their own resources. This demonstrates that with a government’s strong political will it is possible to fight HIV/AIDS in resource-limited countries. To share their valuable experiences, Cuba has proposed helping countries highly affected by HIV/AIDS in building or strengthening their current primary health-care system and in the use of low-cost generic drugs. Such assistance would be performed as part of Cuba’s international development agenda through which it sends doctors and other professionals to other countries.
health-care workers to resource-poor countries as well as trains health care workers in Latin America and Africa (Castro, Farmer, Barberia, 2002). Despite these accomplishments, the Ministry of Public Health needs to focus on sustaining the low HIV-prevalence rate. At the same time it must reduce the rate of new infection that has been on the rise since the mid-1990s. Particular attention to strategies that address the group of men who have sex with men are expected to achieve improved results.

Scaling Up

The Cuban Government was granted US$26.5 million for the next five years from the Global Fund to fight AIDS, Tuberculosis, and Malaria. With help of these substantial additional funds, the National HIV/AIDS Programme will be able to address the challenges by further increased training and prevention activities.

Furthermore, a greater choice of ARV drugs will permit different therapeutic regimens, including for patients who develop resistance to commonly used ARVs. Improved technology and increased accessibility to laboratory analysis, and the greater variety of ARVs will all contribute to providing better care to more patients and hence to improving ethical aspects of care for people living with AIDS.

REFERENCES


This report was first published as part of Perspectives and Practice in Antiretroviral Treatment, by the World Health Organization, 2004.

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CUBAN MEDICAL LITERATURE

Dengue IgM Detection UltramicroELISA Test with Ready-to-Use Reagents

Regla de la Caridad Herrera(1);
Carmen Acosta(2);
Antonio Melchor(3);
Vivian Alonso(3);
Rosa Lidia Solís(4);
Susana Vázquez(5)

ABSTRACT: Dengue is currently the most important human arbovirus. It is reported in more than 100 countries, and 2.5 billion people are at risk of infection. Annually, there are an estimated 50 million people infected, with more than 500,000 hospitalized, and 25,000 to 50,000 deaths. Because of the emergence and re-emergence of dengue and hemorrhagic fever, the diagnosis of this disease by laboratory tests to distinguish dengue from other diseases, as well as to support surveillance systems, is of upmost importance. The best choice for the diagnosis of dengue fever is an immunoglobulin M-specific capture enzyme-linked immunosorbent assay (ELISA), due to its specificity, sensitivity, and fast performance. An example of this technique is IgM dengue ultramicroELISA. We present the standardization results of dengue ultramicroELISAs' new format, which includes strip plates and ready-to-use reagents. The original conditions of coating and conjugate dilution of the UMEELISA Dengue IgM kit were maintained. Both within-run and between-run precision values were below 10%; the stability of all reagents was higher than 90%. There were no significant differences when comparing the previous reagents and plates with the new ones. Compared to hemagglutination inhibition, the sensitivity was 94.3%, the specificity was 94.1%, and the kappa concordance index was 0.91.

Results indicated the ultramicroELISAs' new format maintains its reliability for early detection of dengue.

Keywords: DENGUE; ULTRAMICROELISA; IGM; DIAGNOSIS
INTRODUCTION

Dengue is an infectious disease caused by an RNA virus of the *Flaviviridae* family. There are four known serotypes (DEN-1, DEN-2, DEN-3 and DEN-4).[1] It is transmitted by the *Aedes aegypti* mosquito as its main vector.[2] In terms of morbidity, mortality and economic cost, it is the most important arbovirus globally, with an estimated 100 million cases annually.[3,4]

In acute dengue infections, two patterns of serum response can be observed: primary and secondary. The first is observed in persons who are not immune to flavivirus. In this response, IgM antibodies increase between the third and fifth day after onset of the symptoms, reach a peak at two weeks and at three months, are reduced to practically undetectable levels, although they may persist up to 90 days in some cases. The IgG antibody increase takes place between the 10th and 14th days, where they remain for life. The secondary response is observed in persons with an acute dengue infection that have previously suffered a flavivirus infection. In this case, IgG antibody titters rise to high levels between the first and second day, while the IgM antibodies rise more slowly and to a lower level than in primary infections.[5-9]

Most primary infections result in dengue fever (DF), a mild disease characterized by biphasic fever, intense headache, myalgia, arthralgia, skin rash, lymphadenopathy and leukopenia.[10] The severe forms of the disease, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), are usually associated with secondary infections.[11] DHF is characterized by high fever, associated hemorrhagic phenomenon with reduction of the number of platelets, increase in capillary permeability and hepatomegaly. In DSS, the state of the patient suddenly deteriorates and signs of circulatory failure appear.[12]

Despite advances in the knowledge and clinical epidemiological characterization of DF, DHF and DSS, laboratory support is essential in the differential diagnosis by virus isolation, serological diagnosis or molecular detection. Routine serological diagnosis includes hemagglutination inhibition (HI), complement fixation (CF), neutralization (N) and IgM capture ELISA (MAC-ELISA).[13]

The dengue IgM ultramicroELISA (UMELISA) is an example of MAC-ELISA.[14] With the objective of improving its use and manipulation, the kit format was modified to strip plates and ready-to-use reagents. Results in the standardization of the new format are presented in this study.

MATERIALS AND METHODS

**Samples of human sera:** Fifty-two pairs of sera from patients clinically suspected of dengue infection were evaluated. The samples were collected during the dengue epidemic that took place in the first semester of 1997 in Santiago de Cuba, Cuba.[15,16] The sera were preserved at -20°C. They were classified into primary infection (*n* = 4), secondary infection (*n* = 31), and not dengue (*n* = 17), according to HI criteria.

**Solid Phase:** Rigid ultramicroELISA (10 μl per well, 96 wells) plates and strips (8 wells x 12 strips; Greinerlaborteknik, Germany) were used.[17]
tions of human anti-IgM in 10 mM Na2CO3/NaHCO3, pH 9.6. They were incubated during 4 hours at 45°C and were finally blocked with PBS containing 0.1% bovine seroalbumin (BSA).

**Preparation of the control sera:** Two variants were used: concentrated (control variant) and ready-to-use (test variant). At the time of the test, the concentrated control was diluted 1:21 with a sheep serum solution in 5% 15mM Tris-HCl, 0.05% Tween-20, pH 7.8; while ready-to-use sera were provided in the 1:21 dilution and used directly as supplied in the kit.

**Preparation of the conjugate:** As for the control sera, two variants were used: a concentrated (control variant) and a ready-to-use one (test variant). In the first case, the conjugate working dilution was prepared just before carrying out the test. Meanwhile, in the ready-to-use variant, a ready-to-use conjugate solution was supplied in the test kit.

**Selection of the test conditions:** The use of strip plates required a reevaluation of the coating concentration and the conjugate dilution. A crossed titration was done for the simultaneous evaluation of different coating concentrations (from 4.5 to 17.5 μg/ml of human anti-IgM) using different conjugate solutions (from 1:1000 to 1:9000).

To select the optimal combination of coating concentration and conjugate dilution, the selected concentration had to be within the plateau zone, which is defined as the range of concentrations for which the FU of each control sera remained constant. And there had to be an adequate difference between the control sera, values under 10 FU for the negative, and between 130 and 150 FU for the positive.

**Reproducibility Study:** In this study, the 2 solid phases were used and 5 samples with different positive levels. The samples were applied 10 times in each plate in five consecutive days to determine the within-plate and between-plate variation coefficients (VC).

**Shelf stability:** This study was carried out on the strip plates and the ready-to-use control sera and conjugate. The results obtained on the initial day of the study (time zero) for the control sera, under each of the analyzed conditions, was considered the control while the test condition was the monthly results during the following 24 months. The stability criterion was maintained as long as no significant differences were observed. Storage temperature was 4°C.

**Comparison of the plates, the control sera and the conjugate:** A comparison was made between the strip and rigid plates and the ready-to-use control sera and conjugate with respect to the concentrated ones, using 20 replicas of each.

