

Aster Medical Journal

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Health Tech

India Fights Diabetic Retinopathy with AI

Clinical Medicine

Clinical Protocol for Nipah Virus Disease

Start-up

54gene - Unlocking the African Genome

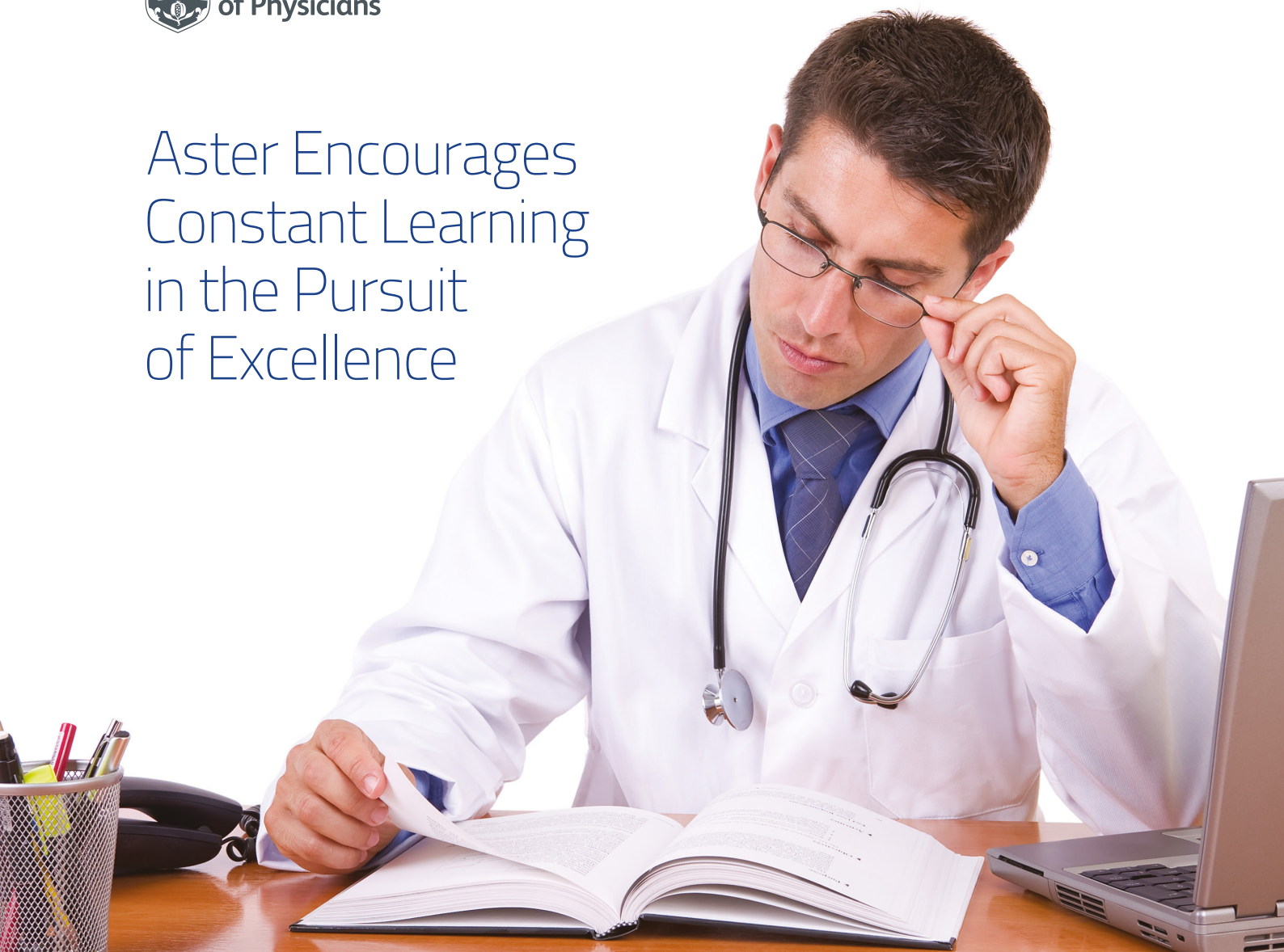
Chasing NIPAH

Nipah is one of the eight diseases the WHO has identified as epidemic threats in need of prioritisation. The list includes Ebola, SARS and Zika. Here is the journey of Nipah traced from the first outbreak in Malaysia to its latest outbreak in India.



Dr Kaw Bing Chua was the first to discover the Nipah Virus In 1998

Aster Encourages Constant Learning in the Pursuit of Excellence



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A young mother in northern Bangladesh's Lalmonirhat District still grieves over the death of her two young children during the 2011 Nipah outbreak there.



It's because of so many health officials, doctors, nurses and support staff, who tirelessly worked day and night, that we have been able to contain the outbreak so swiftly. This is unprecedented when compared to the outbreaks seen across the world. Be it private hospitals or government, or the state and central governments - all worked as a team.

— **K. K. SHAILAJA**, MINISTER OF HEALTH AND SOCIAL WELFARE OF KERALA, INDIA

Conversation



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Prologue



Rapid Detection is the Key in any Epidemic

It gives me immense pleasure to dedicate Aster Medical Journal (AMJ) to the medical fraternity. As a multi-channel knowledge-dissemination platform, the mission of AMJ is to advance healthcare by sharing knowledge and expertise.

Tracing the Nipah outbreak right from its first occurrence in Malaysia to the recent outbreak in India, this issue of AMJ offers comprehensive coverage of this zoonotic virus epidemic. Documentation of Kerala's encounter with Nipah is significant for the many lessons it offers to the world. Especially, the collaborative work across the public and private sectors, the interdisciplinary coordination, and the cooperation across all levels of governments, which have set a benchmark for the future.

I would like to congratulate the Government of Kerala and the Honourable Minister for Health, Smt. K.K. Shailaja. They stepped in with full alacrity and handled the epidemic with a gravity, deftness and promptness that prevented a potential catastrophe.

In any epidemic, quick detection is the key. The first part of the detection of the epidemic rests with the clinical acumen and alertness of the doctors. Here, definitely, it is our medical men who played a vital role in managing both the 2018 and 2019 Nipah outbreaks in Kerala. A round of standing applause to the outstanding clinicians of Baby Memorial Hospital Kozhikode, Government Medical College Kozhikode and Aster Medcity Kochi for early detection of the epidemic and excellent management of the Nipah patients and suspects.

Without a staunch support system, dealing with epidemics is a challenge of the top order. The healthcare professionals, media and the civic society in Kerala have rendered yeoman service during the Nipah epidemic, and we applaud their efforts here.

While we recognize the efforts of healthcare professions for containing the Nipah outbreak, it's important to mention the challenges in laboratory diagnosis in the event of an outbreak. Laboratory diagnosis is an essential element of infectious disease surveillance, both for routine confirmation of infections and the rapid identification of the cause of epidemics. Therefore, it's also imperative that we have increased access to cutting-edge virology labs.

I would urge stakeholders to pay attention to establishing BSL 4 labs in Kerala. It can improve detection capability and enhance efficiency of surveillance programs.

Dr Azad Moopen, MBBS, MD
Founder & Chairman, Aster DM Healthcare



1. K.K. Shailaja — a high school chemistry teacher-turned-politician, a third-time MLA, and Kerala's health minister. As health minister, she had a big role to play in dealing with the outbreak. Kerala has received international recognition for its effective prevention measures against Nipah virus outbreak.

2. Dr Anoop Kumar — critical care chief at Baby Memorial Hospital Kozhikode. Dr Anoop Kumar noticed strange symptoms in one of the patients admitted to the Baby Memorial Hospital during the first Nipah outbreak in 2018, which was later confirmed as Nipah.

3. Dr Bobby Varkey Maramattom
4. Dr Anup R Warriar **5. Dr Anuroop Balagopal** — a team of Doctors at Aster Medcity diagnosed Nipah in 'Patient Zero' during the 2019 outbreak and successfully managed the case to a complete recovery.



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"Key to the response was Kerala's past investments in education and health—the state ranks 10th in GDP among Indian states and territories, but first in human development."

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Editorial



Reimagining Scientific Journals

Scientific journals debuted in the 17th century with the French *Journal des Savants* and the *British Philosophical Transactions of the Royal Society*. These journals complemented scientific meetings, which had been, until then, the primary way of communicating science.

Medical journals have gone a long way since then. Now, they influence the quality of patient care and increase the clinical and academical acumen of healthcare professionals. They also help to remove practices that are not evidence-based. Ideally, medical journals are intended as a platform for the exchange of ideas at any level. Unless there is a free exchange of health information worldwide, the patients will tend to be the victims.

I am happy to introduce the inaugural edition of the Aster Medical Journal, which will soon emerge as a landmark publication covering a wide canvas within the health sector. It is different in many ways from a traditional medical journal. It aims to be an engaging platform for the exchange of ideas between the developed and developing world, a practicing physician and an academic researcher, a medical journalist or a scientist. Even if you don't work in science, or dislike long reads, AMJ would have something for you as the focus would be to shed new light and act as a catalyst to trigger new thoughts and actions amongst its readers.

The current issue of AMJ traces the journey of Nipah, offering perspectives from three Asian countries which reported a Nipah outbreak - Bangladesh, Malaysia and India. We also showcase an array of global experts on Nipah for an in-depth analysis of the epidemic.

I encourage contributions from the medical fraternity in our mission to advance healthcare by sharing knowledge and expertise. I am confident that the Aster Medical Journal will live up to the high, exacting standards we set for ourselves, and also evolve into a publication that is respected globally, showcasing expertise from some of the best of authors.

On the occasion of the release of AMJ, let me also thank Dr Azad Moopen for incubating this Vision and empowering Dr Shihad to go ahead and make this a reality.

Happy Reading!

Dr Harish Pillai
Editor & Publisher



ON THE COVER



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At \$2.1 Million, Zolgensma is the world's most expensive drug ever

Zolgensma® (onasemnogene abeparvovec-xioi) a new drug approved by the FDA, costs more than \$2.1 million. Zolgensma® is a gene replacement therapy indicated for the treatment of spinal muscular atrophy (SMA) in paediatric patients. Originally developed by Avexis, the drug became a part of Novartis' portfolio after it acquired Avexis in May 2018. Zolgensma can be a one-time, life-saving treatment that allows for children with SMA to function in ways unimaginable just a few years ago.



ICMR launches TB vaccine trial

Indian Council of Medical Research (ICMR) launched a vaccine trial to prevent the occurrence of tuberculosis (TB) among close contacts of a TB patient. The study would enroll over 12,000 healthy household contacts of sputum smear-positive TB cases that are at high risk of contracting the disease, from seven sites in six states -- Delhi, Karnataka, Maharashtra, Odisha, Tamil Nadu and Telangana. This is the first-ever government conducted vaccine trial after the BCG vaccine trial that was undertaken decades ago.

20 Million children miss out on life-saving vaccines, U.N. warns

More than one in 10 children - or 20 million worldwide - missed out last year on vaccines against life-threatening diseases such as measles, diphtheria and tetanus, the World Health Organization and the UNICEF children's fund said. In a report on global immunization coverage, the U.N. agencies found that vaccination levels are stagnating, notably in poor countries or areas of conflict.

India government doing the best possible for cancer research



The government is doing the best possible for research on cancer and the Department of Biotechnology's funding for such activities has resulted in vastly improved understanding of the disease, Union Minister Harsh Vardhan said. Observing that cancer is a serious disease, the Science and Technology Minister told the Lok Sabha that the best possible is being done for research on cancer. All future health programmes would focus on preventive and promotive healthcare, Vardhan, who also helms the Ministry of Health and Family Welfare, said during the Question Hour.

Bayer's MRI contrast agent gets FDA approval

Bayer AG said U.S. regulators approved its contrast agent for use in magnetic resonance imaging (MRI) to assess patients with known or



suspected coronary artery disease. The injection, Gadavist, is an approved agent for use in MRI of the central nervous system and breasts. Gadavist is the only contrast agent approved by the FDA for use in cardiac MR, Bayer said.

GSK drug helps ovarian cancer patients live longer

GlaxoSmithKline Plc's cancer treatment Zejula met the main goal of helping patients



with ovarian cancer live longer without their disease worsening says a late-stage study. The study, called PRIMA, tested the treatment as maintenance therapy in women who have undergone platinum-based chemotherapy and met the main goal for women regardless of their biomarker status, GSK said. For GSK, the success of Zejula would help it access a wider population group and give it an edge over rival PARP inhibitors such as AstraZeneca and Merck & Co's Lynparza and Clovis Oncology's Rubraca.



Lynn Johnson/Wellcome Photography

Katie's New Face, A full-face Transplant

At the age of 21, Katie became the youngest person ever to receive a full-face transplant. This was the critical moment after the donor's face was surgically removed before being transferred onto Katie. There was complete silence in the room as the surgical team absorbed the gravity of their mission. The transformational procedure took over 30 hours and was undertaken by a team of around 30 medical professionals at the Cleveland Clinic in Ohio.

China reports new African swine fever outbreak

China's southwestern region of Guangxi has confirmed a new outbreak of African swine fever. The new outbreak has killed 1 pig and infected 42 more on a farm in Guigang city, the Ministry of Agriculture and Rural Affairs said in a statement on its website.

China, the world's largest pork consumer, has reported 144 outbreaks of the incurable disease since August last year and culled almost 1.2 million pigs.



WHO: The Ebola crisis is an international emergency

The year-long Ebola outbreak in the Democratic Republic of Congo is a public health emergency of international concern, a WHO emergency committee has declared. It is only the fourth incident to receive the rare designation, including the 2014-2016 West Africa Ebola outbreak.



Africans are more genetically diverse than all other populations combined. Yet, African DNA makes up less than 2% of genetic research material.

54gene is building the world's first pan-African biobank to unlock the African genome

A Nigerian health tech genomics and AI start-up, 54gene is building Africa's largest biobank to tap into the multi-trillion-dollar global pharmaceutical industry. Africans are more genetically diverse than all other populations combined. Yet, African DNA makes up less than 2% of genetic research material in Genome-wide Association Studies [GWAS]. 54gene is now positioned to build the largest database of genomic and phenotypic consented data of Africans. The unique data sets will be used exclusively for research; to proactively address the significant gap the genomics market currently poses for Africa, using African DNA to focus on drug discovery opportunities that will improve access.

54gene was founded in 2019 by Dr. Abasi Ene-Obong and named for the 54 countries that make up the African continent. Born in Calabar, Nigeria, to parents who were both researchers and academics, Ene-Obong is uniquely qualified for the job. He has a doctorate in cancer biology from the University of London, a master's degree in business administration from Claremont College in California and a master's degree in human molecular genetics from the Imperial College of London.

The company is currently collecting data from ten of the largest research and public hospitals in Nigeria and expects to hold 40,000 samples of participants in its biobank. The current focus is on sampling the genetic material of cancer patients, patients with cardiovascular diseases and metabolic diseases like diabetes and sickle cell anaemia.

Ene-Obong says he became fascinated with genetics from the first moment he took a class in the subject in university. He believes African genetic data may hold the key to unlock medical discoveries in the future. "The osteoporosis drug Romosozumab was discovered by investigating a genetic mutation in South African Afrikaner patients, and Alirocumab, a cholesterol drug, was discovered by researchers at the University of Texas at Austin, who identified a genetic mutation in an African population," says Ene-Obong.

The thesis behind Ene-Obong's company was enough to attract \$4.5M seed round from several investors — including Y Combinator, Fifty Years, Better Ventures, KdT Ventures, Hack VC and Techhammer, among others.

In focus

CHASING NIPAH

Nipah is one of eight diseases WHO has identified as epidemic threats in need of prioritisation. The list includes Ebola, SARS and Zika. We are tracing the journey of Nipah from the first outbreak in Malaysia to its latest outbreak in India.

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LESSONS IN HISTORY THE NIPAH STORY

It's a myth that Nipah is seen only in Kerala. To date India had 3 outbreaks the first being in January and February 2001 at Siliguri, West Bengal causing 45 deaths and subsequently in 2007 at Nadia District causing 5 deaths.

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HOW ONE MAN SAVED THE COUNTRY FROM NIGHTMARE VIRUS

It was a balmy Sunday evening in early 1999, and Dr. Kaw Bing Chua hadn't had lunch or dinner. There wasn't time to eat. Chua was chasing a killer.

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Nipah Outbreak



Member of a Nipah-focused team of doctors and scientists based at the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B), Hossain M. S. Sazzad and Farasha Bashir discuss one of the organization's initiatives. They both are part of a 20 member team charged with investigating and following up on suspected Nipah outbreaks across the country.

PHOTOGRAPHY BY A.M. AHAD



Chasing Nipah

Undoubtedly, the progress that's been made over the past two decades in understanding Nipah virus and implementing infection control interventions has saved countless lives. Still, the potential for a catastrophic outbreak looms large.

by **Steven Bedard**

The young man shifts nervously in the front seat of the van as it turns down increasingly narrow roads, then alleyways, and eventually dirt tracks. His broad grin and swagger have faded since he first volunteered to lead us to the home of a local gachhi, a collector and seller of date palm sap. Leaning out the open window, he asks for directions from three men standing over the parts of a disassembled engine scattered on a dusty concrete floor, then from a man butchering chickens on a wood block out front of a roadside stand.

Whether our guide's waning confidence is due to the fact that he doesn't know the area as well as he first let on, or because revealing a local secret to a vanload of outsiders might be frowned upon isn't clear. But after casting a few wary glances over his shoulder, he resigns himself to continuing our quest.

The gachhi we're searching for is not just any sap collector. He's rumored to make and sell tari, a fermented brew that's popular among men in this part of northern Bangladesh—especially bus drivers, truckers, and day laborers—but one that's prohibited for two reasons. In this predominantly Muslim nation tucked under the crook of India's east arm, consumption of alcoholic beverages is forbidden (except by foreigners), so tari has always been technically off-limits. But now, even fresh date palm sap is banned because of its connection to an emerging infectious disease that is threatening to become the next global epidemic.

In 2005, scientists drew a link between this nearly universally loved local delicacy and Nipah virus encephalitis, a disease that has killed nearly 75 percent of those who have contracted it since 2001, when Bangladesh's first outbreak occurred. Scientists' understanding of the link between the sap—fermented or otherwise—and Nipah infection grew stronger as subsequent outbreaks mounted. But it wasn't until 2011, in the wake of a particularly deadly winter, that the Bangladesh government declared a ban on the sale of date palm sap, an act akin to the U.S. government prohibiting the sale of apple cider.

Of course, banning a substance that's loved by so many and enforcing such an order are two different things, particularly when the risks of consuming that substance are poorly understood. Which is precisely why this team of public health investigators from an organization funded in part by the U.S. Centers for Disease Control and Prevention (CDC) has come here to the village of Mohonpur, near Bangladesh's northeast border.

The team's lead, Hossain M. S. Sazzad, a physician who also holds a Master's degree in health economics, leans forward and addresses the young man in the front seat in a calm, measured tone. He explains that he and his

colleagues are not here to enforce the ban. They're health workers, he says, and only wish to talk and learn.

When the track narrows to a width the van can no longer squeeze through, the team sets off on foot. We follow a path that cuts between thatch- and tin-roofed homes, past goat pens, and along spindly fences lined with reeds that have had dung hand-molded along their lengths and been left to dry in the sun—fuel for another day. Dogs bark, and women and children wrapped in brightly colored cloths come to observe the spectacle of city folk traipsing through their village. Eventually, the team turns down a narrower side path leading to a dwelling that several villagers have pointed them toward. The whereabouts of the local gachhi, it turns out, is not a particularly well-kept secret.

They find the sap collector behind his house hacking at a stack of thick, green bamboo cuttings piled on the ground. While his greeting is less hospitable than is customary in Bangladesh, he seems more perplexed than annoyed by the unannounced visit.

As if amiably chatting with a farmer about the weather and his crop, Sazzad asks the man about his daily activities, his health, his method of sap collection, if he's heard about Nipah virus, if he ever observes bats near the trees he taps.

Standing a pace or two away from the group, the old man, his white hair and beard glinting in the dappled sunlight, says that he's been climbing and tapping date palms on this land since before the country's 1971 War of Independence. He's now 85. As evidenced by more than a dozen clay pots lying on the ground behind him, he admits that he still collects sap daily during the winter, but now only for personal consumption, and claims he doesn't ferment it to make tari.

A few moments later, though, the man asks if anyone in the group wants to purchase sap from the haul he collected the night before. When they decline, his scant interest in the conversation vanishes entirely. He turns, gathers up his tools—a handful of clay pots, a long, curved knife he uses to carve away the bark of date palms, and a rope that

will loop around his waist and the trunks of the trees as he climbs them—and sets off to make his afternoon rounds.

This brief exchange feels anticlimactic to me, especially after our long search for the source of a potentially fatal outbreak. Sazzad and the others don't seem fazed, though. In a way, it's emblematic of the inconclusive and unfinished nature of the work they do—and its importance. Yes, the gachhi will continue collecting, and likely selling, date palm sap. But now they know exactly where he lives, and that this is an area they will need to keep an eye on.

While the man is not the villain I may have envisioned when we were searching for him—just an old man looking to make a few extra Taka by tapping the local trees—these health workers, and health officials around the world, know that the next outbreak could begin with him, or someone just like him. And although Nipah virus has killed fewer than 400 people since it was first identified 20 years ago, they also know that the pathogen's persistence in the environment, its ability to change quickly, and its potential, under the right set of conditions, to spread like wildfire could enable the next outbreak, or the one after that, to become a pandemic. Many experts think that the right set of conditions might already be in place here and across a vast swath of western Bangladesh known as the “Nipah Belt.”

As we make our way back through the village, I can't help retracing the steps I took to get here. It's just a few kilometers and a very plausible route from this tiny village to a city center and onto a crowded bus through one of the most densely populated countries in the world, then on to the country's capital of nearly 9 million, and possibly onto an international flight bound for another metropolis. It took me two days to travel that route in the other direction—well within the virus's incubation period.

Nipah virus encephalitis is one of eight diseases that the World Health Organization (WHO) has identified as epidemic threats in need of prioritization. The list includes Ebola, SARS, Zika, and an as-yet unknown affliction referred to as “Disease X.” All eight have been prioritized because of their inherent epidemic potential, and also the fact that there are currently insufficient measures in place to prevent them.

While the WHO's “priority pathogens” vary in terms of their geographic distribution and the havoc they inflict on the human body, they have a couple of things in common that enhance their epidemic potential. First, they're all viruses (or likely to be in the case of Disease X). Second, they're all zoonotic, which means that they all reside in another animal, but are capable of jumping, or spilling over, into humans. These characteristics are important,



PHOTOGRAPHY BY A.M. AHAD

because viruses reproduce very quickly, which amplifies their potential to change into more pathogenic forms. And a reservoir host acts like a bunker, a safe haven between outbreaks, in which the pathogen can regroup and potentially undergo a change, a random mutation that will better prepare it for the next spillover opportunity.

Nipah virus's safe haven is the fruit bat, or more accurately, several species of bat in the genus *Pteropus*. Fruit bats, also known as flying foxes, are small- to medium-sized herbivorous mammals that roost in trees by day and take to the wing by night in search of nectar, pollen, and fruit. According to Emily Gurley, an epidemiologist at Johns Hopkins Bloomberg School of Public Health who has been studying Nipah in Bangladesh since 2004, most bats in the genus *Pteropus* carry antibodies for Nipah or other closely related henipaviruses. That means the bats have at least been exposed to the pathogen, and many harbor live viruses in their tissues.

Gurley and other scientists think that fruit bats have carried Nipah virus for a very long time. “The bats have always had it,” she says. Not only that, she suspects that the virus began spilling over into humans hundreds of years ago, if not more. Until recently, though, there were likely fewer opportunities to do so. There was also no diagnostic test for the virus, and so, like trees falling in the forest with no one to hear, when spillover events did occur, they went unnoticed.

After its early, unheralded debuts, Nipah virus found its big opportunity in 1998 in the tiny Malaysian village of Sungai Nipah from which the virus acquired its name. The factors that led to that first big spillover event are unfortunately all too familiar in the histories of zoonotic pathogens, currently responsible for 75 percent of all emerging infectious diseases. As the number of humans on the planet has exploded toward and then beyond 7 billion, we've increasingly pushed into and degraded natural ecosystems, causing many organisms to go extinct, and putting ourselves into close contact with those that remain. The lifeforms we now cohabitate with include both the animals and plants we can see, and the microbes they harbor, which we can't.

Ecologist and epidemiologist Raina Plowright prepares to release a little red flying fox (*Pteropus scapulatus*) after collecting tissue samples from the animal.

According to Kevin Olival, an ecologist and evolutionary biologist for the non-profit organization EcoHealth Alliance, it was this type of ecological shift that led to Malaysia's 1998 outbreak. Olival, who has studied routes of transmission from bats to humans all over the world, says that "contact between these animals and people has probably always happened to some degree because we both eat fruit—so there's always been some overlap." But, he says, industrialized agriculture near forest edges over the past several decades has dramatically altered that interface, intensifying contact between bats and humans.

In the mid- to late-90s, pig farming was booming in Malaysia. Farmers cleared forest to make way for more and larger operations. This not only put the farms in closer proximity to the wildness of the rainforest, it reduced the number of fruit and nectar trees available to bats. Drought and fires in Indonesia in preceding years also contributed to food shortages and caused bats to migrate greater distances in search of flowering and fruiting trees. Many of them found what they were looking for around Malaysian pig farms, which were often lined with mango trees. The bats, at least some of which carried Nipah, feasted on the cultivated fruit. And if a bat-nibbled mango dropped into a sty from the tree above, a pig had a chance of picking up the virus along with a tasty snack.

Infected pigs suffered acute respiratory distress, like a horrible case of the flu. The vast majority of animals on stricken farms became infected, and 20 percent of those that fell ill died. Farm workers who handled sick and dying pigs fared even worse. After an incubation period of several days to more than a week, many workers who were exposed developed encephalitis, an often-deadly inflammation of the brain.

Encephalitis is common in Nipah sufferers. But in 1998, no one had ever heard of Nipah virus, and it wasn't clear how people were getting sick in the first place. Doctors initially suspected an outbreak of Japanese encephalitis, a mosquito-borne disease. Eventually, though, when the infections were linked to direct contact with pigs, they realized they had something different on their hands. Identification of the virus in the cerebrospinal fluid of an outbreak victim confirmed that the pathogen was not only new to science, it was of a type known to be carried by mammals, not mosquitoes.

With this telling but incomplete knowledge in



PHOTOGRAPHY BY GARY TABOR

hand, the Malaysian government took a bold step. It ordered the slaughter of more than a million pigs in the hope of preventing a national or global health crisis. Like amputating a limb to stop a rampant infection, the move crippled the country's booming pork industry in a matter of weeks. But it also stopped the Nipah outbreak in its tracks. By May 1999, the nightmare was over. Unfortunately, this would not be the last the world had seen of Nipah virus.

The pathogen reemerged in two separate outbreaks in 2001, one in Siliguri, India and another in Meherpur, Bangladesh. Although the infectious agent was confirmed to be Nipah virus, there were some alarming differences in these new outbreaks. First, neither India nor Bangladesh had large-scale pig farming operations, so there was no obvious intermediate host. More troublingly, the new outbreaks, though significantly smaller than Malaysia's, had much higher fatality rates—about 70 percent. What's more, a number of cases in Siliguri resulted from caregivers being infected by patients. The virus had jumped from person to person.

Although Nipah was at the heart of each case, the virus was clearly behaving differently from place to place, outbreak to outbreak. And that pattern, or lack thereof, has continued over the past 17 years. Bangladesh has seen at least one new Nipah outbreak nearly every year since 2001. India has documented several more as well, including the last outbreaks in 2018 and 2019 that killed 17 of the 19 people who were infected.

What this variation and regular recurrence means is that health workers like Sazzad and Gurley never quite know what to expect from their moving target. "In Bangladesh, we have documented closing in on a hundred different spillover events," says Gurley. "So, that's a hundred different opportunities for a more transmissible strain to be introduced into people. And that's scary."

A lone figure in a long silk shirt and tupi hat pedals silently down a road of damp, red clay packed hard by ages of foot and wheeled traffic. He rides past a great egret probing the surface of a flooded rice field, and between towering fig trees and houses still quiet under a blanket of cook-stove smoke and pre-dawn mist.

In the morning stillness, it's hard to believe that the chaotic crush of Rangpur City is just a short, harrowing 5-kilometer drive from here. There, pushcarts and auto rickshaws and lumbering trucks filled with bricks will soon begin jockeying for position in front of merchant stalls, some peddling mobile phones, others cooking biry-

“Maybe we see high rates of excretion in winter because there’s less food available. We just don’t know.”

—Raina Plowright, Ecologist & Epidemiologist

ani and flatbread over open fires. Here, the chaotic competition is of a different kind—ecological, otherworldly.

Above our heads, hundreds of fruit bats are coming home to roost. Their translucent wings stretch wide as they maneuver between careening bodies and twisted tree limbs before braking hard, grasping with outstretched feet, and awkwardly hanging themselves upside down for the day. As disorderly as the bats’ morning approach may seem, the real scrum begins when they land. Someone’s always too close, or hanging in a prime patch of sun or shade. Often the only way to regain one’s rightful place in the roost is with a warning screech or a swift nip or wingslap.

Fortunately for these bats, the antagonism remains within the colony. This group of Indian flying foxes (*Pteropus medius*) has been lucky enough to take up residence in an enormous sacred fig tree (*Ficus religiosa*), which sits at the center of a local Hindu temple. Though the fig’s twisted trunk brings to mind the menacing trees from *The Wizard of Oz*, the temple’s low, deteriorating walls demarcate a peaceful place in which the tree and its many inhabitants can live out their existence free from harassment.

While the temple offers an extra level of protection, people in Bangladesh are generally resigned to living among bats. “They’re everywhere,” says Gurley. “There’s hardly any village, among the hundreds we’ve visited, that doesn’t have a bat roost.”

Driven by a lack of primary forest and reliable food resources across much of their native range, the bats likewise seem resigned to living near people. Just like their relatives in Malaysia, bats in this region frequently take advantage of cultivated crops such as mangoes and figs to make up for the native fruit and nectar missing from their diets. Many have also developed a taste for date palm sap.

In 2004, when Gurley first began studying Nipah in earnest, she and her team of investigators quickly zeroed in on that bat-sap connection. They asked Nipah survivors and loved ones of the deceased about direct contact with bats, about tree climbing, about living near bat roosts and eating fruit that had fallen from trees. They also asked about consumption of date palm sap. Of all the activities the team explored, sap drinking was one of the most consistent among those who had fallen ill.

The clearest evidence of sap contamination, though, came in 2010 when researchers set up infrared cameras trained on the collection pots that gachhis had hung on date palm trees. The results of this study couldn’t have been more telling. Over 20 nights of observation, the cameras captured 132 visits from fruit bats on 14 separate nights. Bats could be seen lapping up the sweet sap oozing from the sections of tree trunk where the gachhis had shaved the bark away. In some instances, the images captured bats in the act of relieving themselves directly above the collection pots. The contamination was unintentional, of course, but the possible route of transmission was undeniable.

Among mammals, bats rank number one in terms of their role in spreading zoonotic diseases. Scientists have linked them to at least a dozen human afflictions, including four of the eight diseases the WHO has prioritized. Exactly what makes bats such good hosts for disease-causing agents—or if in fact they are particularly suited to carrying and transmitting disease—has been poorly understood for decades. But new research suggests that the answers may have something to do with flight.

While a number of mammals can glide, bats are the only members of the group capable of sustained flight. This feat requires a huge amount of energy—a 16-fold increase in metabolic rate, according to Raina Plowright, a veterinarian and professor of epidemiology at Montana State University. That high sustained output would typically be associated with oxidative damage to cells, she says, but somehow bats have developed mechanisms to prevent or repair the damage.

Bats are also long-lived compared to similar-sized mammals. As a general rule, the more you weigh, the longer you live. But bats are complete outliers in that respect, Plowright says. For example, the oldest known bat, which lived 41 years, weighed less than 8 grams. This suggests that bats have a way to combat the cell damage that typically leads to senescence. “We think that somehow this ability to not have oxidative damage and the ability to repair DNA and not go into senescence are tied up,” she says, “and perhaps even tied up with their ability to host viruses.”

Because bats typically live in large colonies and roost in close proximity to one another, microbes are easily passed among members of the group. While virus numbers are typically kept in check by each bat’s immune system, when an animal

is stressed, its defenses can become compromised. Much as a cold might make us cough and sneeze, a bat's weakened immune system can cause the animal to shed viruses into its surroundings through saliva, urine, and feces.

According to Plowright and Gurley, bats tend to shed viruses in pulses, high concentrations of the pathogens excreted by a colony into the environment over a short period of time. These pulses seem to coincide with Nipah outbreaks, but what stresses the bats in the first place is unknown. Plowright suspects an ecological cause, possibly related to food. "We don't know much about their response to the environment and nutrition," she says. "Maybe we see high rates of excretion in winter because there's less food available. We just don't know."

Those unknowns are of course what flash through my mind on this winter morning as I stand there gawking up at hundreds of bats that have just returned from a night of foraging. I glance down at the backpack I carelessly dropped into the perpetually damp soil at the base of the tree when I first arrived. Now I can't help wondering: How much virus does it take to get sick? How much am I breathing in now? Unfortunately, not even the experts have the answers to these questions.

Two weeks from now, when I'm back in the U.S. and most likely safely outside the virus's incubation period, I'll quiz Gurley about my activities that morning—and the mist that I may or may not have felt as I stood under the roost. Choosing her words carefully, she'll explain that bats do tend to urinate more frequently in the morning. "So, they leave the roost at night to feed, right? And when they come back, that's typically when they urinate so... yeah, I probably wouldn't do that again...."

“Bats are now staying closer to their food sources because the habitats that provided high-energy nectar in the winter are mostly gone.”

—Peggy Eby, Bat Ecologist

In January of 2010, Sazzad found himself in the midst of one of the most uncomfortable moments of his career. Sitting in an isolation room at the Faridpur Medical College Hospital, wearing gloves and an N95 surgical mask designed to prevent the spread of airborne viruses, the soft-spoken, then-33-year-old doctor was interviewing a patient who suffered from fever, dizziness, and shortness of breath. The man's nephew had died from Nipah virus encephalitis about a week earlier, as had three other people from the same village. By the time the patient arrived at the hospital in Faridpur, he was so disoriented that his responses to Sazzad's questions were mostly nonsensical. In 2010, knowledge was limited about how Nipah manifests in the human body or how it spreads. Still, Sazzad knew more than enough to be cautious.

But it was stuffy in the isolation room, and Sazzad, who was coming down with a cold and was feeling pretty lousy himself, felt like he was suffocating behind his mask. Twice during the stifling, hour-long interview, the urge for fresh air became so overpowering that he slipped the back of a pen under the edge of his mask to create a small gap. Just a quick breath, he thought.

The next morning, Sazzad learned that the patient had died, and a diagnosis was confirmed. Nipah virus had been raging through the man's body during the interview. When the young doctor started coughing that night, a concerned colleague called Sazzad's advisor Stephen Luby, a professor of medicine at Stanford University who at the time was stationed at the CDC office in Bangladesh, to ask what to do. They all told themselves it was just a cold, but Sazzad couldn't stop thinking about those two breaths. Or about his wife and one-year-old son at home. Eventually, a blood test put their anxieties to rest. But all these years later, when he tells me the story as we tour a hospital ward just two floors above that isolation room, he still visibly shudders.

A member of a Nipah-focused team of doctors and scientists based at the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), Sazzad is one of about 20 staffers charged with investigating and following up on suspected Nipah outbreaks across the country—all on an annual budget of \$150,000 per year. That's no small task in a nation that's roughly the size of the state of Illinois and packed with a population that's more than half that of the entire U.S.