**Comparison of HI and the new UMELISA format:** Using the results of the 52 paired sera, the specificity and sensitivity of the new Dengue IgM UMELISA format was determined with respect to the HI test, as well as the concordance between both tests by the κappa statistic. The capacity of one or the other technique to diagnose dengue infection using the first serum in the pair (S1), taken during the acute disease phase, was also evaluated.

**Statistical Analysis:** In the shelf stability test, the comparison was performed by the X² test. The comparison of plates, control sera and conjugate was done using the Student t test.

Both tests were carried out for a = 0.01 using the Microsoft Excel 2002 program.

**RESULTS**

**Selection of test conditions**

Using the strip plates, both the coating concentration (12.5 μg/ml human anti-IgM) and the conjugate dilution (1:7000) agreed with the ones used for the rigid plates. In Figures 1 and 2, control sera results are shown for the different coating concentrations evaluated and the 1:7000 conjugate in both types of plates. Figure 3 presents the control sera results for both plates using 12.5 μg/ml human anti-IgM and different dilutions of the conjugate tested.

**Figure 1:** Evaluation of different coating concentrations in the rigid plates using the positive control serum (PCS) and the negative control serum (NCS)

**Figure 2:** Evaluation of different coating concentrations in the strip plates using the positive control serum (PCS) and the negative control serum (NCS)

Key:
- **UF** - Fluorescence Units
- **SCN** - Negative Control Serum
- **SCP** - Positive Control Serum

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**Statistical Analysis:** In the shelf stability test, the comparison was performed by the X² test. The comparison of plates, control sera and conjugate was done using the Student t test.
FIGURE 3: Evaluation of different conjugate dilutions in the rigid and strip plates using positive (PCS) and negative (NCS) control sera

Key:
UF - Fluorescence Units
Dilución - Dilution
SCP Placas rígidas – PCS Rigid plates
SCP Placas de tiras – PCS Strip plates
SCN Placas rígidas – NCS Rigid plates
SCN Placas de tiras – NCS Strip plates

Reproducibility Study

The within-plate and between-plate variation coefficients did not exceed 4% and 7%, respectively (Table 1).

TABLE 1: Reproducibility results using rigid and strip plates

<table>
<thead>
<tr>
<th>Samples</th>
<th>FU</th>
<th>VC within-test (%)</th>
<th>VC between-test (%)</th>
<th>FU</th>
<th>VC within-test (%)</th>
<th>VC between-test (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.4</td>
<td>3.5</td>
<td>6.7</td>
<td>17.5</td>
<td>2.3</td>
<td>7.0</td>
</tr>
<tr>
<td>2</td>
<td>25.8</td>
<td>2.7</td>
<td>7.1</td>
<td>23.7</td>
<td>4.1</td>
<td>5.7</td>
</tr>
<tr>
<td>3</td>
<td>30.8</td>
<td>3.3</td>
<td>6.8</td>
<td>31.0</td>
<td>3.6</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>58.6</td>
<td>2.8</td>
<td>6.6</td>
<td>50</td>
<td>5.3</td>
<td>6.1</td>
</tr>
<tr>
<td>5</td>
<td>102.3</td>
<td>4.0</td>
<td>5.2</td>
<td>104.4</td>
<td>2.9</td>
<td>6.4</td>
</tr>
</tbody>
</table>

FU: Fluorescence Units
VC: Variation Coefficients

Shelf Stability

Throughout the study, the FU results of the control sera did not show significant differences with respect to time zero (data not shown). Table 2 shows the averages of the FU obtained at time zero and after 24 months.

Comparison of HI and the New UMELISA Format

The distribution of the results using the new UMELISA format and the HI are shown in Table 4. Using the paired sera classified as not dengue by the HI test, there was concordance in 16 out of 17, while one pair (number 21) was evaluated as positive by UMELISA. Using this test, 4/4 pairs of primary infection cases were detected and 29/31 secondary infection cases. In this test, the discordant pairs were numbers 12 and 50, diagnosed as negative with UMELISA. The data for the differing samples are shown in Table 5. The S1 samples used to study the capacity of both tests for diagnosing dengue infection using only an acute phase serum were obtained between day 1 and 5 of symptom onset, when the patients first went to the doctor. The UMELISA test detected 2 cases of primary infection with S1 sera, while none was detected by the HI. In the sera pairs of secondary infection cases, the UMELISA test was capable of establishing the diagnosis of infection in 11, which were included in the 13 detected by HI.

The sensitivity, specificity and kappa index were 94.3%, 94.1% and 0.91, respectively.

DISCUSSION

The Pan American Health Organization (PAHO) states that every country endemic for dengue must have a passive surveillance system based on clinical diagnosis, which considers dengue a notifiable disease.[6] However, since it is frequently impossible to clinically differentiate dengue from other diseases[23] caused by several viruses, bacteria and even some protozoa, by the time cases are detected and reported by doctors, a considerable transmission of dengue has already taken place that may have even reached the maximum.

The similarity of clinical symptoms to those caused by other pathogens, as well as the increase in the prevalence and incidence of dengue fever, dengue hemorrhagic fever and dengue shock syndrome,[24] have made clear the importance of an active surveillance based on laboratory tests. With this surveillance, the necessary information regarding onset, location, viral serotype and the severity of the disease may be obtained.[25]

The techniques generally used for dengue diagnosis are HI[18] and ELISA to detect IgM or IgG antibodies.[26] The HI test, as well as the IgG ELISA, requires paired samples collected with an interval of at least 7 days for a final diagnosis when a four times or greater titer increase is found.[6] On the other hand, the IgM ELISA (MAC-ELISA), can frequently diagnose the disease with only one acute phase serum. Several studies have demonstrated that IgM antibodies are detectable between the sixth and tenth day in 95% of the cases, whether primary or secondary.[27] For this reason, IgM capture ELISA is presently the most useful technique for active surveillance and its use has become widespread in recent years.

At present, the development and production of different reagent kits based on MAC-ELISA is being promoted,[24] the Dengue IgM UMELISA among them. Its original format consisted of rigid plates (96 wells), lyophilized antigen and concentrated control sera and conjugate. Considering that the current trend in kit formats is directed towards using lyophilized antigen and the remaining reagents in ready-to-use form,[28] the objective of this work was to evaluate the substitution of the concentrated control sera and conjugate by ready-to-use
ones, as well as analyzing possible replacement of the rigid plates by strips.

During the evaluation of the coating concentration and the conjugate dilution in the strip plates, the coating plateau started at 10 ìg/ml, that is the fluorescence values for each of the control sera remained unchanged. Considering that other researchers have stated,[29] that it is necessary to work in the coating plateau zone, the value selected as optimal concentration was 12.5 ìg/ml. This concentration is in the zone mentioned, and besides, by using this concentration and the 1:7000 conjugate, it was possible to obtain a good separation between the positive control serum and the negative one (8 and 137 FU, respectively). Thus, it was not necessary to change the previous coating and conjugate concentrations.

With respect to reproducibility, the variation coefficients within-plates and between-plates did not exceed 10%, indicating that there was adequate precision, which guarantees the homogeneity of the results for the same sample evaluated at different times.[30]

The statistical analysis of the stability results evidenced that the strip plates as well as the ready-to-use control sera and conjugate were stable during 24 months when preserved at 4ºC.

In the evaluation of the plates – in which no significant differences were found when comparing the strip to the rigid ones - showed that the results were equally reliable if the previous conditions of time and storage temperature were maintained. This result is of vital importance since it increases the possibilities of UMELISA use. The introduction of strip plates allows the kit to be used both in massive screening laboratories, as well as in those where a small number of samples is processed, without wasting determinations or delaying the diagnosis waiting for the number of samples (90) required to complete the rigid plates.

When the ready-to-use control sera and conjugate were compared with the concentrated reagents, there were no significant differences either, so it is possible to eliminate the final dilution step in the preparation of these reagents, thus eliminating possible changes in the test derived from their preparation.