What was once pristine rainforest, the Bukit Pelandok region of Malaysia now lies in ruin, the victim of industrialized agriculture such as pig farming.

Interviews with sap collectors, potential Nipah victims, and past outbreak survivors are a key part of the team's efforts to understand the disease and its transmission. Despite having conducted more than a hundred of these high-stakes conversations, Sazzad still sometimes feels nervous. "When you are just inside an outbreak," he explains, "when you don't know the whole picture of who's transmitting to whom, you feel very unsafe, because you don't know if you have been exposed or not. You could be part of the chain."

Despite the risks, Sazzad and his colleagues persist, because they know the next conversation they have or observation they make may mean the difference between life and death for someone—or many. They also know their front-lines work is leading to a much clearer picture of the way the virus works, providing the basic information necessary to help stop a future epidemic.

The symptoms of the disease are now well documented, although they vary considerably from patient to patient and strain to strain. While some infected humans are completely asymptomatic, most initially develop symptoms including fever, headaches, vomiting, and sore throat. Some develop acute respiratory infections in the early stages of the disease; others never do. After a few days to a couple of weeks, many patients start to exhibit more serious signs of encephalitis—dizziness, drowsiness, altered consciousness, and other neurological changes. Within another day or two, the disease often progresses to coma, then death.

Transmissibility is also highly variable. While the world has yet to see a strain of Nipah virus that is especially proficient at jumping from human to human, many past spillover strains have managed to make that leap, traveling in fluids spewed from a mouth or nose, or through urine or blood. "Immunological studies have shown that the primary route of human transmission is through saliva," says Sazzad, "but we still don't know if a fraction of cases are caused by airborne transmission. Is there any additional route of transmission? We don't know."

So far, most documented person-to-person transmission has been from patient to family caregiver. Even in hospitals, patients are more likely to receive direct care from a family member than a doctor or nurse, partly because of staffing levels at the hospitals and partly because of cultural taboos around physical contact with strangers.

As Sazzad and I walk the concrete halls of the Faridpur Medical College Hospital, I recall a pre-trip conversation with Gurley, who told me that one of the biggest challenges her team faces in their infection-control work in Bangladesh is that family members, and

in many cases even the health workers, caring for Nipah patients "don't understand contagion and how diseases are being transmitted." Mothers hand-feed food to sick children, then finish the leftovers themselves. Daughters use the long folds of their skirts to wipe mucus from a dying parent's face, then use the same skirt to wipe their own tears moments later.

Now that I'm here, it has become abundantly clear that it's not only possible for person-to-person transmission to happen inside hospital walls—it's likely.

According to Gurley, who led the Surveillance and Outbreak Investigation Unit and directed the Programme on Emerging Infections at ICDDR,B from 2003 to 2015, it's not a matter of if there will be another pandemic on our crowded and degraded planet, it's a question of when, and which disease it will be—Ebola, Disease X, Nipah? She's spent the past 15 years, first at ICDDR,B and now at Johns Hopkins, doing everything in her power to make sure it's not Nipah.

After my trip, having seen everything she's up against, I comment that I'm amazed by her ability to stay motivated in the face of such monumental challenges.

She laughs. "I think the word you're looking for is 'stubborn,' right?"

Her persistence is unquestionably derived, in part, from her self-described love of big, hairy problems. "I guess I run under the assumption that if there's a good reason to do something, then there's gotta be a way to figure it out," she admits. But she reminds me that she has reasons to be optimistic about the progress they're making.

While there's never enough money to go around, and while Gurley and Sazzad both lament the fact that sexy projects like vaccine development are much easier to secure support for than things like hospital infrastructure and disease surveillance, total funding for Nipah research and response is at an all-time high. Most of the other diseases on the WHO watch list still attract far more attention than Nipah, but at least, says Gurley, "it's on the radar."

Additionally, thanks to intensive surveillance efforts over the past 15 years, Gurley says we now know more about how to stop Nipah than we do many other emerging infectious diseases. "We know how to prevent transmission of Nipah from wildlife to people," she points out. "Can we do that

for Ebola? No. And it's because we haven't spent the same time with other diseases monitoring every single case and looking into it."

But knowing what needs to change and convincing people to make those changes are two very different matters.

Once Gurley's team determined that bat-contaminated date palm sap was the culprit in most, if not all, Nipah outbreaks, they launched an educational campaign urging people to stop drinking raw sap. But since they knew most people would continue to risk drinking the delicacy, they also started looking into possible "safe sap" options.

For decades, some gachhis have wrapped their sap collection pots in protective shields that resemble bamboo placemats. They've done so not because they were worried about disease transmission, but because they wanted to keep bats and birds from drinking and dirtying their hard-earned sap. Most gachhis rarely took this precaution, presumably because scaling towering date palm trees is hard enough without lugging extra equipment up the trunk. But when field studies proved that the skirts reliably kept bats out of the sap, Gurley's team began campaigning to make that practice the norm.

They visited dozens of gachhis in many dozens of villages to pitch them on the benefits of safeguarding their sap collection pots with bamboo skirts. They produced posters and aired docudrama PSAs with soap-opera-style storylines warning people of the dangers of drinking unprotected sap. They hired locally trained anthropologists to help them frame their messaging in the best possible way. And their efforts have helped, a bit. But, says Gurley, "getting people to change what they do when it's culturally ingrained is really hard. Really, really hard. I mean, people still smoke cigarettes. People still

start smoking cigarettes!" In Bangladesh, gachhis still collect sap all across the Nipah Belt, most often without bamboo skirts. And in each of those villages, people still consume unsafe sap.

Behavior change is also a major factor in the team's efforts to prevent person-to-person transmission. Installing portable hand-washing stations, or even running water, in hospitals, for instance, will only help control infection to the extent that health workers can convince people to start washing their hands. The same is true for ongoing efforts to develop faster diagnostic tests that would allow for earlier diagnosis and reduced transmission opportunities—those tests will only matter if health workers can convince more people to seek treatment. "A hospital in Bangladesh, it's a really unpleasant place," says Gurley. "If you're in the context of an outbreak, and everybody who's gone to the hospital has died, why would you go?"

One key to incentivizing hospital visitation, says Gurley, is the development of therapeutic drugs that could at least treat, if not cure, the disease. "Realistically, medical facilities currently have very little to offer people with Nipah. They can provide some basic supportive care, but most of these people are going to die," she says. If better treatment options were available, more patients might be motivated to seek medical care, which would improve both surveillance efforts and the potential for better infection control.

As a member of WHO's Nipah Virus Taskforce, Gurley is currently advising on efforts to develop both therapeutic drugs and vaccines. The latter now has the benefit of a \$25 million grant from the Coalition for Epidemic Preparedness Innovations (CEPI) for the development of a candidate vaccine, which is projected to be ready for human trials within the next five years.

When asked if a vaccine is likely to solve the Nipah problem, Gurley is quick and decisive with her response. "A vaccine itself is never going to be the only answer. The only disease we've ever eradicated with a vaccine is smallpox." It would certainly help, especially to be able to inoculate the health workers, like Sazzad and his medical technicians, who regularly come into contact with or treat Nipah patients. But, she says, infection control and surveillance are always going to be important, as are diagnostics and therapeutics. "All these issues are linked together. In some ways that's daunting, and in another way, it can give us some

“We have documented closing in on a hundred different spillover events. So, that’s a hundred different opportunities for a more transmissible strain to be introduced into people. And that’s scary.”

—Emily Gurley, Epidemiologist



Arifa Nazneen and Hossain M. S. Sazzad, members of ICDDR,B Nipah surveillance team, conduct a physical examination of a gachhi in Bangladesh's Faridpur District.

optimism that if we make progress in just one area, it will reinforce all the others."

Undoubtedly, the progress that's been made over the past two decades in understanding Nipah virus and implementing infection control interventions has saved countless lives. Still, though, the potential for a catastrophic outbreak looms large.

In 1994, Hendra virus—a deadly, bat-borne disease that is closely related to Nipah—jumped from bats to domesticated horses for the first time (at least as far as anyone knew). Endemic to Australia, the virus has since killed more than a hundred horses and has made the leap from livestock to humans on seven occasions. As the outbreaks began to mount, Raina Plowright returned to her native Australia to study the dynamics of Hendra virus transmission. Since her path to infectious disease research included a degree in veterinary medicine, and a Master's in epidemiology, she was quite possibly the perfect person to take on this challenge for her PhD.

After assembling a diverse team of collaborators, including veterinarians, range managers, behavioral ecologists, and virologists, Plowright set out to identify the factors that had regularly, but so far unpredictably, led to Hendra spillover. As the research progressed, she observed that each of her colleagues viewed the virus through the lens of their particular specialty, and most seemed to view the piece they studied as the most important one—the factor ultimately responsible for spillover.

To gain a more complete view of Hendra transmission, Plowright forced herself to step back a pace or two. Suddenly she began to see the virus's route from bat to human as a series of barriers through which the pathogen must pass to move from reservoir host to recipient. The concept that Plowright sketched that evening before it could once again fade from view was a stack of widely spaced layers. Like slices of Swiss cheese, each layer was pockmarked with holes that represented potential routes the virus might exploit to move on to the next step.

The arrangement of the layers in Plowright's mind was anything but arbitrary; it was hierarchical. In other words, if a virus was unable to circumvent any one barrier, spillover would be impossible—and none of the other barriers in the chain would matter, regardless of how porous they might be. The uppermost layer in Plowright's model, for example, represented the distribution of a reservoir host

population, specifically its proximity to people or domestic animals. No matter how transmissible or virulent a virus might be, if a reservoir host had no contact with a recipient, spillover couldn't happen.

The many layers that Plowright sketched that evening illustrated why spillover isn't inevitable; it's actually quite difficult, and rare. Not only does a virus need to find a route through each barrier, but those Swiss cheese holes need to be aligned with one another in space and time. The virus can only get through if it has a straight shot. "It's kind of a no-brainer," Plowright says now. "Of course that's how it works."

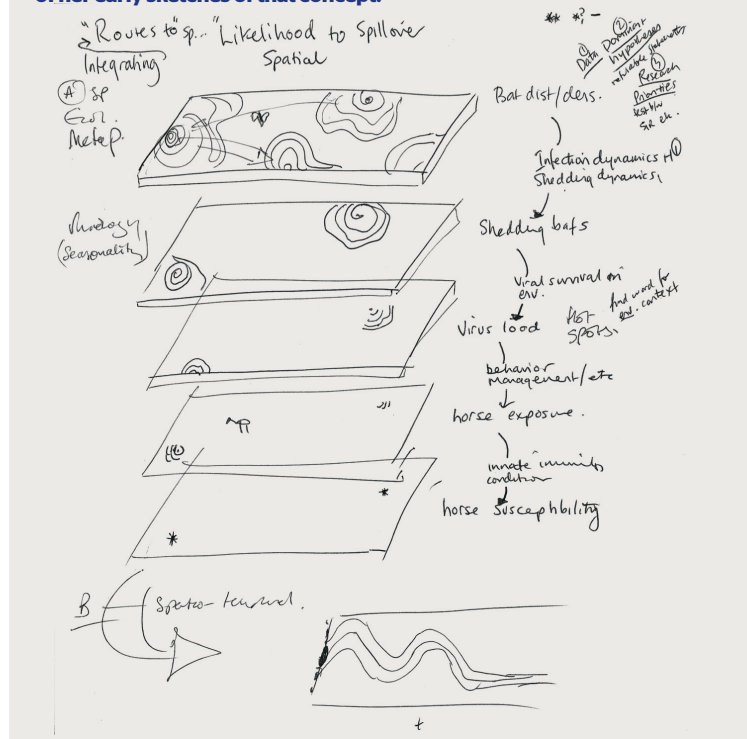
Still, the more she looked at her sketch, the more she felt like she was onto something important. She could see how various changes in the environment, or the virus's genetic makeup, or the recipient host's immune response could influence the size and position of those holes, making it easier or more difficult for spillover to occur. The framework was not only an intuitive way to think about zoonotic disease, Plowright thought, it might also help researchers pinpoint the most effective ways to close off those routes of transmission and prevent spillover from happening in the first place.

Historically, our battles against infectious diseases have largely been waged at the level of the recipient host—the person who has fallen ill or who might become infected in the future. That's the level that medical care, drug therapies, and vaccines target. Plowright is quick to acknowledge the critical role that medical and public health workers play in disease prevention. "But," she says, "we think we could probably prevent spillover at the top, at the level of the reservoir host... rather than at the lowest level of recipient-host susceptibility."

For the past 25 years, one of Plowright's collaborators, a bat ecologist named Peggy Eby, has documented the rapid decline of native forests in eastern Australia, and the dramatic shifts in bat populations that have followed. Plowright suspects that this ecological degradation has been a major cause of the increased incidence of Hendra virus outbreaks. "Something has switched in the system," she says. "Bats are now staying closer to their food sources because the habitats that provided high-energy nectar in the winter are mostly gone." That switch has put Australia's bats in closer contact with people and domestic animals as the bats supplement their diets with cultivated fruits and ornamental flowers.

Spillover Diagram >

When Raina Plowright began to look at the many factors that influence the spillover potential of viruses like Hendra and Nipah, she began envisioning the route a virus must take as being punctuated by a series of layers whose holes can open or close to make transmission easier or harder. This is one of her early sketches of that concept.



Although there are surely many environmental factors involved in Hendra transmission, the timing and location of several recent outbreaks has led Plowright to key in on one in particular: food. “For some reason, it’s the winter after nutritional stress events that seems to be the worst for Hendra spillover.”

Another observation that supports the connection between food availability and Hendra outbreaks also hints at a potential ecological intervention—one that could reduce viral shedding and pull bats back out of cities and into more natural habitats. Eby observed that when spotted gum trees flower, an event that occurs every few years, the bats empty out of cities to take advantage of this rich food source. Now the scientists are exploring ways to mimic this effect by encouraging agencies and organizations working on reforestation projects to incorporate winter-flowering trees into their replanting efforts. Plowright imagines that a similar type of intervention might also be possible in Bangladesh, encouraging bats to rely more on natural sources of food.

Such speculation will soon be put to the test as Plowright, Gurley, and more than 20 other collaborators begin an ambitious \$10 million research project that will span eastern Australia and Bangladesh’s Nipah Belt, as well as Ghana and Madagascar, where closely related bat-borne viruses are also found. The aim of this research, funded by the Defense Advanced Research Projects Agency (DARPA), is to understand the ecology of Hendra, Nipah, and other henipaviruses, how they’re sustained within bat populations, and why they’re excreted. The hope is that this information will help scientists, doctors, and

public health workers identify bottlenecks in the spillover process, where applying relatively little effort and expenditure could have a significant impact on reducing a virus’s epidemic potential.

With research teams going into the field this month, just as Bangladesh’s Nipah season gets underway, it’s impossible not to view this work as a race against the clock—albeit one with significantly better odds of success with a new influx of funding.

Back under the sacred fig tree, as I watch the light and color drain from the sky, it strikes me that this is an appropriate place to begin my journey back home. Among all the experiences I’ve had in this fascinating, beautiful, and troubled country, this is perhaps the most bewildering and overpowering. With the roots of the local Hindu’s venerated tree under my feet, I hear the Muslim call to prayer burst from a loudspeaker in the unseen distance. High above, the bats stir, their urge to feed now undeniable.

As a crowd of villagers gathers, I’m struck by the amalgam of nature and people and tradition and modernity all gathered together in this one tiny plot. This, I think, is why Nipah’s epidemic potential is so great—potentially. The old gachhi’s unprotected collection pots hang from date palm trees just 4 kilometers away as the bat flies. There, a new strain of Nipah virus could jump to a little girl or an entire village tomorrow morning, or next week. Days later, a doctor—or a journalist—who has visited those villagers in their homes and hospital wards could board a plane bound for Hong Kong. And this is just one of countless ways that a small spillover event could metastasize into a pandemic.

I shudder to think of the possibilities as I make my way back to the van with Sazzad and the others. Just before we climb in, several dozen bats drop from their perches, open their wings, and head off into the remaining orange light above the horizon. In this moment, it’s hard to imagine the bats going anywhere other than the many sap collection pots nearby. But maybe someday, if an ecological intervention takes root, a future flight path will carry these reservoirs toward native fruits and flowers instead.

As the bats dissolve into the darkness, Sazzad and several of the others bid them adieu. “*Ḍnāra samaḌa*,” they say in unison. “Dinner time.”

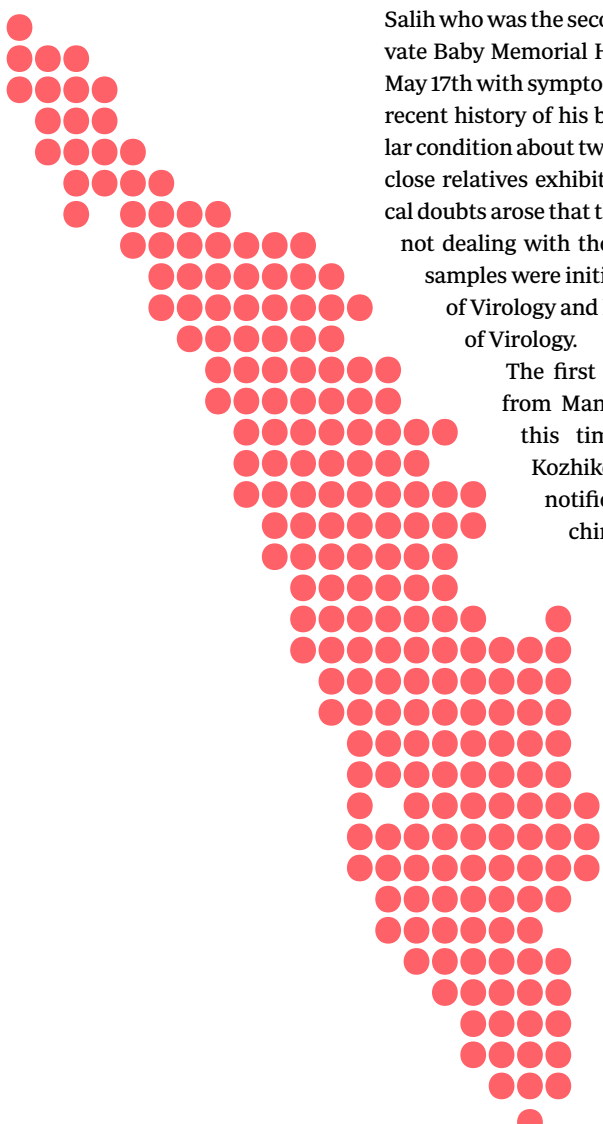
Steven Bedard, Editor-in-Chief, bioGraphic’s
by California Academy of Sciences.



Lessons in History The Nipah Story

The State of Kerala with its experience of handling the 2018 Nipah outbreak and its high alert and proactive deployment of key resources in 2019 is best placed to share inputs for a draft national policy

by **Dr Harish Pillai**



It was on May 2nd 2018 when the first Index - Mohammed Sabith - was taken to a Kozhikode Sub divisional hospital and from where he was referred to the Kozhikode Medical College for better care. During the care process in the Casualty, CT room and ICU, the infection spread through direct contact to other people who later succumbed and took the final total death toll to 16. His brother Mohammed Salih who was the second case, was taken to the private Baby Memorial Hospital in the early hours of May 17th with symptoms of encephalitis. Due to the recent history of his brother's demise from a similar condition about two weeks prior and three other close relatives exhibiting similar symptoms, clinical doubts arose that the treating medical team was not dealing with the usual case of encephalitis ; samples were initially sent to Manipal Institute of Virology and later to the National Institute of Virology.

The first positive identification came from Manipal on May 18th. It was at this time that the authorities at Kozhikode Medical College were notified and the state health machinery under the leadership of the Health Minister K.K Shailaja Teacher and then Additional Chief Secretary Rajeev Sadanandan rose up to the daunting challenge in isolating and containing the outbreak to just two state districts -Kozhikode and Malappuram. A total of 18 people was infected of which 16 died and 2000 people who were in direct contact with the infected cases were kept under close observation and verified twice daily. Any person showing symptoms were

immediately shifted in specially prepared ambulances to the specifically designated two buildings within the Kozhikode Medical College (away from regular Outpatient activities) where facilities for triaging, observation and isolation were created with clear segregation zones.

The deployed healthcare workers had undergone an intense course in safe and protective handling procedures and the exact standards for Ebola cases were adopted. Finally, the State government declared the outbreak over on June 10, 2018. Subsequent studies by Indian Council of Medical Research (ICMR) showed that Fruit Bats at the Changorath village in Kozhikode district were found positive for Nipah.

It's a myth that Nipah is seen only in Kerala. To date India had 3 outbreaks the first being in January and February 2001 at Siliguri, West Bengal causing 45 deaths and subsequently in 2007 at Nadia District causing 5 deaths. In 2001 the doctors at Siliguri were clueless as to what hit them, the infection initially was said to have spread from a nursing home through health care workers, patients and their relatives. Utter panic spread throughout the town and it was almost deserted. The state government had to deploy health care resources from Kolkatta to contain and isolate the outbreak. Later investigations by the National Institute of Virology showed a case fatality ratio of 74%.

Like mentioned before even in the first episode in Kerala, it was the clinical insight of the medical team at the private hospital that helped in the correct diagnosis. As per ICMR scientists about 20% of wild fruit bats are known to be carriers of Nipah virus and hence they are present across the country. Unfortunately, no proper epidemiological studies have been conducted at the annual seasonal fever related deaths nor do we have a national policy or guideline in the management of Nipah. The State of Kerala with its experience in handling the 2018 Nipah outbreak and its high alert and proactive deployment of key resources in 2019 is best placed to share inputs for a draft national policy. Interestingly the State government had to borrow the national guidelines of Bangladesh to manage the situation in 2018!

A combination of climate change and rapid urbanization is increasing the acceleration of bat-human interfaces, with the virus crossing from Bat to Human in the Index case and then spreading aggressively from human to human. The most effective way to control the spread and prevent future outbreaks is through widespread education and public health activities focussing on prevention. Once infected it is now known that hospitals both in public and private sector will play a key role in early diagnosis/ detection and isolation of cases.

Stringent adoption of infection control protocols, use of personal protection equipment (PPE's) and setting up of fever clinics with triaging facilities specially during the times of seasonal outbreaks and immediate notification to public health authorities of suspected cases can go a long way to control outbreaks. It's also essential to have low cost point of care PCR diagnostic kits made available to designated nodal public hospitals. The clinical, epidemiological, administrative and political experiential learning that is currently available in Kerala needs to be documented and used in the preparation of the national guidelines.

The current index case was referred to Aster Medcity from a peripheral hospital with a history of fever since 10 days. He arrived early morning on May 30th at the emergency department with fever and showed all signs and symptoms of encephalitis including slurring of speech and altered sensorium. Further work up by the Consultant Neurologist including blood markers and a MRI Brain showed an atypical clinical picture for encephalitis that necessitated the dispatch of CSF sample to an NABL accredited lab for testing of a viral panel that included Nipah.

The Infectious Diseases Consultant was also notified who helped in analyzing the various differential diagnosis based on available clinical information. Within 48 hours of the arrival of the patient a positive result for Nipah was obtained that triggered the next chain of events. Immedi-

ately the patient was isolated to a negative pressure isolation room and all barrier precautions put in place. The District Medical Officer - DMO was notified and through him the District Collector and consequently the State Health Secretary and Health Minister. The rapid response of the public health authorities was remarkably quick and efficient and all possible support was given to the hospital in form of management guidelines, supply of anti-viral medicines. Further samples were taken and send to nodal labs at Allepey, Manipal and to the National Institute of Virology, Pune. The test results were all positive for Nipah and the rest as they say is history.

As I write this piece, the Index case is clinically stable and the 3 healthcare workers who were direct care givers and quarantined in the Government Medical College, Ernakulam have all tested negative for Nipah. It's a much-needed good news to the entire hospital and also to the state at large and reflects strongly on the stringent infection control protocols practiced at Aster Medcity. The most important take away lessons from this experience is the critical importance of early diagnosis, isolation containment of the patient and the adoption of infection control norms by hospital workers. As seen in the two instances in Kerala, the initial clinical suspicion resulted due to the alertness and clinical acumen of consultants at private hospitals. This may also hold true for a large number of patients across India, hence it will be most help for the clinicians involved to publish their findings in peer reviewed journals so that the larger community of doctors especially the general practitioners have a good reference point to make an early diagnosis. Thankfully to date, unlike in 2018 even though the state is on full alert no fresh cases have turned positive.

The early governmental response, decisive leadership, quick mobilization of resources, active vigilance posture, coordinated communication to the public through all media channels and the highly mature and responsible actions by them have all resulted in a state of calm that is truly laudable. A large deployment of central and state teams are already at work to understand the how's and why's of transmission to the Index case and hopefully the country at large will be better prepared for handling any possible future events of a similar nature.

Dr Harish Pillai, CEO - Aster India

It will be most help for the clinicians involved to publish their findings in peer reviewed journals so that the larger community of doctors especially the general practitioners have a good reference point to make an early diagnosis.

HOW ONE MAN SAVED HIS COUNTRY FROM A NIGHTMARE VIRUS

IT WAS A BALMY SUNDAY EVENING IN EARLY 1999, AND DR. KAW BING CHUA HADN'T HAD LUNCH OR DINNER. THERE WASN'T TIME TO EAT. CHUA WAS CHASING A KILLER. AND HE THOUGHT MAYBE HE HAD FINALLY TRACKED IT DOWN.

HE SLID THE SLIDE UNDER THE MICROSCOPE LENS, TURNED ON THE SCOPE'S LIGHT AND LOOKED INSIDE. "A CHILL WENT DOWN MY SPINE," CHUA SAYS. "THE SLIDE LIT UP BRIGHT GREEN, LIKE BRIGHT GREEN LANTERNS."

Right there, in Chua's hands, was a virus the world had never seen before. And as he soon learned, it's also one of the most dangerous ones.

Now Chua had enough of the virus to kill everyone in the lab. Maybe worse.

The new virus — eventually called Nipah — is on the World Health Organization's list of viruses most likely to cause a global pandemic. It's the virus that inspired the 2011 movie *Contagion*. And just this past January, governments and philanthropists

pledged hundreds of millions of dollars to develop a Nipah vaccine because it poses such a big threat.

Back in 1999, Nipah was spreading across Malaysia. And Chua was the only one who knew it.

But nobody believed him. Chua was still training in virology at the University of Malaya in Kuala Lumpur and didn't have clout or confidence.

"I called my department head at his home. I said, 'Prof, please come. I want to show you something,'" Chua says.

by **Michaeleen Doucleff / Jane Greenhalgh**

Today **Dr. Kaw Bing Chua** is a scientist at Temasek Life Sciences in Singapore. When he discovered the Nipah virus, he was a graduate student at the University of Malaya in Kuala Lumpur, Malaysia.



Photography By Sanjit Das

Chua's professor told him to throw away the experiments — that Chua was wasting time. But Chua didn't throw away the virus. Instead he packed it up and brought the samples to the U.S.

Living in a nightmare

An hour south of Chua's laboratory experiments, a mysterious disease was devastating a farming town called Nipah. The disease was as deadly as Ebola, but instead of attacking blood vessels, it attacked the brain.

"I was practically begging people to believe me."

It felt like living in a nightmare, says Thomas Wong, who was a pig farmer in Nipah at the time. "Every day we were seeing in the newspaper that people were dying," Wong says. "I lost many friends. Many friends."

The disease struck lightning fast. Young men would be healthy one day.

The next day their brains would swell up. They couldn't walk. Or talk.

"They'd become comatose, and some of them became paralyzed," says Dr. C.T. Tan, a neurologist at the University of Malaya, who took care of patients from Nipah.

There was nothing Tan could do. No cure, no treatment. About half the patients died.

"We didn't know what it was," he says. "It was terrifying."

Nearly 1 in 3 families in Nipah had already lost someone. And the window of opportunity for keeping the disease contained was quickly closing. It had already spread to several states and

hopped over the border into Singapore — where 4 million people lived.

Yet the Malaysian government told people not to worry. It said the disease was coming from mosquitoes. And it had it under control because it was spraying for mosquitoes.

Both Tan and Chua thought the government was wrong. And there was one big clue: "No Muslims were getting sick," Tan says.

Mosquitoes don't care which religion you practice. "So if the disease was coming from mosquitoes, you would have Muslims, Hindus and Christians getting sick," Tan says.

But only Chinese Malaysians were catching the disease — and even more specifically, only Chinese farmers raising pigs.

"As you know, Muslims don't handle pigs," Tan says.

Pigs were crying

At this point, Chua agreed with Tan: This disease wasn't coming from mosquitoes. "No, no I knew it was something else, and people were dying!" he exclaims.

"But no one would believe me," he says. "I was practically begging people to believe me."

So Chua had to get crafty.

He persuaded his professor to send him to a Centers for Disease Control and Prevention lab in Fort Collins, Colo. Scientists study mosquito-borne diseases there. They also have a powerful microscope that would show exactly what type of virus was causing the problem.

Chau wrapped up samples of the virus in special packaging, put them in his carry-on luggage and hopped on a plane.

"It was an emergency," Chua says. "I had to get the samples there very quickly."

When a scientist put the samples into the microscope, Chua says a sense of great fear rushed through him: "The moment I saw the screen, I said 'Goodness! It's a paramyxo!'"

The image revealed the telltale signs of a frightening group of viruses: paramyxoviruses.

These viruses come from livestock, not mosquitoes. And they often infect the lungs. So they can spread rapidly through the air. Measles is a type of paramyxovirus, and it's one of the most contagious viruses on Earth.

Chua quickly realized just how dangerous this virus could be. He rushed to a phone and called

The entrance to the town of Nipah, which the Malaysian government quarantined in 1999 to try to stop the spread of a new deadly virus. "It was like a ghost town," says Thomas Wong, a former pig farmer in Nipah. "No one could come in. No one could leave."



Photography By Sanjit Das

Pig farm workers push live pigs into a large grave in Nipah in 1999. To stop the outbreak, the Malaysian government culled almost 1 million pigs, nearly destroying the country's pork industry.

officials in Malaysia. "Stop fighting mosquitoes!" he told them. "It's coming from pigs."

The Malaysian government listened. And it did something very drastic.

"Malaysia's army moved in for the country's biggest-ever animal culling," Journeyman Pictures reported in a documentary back in 1999. "Almost 1 million pigs, shoved into pits and shot."

Awali Muniandy helped with the pig culling. He says it was a horrific scene.

"The pigs were screaming, and you could see some tears on their faces," says Muniandy, who's with the Department of Veterinary Services Malaysia. "It was pitiful."

But the culling worked. The outbreak completely stopped. The new killer virus appeared to have vanished.

And the world was left with a mystery: Where did the pigs get the virus?

Huge pig farms turned into virus factories

It took more than a decade to figure all out, but eventually scientists realized that pigs had been getting Nipah virus for years. Maybe more. They very likely picked it up from bats.

But the outbreaks were small. And no one really noticed because the farms were small.

"In the olden days, the pigs were running and the family would look after a few pigs," neurologist Tan says.

Then in the '80s and '90s, Malaysia went through a massive economic boom. Families were entering the middle class. They could afford to eat pork several times a week.

So farmers changed the way they raised pigs. They started packing the pigs into tight quarters and industrializing the farms. They could produce more meat with fewer resources. But the productivity bump came with a cost: "When a virus got into the pigs, it could multiply very quickly," Tan says.

When you have thousands and thousands of pigs on one farm, there's a seemingly endless supply of new piglets to infect. The pig factory becomes a virus factory. The virus spreads like wildfire through the whole farm. Hops to another farm. And eventually jumps into farmers.

"The way people grow their food has changed; so has the way diseases spread," Tan says. "Agri-



Photography By Andy Wong/AP

cultural industrialization was part of what triggered the outbreak."

This pattern has occurred throughout human history. When we change the way we interact with animals, we unleash new diseases.

For example, when people first started raising cows and farming, thousands of years ago, we very likely started catching something like the measles from cows.

Now we're in a new phase of agriculture: factory farming. From it, we've gotten a new strain of the flesh-eating bacteria disease MRSA, a slew of bird flu, swine flu and Nipah.

In Malaysia, pig farms have gotten cleaner. Farmers break large farms into smaller ones and keep pigs isolated from other animals and people. As a result, Nipah has stayed away.

But across Asia, there have been at least 16 outbreaks of Nipah since 1999 — in India, Bangladesh and the Philippines.

And there are signs the virus is becoming more dangerous. In the Malaysian outbreak, the fatality rate was about 40 percent, and the virus didn't seem to spread between people. But more recently, Nipah has killed up to 70 percent of those infected — and can spread not only from animals to people but also between people.

"The world is changing so fast," says Tan. And sometimes the only way to keep up is when a scientist like Chua isn't afraid to challenge the status quo.



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Vinod Thomas



Key to the response was Kerala's past investments in education and health—the state ranks 10th in GDP among Indian states and territories, but first in human development.



Lessons from the Nipah outbreak in India.

Vinod Thomas is visiting professor at the Lee Kuan Yew School of Public Policy, National University of Singapore, and Asian Institute of Management, Manila, and former Senior Vice President, Independent Evaluation, The World Bank.

Health experts are rightly alarmed that the world is unprepared for the next pandemic. So, when the rare and deadly Nipah virus broke out in the southern Indian state of Kerala, many feared that it would spread on the scale of SARS in China or Ebola in West Africa. But the authorities and the public controlled its spread. Key to the response was Kerala's past investments in education and health—the state ranks 10th in GDP among Indian states and territories, but first in human development.

A Nipah infection leads to acute respiratory problems and brain inflammation. The virus—of which there is no vaccine yet—was first identified in among pig farmers in Malaysia, when it killed over 100 people in 1998. Cases now appear almost yearly in Bangladesh, and there were two previous occurrences in West Bengal, India. Its containment in Kerala was impressive because this Nipah strain was more deadly and infectious than the one in Malaysia.

Much has been learned about the links between the degree of preparedness and the effectiveness of the response to a breakout of infectious diseases. Being prepared involves vital elements ranging from labo-

ratory surveillance to communication about the risks.

The key to containment in Kerala was the speed of detection. One reason the virus was contained was the relatively high proportion of doctors and nurses in Kerala, and that private spending on health is the highest in India. Kerala's high literacy rate may not have the expected economic payoffs, as heavy regulations and labor laws have stifled growth. But its contribution to health care and participatory responses comes through in this recent experience.

The equal presence of women in the workforce enables the use of the full potential of the society's human capital. Girls are educated as much as boys; a girl born in Kerala can expect to live to 78 years, comparable to upper middle-income countries. The line of command in the Nipah campaign included both men and women not only in senior health management but also among the doctors and paramedics involved in containing the spread of the virus.

Community spirit and societal resilience, underscored by a high degree of participatory style of governance, played a part as well. Kozhikode Medical College's doctors, nurses, and administrators went into high gear. Notable was the mutual trust and social cohesion beyond religious divides in India's most religiously diverse state.

Against these positives was the environmental destruction in Kerala, particularly related to garbage disposal in urban areas. Had the authorities not been able to quickly contain the virus, ecological factors would have spurred its spread. Worsening environmental degradation was connected to outbreaks of the mosquito-borne Chikungunya virus in Kerala and the Zika virus in Brazil. In both instances, reckless deforestation and urban decay played a role.

In the wake of worldwide threats of new viral outbreaks, Kerala's experience holds lessons going forward. Disease prevention and rapid response, coupled with environmental protection, should be bigger priorities everywhere.

Conversation



**“I hope India will
set up a longterm
surveillance
programme on
Nipah”**
- Dr Emily S Gurley

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**“Nipah outbreak
should be a wake-
up call for AES
surveillance in
India”**
-Dr G Arunkumar

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**“If we know that
the bats are there
and they have the
virus, why would
we be surprised
that humans are
infected?”**

“I hope India will set up a long-term surveillance programme on Nipah”

Dr Emily S Gurley is an infectious disease epidemiologist at the Department of Epidemiology, Johns Hopkins University and a member of WHO's Nipah Virus Taskforce.