In the analysis of the samples by UMELISA and HI, we obtained three pairs of sera for which results differed. The first discordant pair was number 21, classified as not dengue by HI (titers below 1:1280, without seroconversion),[31] and weakly

<table>
<thead>
<tr>
<th>Control Sera</th>
<th>Plates</th>
<th>Control sera</th>
<th>Conjugate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>6.3</td>
<td>6.5</td>
<td>100</td>
</tr>
<tr>
<td>Negative</td>
<td>8.0</td>
<td>7.8</td>
<td>97.5</td>
</tr>
<tr>
<td>Positive</td>
<td>142.5</td>
<td>141.1</td>
<td>99.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Controls</th>
<th>Control</th>
<th>Strip</th>
<th>t</th>
<th>Control</th>
<th>RU t</th>
<th>Control</th>
<th>RU t</th>
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</thead>
<tbody>
<tr>
<td>Negative</td>
<td>5.75</td>
<td>5.91</td>
<td>0.31</td>
<td>6.23</td>
<td>6.32</td>
<td>0.23</td>
<td>6.11</td>
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<tr>
<td>Positive</td>
<td>139.24</td>
<td>138.24</td>
<td>1.04</td>
<td>140.91</td>
<td>140.82</td>
<td>0.01</td>
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<table>
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<th>DEN-2</th>
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<th>M-B/P-B</th>
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<td>Secondary</td>
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<td>Negative</td>
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<tr>
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<td>&lt;20</td>
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<td>Negative</td>
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<td>50a</td>
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</tbody>
</table>

<table>
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<th>Secondary infection</th>
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<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>4/4 (100%)</td>
<td>29/31 (93.5%)</td>
<td>1/17 (5.8%)</td>
<td>34</td>
</tr>
<tr>
<td>Negative</td>
<td>-</td>
<td>3/31 (6.4%)</td>
<td>16/17 (94.1%)</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>34</td>
<td>17</td>
<td>52</td>
</tr>
</tbody>
</table>

| Table 2: Results of the shelf stability test for the strip plates using control sera and conjugate |
| T0: Time zero evaluation |
| T24: Evaluation after 24 months |
| %: Percentage of recovery |
| 24 months after time zero |

| Table 3: Averages and Student t test comparison |
| RU: Ready-to-use reagent |
| t (0.01) = 2.86 |

| Table 4: Distribution of positive and negative sera by HI and UMELISA |

| Table 5: Results of the discordant samples |
positive by UMELISA. This result could be due to the higher sensitivity of the ELISA techniques with respect to HI.[32] The other two discordant pairs were numbers 12 and 50, which showed seroconversion by HI and the titer of the convalescence serum was 1:2560, compatible with a secondary infection.[31] In such cases, a small number of persons have been reported in which IgM antibodies may not be detected.[33,34]

Considering that one of the main disadvantages of the HI is the need for paired sera to carry out dengue infection diagnosis (except in those cases in which the first serum has titers over 1:2560), the capacity of both techniques to carry out the diagnosis with sample S1 was evaluated as part of the comparison between UMELISA and HI. Neither of the techniques, UMELISA or HI, was particularly efficient in dengue infection diagnosis using the acute phase serum. Of the 33 paired sera evaluated as positive by HI, UMELISA diagnosed 31% of them using the acute phase serum (13/33).

Two of them were from secondary infection and 11 from primary infection cases. On the other hand, HI allowed reaching a diagnosis in 13 samples of secondary infection. The two primary infection samples that were not detected by UMELISA were taken on the first and second day of symptom onset, earlier than the time required for IgM antibodies to reach detectable levels in primary dengue infections.[35] In the secondary infection cases, HI excelled UMELISA, which could be because HI detects total antibodies[18], IgM, as well as IgG. The latter predominate in this type of infection and that is why in reinfections they are considered the gold standard of markers.[28]

The agreement between the new UMELISA format and the HI was 94.2%, similar to the 92.85% when the original format is compared to HI.[14] This result reaffirms that the format change does not have any effect on the previously established kit quality.

The kappa index (0.91) showed good concordance with the HI.[22] The percentages of sensitivity (94.3%) and specificity (94.1%), were comparable to those of other diagnostic kits designed for the same purposes[33] and allowed the application of the test for massive screenings in populations suspected of being infected by dengue.

CONCLUSIONS

The UMELISA Dengue IgM kit with strip plates and ready-to-use reagent format improves present conditions of manipulation and use. This test, performed in four hours, is a favorable alternative for the serological diagnosis of dengue infection from a single serum sample and does not have any of the HI limitations.

REFERENCES

The plenary session began with a wide and detailed conference including, briefly, the main issues and management of the epidemic in Cuba. Several experiences of epidemic management in the provinces were presented as well.

Thereafter, a series of ideas was presented based on different hypotheses on the role of vitamins in the development of the epidemic and of vitamin therapy in reducing its incidence. The presence of toxic substances related to the epidemic was also discussed.

Participants highlighted the special protection of priority groups - children, seniors and pregnant women.

Data on the present state of the 50,945 patients reported by the end of May 1994 were presented. The illnes was controlled in 85.9% of the patients, 87.2% of those with optical neuropathy, and 84.4% with peripheral neuropathy.

During the afternoon, sessions were held in three work groups: clinical-therapeutic, toxic-nutritional and virological. The main papers presented at the workshop were analyzed in the groups, as well as the research results related to the subjects discussed.

Clinical-Therapeutic Group

This group debated aspects related to the characterization of the disease. The fundoscopic and electrophysiological findings in optical neuropathy and the clinical neurological, physiopathological and systemic symptoms of peripheral neuropathy were summarized. The anatomo-pathological and neurophysiologic results were presented. The pathogenic outline of the damage was explained. The session concluded with a summary of the multi-center controlled therapeutic trials.
Due to the similarity of the clinical picture and the fundoscopic appearance to Leber's optic neuropathy, an inherited mitochondrial disease, a DNA study was carried out by Wallace et al. on a group of these patients and their controls, looking for the mutations in this neuropathy. They concluded that there was no relation between the epidemic neuropathy and this disease.

Peripheral neuropathy includes all clinical symptoms, except those dependent on the lesion of the optical nerve. The fundamental symptom was general irritation, along with irritability and passivity, which marked the beginning of the clinical picture early on. In the groups with visual and peripheral neuropathy, a short-term memory problem was found.

The uniformity of the morphological lesions described in patients with different clinical pictures suggests that all the clinical types correspond to a common pathogenic mechanism. In the material studied, there are no elements indicating an inflammatory or infectious cause. The morphological changes correspond to an axon type of neuropathy, similar to the one observed in toxic-metabolic, or nutritional deficiency processes, with changes in the myelin sheath, probably of a secondary nature.

A basic treatment of vitamins and, in severe cases, of hydroxocobalamin is recommended.

Patients with unsatisfactory evolution merit in-depth study to determine the existence of individual predisposing factors, toxic habits, or other risk elements that may explain this response; epidemiological control involving primary care is also required.

Virology Group

In the virology group, the main report was presented with results obtained by Cuban institutions; participants also debated illustrative lectures related to the subject. Certain similarities between the Japanese and the Cuban epidemic were shown.

Researchers from the Pedro Kourí Institute of Tropical Medicine (IPK, according to the acronym in Spanish), the Center for Genetic Engineering and Biotechnology (CIGB), and Labor 1 presented 15 papers. They all showed the unquestionable presence of viral agents (Coxsackie A9, IMV) and an agent that was not classified, but that produced a slow cytopathogenic effect.

Results obtained by three Cuban laboratories working independently coincided almost completely. There were clear virological, serological, molecular, electron microscopy and pathological evidence in human samples, demonstrating the unmistakable presence of viral agents involved in the epidemic neuropathy. Samples taken from laboratory animals showed the same results.

Antibodies that recognize Coxsackie A9 virus have been detected in apparently healthy populations, which speak in favor of its increasing circulation during the last years.