Dr Emily S Gurley has worked in public health research in Bangladesh since 2003 and spent 12 years at the ICDDR-B (International Center for Diarrheal Diseases Research, Bangladesh) where she led the Surveillance and Outbreak Investigation Unit and served as Director of the Program on Emerging Infections. She worked closely with the US CDC and the Government of Bangladesh to establish national surveillance for meningoencephalitis, respiratory infections, acute gastroenteritis, acute hepatitis, and hospital-acquired infections, with a focus on developing junior scientists. Dr Gurley leads multi-disciplinary studies on the

transmission, burden and epidemiology of a variety of emerging and established diseases, taking into account the ecological context in which human disease occurs. She has been working on describing the ecology and epidemiology of Nipah virus since 2004, including identifying transmission pathways and drivers of person-to-person transmission, and designing and testing interventions to prevent human infection. She currently serves on WHO's Nipah Virus Taskforce, advising on the research and development of medical countermeasures. Her research adopts a One Health approach to the study and prevention of Infectious Disease, taking into account the ecological context in



PHOTOGRAPHY BY GMB AKASH

which human disease occurs. Emily is the lead for the Bangladesh component of Preventing Emerging Pathogenic Threats (PREEMPT) program to study henipaviruses in bats, and the Co-Director for the Child Health and Mortality Prevention Surveillance (CHAMPS) site in Bangladesh, which aims to determine the aetiology of and prevent child deaths.

AMJ: Where did it all begin, your association with the Nipah outbreak in Bangladesh?

Dr Gurley: The first time that I moved to Bangladesh I was 11 years old. It was 1986. It's been like a second home for me. I moved there again in 2003, and that's when I first began working at the ICDDR-B, an international health research organization located in Dhaka. And at that time, I was a young public health researcher starting to work in infectious diseases. It was in January 2004, right after I began, that one of the early outbreaks in Bangladesh was identified, and that was the first outbreak of Nipah that

was investigated in real time. I remember it was a very traumatic community event, traumatic to bear witness to the destruction of this Disease. It is a terribly compelling Disease. After the first outbreak, it was clear to me that I would be studying that disease for a long time, so, I've been working on it since 2004 in Bangladesh, and I lived there for most of that time. I came back to the US for my doctoral studies and then went back to Bangladesh. I relocated to Baltimore in 2016 after the terrorist attack in Dhaka, but my work is still there. I'm usually in Dhaka every three months.

AMJ: The first outbreak in India was close to the Nipah belt of Bangladesh, but Kerala is much further from the Nipah Belt. It came as a surprise to the majority of the people in Kerala, so what might have caused a spillover event in the Kerala outbreak?

Dr Gurley: I know many people found this shocking or surprising. How do we have Nipah when the other outbreaks are so far away? Also, we are far from West Bengal, so why is it here? This is very surprising.

We know that the bats that carry this virus are all over India, around South Asia, Madagascar, Ghana, and throughout Southeast Asia. So, if we know that the bats are there and they have the virus, why would we be surprised that humans are infected? Sometimes we confuse the absence of observing something with the absence of it happening. If you have a surveillance system in place and you are testing everyone for Nipah, and no case were reported for five years and all of a sudden, a case occurs, that would be surprising. But if you've never tested anyone before yet the reservoir species exists in the region then why would you be surprised to find it if you start looking?

“Only 10 per cent of Nipah patients in Bangladesh have ever transmitted the virus to someone else.”

How can you tell if it's Nipah or not unless you are doing a diagnostic test? If there is a major outbreak, you ask some questions and you do more testing. All these years it could have been misdiagnosed as Japanese Encephalitis (JE). In fact, in Malaysia, the whole outbreak was misdiagnosed as JE for many months before they found the new virus. That's often the case, then as we have seen in Kerala, we have a doctor saying “wait a minute, this doesn't seem right. I need to investigate. I need to do something more”.

AMJ: How do you compare and contrast the spillover dynamics and transmission pathways of the Kerala and Bangladesh outbreaks?

Dr Gurley: Each time a bat virus infects a human, we call this a spillover event. It's a new chance for that virus to adapt to a new host, to try that species and see if it can do well in that species. So, if you look at the example of Malaysia, how were humans affected? Through infected pigs. The evidence suggests that there were one or two spillover events from bats to pigs.

In commercial pig farming, many new piglets come in all the time, meaning the outbreak was able to be sustained within the pigs, then that virus causing an outbreak in the pigs also infected the people. So, it was really one virus that took off in pigs and then infected people. That's our best understanding of Malaysia.

Each spillover event is a risk and carries a risk in itself. In Bangladesh, we see multiple spillovers every year. There are many more viruses spilling over into people, and there's diversity even among those viruses within Bangladesh. Considering the potential for a new virus to emerge that is more transmissible, that's our biggest fear for Nipah viruses.

In Kerala, there were only two outbreaks until now, and we don't know how the index cases were infected. We have hypotheses but we do not know, and probably will never know. And then you had the propagation of person to person transmission. The outbreak in Kerala looks very similar to the first outbreak identified in Sili-guri, India during 2001, and it seemed very similar to the large 2004 outbreaks seen in Faridpur, Bangladesh. In many ways, it is a stereotypical super-spreader outbreak and super-spreaders as first outbreaks are very common because those outbreaks are hard to miss.

AMJ: What was the nature of the transmission in Bangladesh? I believe, after the first major outbreak in 2004 in Fardipur, most of the outbreaks were smaller in scale?

Dr Gurley: In Bangladesh, our goal was to find the occurrence of singular cases, but we don't see them unless we're testing for Nipah. Since most cases don't cause a major outbreak, we set up surveillance systems to test



PHOTOGRAPHY BY A.M. AHAD

every individual patient who comes to the hospital with certain symptoms during the Nipah season. From this study, areas with higher risk can be identified. We found that almost all of the patients happened to be singular cases. Only 10 per cent of Nipah patients in Bangladesh ever transmitted the virus to someone else.

Case-control studies can be done with individual cases to find out how they are different from other people in their village who did not get Nipah, to identify how the virus is spilling over. This information is crucial. We have published a paper in the New England Journal of Medicine in May 2019, which is a comprehensive view of person to person transmission in Bangladesh. It's a report of 14 years of investigation and that may be useful if you want to read up more about that.

I would say my guess is that the same thing is happening in Kerala – that there are more frequent spillover events occurring, with only a few leading to larger outbreaks. There's no reason to think this wouldn't be the case. Based on our experience in Bangladesh, it is very unlikely that a single spillover led to this large outbreak in 2018. It's probably still present with a lower level transmission, but is not being recognized. So, with improved surveillance, I expect that you will continue to find cases.

AMJ: To what extent do bat biology and immunology drive spillover dynamics in Nipah spillovers from bats to humans? Are there any environmental factors triggering or influencing these dynamics? Is there any active research to understand this?

Dr Gurley: There is an ongoing global study in collaboration with researchers in many other countries. I'm leading the efforts for Bangladesh. There are also field

studies in Australia, Ghana and Madagascar. The overarching goal of that work is to understand when and where these bats shed Henipaviruses. We have very good evidence from Australia that the bats which carry the viruses tolerate the infections well. Sometimes when they shed these viruses, it seems that antibody levels can wane in the bats and they can become reinfected or start shedding the virus again. It is an interesting biological system of infection, and it looks different than other diseases that we study in humans. We're trying to understand what's going on with the bats and how they get infected and how

they transmit the virus to each other.

In Australia, they have good evidence about what they call shedding pulses. There are certain times of the year when the bats are shedding more of these viruses than usual; they call it a shedding pulse. They have very good data to suggest that this happens when their immune systems are stressed due to the unavailability of high-quality food sources. So, their understanding is that in times and places where bats don't have good food, their immune systems are suppressed, and that's when they shed these viruses.

In Australia, it also happens to be the time when they move into more urban areas looking for food, because they don't have enough food. In fact, last year, based on this information, they were able to predict when bats were going to be shedding Hendra virus, and their prediction was correct. In public health, when you're able to predict when and where something is going to happen, it is very powerful because that allows you to put in interventions to try and stop transmission.

The goal of our study is to see if the same thing is true in other countries. To find the same kind of shedding pulse as is described in Australia with the same type of ecological predictors of those pulses is the first thing. The second part is to see if all these different Henipaviruses have the same or diverse genetic characteristics of the viruses. And how do those genetic characteristics translate into clinical disease? We often do this using animal models.

Ultimately, we want to predict when and where the bats are going to be shedding. Are there vaccines we could design to keep the bats from shedding? Using rabies as one example where we often vaccinate wild ani-

imals to protect human health, could we do the same in the Henipavirus system? Could we give bats better food sources? Could we have an ecological intervention to improve their habitat, so they don't shed the viruses as much? There's a lot of scientific work we have to do first to understand the process.

Our typical understanding of the way infectious diseases work is that, for example from the perspective of measles in humans, there can only be three states - a human can be susceptible to measles, or the person is infected, and then they recover and become immune for the rest of their life. You are never going to be infected again. You are never going to be susceptible again. We often think about infectious diseases in that way, and if we consider it in sort of conceptual model of how infections work, you can think about a bat being susceptible or infected and shedding or immune.

In the case of measles, who are the most susceptible to measles? It's babies after maternal antibodies wane, and the same is true for bats. When they are born, they have some antibodies against the Nipah virus, usually. Those antibodies wane, and then the new juvenile bats are susceptible to infection. Those new susceptible bats could be playing a role in outbreaks in bats. However, unlike measles in humans, bats who have been infected with Nipah may be immune for some time, but then they lose their immune status, and can lose their antibodies. They can become reinfected or shed the virus again. So, you have this scenario where the new juvenile bats are susceptible to infection, and the adult bats can also become susceptible again. The bats don't become sick, but can shed the viruses more than once.

The second paradigm is that these viruses look more like herpes virus in humans, so let's think about that model system when many people are infected with herpes viruses, Herpes Simplex Virus - Type1. The person is infected early in life and is infected for the rest of their life. However, the person is not always shedding that virus. You are shedding it when your immune system is down for some other reason, then you'll get a cold sore.

Another example of infections that don't cause illness in wildlife could be pathogenic influenza viruses in wild ducks. They typically don't make ducks sick at all, but they can infect poultry and make all the poultry die. They can be pathogenic for people, but the ducks are fine.

The short answer is, it's complicated. Both of these dynamics are probably happening, and it's just going to take us some more time to figure it out.

AMJ: Is there any evidence suggesting that the frequency of transmission changes over time, or is it linked to the strain of the virus?

Dr Gurley: Almost every outbreak at some point will stop, even without any intervention. Sometimes we try to over-interpret and say that the virus has changed and is not as infectious, but often what we're seeing is just the normal process of an infectious disease. I don't want to over-interpret, and again I would say that in our experience in Bangladesh, only one out of every 10 Nipah patients will infect someone else. Let's take this outbreak in Kerala last year as an example. There was one super spreader. These are outliers. But then, among the patients that he infected, only maybe two or three infected someone else. Approximately 10 per cent of those patients affected someone else. So, it's true to our experience that among those infected, few new people were affected. So if only 10 per cent are going to infect someone else and you have less than ten, you may not see an onward transmission. Our prior experience would tell you that you wouldn't expect to see on average any more transmission events after that, and it doesn't have anything to do with that attenuation of the virus, it's just what we expect, that only 10 per cent will transmit.

Now if we have good data on the viruses through each transmission chain, and we found differences in the genetics of those viruses, and we could show through laboratory experiments that those genetic changes also cause some kind of attenuation in the ability of the virus to transmit to others, that would give us some strong evidence. But, we don't have anything like that so far, the outbreaks that have happened including last year in Kerala have behaved

“If we know that the bats are there and they have the virus, why would we be surprised that humans are infected?”

precisely as we would predict without any changes in virus strains.

AMJ: To what extent are ecological factors and climate change contributing to these zoonotic spillovers?

Dr Gurley: For one spillover event to happen, many different things have to align. Not only do you have to have shedding in the reservoir species, but that virus has to survive long enough outside the reservoir species or in fluids or something else on order to infect another species, and the virus has to get access to the right cells where it can bind. It has to be able to replicate. It has to overcome the innate immune response of that animal. If this is very swift and identifies this virus quickly to shut it down, you're not going to have an active infection in the new host. So, all of these things have to line up. Once a virus has spilt over, there is something that may be unique about that virus that means it was able to create that spillover.

Some people like to think that spillovers are the fault of the bats. I think it's the fault of humans. We're creating new transmission pathways, for example, with the Nipah virus in Bangladesh. The major pathway of transmission is through consumption of date palm sap. This is an agricultural product. If humans weren't shaving and tapping these trees, the bats would not have access to the sap. The only way they can drink it is if humans are making it available. Humans are the ones that are generating this transmission pathway.

We know that before the Malaysian outbreak, there had been a massive expansion of the commercial pig raising industry, and there was deforestation to help to accommodate that. If you have destroyed part of the bat habitat, then they have to go and live somewhere else. If you have destroyed the trees where they prefer to feed, they need to go somewhere else to look for food. We have seen this in Australia. They actually have very good data going back more than 30 years now where they show that the destruction of natural bat habitats has led to bats relying more on food sources around human settlements.

AMJ: Are there lessons from Bangladesh that you would like India to follow in implementing a Nipah surveillance plan?

Dr Gurley: I had the opportunity to be a part of a team that worked to build the first Nipah surveillance platform in Bangladesh. I'm only one part of that team, and many other dedicated, talented people working in Bangladesh worked for many years to maintain that platform and continue to do so now. It's run in collaboration with the Institute of Epidemiological Disease Control and Research, which is part of the Directorate General of



Health Services and the Ministry of Health, in collaboration with ICDDR -B and also with support from the U.S. Centers for Disease Control and Prevention.

I think we do have one major lesson that I hope we can disseminate far and wide, and this lesson is that systematic surveillance is essential for monitoring this virus. The closer you look, the more cases you find, and the faster you can be in responding to outbreaks. Imagine in Kerala if they had found the first case and they had put him into isolation, would you have seen the super-spreading effect? It could have been mitigated somehow.

With viruses like Nipah, it's crucial to think about transmission over multiple years. This is possible if you have surveillance in place as we have had in Bangladesh since 2007, with the same three hospitals testing every patient during NIPAH season. It is seasonal in Bangladesh because of the spillover pathway. It spills over because humans and bats share date palm sap, and that's a very seasonal activity. So, in the Nipah season, we test every patient.

It's a huge activity. Only 1 per cent of all the patients we test have Nipah. It's a small proportion, but partly because we do that, and every time we find a case, we go back to the village to look for other cases. We do contact tracing as a routine activity, so even if there was a larger outbreak, there wouldn't be such big reports, because we're investigating this as a routine thing. What this allows us to do is to track the important epidemiologic characteristics of the virus over time. Since 2007 every year, we can see how incidence and mortality changes. Does the person to person transmission change? Does the geography of these spillover events change? Does the number of spillover

We have to address the emerging pathogens that give us the best reason to believe they could cause a pandemic or a massive outbreak. Nipah is on that list. SARS is on that list. We have to focus on the ones we know are causing problems.

events each season change? Unless you have the same systematic surveillance over decades, you cannot do that, you can't make any sense of the patterns.

AMJ: The count of lives that the Nipah virus has claimed so far, from the first outbreak to the last outbreak in India, is less than 400 worldwide. However, WHO has classified Nipah as a priority pathogen, which can potentially cause large outbreaks or even a pandemic — are we becoming overcautious?

Dr Gurley: There are many health problems in India. There are many health problems in Bangladesh. Did more people die last year in India from Nipah or Japanese Encephalitis or from traffic accidents? Nipah does not kill more people than these other diseases. However, from a global health perspective, the reason why we care about Nipah is that we have a fear that a strain could emerge that is more easily transmissible between people, and this could cause a massive outbreak or even a pandemic. So, the outbreaks themselves are devastating for a particular community, but the global interest in Nipah is not in those individual outbreaks, it is in the emergence of a more transmissible strain.

The only thing that we know for sure is that we will have more pandemics. If you ask which Disease is going to cause it, we have no idea. But this I want to emphasize, just because we don't exactly know which one it will be, does not give us an excuse for inaction.

What does this mean? It means that we have to address the emerging pathogens that give us the best reason to believe they could cause a pandemic or a massive outbreak. Nipah is on that list. SARS is on that list. We have to focus on the ones we know are causing problems. It also means that we have to constantly be vigilant and be looking for the next emerging disease. Twenty years ago we didn't

know about Nipah. Does that mean that Nipah was not there? There is no reason to believe that there haven't been cases, but we just didn't see them.

How do we know if a more transmissible strain is emerging, or if we're seeing changes in epidemiology over time that suggest it's becoming worse? You can only do this through this systematic surveillance. That's why systematic surveillance is so important. We can look at changes in those vital epidemiologic parameters over time and it will help us to be smarter. Imagine there is an outbreak next year in a different country, Not India or Malaysia, but another place where bats live. The clinicians there are not familiar with Nipah. They don't have any experience to draw upon, but if we have some data over time from other places, we can give them our advice, and they can start to build on their own experience.

Right now, Bangladesh is the only place with this long-term surveillance experience, but I hope that India will take this up and they will set up similar long-term surveillance platforms so that we can see if we are finding the same things. Bangladesh is just one place, and we don't know if that place represents what's happening in other locations. I hope that more places will take up this responsibility to set up surveillance and report the results. I have been so impressed with India's transparency on this issue, and as I mentioned to you earlier, this is essential for our Global Public Health good.

Lastly, I don't think it's a coincidence that the outbreak in India was diagnosed in an Indian state that already had a very well-developed healthcare system and a scientific community. Kerala found and diagnosed the outbreak so quickly. Why? Because you have an excellent medical system. You have well-trained clinicians. You have the capability to find it.

“Nipah Outbreak Should Be A Wake-Up Call For AES Surveillance In India”



Dr G Arunkumar, *Director of Manipal Institute of Virology*, was the scientist at the forefront of the identification and diagnosis of NiV in the 2018 outbreak in Kerala, India. For the first time in India, Arunkumar and his team at Manipal Institute of Virology detected the virus using Real-time PCR. The eminent virologist, who has been part of the myriad of encephalitis outbreak investigations in India talks to *Aster Medical Journal*.

AMJ: Rapid Detection of Nipah Virus helped to contain the outbreak in Kerala. As the first person to detect the Nipah virus in India, could you please tell us what made you test for Nipah?

Dr Arunkumar: For the past few years, we have been conducting a study to understand the etiology of hospitalised febrile illness cases in rural India. So as part of that, we have sentinel sites in 10 states. We had sentinel sites near to Bangladesh, i.e. in Tripura and Assam. In these two places, we were actively looking for Nipah among the febrile illness causes, but none were previously found. Because of that, we had the test ready, and our team was prepared. When the Kerala case came what led us to check for Nipah was a cluster of Encephalitis.



An adult cluster of Encephalitis is the classical epidemiological presentation of Nipah in south-east Asia. The only virus that can cause Encephalitis in a family cluster is Nipah. With other Encephalitis viruses like herpes or Japanese Encephalitis virus, you don't see family clusters. In Japanese Encephalitis, a mosquito borne disease, typically for every 300 people infected, only one person develops Encephalitis. You may see one case per village. Instead, in the 2018 outbreak of Nipah in Kerala, we had a family cluster.

Moreover, the epidemiological report from Bangladesh clearly showed the family pattern within the adult cluster. This was the reason for the Nipah testing. We used a Real-Time PCR, wherein a sample is inactivated to reduce the risk, to screen the RNA.

AMJ: In most of the previous Nipah outbreaks, detection and diagnosis happened retrospectively. It took months or years to detect the virus. For instance, in Siliguri, it took five years to identify the infectious virus as Nipah, whereas in Kerala the virus was detected and the diagnosis was confirmed while the outbreak was still active.

Dr Arunkumar: Yes. That's true. Unlike the past outbreak, this is the first time in the history of Nipah that the diagnosis was made in the outbreak country. All the previous diagnoses were made at CDC Atlanta. The issue in Malaysia when Nipah appeared was that it was a totally new virus, meaning it took some time to figure it out, in total six months because the samples were finally taken to the US. The Malaysian team had a good connection with the CDC, so they could send them the sample to identify. The availability of another virus, Hendra virus from Australia really helped. The Malaysian team were able to grow the virus in their

laboratory and the antibodies of Hendra were reacting to it, which finally clinched identifying Nipah in Malaysia.

In Bangladesh, again there was unusual deaths which were not explained by the routine Japanese Encephalitis story. There were no pigs involved, but Malaysia, there were pigs involved. So again, it took some time to understand that there was something wrong, and the samples again had to go to the US. It took around three years for them to diagnose it as Nipah.

In 2001, India had the Siliguri outbreak, and only some time into the outbreak was it noticed. Again, clinically it did not fit stories such as it being a modified form of measles, or measles without rashes. Unfortunately, they could not identify it, so again CDC was involved. It took some time to transfer the samples out of the country, therefore the diagnosis was a retrospective one which took five years. Only after five years, it was confirmed that this was Nipah, and in 2006 the team published a report. In 2007 there was another small outbreak in Siliguri, but by 2007 the outbreak reportedly involved five people and all five were dead. That outbreak was confirmed in India, and again was a retrospective confirmation rather than identification in real time.

When Nipah struck in Kerala, two things were different; We had two trained laboratories in India, both of which were ready to do the test, and we were already regularly looking for this virus so that we could analyse it. In fact, we were anticipating that this virus would surface in other places in different ways, but when the cluster of Encephalitis came, we were in a position to quickly test it. This case came from a private hospital, the Baby Memorial Hospital in Kerala, from Dr. Anoop, Critical care Physician.

By 2009, H1N1 pandemic flu had come to India. As a response, India had to establish influenza testing facilities nationwide. From 2007 onwards there was some activity in preparation for a bird flu outbreak, if bird flu affected humans, the government had plans preparing some laboratories to test bird flu, so we were part of that program. Our labs were prepared for testing influenza, but when pandemic Influenza A H1N1 arrived in India in May 2009, we became the regional laboratory for testing influenza in Kerala, Karnataka and Goa. As part of the acute febrile illness surveillance program under the Global Health Security Agenda (GHSA), CDC shared technical expertise, specific reagents, and training for diagnosis of dangerous viruses including Nipah.

“The genome of the virus recovered from the bat in Kerala and the genome of the virus recovered from human cases in Kerala was a 100% match.”

From 2009, because of this testing facility, many of the hospitals were connected to us. So they did send samples for influenza testing. Apart from that, whenever they spotted something unusual, they used to contact us, and we would provide diagnostic services. Slowly from 2009, we had around 10-15 diagnostic tests coming from these peripheral hospitals, and by 2018, it was almost 100 tests. Our capacity had increased. These kinds of relationships between hospital and lab were one of the reasons that Dr. Anoop could alert us about this unusual cluster of Encephalitis and we could identify it quickly.

The case study was described to me by Dr. Anoop, and then samples were collected and sent. That is how things become faster. All of these things contributed to rapid detection. If the clinicians were not alerting us, then there would have been no question of anybody knowing what was happening. Also, in the 2018 outbreak, if each member of the family had gone to three different hospitals, then we may not have even recognized Nipah. Since all members went to the single hospital, to the same doctor, he saw it as something unusual, which was the real indicator.

AMJ: In the 2018 outbreak in Kozhikode, Nipah was spotted in the second case and in 2019 in Kochi, Nipah was diagnosed in the index case itself. The rapid detection of

Nipah in patient zero accelerated Kerala's response to the outbreak. Additionally, there was no transmission from the index case, and all other suspected cases proved Nipah negative. What has changed since the first outbreak in Kerala - is it because of the change in the strain of virus or in pathogenicity?

Dr Arunkumar: We cannot say this strain is different or pathogenically changed based on clinical situations, because death typically occurs when the disease becomes a severe condition and affects the respiratory system or the CNS, but in the current case, only the cerebellum was affected. Last year there was a case with only upper respiratory symptoms, not even pneumonia or any altered sensorium, and the patient recovered. So, we will definitely have a spectrum of clinical presentations, and also if we look at the transmission dynamics, every Nipah case is not going to transmit, but there will be some cases where it will transmit more readily.

In last year's outbreak, only two infected people survived. One person had only mild illness, and he was picked up only because his wife died of Nipah. If that wasn't the case, he wouldn't have been picked up, because he had only upper respiratory illness. Obviously, we can't identify every upper respiratory disease as Nipah. The second case was an Encephalitis case, and she was a nursing student. She went through the whole spectrum, but she recovered. She was not given any monoclonal antibody, but she was given supportive therapy and ribavirin. In that case, the patient was not admitted immediately because she was a nursing student with fever and went home and later vomited and was admitted, because initially there was no apparent connection. The connection was later established because she was in the ER to which the index case was brought. Last year we had a case which was very mild, but also other fatal cases although the virus strain was the same.

AMJ: In 2003, the eminent epidemiologist Jonathan Epstein et al. conducted a serological study in north India to check for the presence of Nipah. The investigation was later published in the Journal of Emerging Infectious Disease. Jonathan Epstein et al. captured 41 *Pteropus giganteus* bats from a colony in Haryana from June 24 to June 30 2003, using mist nets. The bats were tested for antibodies against Nipah and Hendra viruses to determine whether henipaviruses circulate in Pteropid fruit bats (*Pteropus giganteus*) in northern India. The result proved twenty bats were seropositive for Nipah virus. However, there was no reported case of Nipah in this region until now. Does this

suggest that while in Kerala, we found Nipah because we tested for Nipah, whilst in other states in India, Nipah may be misdiagnosed or provisionally diagnosed as Japanese Encephalitis?

Dr Arunkumar: Nipah outbreak should be a wake-up call for AES surveillance in India. Our Encephalitis surveillance is primarily based on Japanese Encephalitis (JE) because that is a vaccine-preventable disease and has a vaccine. Hence, the whole national program moves around JE surveillance. It's true that Nipah is not tested for in most of the Encephalitis cases in India. Wherever fruit bats were tested for Nipah in India, we found it. Jonathan's study reported antibodies in bats in Haryana, and the National Institute of Virology, Pune found Nipah virus among fruit bats in West Bengal, Assam and in Kerala. These are the only places where they tested, and if they increase the survey and test in other places, you will find the presence of Nipah in many states.

In Kerala, it is definitely because of testing that we were able to detect Nipah. When there was a family clustering in an Encephalitis case we have tested Nipah as a first line of action. Where there was not a familial cluster Nipah would have been tested not as a front line, but as a 3rd or 4th line option.

Many times in hospital-based outbreaks, even in Kozhikode, only because we were able to test and

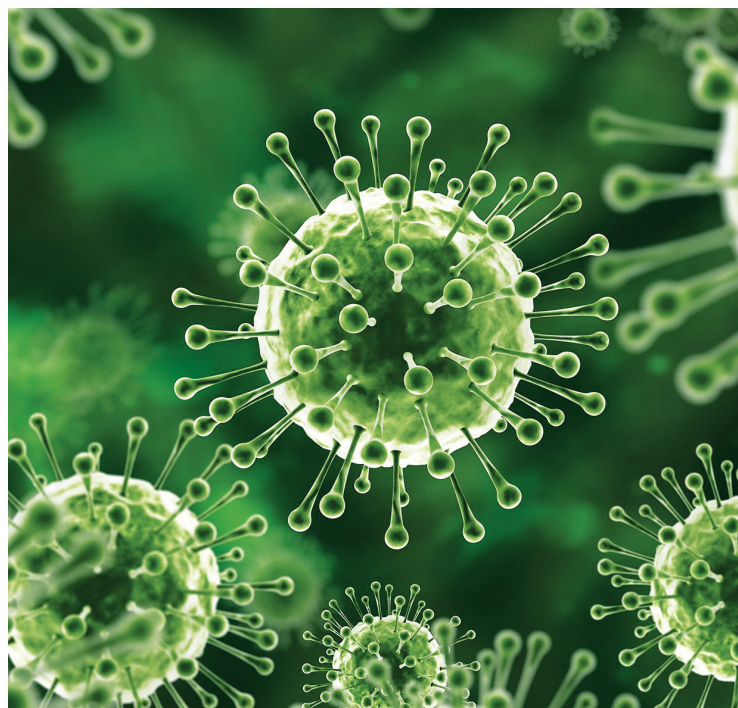
connect the deaths, we were able to make the links. Because in the hospital when a patient comes with Nipah and transmits it to others, these people may be bystanders or other patients, it may not be seen as a cluster. However once one healthcare worker is involved it can raise a very high level of suspicion.

AMJ: During a new infectious disease outbreak, the source of infection and the route of transmission is always a mystery. How does this virus directly affect humans? Looking at the past outbreaks, transmission pathways in each country were different. In Malaysia it affected the pigs and was transmitted from pigs to pig farm workers, whereas in Bangladesh, bats contaminated the date palm sap and people drank date palm sap and got infected. In the Philippines, it was from bats to horses. When it comes to Kerala, the transmission pathway is not confirmed. It's still puzzling- how did the index case get infected from the natural reservoir when, moreover, there was no evidence of other animals involved.

Dr Arunkumar: No, It is not completely clear, but it is assumed that because he came from this community, there was a very high probability that it would have been a direct transmission from a bat. The genome of the virus recovered from the bat in Kerala and the genome of the virus recovered from human cases in Kerala was a 100% match, but they were not the Nipah virus strain which was circulating in Bangladesh. They were of the Bangladesh lineage but not the same strains. This was a Kerala specific strain, and so that clearly shows that the virus came from a bat. How that virus came from bat to humans is difficult to trace because the index case in the Kozhikode outbreak died before we could trace the epidemiology. This year, the index case is alive, so we can get some information.

AMJ: Considering the poor AES surveillance in India, do you subscribe to the point of view that every case of Encephalitis should be investigated for Nipah?

Dr Arunkumar: Not every case of Encephalitis. But you should look at the epidemiology and clinical presentation. I have investigated Gorakhpur Encephalitis and Orissa encephalopathy, it is all children, and because of the Acute Encephalitis Syndrome (AES) surveillance definition, people get confused with JE. To increase the sensitivity of JE case detection, they have provided a broad definition, but unfortunately, once you diagnose AES, which is a combination of syndromes including Encephalitis, meningitis, altered sensorium and seizures, people get confused hence further investigation is blocked.



“last year we had a case which was very mild and other cases with high mortality and the virus strain was the same.”

People in these situations immediately start with a JE vaccination. Many times they check serum antibodies for JE IgM and this creates problems when they give false positive results.

AMJ: They don't do CSF?

Dr Arunkumar: No, in many of these places they don't do CSF initially. Because it is done only in higher or tertiary care centres. Of course, there is region specific variation in practice, but still, diagnosis is mostly around JE.

AMJ: There are survivors of Nipah virus disease in many countries. What are the common sequelae of Nipah virus disease and recommended evaluations in the survivors? Are you aware of any studies monitoring the NiV survivors?

Dr Arunkumar: Survivors will develop antibodies against Nipah. Even last year's survivor in Kozhikode had antibodies. The survivors must be monitored for a longer time to look for potential sequelae. Until now they have had no problems, they are doing fine.

In Malaysia, very rarely they found some cases having recurrent Nipah again after around 11 years, so there is a remote possibility of recurrence. Since the numbers of survivors are not very high in our current Indian situation, it may not be a big problem, but these people have to be monitored for a long time to understand whether something is happening. Generally, the viremia lasts only for 8-10 days post onset of illness and by then, the case will have sufficient antibodies and a good immune response. With the present case in Kochi, they could not detect the virus in the blood, but were able to detect the virus in the urine. That clearly shows that the person would have already developed

the antibody, that's why he survived. The moment that we reach 6-8 days post-onset, the survival chance of the patient significantly increases as the immune response including antibodies will clear the virus. However, we have showed that Nipah virus RNA could be detected in semen of the last years male survivor for up to 26 days. This does not imply that it is infectious virus. Further, it may not be like Ebola or Zika which can persist for up to several months. Only in one case was the semen tested. But definitely, the virus remains in semen for some time, because it is an immunologically privileged site and hence has delayed clearance. Additional studies are required to understand the potential of the sexual mode of transmission of Nipah.

AMJ: In the last two decades, several zoonotic disease outbreaks have been linked to bat-borne viruses. These include the SARS coronavirus, Hendra virus Nipah virus, Ebola viruses and MERS coronavirus. Bats are potential reservoirs of a large number of known and unknown viruses, many of which could spillover into animal and human populations. However, our knowledge about bat biology and immunology is very minimal, and we have little understanding of major factors contributing to the risk of bat virus spillover events.

Dr Arunkumar: We are increasingly understanding the bats. They may be harbouring much more dangerous viruses also. We can do very limited things with the natural environment, but we can do much more as a community and even in the health-care system. We cannot avoid or disturb the bats' habitats because they do a lot of good things within the ecosystem such as pollination, but we can create awareness to avoid close contact with bats as well as fruits which have been bitten by bats.

We have a minimal risk when it comes to the direct transmission from the natural reservoir, but we can very effectively control human to human transmission in hospitals. Last year, only one case was from the community, the remaining cases of transmission all happened in the hospital.

If a mask was put on coughing patients and if the nurse and other healthcare workers were using appropriate personal protection, then the transmission wouldn't have been as high. That is an area where intervention is really possible, along with early detection and increased surveillance i.e., case surveillance and event-based surveillance with laboratory support. So, as lab tests increase, the ability to detect cases in the hospital should also increase.

people have to be monitored for a long time to understand whether something is happening. Generally, viremia lasts only for 8-10 days post onset of illness and by then, the case will have sufficient antibodies and good immune response.

The first case in Kerala last year came to Kozhikode Medical college and died, although otherwise an apparently healthy patient with two days severe illness. No samples were taken, no investigations were mounted. I think that part also has to improve. We need to increase the surveillance. If that could have been detected early, it would have definitely helped in preparedness, containment, contact tracing etc. All unexplained deaths in otherwise healthy people should be investigated.

AMJ: As we know, the first part of detection comes from the clinical acumen and alertness of doctors to suspect the clinical presentation, and this has played a vital role in both the 2018 and 2019 Nipah outbreaks in Kerala. At the same time, laboratory diagnosis is an essential element of infectious disease surveillance, both for routine confirmation of infections and the rapid identification of the cause of outbreaks. In many instances, only the laboratory can confirm an infectious agent. Do you agree that we could improve detection capability by reducing the waiting time to confirm the diagnosis and also increase the accessibility to advanced laboratories?

Dr Arunkumar: One of the limitations in virus diagnosis is that most of these organisms are classified as risk group 4 pathogens. We are confused with this risk group 4 pathogens and containment level 4 for handling samples. But over the years, technology has changed. We need to rethink the basic concepts of risk groups and laboratory biosafety. We are still talking about culturing the virus, which means increasing the quantity of virus in the laboratory, but currently we are not doing that, we are inactivating the virus in specimen, and we are only amplifying the nucleic acid. This actually reduces the risk and makes it possible to do tests at biosafety level 2, enabling near-patient testing.

When you use serological diagnosis, the antibodies are detectable only after 8-10 days after the onset of illness. Nipah is an acute and fatal disease. Many people may die before they develop the antibody, so we need to use a combination of real-time PCR and antibody detection assays. Hence the accessibility of real-time PCR should be increased.

Increased accessibility of Real-time PCR or even single sample testing devices like point of care tests will help to pick up Nipah cases in tertiary care centers. The disease is not transmissible in the early stage. In last year's case in Kozhikode, none of the patient's household had any infection. Only during the last 48 hours did he transmit the virus. His brother and father looked after him in the hospital. No children or other people at home were infected. The transmission happened towards the end of the illness, by which time he was already in the tertiary care centre. So, the major tertiary care centre should have these facilities to test at the point of care. Last year in collaboration with a company, MolBio, we had developed a point of care PCR device for Nipah diagnosis. Currently it is undergoing evaluation and awaiting regulatory approval. I am happy to note that this device was put into use during this year's Nipah outbreak response in Kochi. Unless we follow these steps and make diagnostics more accessible, we cannot detect these things easily.