It was concluded that:

- There are viruses in the CSF of most patients with epidemic neuropathy;
- These viruses require further studies to characterize them correctly, to know their reactions, and definitively identify them and;
- The unusually high percentage of isolates and the serological studies indicate that these agents play an important role in the etiopathology of the disease. Nevertheless, the group was not able to put forward a conclusive course of action.

The cause of epidemic neuropathy was considered multifactorial. Furthermore, there was no contradiction with the presence of toxic-nutritional and metabolic factors since there are many interrelating elements between these and the appearance of infections in humans. Besides, certain deficiencies in the host may trigger the virulence of viral agents.

The group considers that, despite the apparent contradictions, we may be facing new situations, and that the presence of viruses in most patients forces us to consider them as a co-factor in the cause of epidemic neuropathy.

Toxic-Nutritional Group

In the roundtable of the toxic-nutritional group, the main work carried out by participating institutions was presented, including a summary of the different epidemiological studies performed and the main results. These showed that major associations were found with diet-related factors; smoking was found to be an important risk factor.

They analyzed how the disappearance of the socialist bloc and the worsening of the U.S. embargo critically reduced food supplies since 1990, and how this was more evident in the western provinces, even though historically the eastern provinces had lower consumption levels.

The diet study showed a major effect on food consumption, a less varied diet, a smaller body mass index and greater loss of body weight.

The main findings of the PAHO-Ministry of Public Health-CDC study carried out in Pinar del Río were presented (see Abstract). Their analysis demonstrated that the patients consumed less meat, milk products, cereals, eggs and leafy vegetables than the control group.

Nutrients and energy consumption, animal proteins, animal fats, methionine, retinol and all the vitamins in the B complex were lower in patients than in the control group.

Cigar and cigarette smoking is the most important risk factor in these analyses. Eating yucca [cassava, eds] is a risk factor only in energy-adjusted models. Although it may have a direct effect, an alternative explanation is that it is a marker of a diet pattern associated with risk.

Several nutritional factors were protective. Lycopene and other carotenoids having antioxidant effects displayed a very strong protective association. The administration of B complex vitamins, especially riboflavin and nutrients associated with consumption of animal products, gives strong protection, but as they are interrelated, it is difficult to separate their effects.

Biochemical tests showed much higher serum creatinine levels in the urine of the patients than the controls; lower serum levels of alpha carotenoids, lycopene, beta carotenes, cryptoxanthins and selenium were found in the patients than in control groups.

The results of ecological studies carried out in Pinar del Río were also shown. They indicated that rural areas with high
disease rates had a higher population density, substantial state tobacco production with little land access for production of food to complement limited food supplies, and a monotonous carbohydrate-based diet. The adjacent areas with low disease rates were less populated, had private-farms or aquaculture. They sold their surplus in the market and had a less monotonous diet.

At the same time, significantly higher disease rates were confirmed in areas dominated by state tobacco plantations as compared to areas with mainly private farms, after population density stratification.

After temporal and social distribution was explained, a possible causal chain was discussed. It started with economic recession, changes in food distribution and little access to complementary sources of food. This led to a monotonous carbohydrate diet and an unbalanced nutritional state, where tobacco and other toxins may have interacted with the metabolic disorder to induce neuronal damage.

The disease distribution found was difficult to explain as the isolated effect of a toxin or infectious agent.

The conceptual outline of the toxic-nutritional hypothesis was also expounded, using the works of Dr. Madam as historical background. The disease was considered an optic-peripheral neuropathy, that could be associated to dorsal lateral myelopathy.

Starting from the known causes of optic and peripheral neuropathies, other causes of genetic origin were ruled out, as well as those due to systemic metabolic diseases, since they are not epidemic. Acquired causes of epidemic behavior were proposed, such as: toxics, deficiencies, association of both (toxic-nutritional) and infections. In this sense, the etiopathogenic hypothesis proposed that the altered nutritional state adversely affected the detoxification mechanisms and the antioxidizing systems. Together with the aforementioned exposure to toxic substances from smoking, which contributes to depressing defense mechanisms, this may have triggered metabolic stress at the cellular level, disturbing the energy-producing mechanisms required to maintain adequate functioning of the nerve fibers.

Considering the results obtained in the multiple studies carried out, two pathogenic mechanisms may be responsible for the neuronal damage characterizing this disease: oxidative stress, because of a lack of antioxidants and a disturbance of the antioxidizing systems, and the exposure to toxic substances from smoking that causes an increased depression of the cyanide detoxifying mechanisms.

To sum up, the neuropathy epidemic in Cuba cannot be attributed exclusively to the damage caused by depressed nutritional state. However, this state created the conditions necessary for the development of the aforementioned mechanisms. Thus, we can define it as a toxic-nutritional neuropathy.

Toxic-Nutritional Neuropathy

The joint discussion session exceeded all expectations. Different and controversial ideas were exchanged, which, at times, were compared to the Italy-Brazil World Championship soccer match. The essential discussion dealt with the primary hypotheses about the cause of the disease: toxic-nutritional and viral.

According to some, the methodology for demonstrating the presence of viruses was correct: the virus may be latent and act as a cofactor, together with the nutritional or toxic factors.

Another aspect discussed was patient follow-up, which will clear up some unknown facts. In this regard, continued collaboration would be helpful.

The National Follow-up Program for epidemic neuropathy patients includes three main elements:

- guarantee of adequate medical care for all persons affected;
- establishment of a Health Surveillance System on the course of the disease in these people and their general status; and
- a special protocol for severe and therapeutic failure cases.

Despite follow-up and the best therapeutic protocols, some patients do not recover. Patients maintaining a static course is presented. It is necessary to analyze the causes contributing to this.

The participation of the Cuban President, who took interest in the results of other treatments including spa treatment, the role of vitamin therapy in disease control, the behavior of new cases and whether they were taking vitamins prophylactically, led to new explanations on this subject. The Cuban President pointed out how much has been achieved since the beginning of the epidemic and the need to continue looking closely into the causal factors, as well as follow-up and control of the patients.

The role of the family doctor was analyzed—follow-up, control and prevention of cases, as a researcher into the epidemic’s causes and as a care provider for the patients. About spa therapy, some data demonstrated positive results in patients treated at the San Diego de los Baños spa in Pinar del Río province. A therapeutic protocol including vitamins, methionine and sulfur baths was used. The application of rehabilitation protocols for the most severe cases was recommended here, as it was in the Elguea spa in Santiago de Cuba province. Collaboration projects with international organizations were detailed and rehabilitation was emphasized.

Final Considerations

This meeting efficiently summarized studies of this disease to date by specialists from prestigious national and international institutions. The results obtained will enrich knowledge about the different aspects related to it, as well as enable their application to the integral development of science.

The objectives of the workshop were achieved and expectations exceeded. Nevertheless, pursuing investigations and designing other research that responds to present needs was recommended. A more integral character in the multidisciplinary and multi-centered approach with which these studies have been carried out was also recommended.

These four days of work have signaled the climax of a prolonged, intense and fruitful stage of scientific and medical cooperation. At the same time, the workshop defined new joint tasks to be developed in the future, both as regards organization, medical care and research.

CUBAN MEDICAL LITERATURE

Malaria Surveillance of International Travelers Living in Havana City, 2000-2001

Carmen Julia Suárez Miranda(1);
Antonio Pérez(2);
Alina Pérez Carreras(3);
Omar Fuentes González(4)

ABSTRACT: A prevalence study was made of Cuban international travelers and foreigners living in Havana, who arrived in Cuba either by air or sea between January 1st, 2000 and December 31st, 2001, as well as of students in the Latin American School of Medicine (ELAM) in the 1999-2000 and 2000-2001 school years.

Malaria prevalence calculations were made by continent and country of origin. General (by continent), and specific (by country), rates were calculated. The same procedure was used for ELAM students. The main source of malaria was found among Cuban passengers coming from the African continent in the period 2000-2001, with the highest rates of incidence and risk of introduction in the passengers coming from Nigeria and Cameroon.