Nipah and other zoonotic viruses are here to stay, and we need to learn to live with them to ensure global health security.

Dr Shihad, Managing Editor, Aster Medical Journal

Research

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Chronic Kidney Disease (CKD) has a global prevalence of approximately 11–13%, and is a key health indicator, being intrinsically linked to comorbidities including diabetes and cardiovascular disease.

Determining the prevalence of risk factors of chronic kidney disease in the United Arab Emirates population: Results from the pilot phase of the community screening program

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ABSTRACT

There is limited data available about the prevalence of chronic kidney disease (CKD) and its risk factors in the general population of The United Arab Emirates (UAE). To estimate the prevalence of CKD and its associated risk factors in the UAE, which has a predominately expatriate population, we conducted a pilot community-based screening program in two hospitals in Dubai, taking blood and urine samples for analysis. The sample included 491 adults (75.7% were males), predominantly expatriates with Indian (61.9%), Pakistani (10.7%) and Filipino (10.6%) nationality. The mean age was 37.0 ± 11.3 years. Multivariate regression was used to establish correlations between

dysfunction and demographic data. The overall prevalence of low eGFR (<60) was 0.92% and 0.76% using the MDRD-3 and CKD-EPI glomerular filtration equations, respectively, but the prevalence of microalbuminuria was much higher (13.61%), giving an estimate of high CKD risk (combined low eGFR or microalbuminuria) of 13.76%. Male gender and increased age were significant predictors of low eGFR. We recorded pyuria in 65.51% of patients, haematuria in 6.89% and glycosuria in 11.62% despite the patients being asymptomatic. Pyuria incidence was particularly high in the young and elderly, and may point to early urine infection, renal calculi, or poor water intake.

INTRODUCTION

Chronic Kidney Disease (CKD) has a global prevalence of approximately 11-13%¹, and is a key health indicator, being intrinsically linked to comorbidities including diabetes and cardiovascular disease². CKD incidence has increased by an estimated 32% globally between 2005 and 2015, and in many populations, it is expected to continue to rise³. The true incidence and prevalence of CKD within a community are difficult to ascertain, because early to moderate CKD is usually asymptomatic. However, various epidemiologic studies suggest a prevalence of CKD ranging from 7% to 14% in various populations¹.

Albuminuria (mostly microalbuminuria or A2) has been reported in 7-10% of patients in the USA^{3,4} and as many as 19.5% of patients in China (5). In the USA, glomerular filtration rate (GFR) falls below 60 ml/min/1.73 m² in approximately 3% to 5% of patients⁴, however no population level data is available detailing the prevalence of low eGFR or CKD in the United Arab Emirates (UAE). The UAE is known to have a high prevalence of CKD risk factors including hypertension, but previous studies indicate a prevalence of end stage renal failure (ESRF) that is lower than that of neighbouring countries⁶. As 89% of the population are expatriates⁷, studies reporting CKD prevalence in the Middle East and South East Asia are not necessarily comparable.

The three-year incidence of CKD levels 3-5 has been determined as 11.4% in a subgroup of UAE patients at high risk of cardiovascular disease⁸, and the overall prevalence of CKD 3-5 was recorded as 3-5% in the Emirate of Abu Dhabi in 2011-2012 in patients presenting with symptoms prompting serum creatinine testing⁹. Late presentation of CKD patients is currently typical in the UAE, which negatively impacts patient outcomes and increases costs¹⁰.

Appropriate and timely lifestyle choices for persons with CKD can hamper the progression of kidney function deterioration as well as prevent the development or progression of CKD-related diseases¹⁰, but this is only possible if patients are aware of their condition and if high risk subgroups of the population can be identified and encouraged to attend monitoring. Establishing a picture of renal health in countries such as the UAE is therefore an immediate priority⁶.

A pilot study to follow the prevalence of proteinuria, haematuria, and low estimated GFR (eGFR)

Table 1. Demographic information for study participants

Number of study participants	654	Sri Lankan	12 (1.83)
Number of men (%)	495 (75.69)	Sudanese	2 (0.31)
Nationality (%):		Syrian	4 (0.61)
Afghan	2 (0.31)	Tanzanian	1 (0.15)
Albanian	1 (0.15)	Turkish	1 (0.15)
American	1 (0.15)	Ugandan	1 (0.15)
Australian	3 (0.46)	Uzbekistani	1 (0.15)
Bangladeshi	14 (2.14)	Yemeni	2 (0.31)
British	5 (0.76)	Zimbabwean	2 (0.31)
Cameroonian	1 (0.15)	Unknown	1 (0.15)
Canadian	5 (0.76)	Age (years) (%):	
Chinese	3 (0.46)	Median age	37.00
Comorian	2 (0.31)	Median age (SD)	38.41 (10.79)
Dutch	1 (0.15)	<18	6 (0.92)
Egyptian	12 (1.83)	>=18 <30	113 (17.28)
Emirati	1 (0.15)	>=30 <40	281 (42.97)
Ethiopian	1 (0.15)	>=40 <50	152 (23.24)
Filipino	69 (10.55)	>=50 <60	67 (10.24)
Indian	405 (61.93)	>=60 <70	29 (4.43)
Indonesian	1 (0.15)	>=70	6 (0.92)
Iranian (Persian)	2 (0.31)	Median mean daily creatinine (IQR)	56.00 (42.00-70.00)
Italian	1 (0.15)	Mean daily creatinine	56.35
Jordanian	1 (0.15)	Median mean daily CKD-EPI eGFR (IQR)	123.23 (112.48-136.20)
Kenyan	4 (0.61)	Mean daily CKD-EPI eGFR	124.79
Lebanese	1 (0.15)	Median mean daily MDRD eGFR (IQR)	139.00 (109.08-160.60)
Malawian	1 (0.15)	Mean daily MDRD eGFR	160.60
Moroccan	2 (0.31)		
Nepalese	12 (1.83)		
Nigerian	5 (0.76)		
Pakistani	70 (10.70)		
Serb	2 (0.31)		

was carried out in the UAE in volunteers undergoing routine testing in response to a CKD awareness campaign for renal testing. We report the baseline creatinine, eGFR and albuminuria results of the study participants alongside other bioindicators of CKD risk.

MATERIALS AND METHODS

Patient selection

Patients were eligible for inclusion in the study if they volunteered for routine testing in response to a CKD awareness campaign at Aster Hospital Al Mankhool (West Dubai) & Aster Hospital Al Qusais (East Dubai). All tests were recorded in March-April 2019. Nationality was declared by

Table 2. Urine test results of study participants

	All patients	Males	Females
No. study participants	654	495	159
Glucose (%)			
Negative	578 (88.38)	430 (86.87)	148 (93.08)
Trace	3 (0.46)	2 (0.40)	1 (0.63)
1+	11 (1.68)	9 (1.82)	2 (1.26)
2+	12 (1.83)	12 (2.42)	0 (0)
3+	8 (1.22)	8 (1.62)	0 (0)
4+	42 (6.42)	34 (6.87)	8 (5.03)
All glycosuria (%)	76 (11.62)	65 (13.13)	11 (6.92)
Protein (%)			
Negative	565 (86.39)	422 (85.25)	143 (89.94)
Trace	7 (1.07)	6 (1.21)	1 (0.63)
1+	56 (8.56)	45 (9.09)	11 (6.92)
2+	14 (2.14)	12 (2.42)	2 (1.26)
3+	8 (1.22)	6 (1.21)	2 (1.26)
4+	4 (0.61)	4 (0.80)	0 (0)
All proteinuria (%)	89 (13.61)	73 (14.75)	16 (11.19)
Pus 1 (%)			
0	202 (30.89)	185 (37.37)	17 (10.69)
1-5	26 (3.98)	22 (4.44)	4 (2.52)
6-20	3 (0.46)	1 (0.20)	2 (1.26)
21-100	4 (0.61)	2 (0.40)	2 (1.26)
101-1000	2 (0.31)	1 (0.20)	1 (0.63)
>1000	417 (63.76)	284 (57.37)	133 (83.65)
All pyuria (%)	426 (65.14)	288 (58.18)	138 (86.79)
Mean daily eGFR (MDRD) (ml/min/1.73m²)			
≥60	648 (99.08)	494 (99.80)	154 (96.86)
≥30 <60	6 (0.92)	1 (0.20)	5 (3.14)
<30	0 (0)	0 (0)	0 (0)
All high MDRD CKD risk (%)	6 (0.92)	1 (0.20)	5 (3.14)
Mean daily eGFR (CKD-EPI) (ml/min/1.73m²)			
≥60	649 (99.24)	494 (99.80)	155 (97.48)
≥30 <60	5 (0.76)	1 (0.20)	4 (2.52)
<30	0 (0)	0 (0)	0 (0)
All high CKD-EPI CKD risk (%)	5 (0.76)	1 (0.20)	4 (2.52)
Median creatinine ratio (1/creatinine, IQR)	1.79-02 (1.43-02-2.38-02)	1.64-02 (1.37-02-1.92-02)	2.86-02 (2.41-02-3.85-02)

Signif. codes: 0 '****' 0.001 *** 0.01 ** 0.05 '.' 0.1 '.' 1

all patients but one, who was omitted from the quantitative analysis, along with 9 further patients who were missing partial test data. The dataset of patients with all tests completed contained a total of 654 patients. Patients with hyperglycaemia were advised regarding lifestyle modifications and regular follow-ups to evaluate the difference.

Statistical methods

For patients for whom more than one mean daily serum creatinine value was recorded, the mean daily creatinine for the first day of presentation was used in the analysis to avoid bias towards patients requiring follow-up testing. For pus 1 (white blood cell) count values, test results recorded as cell count ranges of up to 5 (e.g. "0-2") were assigned 0; higher cell count ranges were assigned the median bin value (e.g. 45 for "40-50"), results of ">100" and "50-170" were assumed equivalent and assigned the median value for the "50-170" bin (110). All cell count values over 170 were analysed as integer values. Patients with a pus 1 cell count of >5/mm³ were considered pyuric. Red blood cell (RBC) count results of "trace" and 1-3 were considered synonymous, as were "many" and 4-100, and "too numerous to count" and >100. Haematuria was defined as urine RBC count ≥3. Proteinuria (albuminuria) was recorded in all cases of presence of protein and glycosuria was recorded in all cases of presence of glucose.

eGFR was calculated using both the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)¹⁰ and Modification of Diet in Renal Disease (MDRD) (11) formulas. For the purposes of adjusting for black African ethnicity within the eGFR calculations, we have assumed that the following nationalities fall within this group: Cameroonian, Comorian, Ethiopian, Kenyan, Malawian, Nigerian, Sudanese, Tanzanian, Ugandan, and Zimbabwean. In order to gain statistical power given the small numbers of individuals representing some nationalities, the following groupings were made to group most nationalities of fewer than five individuals and models repeated before and after grouping: North American (American and Canadian), Other European (Albania, Dutch, Italian, Serbian, Turkish, Uzbekistani), Western African (Nigerian, Cameroonian), Central to Southern African (Zimbabwean, Malawian), East African (Kenyan, Tanzanian, Ugandan, Ethiopian), and Middle Eastern (Lebanese, Jordanian, Syrian).

Generalised linear models (GLMs) were constructed to model eGFR as a response with national-

Table 3. Age-specific prevalence of renal symptoms

Age	All patients	<18	>=18 <30	>=30 <40	>=40 <50	>=50 <60	>=60 <70	>=70
Number of study participants	654	6	113	281	152	67	29	6
Glycosuria (%)	76 (11.62)	0	1 (0.88)	21 (7.47)	23 (15.13)	15 (22.39)	12 (41.38)	1 (16.67)
Proteinuria (%)	89 (13.61)	0	15 (13.27)	40 (14.23)	16 (10.53)	11 (16.42)	5 (17.24)	2 (33.33)
Pyuria (%)	426 (65.14)	6 (100)	79 (69.91)	179 (63.70)	86 (56.58)	45 (67.16)	25 (86.21)	6 (100)
Haematuria (%)	45 (6.89)	0	9 (7.96)	20 (7.12)	15 (9.87)	6 (8.96)	1 (3.5)	0
All high MDRD CKD risk (%)	6 (0.92)	0	0	2 (0.71)	0	2 (2.99)	1 (3.45)	1 (16.67)
All high CKD-EPI CKD risk (%)	5 (0.76)	0	0	1 (0.36)	0	2 (2.99)	1 (3.45)	1 (16.67)

ity, age, and sex as predictors, followed by creatinine ratio and continuous biomarker values (RBC, Pus 1) as responses with the same predictor variables. In order to analyse the RBC count based on the binned categories recorded, the four RBC level bins recorded (negative, trace, many, numerous) were assigned levels 0-3 and the variables were treated as continuous. To analyse glucose and protein results, the categories used to differentiate levels (Negative, trace, 1-4) were recoded as 0-5.

Serum creatinine derived indicators

eGFR generally decreased with age ($p=2e^{-16}$) and was lower in men ($p=8.6e^{-14}$). As only five individuals had a low mean daily CKD-EPI eGFR below 60, it was not feasible to categorically model eGFR indicative of compromised kidney function. However, all five participants with eGFR<60 were Indian, and four of these were female (Table 2). Further research will be needed to discern whether Indian women are generally at a higher risk of kidney impairment or whether this simply reflects the demographic split of patients.

Creatinine ratios were significantly lower in Egyptian participants ($p=0.04$) and Yemeni participants ($p=0.001$), and higher than average in East African patients ($p=6e^{-04}$). In Yemeni patients, creatinine ratio decreased less rapidly with age ($p=9e^{-04}$), and in East African patients, creatinine ratio decreased more rapidly with age ($p=0.03$). A single Indonesian patient had a remarkably high creatinine ratio ($p=1.68e^{-05}$) and therefore also a high CKD-EPI eGFR ($p=0.04$).

Women had a 3-fold larger creatinine ratio (1/ creatinine) interquartile range than men (Figure 1, Table 2). Pakistani and East African women showed an increased creatinine ratio compared to men of the same nationalities ($p=0.01$, $p=4e^{-04}$), but this gap narrowed with increasing age.

Urine test biomarkers

All patient prevalence of pyuria was 65.51%, haematuria prevalence was 6.89%, proteinuria prevalence was 13.61% and glycosuria prevalence was 11.62% (Table 2). Considering age and sex subgroups, sex was highly significant in predicting Pus 1 count ($p=9.74e^{-10}$), with 86.79% of women having pyuria (Figure 2). A U-shaped relationship was evident between age and pyuria with highest prevalence in the elderly and the young (Table 3). Age was associated with significant increases in glucose level ($p=6.0e^{-12}$) and in protein (albumin) level ($p=0.05$) (Table 3).

The only Emirati individual of the study had a significantly increased RBC count ($P=3.8e^{-04}$), and the only Indonesian national had a significantly increased glucose level ($p=0.002$). These results should be interpreted with caution given that they reflect only single individuals.

DISCUSSION

The prevalence of CKD varied from 1.1% to 34.3% across various populations studied since 2000, with a global estimate of 11-13%¹. In the majority of previous studies, the prevalence of CKD increased with age within the same study populations¹, and, consistent with these findings, our model considering demographic variables with CKD-EPI eGFR shows a significant negative correlation between age and eGFR. The mean age of patients with CKD-EPI eGFR<60 in this study was 56.2 years $\pm$ 15.0, compared to a whole study mean of 38.4 years $\pm$ 10.8. The overall prevalence of low eGFR in the dataset was 0.76-0.92% depending on GFR formula. We observed a difference in the individuals indicated as having low GFR using the CKD-EPI and MDRD eGFR equations: among six individuals identified as having eGFR<60 with the MDRD equation (Table 2), one was classified

Table 4. Condition prevalence by frequent patient nationalities (n>10)

Nationality	All patients	Indian	Pakistani	Filipino	Bangladeshi	Sri Lankan	Egyptian
No. study participants	654	405	70	69	14	12	12
Glycosuria (%)	76 (11.62)	55(13.58)	9(12.86)	5(7.25)	0	2 (16.66)	0
Proteinuria (%)	89 (13.61)	51(12.59)	12(17.14)	6 (8.70)	2 (14.29)	1 (8.33)	7 (58.33)
Pyuria (%)	426 (65.14)	252 (62.22)	56 (80.00)	46 (66.67)	6 (42.86)	5 (41.67)	8 (75.00)
Haematuria (%)	45 (6.88)	23 (5.68)	8 (11.43)	4 (5.80)	2 (14.29)	0	3(25.00)
High MDRD CKD risk (%)	6 (0.92)	5 (1.23)	1 (1.43)	0	0	0	0
High CKD-EPI CKD risk (%)	5 (0.76)	5 (1.23)	0	0	0	0	0

Signif. codes: 0 '****' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

as having an eGFR of ≥ 60 ml/min/1.73m² with the CKD-EPI equation (CKD-EPI=68.14 ml/min/1.73m², MDRD=59.18 ml/min/1.73m²). The mean eGFR of the whole cohort was 160.60 ml/min/1.73m² using the MDRD formula and 124.79 ml/min/1.73m² according to the CKD-EPI formula. Such discrepancies are not uncommon, with the CKD-EPI formula typically estimating higher GFRs in women and young people than the MDRD formula¹³.

In this study, 13.6% of patients demonstrated proteinuria. Proteinuria is often the first indicator of progression towards renal failure¹⁴. Only after a prolonged period of increasing proteinuria does the serum creatinine level begin to increase. Although proteinuria can be minimal in CKD, this pattern is commonly seen in CKD patients whose condition is progressing because of increased glomerulonephritis¹⁴. Glomerulonephritis is currently the leading cause of end stage renal failure in the UAE, followed by diabetes⁶.