In Latin America, malaria prevalence was higher in travelers arriving from Nicaragua. In the 2000-2001 school year, the highest rates of infected individuals came from Africa, mainly from Nigeria. ELAM students were found to be a high-risk group in malaria prevalence in the present study.

Keywords: MALARIA, EPIDEMIOLOGICAL SURVEILLANCE, INTERNATIONAL TRAVELERS, HAVANA CITY.

INTRODUCTION

It is estimated that malaria represents 2.3% of the global disease burden, 9% in Africa. According to the World Health Organization, in 1998 more than two billion people - 40% of the world population - live in malaria-risk areas.[1-6] Between 1.5 and 2.7 million people die as a result of this disease every year, while between 300 and 500 million suffer from it.[5-8]

Historically, communicable diseases have spread from one continent to another and from one country to another by land, sea, and air.

International travel has thus increased the risk of arrival of people who suffer from or carry disease, and intermediate vectors or hosts who find in our ecosystem a favorable habitat in which to develop (Ministry of Public Health, International Sanitary Control Program, Havana City: MINSAP, 1998).[9]
The situation gets worse as travel to endemic areas increases. As endemic areas grow, so does the parasite’s resistance to prophylactic regimes, thus causing a significant increase in imported malaria (Valdés García L, Carbonell García I, Delgado Bustillo J, Santín Peña M. *Paludismo: Enfermedades emergentes y reemergentes*. Ciudad de La Habana: MINSAP; 1998). As a result, the disease has appeared in countries like the United States, where autochthonous outbreaks occurred at the end of the 1980s.[6-9] Imported malaria has also been reported in other First World countries like France, the United Kingdom, Germany, Switzerland, Australia and Italy.[10-12]

In Latin America, malaria has been reported in about twenty countries including Mexico, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Guyana, Colombia, Brazil and Venezuela.[8-13]

In the last few decades Cuba has increased its international relations, which is why 40 years ago the Surveillance and International Sanitary Control Program was implemented [a component of the UATS system, eds.]. This program aims at identifying and preventing the introduction of exotic diseases such as malaria into Cuba. Malaria introduction has been the greatest risk in recent years, so special measures were required.

This study aims at presenting the results and experiences of international surveillance of passengers who arrive in Havana and the group of students in the Latin American School of Medicine (ELAM) who come from abroad.

**METHOD**

**Type of Study**

A prevalence study of malaria was carried out.

**UNIVERSE**

The total number of Cuban international travelers and foreigners living in Havana City who arrived in Cuba between January 1st, 2000 and December 31st, 2001, either by air or sea, and all students at ELAM during the 1999-2000 and 2000-2001 school years.

**Sources of Information**

Records from the International Sanitary Control Program at the Epidemiology Department of the Provincial Health and Epidemiology Center of Havana City.

Traveler records of the International Sanitary Control Program at José Martí International Airport.

**PROCEDURE**

Sources of potential malaria were identified by measuring malaria prevalence in international travelers living in Havana City who arrived in Cuba in the period under study. Upon arriving in Cuba, these passengers are assisted by the International Sanitary Control staff in arrival terminals (airport or port). They declare what country they are arriving from and whether they are sick. They receive a warning card and are instructed to contact the health authorities in the area where they live.

If a passenger arrives sick, he is immediately isolated for diagnosis and treatment at the Pedro Kourí Institute of Tropi-

cal Medicine (IPK), which is the institution in charge of exotic diseases in Cuba. IPK informs the provincial health authorities, which in turn advise municipal authorities of the case.

If the passenger is asymptomatic upon arrival, the port or the airport will inform the Provincial Health and Epidemiology Centers by telex, email or telephone. These institutions in turn contact each Municipal Health and Epidemiology Unit, which informs the specific health areas regarding the travelers’ situation and will start epidemiological surveillance through the family doctor and nurse, who apply a thick blood smear test. If the blood sample is positive, the traveler is immediately isolated at IPK. The time frame between the traveler’s arrival in Cuba and his or her visit to their doctor should not exceed 72 hours.

The analysis of this procedure made it possible to determine the total number of passengers, as well as the number of infected travelers, in the period under study. Calculations were made of general (by continent) and specific (by country) rates of travelers infected with malaria by continent and endemic countries of origin.

The same procedure was followed with the special group of ELAM students. Specific rates of sick students were calculated.

**RESULTS**

A total of 10,527 Cuban international travelers and foreigners living in Havana arrived in Cuba either by air or sea, coming from 65 countries on four continents: Latin America and the Caribbean, Africa, Asia and Europe. Of the total, 9,276 passengers arrived from 32 countries in Latin America and the Caribbean; 935 travelers from 20 African countries; 244 passengers from nine Asian countries; and 72 travelers from four European countries. In 2000, the highest percentage of travelers arrived from Latin America and the Caribbean. In 2001, the same airport and port received 7,077 travelers, coming from 75 countries on the same four continents: 5,896 passengers from 30 Latin American and Caribbean countries; 797 from 28 African countries; 341 from 16 Asian countries; and 44 from one European country. In both years the highest number of passengers arrived from Latin America and the Caribbean.

The number of passengers coming from endemic regions for the identification of potential malaria sources (Table 1) showed a total of 8,521 travelers (80.9%) coming from 46 endemic countries in Latin America and the Caribbean, Africa and Asia. Of these, 7,363 passengers (79.3%) came from 19 endemic countries in Latin America and the Caribbean; 925 (98.9%) from 19 African countries; and 233 (95.4%) from eight Asian countries. In 2000, 70% of the countries from which Cuban and foreign passengers living in Havana arrived were malaria endemic.

In 2001, potential malaria sources were related to the arrival of 6,409 travelers from endemic areas (90.5%), coming from the same continents as the year before, and from 60 malaria endemic countries. Of the total, 5,322 passengers arrived (90.2%) from 19 countries in Latin America and the Caribbean; 773 passengers (96.6%) from 26 African countries; and 314 travelers (92.0%) from 15 Asian countries.

It is notable that in 2000 the number of travelers arriving from malaria endemic zones was higher, while in 2001 the
number of passengers coming from these zones diminished and the number of endemic countries increased, especially in Africa and Asia.

In the distribution of travelers from endemic countries in 2000, the highest percentages were found in Mexico (14.2%), Venezuela (12.3%) and Brazil (11.3%) within Latin America and the Caribbean; South Africa (34.8%), Ghana (14.5%) and Angola (8.6%) in Africa; and China (41.6%), Vietnam (28.3%), and India and Iraq (7.7%) each in Asia.

The distribution in 2001 showed the same countries in top positions for Latin America and the Caribbean, and South America and Angola in Africa, with Guinea Bissau now ranked third with 9.3%. China and Vietnam topped the list in Asia again, plus Turkey with 6.6%.

Screening of the total number of passengers from malaria endemic areas (Table 2) identified 38 positive cases of *Plasmodium*, 24 of which were found in 2000 with a general rate for continents of 23.5/10,000 travelers, and a specific rate for endemic countries of 28.9/10,000 passengers. Nineteen infected passengers came from Africa, for a general rate of 203.2/10,000 travelers, and a specific rate for endemic countries of 205.4/10,000 travelers. Five cases were detected in passengers coming from Latin America and the Caribbean, for

TABLE 1: Continental distribution of number and percentage of travelers coming from malaria endemic zones in 2000 and 2001

<table>
<thead>
<tr>
<th>Year 2000</th>
<th>Year 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continent</td>
<td>Number of travelers</td>
</tr>
<tr>
<td>LAC</td>
<td>7,363</td>
</tr>
<tr>
<td>Africa</td>
<td>925</td>
</tr>
<tr>
<td>Asia</td>
<td>233</td>
</tr>
<tr>
<td>Total</td>
<td>8,521</td>
</tr>
</tbody>
</table>

Source: Epidemiology Department, Provincial Health and Epidemiology Center, Havana City

TABLE 2: Number of sick travelers and malaria prevalence rate per 10,000 travelers from endemic continents

<table>
<thead>
<tr>
<th>Year 2000</th>
<th>Year 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continent</td>
<td>Infected</td>
</tr>
<tr>
<td>LAC</td>
<td>5</td>
</tr>
<tr>
<td>Africa</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
</tr>
</tbody>
</table>

Source: Epidemiology Department, IPK

TABLE 3: Malaria cases, number of passengers and prevalence rate per 10,000 travelers from African countries

<table>
<thead>
<tr>
<th>Year 2000</th>
<th>Year 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries</td>
<td>Cases</td>
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<tr>
<td>Ghana</td>
<td>2</td>
</tr>
<tr>
<td>Cameroon</td>
<td>2</td>
</tr>
<tr>
<td>Congo</td>
<td>1</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>1</td>
</tr>
<tr>
<td>Nigeria</td>
<td>8</td>
</tr>
<tr>
<td>Angola</td>
<td>2</td>
</tr>
<tr>
<td>Equatorial Guinea</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
</tr>
</tbody>
</table>

Source: Epidemiology Department, IPK
a general rate of 5.3/10,000 travelers and a specific rate of 6.7/
10,000 travelers. Fourteen cases were detected in 2001 (a gen-
eral rate of 20.9/10,000 travelers and a specific rate of 22.9/
10,000 travelers); with Africa maintaining the highest rates.
No infection was identified in passengers arriving from endemic
areas in Asia during the period under study.

The distribution of malaria cases by country in Africa
(Table 3) included 19 sick travelers from seven countries in
2000 (general rate of 695.9/10,000 travelers), with Cameroon
(10,000/10,000 travelers) and Nigeria (5333.3/10,000 travel-
ers) being the countries with the highest rates.

In 2001, the highest rates of passengers who contracted
malaria in the African continent were found coming from Ivory
Coast (3,333.3/10,000 travelers) and Equatorial Guinea (2,000/
10,000 travelers). In 2000, Nigeria contributed the highest num-
ber of cases, while Cameroon showed the highest rate.

The distribution of infected travelers from Latin America
and the Caribbean (Table 4) during 2000 totaled five, includ-
ing Nicaragua with the highest rate (135.1/10,000 travelers).
The total number of cases dropped to 3 in 2001. The rate from
Haiti was 86.9/10,000 travelers, from Nicaragua 79.3/10,000
travelers and from Colombia 34.6/10,000 travelers. In the
two years considered for the study, Nicaragua showed the high-
est number of cases and the highest rate for this continent.

It is notable that the regional distribution of cases per
year for the special group at ELAM (Table 5) shows that in the
1999-2000 school year, all of the infected students came from
Latin America and the Caribbean, with a rate of 34.3/10,000
inhabitants. In the 2000-2001 school year, eight cases were
reported (general rate of 23.6/10,000 inhabitants), with Af-
rica showing the highest rate (283.1/10,000 inhabitants), and
Latin America and the Caribbean with a noticeably lower rate
in relation to the previous school year.
The specific distribution of sick students by country within the ELAM special group (Table 6) shows that malaria cases were reported from three countries in the 1999-2000 school year. The highest rate was found in Nicaragua (173.2/10,000 inhabitants). In the 2000-2001 school year, Nigeria showed the highest rate (500/10,000 inhabitants). In the two school years included in the study, the highest rates were found in these two countries.

**DISCUSSION**

With regards to Latin America and the Caribbean, we believe that the problem can be approached from another perspective, so that the exact province or town from which the traveler arrived can be traced. It is precisely with this goal in mind that it becomes necessary to specify where the passenger came from, in order to identify the true risk the traveler was exposed to. This can be done in the Health Area to which the traveler should report within 72 hours after his/her arrival. The family doctor can obtain this kind of information, making it possible to expand epidemiological surveillance beyond risk macro-identification by continent and country, to identify specific regions in each where malaria or other diseases are present.

In order to clearly illustrate our criterion, we will refer to facts we found through our research. In Latin America and the Caribbean, Mexico, Brazil and Venezuela - countries where malaria is endemic - showed a significant percentage in terms of number of travelers, but not in number of infected travelers. This is logical if we consider that a traveler may have been in Brasilia and did not visit another city or province. This same analysis may be applied to other travelers who may have been in Honduras’ Mosquitia region, for example. In this sense, surveillance can be made applied more clearly and accurately.

Despite Asia’s considerable number of endemic areas, no infection was detected among travelers coming from this continent. This allows us to suggest that, as for Latin America and the Caribbean, it is worthwhile to identify the exact place where the traveler is arriving from in Asia, to be able to assess the actual risk he/she was exposed to, and to take suitable action in epidemiological surveillance with a more rational use of material resources.

The results of the research carried out by Sabatinelli et al.[14] were similar to ours, as they found Africa to be the continent from which more Italian travelers arrived in 1997 and 1998. Likewise, Romi et al.[15] found similar results in Italian travelers in 1999 and 2000.[16]

Results similar to ours were also obtained by Muentener et al.[17] who argued that French, German, Italian and British tourists came from a larger number of malaria endemic zones in Africa than any other continent.

Couser et al.[18] obtained similar results. They argued that U.S. travelers go to, and come from, more malaria endemic zones in Africa than in America, Asia and Oceania.

Couser et al.[18] obtained similar results. They argued that U.S. travelers go to, and come from, more malaria endemic zones in Africa than in America, Asia and Oceania.

Like us, these authors did not identify the exact location or territory from which the travelers came, so the risk of exposure was thus very generally expressed in their results. This is the reason why we insist that our health system be equipped with the proper procedures to obtain traveler information and orient disease surveillance to be more geographic-specific.

The malaria endemic countries which rendered the highest infection rates in Africa were Nigeria and Cameroon, while Nicaragua showed the highest rates in Latin America and the Caribbean. This allowed us to conclude that these are high-risk countries to take into account for future surveillance action. It would still be necessary to locate the exact zones of origin in Nicaragua, as was pointed out before.

Sabatinelli et al.[14] concurred with us when they found Nigeria a high-risk country for their travelers, as well as Ghana, Senegal and Kenya.

We found results that were similar to those obtained by Couser et al.[18] for whom the highest number of malaria-infected travelers in the United States in 2000 and 2001 came from Nigeria. They also referred to the significant percentage of infected travelers who had visited Latin American and Caribbean countries like El Salvador and Mexico. This information did not match our results, as no cases were reported in our study of travelers coming from these countries.

**Conclusions**

- The main source of malaria among Cuban travelers in 2000 and 2001 was found in those who came from Africa. Nigeria and Cameroon were the countries with the highest rates in the African continent and thus posed the highest risk of this disease.
- In Latin America and the Caribbean, the highest malaria prevalence was found in travelers arriving from Nicaragua.
- ELAM was a high-risk group in malaria prevalence identified by malaria surveillance of international travelers in the period under study.

**REFERENCES**

Factors Associated with Tuberculosis in Patients with Acquired Immunodeficiency Syndrome in Cuba

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OBJECTIVES: To determine the factors associated with the development of tuberculosis in patients with acquired immunodeficiency syndrome (AIDS) and to identify the most frequent signs and symptoms of tuberculosis in this group of patients.

METHODS: This retrospective observational case-control study was carried out with 143 patients diagnosed with AIDS who were discharged from the Pedro Kourí Institute of Tropical Medicine, Havana, Cuba, between January 1997 and March 2001. The cases were 72 patients with AIDS and some clinical form of tuberculosis, while the control group was made up of the first 71 AIDS patients without tuberculosis who were discharged. The following variables were evaluated: AIDS stage before the study; serious opportunistic infections suffered before the diagnosis of tuberculosis (pulmonary pneumocystosis, cerebral toxoplasmosis, systemic candidiasis, isosporiasis, and recurrent pneumocystosis); concentration of CD4+ T lymphocytes, and clinical signs and symptoms of tuberculosis. The primary data were taken from the clinical files of the patients. We calculated the frequency of the nominal qualitative variables and the crude odd ratios (ORs) and their 95% confidence intervals (CIs). The statistical association among the variables was determined with the chi-square test with Yates correction. The individual effect of each variable was assessed through multivariate logistic regression analysis. The level of statistical significance was 0.05.

RESULTS: Tuberculosis in this group of patients showed a statistically significant association with: being ill with AIDS before the study (OR = 3.57; 95% CI: 1.78 to 7.17); a history of systemic candidiasis (OR = 10.47; 95% CI: 1.88 to 170.34); fever of unknown origin (OR = 13.38; 95% CI: 1.06 to 103.5); age diameter of the indurations were calculated for the cohort (pulmonary pneumocystosis, cerebral toxoplasmosis, systemic candidiasis, isosporiasis, and recurrent pneumonia); concentration of CD4+ T lymphocytes, and clinical signs and symptoms of tuberculosis. The percentage of skin tests that were positive and the average diameter of the indurations were calculated for the cohort. The symptoms associated with the diagnosis of tuberculosis were hemoptysis (OR = 7.56; 95% CI: 1.88 to 30.74); fever of unknown origin (OR = 13.38; 95% CI: 5.55 to 32.96); night sweats (OR = 21.95; 95% CI: 4.66 to 142.43); and weight loss (OR = 3.52; 95% CI: 1.63 to 7.55). The associated signs were regional lymphadenopathies (OR = 10.00; 95% CI: 1.22 to 220.33); hematopenia (OR = 5.44; 95% CI: 1.76 to 17.95); and splenomegaly (OR = 5.08; 95% CI: 1.63 to 16.83).

CONCLUSIONS: The signs and symptoms seen most frequently in patients with AIDS and tuberculosis are characteristic of tuberculosis in patients without AIDS. In patients with AIDS, tuberculosis can be associated with other diseases whose symptoms are similar to those of tuberculosis. Nevertheless, these results indicate that the traditional symptoms of tuberculosis can help diagnose tuberculosis in this group of patients.

Keywords: TUBERCULOSIS; HUMAN IMMUNODEFICIENCY VIRUS; CUBA

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Tuberculin Reactivity Among Ninth-Graders in Havana City

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OBJECTIVES: To determine the proportion of 14-year-old schoolchildren in the city of Havana, Cuba, with a positive tuberculin skin test, as an indicator of the prevalence of tuberculosis infection among them.

METHODS: Using single-stage cluster sampling, 1936 Mantoux (tuberculin) tests were carried out with ninth-grade students (cohort born in 1985) during the 1999–2000 school year in 20 junior high schools randomly selected in Havana. The tests were performed according to the standard technique recommended by the World Health Organization, and they were read after 72 hours.

The percentage of skin tests that were positive and the average diameter of the indurations were calculated for the cohort.
RESULTS: Of the tests read, 96% of them were negative (0–4 mm), 2.5% were doubtful (5–9 mm), and 1.5% were positive (> 10 mm). The percentage of reactivity was 0.1% when a cutoff value of 15 mm was used. The mean diameter of the indurations was 0.41 mm. No statistically significant difference was found between the genders.

CONCLUSIONS: In this study the proportion of schoolchildren with tuberculin reactivity, using an induration-diameter cutoff point of 10 mm, was very low (1.5%), and it was much lower (0.1%) when a cutoff point of 15 mm was used.

The skin reactions with an induration diameter of > 10 mm could be the expression of a natural infection if one takes into account the low frequency of bacillary tuberculosis in Cuba and that there is an inverse relationship between the time elapsed from the BCG vaccination and the intensity of the response to tuberculin. Therefore, that would mean that in this case the point prevalence of tuberculosis infection in this group of schoolchildren would be 1.5%.

Keywords: TUBERCULOSIS; TUBERCULIN TEST; CUBA

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The Epidemiology of Dengue and Dengue Hemorrhagic Fever in Santiago de Cuba, 1997

Valdés I; Guzmán MG; Kouri G; Delgado J; Carbonell I; Cabrera MV; Rosario D; Vázquez S

Abstract: A dengue epidemic that Cuba reported in 1997 registered more than 500,000 cases of dengue fever produced by viral serotype 1. In 1981, there was an epidemic of dengue hemorrhagic fever produced by serotype 2 of the virus. This time, 344,203 clinical cases were reported, 10,312 of which were severe cases of hemorrhagic fever that led to 158 fatalities (101 of them children).

The re-introduction of dengue, and specifically of dengue viral serotype 2 (Jamaica genotype), was quickly detected in January 1997 through an active surveillance system with laboratory confirmation of cases in the municipality of Santiago de Cuba, in the province of the same name.

The main epidemiological features of this outbreak are reported in this paper. A total of 3,012 cases were reported and serologically confirmed. These included 205 cases classified as dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), 12 of which were fatalities (all among adults). Secondary infection with dengue virus was one of the most important risk factors for DHF/DSS. Ninety eight percent of the DHF/DSS cases and 92% of the fatal cases had contracted a secondary infection.

It was the first time dengue hemorrhagic fever was documented as a secondary infection 16 to 20 years after initial infection. Whites were more at risk for DHF/DSS, as had been observed during the 1981 epidemic.

During the most recent epidemic it was demonstrated that the so called “fever alert” is not useful for early detection of an epidemic. Measures taken by the country’s public health officials prevented spread of the epidemic to other municipalities plagued by Aedes aegypti.


Construction and Characterization of a Non-proliferative El Tor Cholera Vaccine Candidate from Strain 638

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Abstract: In recent clinical assays, our cholera vaccine candidate strain, Vibrio cholerae 638 El Tor Ogawa, was well tolerated and immunogenic in Cuban volunteers. In this article we describe the construction of 638T, a thymidine auxotrophic version of improved environmental biosafety. In so doing, the thyA gene from V. cholerae was cloned, sequenced, mutated in vitro, and used to replace the wild-type allele. Except for its dependence on thymidine for growth in minimal medium, 638T is essentially indistinguishable from 638 in the rate of growth and morphology in complete medium.

The two strains showed equivalent phenotypes with regard to motility, expression of the celA marker, colonization capacity in the infant mouse cholera model, and immunogeneity in the adult rabbit cholera model. However, the ability of this new strain to survive environmental starvation was limited with respect to that of 638.

Taken together, these results suggest that this live, attenuated, but non-proliferative strain is a new, promising cholera vaccine candidate.

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Source: Infection and Immunity, November 2000, p. 6411-6418, Vol. 68, No. 11 . Available at: http://iai.asm.org/cgi/content/abstract/68/11/6411

MEDICC Review - Epidemics: The Cuban Approach
TOP STORY

Rain & New Initiatives Ease Drought

By Gail Reed and Julián Torres

Traditionally the good luck rite of showering fully clothed in the first rain of May has brought Cubans into the streets in droves, from youngsters to their grandparents. But the sky’s stingy offerings this May - a paltry 56% of the month’s average rainfall, following 18 months of severe drought - forced many to wait until June. The good news is that June rains hit 85% of their average by the last week of the month. The boost was enough to send reservoir levels to 36% of their combined capacity nationally, a modest turnaround on water depletion across the island that had reserves at a critical 27.1% the month before.

The rains, which were at or above traditionally high levels for June in several western provinces, also brought some reservoirs out of mothballs and returned water to the taps of at least 100,000 people in eastern Santiago de Cuba alone.

The more sobering news is that much still needs to be done - and much rain needs to fall - before Cuba’s worst drought since 1901 becomes history. In a country of 11.2 million inhabitants, World Food Program country representative Rosa Inés Antolín estimates that the drought has threatened to leave one of every six Cubans without access to water. Most seriously affected since 2003 are the eastern provinces of Las Tunas, Holguín, Santiago de Cuba, Granma and Guantánamo, as well as the central province of Camagüey. Of the country’s 235 reservoirs, 73 benefited from the June downpours, but another 17% are essentially dry. Nationally, rainfall for 2004 was only 952 millimeters, or just 69% of the historical average.

The severity of the drought has health officials on high alert, since increased health risks are inherent to fluctuations in water supply: drought presents challenges for hygiene and food security, while excessive rains and flooding can lead to an increase in water- and vector-borne diseases. In both cases, coordinated epidemiological surveillance of potential health risks is vital (see Training an Eye on Epidemics: Cuba’s National Health Surveillance System, this issue).

Government Response

Last year, the Cuban government created a high-level national commission to identify short, medium and long-term solutions to bring precious water to the population, livestock and agriculture; and to harness resources to implement these recommendations. As a result, US$20 million was invested in 2004, and another $160 million has now been earmarked for key projects.

In Holguín Province these include:

- The “transvase” project, to bring water from the largest reserve to replenish supplies in the driest zones. This means building a number of dams, plus 160 kilometers (km) of canals. As a result, in the first 2½ years, 800 million cubic meters of water are expected to be shifted westward, with 320 million cubic meters moved annually thereafter.
- A 28-kilometer pipeline to link two reservoirs, sending their combined resources to local towns and resort areas.
- A 52.8-kilometer pipeline and three pumping stations already installed to alleviate shortages in various parts of the province.

Along with Holguín, similar projects are under way in Las Tunas, Camagüey and Havana City, with a total of US$60 million going to rehabilitate water pipelines in these four provinces. In Santiago de Cuba, US$10 million is being invested in refurbishing ailing aqueducts in this city where hydraulic engineers estimate that up to 40% of the water that enters seeps away in leakage. Cisterns are also projected for each of Santiago’s 800 multi-family dwellings. In the meantime, the city’s residents are on a distribution schedule that only brings them water every three to ten days.

In the short run in the most affected areas, 1.4 million people are receiving water from cistern trucks; and special food supplements have been allotted to the most vulnerable in five eastern provinces.

World Food Program Aid

On June 17, the World Food Program (WFP) announced emergency assistance for 773,000 of the people most seriously affected. The aid, beginning in July, contemplates food assistance for children under five, pregnant women and the elderly; donations of water tanks and buckets to families dependent on cistern truck deliveries; and spare parts for the trucks themselves. WFP will fund the first month of the US$3.7 million program, and Ms. Antolín said she expects further support from donors such as the European Union, Canada and Japan. Due to the U.S. embargo, Cuba cannot access funds from the World Bank or the Interamerican Development Bank, according to Jorge Luis Aspiola, President of the National Hydraulic Resources Institute (INRH).

The Institute has estimated losses from the drought so far at US$835 million, or approximately 2.5% of the country’s GDP, plus significant losses of crops and livestock.
Cuban Cholera Vaccine Headed for Clinical Trials

By MEDICC Review Staff

Cuba’s Finlay Institute recently announced it will implement a range of international field trials for its vaccine against cholera. Mozambique, South Africa and Equatorial Guinea topped the list of possible trial locales.

The vaccine, presented recently at Havana’s Health for All Fair, is based on living strains of genetically attenuated cholera-transmitting bacillus, and has already been successfully tested on 100 volunteers in lab tests carried out on the island.

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according to WHO reports. Nor are they effective during epidemics because of the time the body needs to generate antibodies (two to three weeks).

Present-day vaccines are based on disactivated bacteria (with heat or chemical substances), or dead bacteria, to generate antibodies. The Cuban vaccine, however, is based on modifying the bacteria’s genetic makeup to attenuate its effect, and to use it as a short-term (two- or three-day) antibody generator.

Talks have been held with health officials from Mozambique, Equatorial Guinea and South Africa to undertake field trials that will make it possible to pursue studies on the candidate vaccine.

UN Proposes Havana-Based Disaster Prevention Network

By Conner Gorry

Cuba’s hurricane season - predicted to be worse even than last year’s devastating storms - kicked off June 1 with heavy downpours and a three-day workshop designed to more effectively prepare for, confront, and recover from natural disasters. Jointly convened by the Association of Caribbean States, the Cuban Civil Defense, the United Nations Development Program (UNDP) and the Office for the Coordination of Humanitarian Affairs (OCHA), Cuba, with its proven and hopefully replicable, natural disaster response program, was a logical location for the meeting.

Held from June 1st through 3rd, the purpose of the “Seminar Workshop for National Authorities: Risk Management Policies, Systems and Experiences in the Caribbean,” was to define a regional plan of action within the larger goals for international disaster preparedness and risk reduction. Such a plan is long overdue.

Following the deadly hurricanes that ripped through the Caribbean in late 2004 and the December 26 tsunami in Asia, experts from all over the world convened in Japan in January 2005 to draft the Hyogo Framework of Action (HFA). The Framework calls for worldwide strategies to minimize risk and loss due to natural disasters, which is critical as these become both more frequent and more powerful.

Natural Disaster Statistics

- More than 1.5 million people died from natural disasters in the last 20 years.
- In 2003, worldwide economic loss due to natural disasters totaled US$60 billion.
- In 2004, the Caribbean alone lost US$7 billion as a result of natural disasters.
- In September 2004, 3,006 Haitians died during Tropical Storm Jeanne.

Source: United Nations

According to UN Under Secretary General for Humanitarian Affairs, Jan Egeland, Cuba is a leader in the field, with one of the world’s best systems for protecting its citizens and a demonstrated ability to minimize and manage the impact of natural disasters. The meeting highlighted the opportunity for Cuba to transfer its best practices in disaster management to other countries of the Caribbean. Specific areas in which Cuba could help include organizing workshops, sending disaster specialists to countries in need and knowledge sharing about early warning systems, elaborated Egeland.

During the proceedings, a plan was outlined to develop an integrated regional network allowing nations to augment their capacity to confront and mitigate the effects of natural disasters. Proposed by the UNDP and agreed upon by consensus, the Havana-based network - known as the Cross Cultural Network for Disaster Risk Reduction - would have the support of various UN agencies, underscoring the importance of a multilateral, interdisciplinary model to resolve inequalities that exacerbate losses. Improving the social and economic conditions of the poor, who are the most adversely effected by natu-
Another First: 
Cuba Hosts IERASG 2005

By Michele Frank, MD

Some 150 delegates from 25 countries gathered in Havana from June 12-16 for the 19th Biennial Symposium of the International Evoked Response Audimetry Study Group: IERASG 2005. This is the first time the prestigious Symposium has been held in the developing South. Another first for IERASG, this year’s event was organized and chaired by a woman - Cuban neuroscientist María Cecilia Pérez-Abalo of the Cuban Neuroscience Center.

The IERASG is a neuroscience professional society organized to provide an open forum for the discussion of physiologic signals generated within the auditory system, according to its mission statement. The 2005 meeting’s topics included electrically evoked auditory response, cochlear implant evaluations, auditory neuropathy, technology and instrumentation, auditory steady-state responses, and screening for hearing impairment in newborns.

“From a scientific standpoint,” Dr. Pérez-Abalo told MEDICC Review, “this has been a great success. There was even a significant U.S. presence despite severe restrictions currently imposed by the U.S. on U.S.-Cuba scientific interchange.” Dr. Pérez-Abalo also pointed to the contributions of top specialists Dr. Adrian Davis and Dr. Martin Hyde of the United Kingdom and Canada, respectively, who spearheaded national screening programs for the early detection of hearing impairment in their countries.

Dr. Davis of the University of Manchester told MEDICC Review: “We wanted to hold this Symposium in Cuba because Cuba has played an essential and ongoing role in the development of Cognitive Neuroscience, particularly its relevance to children with hearing impairment. Cuban scientists have made quite a substantial contribution to the discussion of how we should screen babies for hearing loss.”

Several companies promoted their products during the Symposium, including Cuba’s Neuronic SA (an ISO 9001-approved company), which exhibited AUDIX, the first commercially available electro-audiometer system with Multiple Steady State Responses (MSSR). Already widely used in clinical practice, this electro-physiological system is designed to facilitate objective hearing assessment in infants and other difficult-to-test patients by including both Transient Auditory Evoked Potentials and MSSR.

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