The prevalence of low eGFR that we observed may be lower than the population wide prevalence, considering that the majority of patients were asymptomatic outpatients volunteering to access preventative healthcare and that CKD is currently most commonly diagnosed on emergency room presentation¹⁰. However, we also recognise that some patients reporting low eGFR may have sustained acute kidney injuries that resolved soon after testing rather than progressing towards chronic disease. Overall CKD prevalence in the UAE is likely to be lower than the 11.4% reported CKD 3-5 incidence in patients with hypertension and/or cardiovascular disease, a high CKD risk subgroup⁸. Comparing our low CKD-EPI eGFR prevalence (0.8%) to that of these patients (8.8%) confirms that the high cardiovascular risk cohort had atypically low eGFRs when compared to the general populace.

A number of studies report 'CKD' prevalence as albuminuria and/or a single eGFR measure-

ment<60^{18,21}. Our combined albuminuria and low CKD-EPI eGFR prevalence is 13.76%. Using this definition, 'CKD' prevalence in this cohort would be double that of Saudi Arabia and equivalent to that of China (Table 4). This value is considerably higher than the prevalence of low eGFR and it is therefore likely that the majority of UAE CKD cases qualify as having CKD based on having albuminuria before reaching low eGFR.

Sex-specific prevalence of low GFR

In most prior South Asian CKD prevalence studies (Table 4), the prevalence of CKD was greater in women than in men, across age categories and various ethnic groups. Our study results are consistent with these findings, with four of the five individuals identified with eGFR<60 being women. A sixth patient identified as having eGFR<60 using only the MDRD formula was also a woman.

Ethnicity-specific prevalence of low GFR

All five patients with low CKD-EPI eGFR were Indian, although a sixth patient identified as having eGFR<60 using only the MDRD formula was Pakistani. Both the CKD-EPI and MDRD formulas calculate eGFR differentially in black African and Caucasian patients, and it is arguable that these should be further developed and modified to reflect the baseline eGFRs of additional ethnic groups. There is therefore significant uncertainty as to how well eGFR reflects renal function in non-Caucasian patients¹⁵.

Considering Indian patients, who made up the largest proportion of the cohort, Varma et al.¹⁶ reported a high incidence of CKD (13-15%) in apparently healthy Indian subjects with a mean age of 36 years and no history of renal disease, a 3.95 prevalence of haematuria and a 9.9% prevalence of microalbuminuria, while The SEEK India cross-sectional study¹⁷ recorded 17.2% CKD, 8.6% glycosuria, 19% haematuria and 13.7% proteinuria in the

general population (Table 4). Our haematuria and proteinuria results for Indian patients are intermediate to these two studies, but the glycosuria prevalence we recorded (11.6%) is higher than that of the SEEK study, potentially reflecting lifestyle differences.

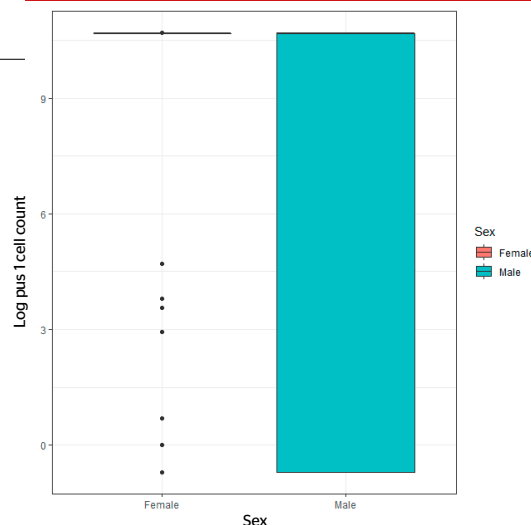
Age and nationality-specific prevalence of renal dysfunction markers

There were age-based differences in how commonly patients displayed renal decline symptoms. For example, all 6 individuals aged over 70 had pyuria, with Pus 1 counts of 43,000-44,000 (Table 2) and all 6 patients aged under 18 also had pyuria, creating a U-shaped relationship, which could potentially be explained by the vulnerability of young and old patients to urinary tract infections (UTIs). Increasing age was associated with a significant increase in urine glucose level (Table 3, $p=4.2 \times 10^{-12}$), and with progressive proteinuria ($p=0.05$).

Little variation was detected in renal dysfunction symptoms according to nationality, although this may reflect the small sample size. Although the overall prevalence of proteinuria (58%), haematuria (25%) and pyuria (75%) was atypically high in Egyptian patients (Table 3), this was explained when modelling nationality alongside sex, as there were more men in the Egyptian subgroup. Pyuria frequency was highest (80%) in the Pakistani patients and glycosuria in Sri Lankan patients (17%), but again these relationships were non-significant (Table 3).

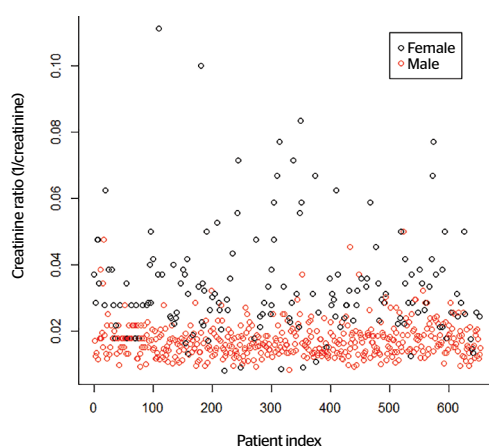
It is likely that further links between renal dysfunction biomarkers and nationality and/or sex

Figure 2



could be determined in the future, as more individuals from minority nationalities contribute their data to the project, and if more women can be recruited to the study. Extending the data capture will enable baseline values to be created for individual patients and for nationality groups to determine general or specific differences between patient groups. For example, there was low participation from individuals over 70 years, who are likely to be at higher risk of CKD¹, and significantly different values in some symptoms were observed for Indonesian and Emirati individuals, who represent ethnic groups in which limited population-level renal research has been conducted. CKD progression speed typically positively correlates with age and male sex and varies by ethnicity (progression has been shown to be more rapid in non-Caucasian ethnicities in the West, including African Americans and Asians [South Asians and Pacific Asians])¹³. It is therefore imperative to encourage older people and those from ethnic minorities to attend screening.

Figure 1



The main observations of the study:

Most of the study group were of South Asian nationalities, including Indian (62%), Pakistani (11%) and Filipino (11%), and most were 18-50 years old (84%). Glycosuria was detected in 11.6% of the population studied. Proteinuria (albumin in the urine) was found in 87 patients (13.6% of the study sample), and microscopic haematuria in 45 (6.9%).

Considering differences by nationality, asymptomatic Haematuria (blood in urine) was found in 11.4% of Pakistani participants and in 5.7% of Indians. The incidence of proteinuria was 17.1% vs 12.6% respectively. Most participants (65.1%) had pyuria (pus cells in urine), which was unexpected as most of them were asymptomatic. eGFR was found

Table 5. Prevalence of chronic kidney disease (CKD) in population-based studies from South Asia

			Prevalence of CKD		
Author [ref.] year	Country	Study population, study design, number of participants, response, age, gender	MDRD equation	CKD-EPI equation	
Imtiaz et al. [15] 2018	Pakistan	Review of studies from Pakistan	NR	Overall 5.0-31.20%	
Alsuwaida et al. [18] 2010	Saudi Arabia	Participants from SEEK Thailand attending testing camps in public areas, 2008, N=aged ≥18 (mean age 37.4 yrs), 49.9% males ('CKD' defined from single measurements)	Overall: 5.7%	Overall: 5.3%	
Chen et al. [19] 2005	China	Participants of the International Collaborative Study of Cardiovascular Disease in Asia (InterASIA), random sample, cross-sectional study, N = 15540, response 83.3%, aged 35-74 yrs., 48.5% males.	Overall: 2.5% Men: 1.3%, Women: 3.8%		
			Age (yrs.)	Men	Women
			35-44	0.2%	1.2%
			45-54	0.7%	2.7%
			55-64	1.6%	6.4%
			65-74	5.8%	10.4%
Ingsathit et al. [20] 2010	Thailand	Participants from the SEEK Thailand cohort, cross-sectional study, N=3459, mean age 45.2 yrs, 45.5% males	Overall 17.5%	Men: 16.3%	Women: 18.5%
omen: 1					
Zhang et al. [21] 2012	China	National cross-sectional survey, N = 47204, response=93%, Overall: 10.8% mean age= 42.3 yrs, 49.5% males. ('CKD' defined from single measurements)			
Ninomiya et al. [22] 2005	Japan	Participants from study of Cerebrovascular and Cardiovascular Diseases, prospective cohort study, N = 2634, response 80.7%, aged ≥ 40 yrs., 42.1% males.	Overall: 10.3% Men: 5.3%, Women: 13.8%	NR	
Singh et al. [17] 2013	India	Participants from the SEEK India cohort, cross-sectional study, N= 5588, aged 18-98 yrs (mean age: 45.2 yrs), 55.1% males.	Overall: 17.2:	Overall 16.4%	
Wong et al. [23] 2018	Singapore	National database of health records, N =2m	Overall: 12.2% Men: 7.1%, Women: 6.2%	NR	

MDRD: simplified equation of the Modification of Diet in Renal Disease Study.

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation

eGFR: estimated glomerular filtration rate.

NR: Not reported.

to be <60 ml/min/1.73m² in only 6 people (0.9%) using the MDRD method and 5 (0.8%) using the CKD EPI formula. There were more women than men in this low eGFR group. Creatinine ratios were significantly lower in Egyptian participants (p=0.04) and Yemeni participants (p=0.001), and higher than average in East African patients (p=6e-04).

Limitations

CKD prevalence could not be assessed based on single measurements from the study patients, as CKD is defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria based on persistent low GFR (<60 mL/min/1.73 m²) and/or albuminuria over

a period of at least three months (Levey et al 2012). Establishing CKD prevalence is a primary goal of this research programme as it continues. A further limitation of this study was that all participants with abnormal urine findings could not undergo detailed imaging and laboratory work to ascertain the cause of the findings.

CONCLUSIONS

The high incidence of pyuria in this study (65.1%) points towards the possibility of early urine infection, renal calculi, or poor water intake. It may also point towards occult infections of the genital tract. The female population is at a bigger risk for

infection due to the shorter female urethra and may also be more prone to inadequate hydration. The incidence of hyperglycaemia was 11.6%. The prevalence of hyperglycaemia, lack of awareness about fluid intake, and inadequate personal hygiene may all have contributed to pyuria.

This study has helped to understand the need for frequent population screening to detect early onset of the chronic illnesses. Early detection would help to initiate life style modifications, which could help to retard the progression of major diseases. The importance of hydration among individuals needs to be emphasized; moreover, proper dietary habits and regular check-ups help to maintain the health of the general public. Women have an elevated risk of pyuria, low eGFR and therefore CKD, and should be encouraged to attend routine health screening.

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Microeconomic Costs, Insurance, and Catastrophic Health Spending Among Patients With Acute Myocardial Infarction in India

Substudy of a Randomized Clinical Trial

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KEY POINTS

Question What are the costs and risks of impoverishment for patients with acute myocardial infarction and their families in Kerala, India, and how do these factors vary by health insurance status?

Findings In this prespecified cross-sectional substudy of a randomized clinical trial, 2114 respondents reported \$480 international dollars in out-of-pocket costs per acute myocardial infarction, with \$400 international dollars in higher costs among individuals without insurance vs those with insurance. Catastrophic health spending was also higher among individuals without insurance (58.1% vs 39.9%) as was distress financing (9.7% vs 3.1%).

Meaning Survivors of acute myocardial infarction in Kerala may face high costs and risk for impoverishment, and expansion of insurance access and coverage should be considered for financial risk protection.

ABSTRACT

IMPORTANCE Ischemic heart disease is the leading cause of death in India, and treatment can be costly.

OBJECTIVE To evaluate individual- and household-level costs and impoverishing effects of acute myocardial infarction among patients in Kerala, India.

DESIGN, SETTING, AND PARTICIPANTS This investigation was a prespecified substudy of the Acute Coronary Syndrome Quality Improvement in Kerala study, a stepped-wedge, cluster randomized clinical trial conducted between November 2014 and November 2016 across 63 hospitals in Kerala, India. In this cross-sectional substudy, individual- and household-level cost data were collected 30 days after hospital discharge from a sample of 2114 respondents from November 2014 to July 2016. Data were analyzed from July through October 2018 and in March 2019.

EXPOSURES Health insurance status.

MAIN OUTCOMES AND MEASURES The primary outcomes were detailed direct and indirect cost data associated with acute myocardial infarction and respondent ability to pay as well as catastrophic health spending and distress financing. Catastrophic health spending was defined as 40% or more of household expenditures minus food costs spent on health, and distress financing was defined as borrowing money or selling assets to cover health costs. Hierarchical regression models were used to evaluate the association between health insurance and measures of financial risk. Costs were converted from

Indian rupees to international dollars (represented herein as “\$”).

RESULTS Among 2114 respondents, the mean (SD) age was 62.3 (12.7) years, 1521 (71.9%) were men, 1144 (54.1%) presented with an ST-segment elevation myocardial infarction, and 1600 (75.7%) had no health insurance. The median (interquartile range) expenditure among respondents was \$480.4 (\$112.5-\$1733.0) per acute myocardial infarction encounter, largely driven by in-hospital expenditures. There was greater than 15-fold variability between the 25th and 75th percentiles. Individuals with or without health insurance had similar monthly incomes and annual household expenditures, yet individuals without health insurance had approximately \$400 higher out-of-pocket cardiovascular health care costs (median [interquartile range] total cardiovascular expenditures among uninsured, \$560.3 [\$134.1-\$1733.6] vs insured, \$161.4 [\$23.2-\$1726.9]; $P < .001$). Individuals without health insurance also had a 24% higher risk of catastrophic health spending (adjusted risk ratio, 1.24; 95% CI, 1.07-1.43) and 3-fold higher risk of distress financing (adjusted risk ratio; 3.05; 95% CI, 1.45-6.44).

CONCLUSIONS AND RELEVANCE The results of this study indicate that acute myocardial infarction carries substantial financial risk for patients in Kerala. Expansion of health insurance may be an important strategy for financial risk protection to disrupt the poverty cycle associated with cardiovascular diseases in India.

INTRODUCTION

Ischemic heart disease is the leading cause of death and disability in India,¹ and treatment of acute and chronic manifestations of ischemic heart disease can be costly for patients and their families.² Although the stepwise, inverse relationship between baseline socioeconomic position and incident cardiovascular disease (CVD) has been well described,³ including in Asia,⁴ the impoverishing effects of CVD have not been as widely reported. High-functioning health systems need to not only be accessible and responsive to patients' needs but also provide financial risk protection for short- and long-term treatment. As a result, the United Nations Sustainable Development Goals includes target 3.8: “Achieve universal health coverage, including financial risk protection, access to quality essential health care services and access to safe, effective, quality, and affordable essential medicines and vaccines for all.”⁵

Individuals' abilities to pay for health care expen-

ditures are estimated by comparing out-of-pocket health care expenditures with household expenditures after accounting for subsistence, or food, expenditures. Catastrophic health spending occurs when individuals spend a high proportion of overall expenditures on health care with variable thresholds set, ranging from 10% to 40%,⁶ with subsequent poverty incidence rates ranging from 0.5% to 14%.⁶ Distress financing occurs when individuals try to buffer spending shocks by selling or mortgaging assets or borrowing money to cover health expenditures. A 2011 report from the south Indian state of Kerala (500 respondents) demonstrated a more than 60% prevalence rate of catastrophic health spending and distress financing among individuals with a recent acute myocardial infarction or stroke.² India has subsequently enacted and scaled a social health insurance program, Rashtriya Swasthya Bima Yojana, to 36 million households to cover hospital expenses, with 2.1 million families covered in Kerala.⁷ However, this program does not seem to have reduced out-of-pocket spending.⁸

The Acute Coronary Syndrome Quality Improvement in Kerala (ACS QUIK) study was a stepped-wedge, cluster randomized clinical trial evaluating the effect of a quality improvement toolkit on clinical outcomes.^{9,10} As a prespecified substudy of ACS QUIK, the present study collected data on individual- and household-level expenditures associated with acute myocardial infarction. We sought to describe the individual and household costs associated with acute myocardial infarction; to assess how these costs compare with an individual's ability to pay; to explore other patient-, hospital-, and treatment-level factors; and to evaluate the degree to which insurance mitigates risk for catastrophic health spending, distress financing, or both.

METHODS

Overview of ACS QUIK

The methods and results of ACS QUIK (ClinicalTrials.gov identifier, NCT02256657) have been reported.^{9,10} In brief, 21 374 eligible participants with acute myocardial infarction were recruited from 63 hospitals in Kerala, India, from November 2014 to November 2016. The trial used a stepped-wedge cluster randomized design to evaluate the effect of a locally adapted quality improvement toolkit on the rate of 30-day major adverse events, defined as death, reinfarction as defined by the Third Universal Definition of Myocardial Infarction,¹¹ stroke, and major bleeding as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria.¹² The unadjusted difference between the intervention and control groups (5.3% vs 6.4%) was no longer observed after adjustment

Table 2: Table 1. Demographics, Clinical Presentation, and Laboratory Data From 2114 ACS QUIK Respondents Who Completed Microeconomic Questionnaires, Overall and by Insurance Status

Characteristic	Respondents, No.	Overall (N = 2114)	No Insurance (n = 1600)	Insurance (n = 514)	P Value ^a
Demographic at hospital presentation ^b					
Age, mean (SD), y	2114	62.3 (12.7)	62.9 (12.9)	60.3 (11.7)	<.001
Male, No. (%)	2114	1521 (71.9)	1162 (72.6)	359 (69.8)	.22
History of tobacco use, No. (%)	2114	618 (29.2)	456 (28.5)	162 (31.5)	.19
History of diabetes, No. (%)	2114	901 (42.6)	699 (43.7)	202 (39.3)	.08
Transferred, No. (%)	2114	907 (42.9)	709 (44.3)	198 (38.5)	.02
ST-segment elevation myocardial infarction, No. (%)	2114	1144 (54.1)	838 (52.4)	306 (59.5)	.005
Symptom-to-door time, median (IQR), min	2015	260 (120-960)	272 (120-980)	240 (130-879)	.82
Body weight, mean (SD), kg	2113	60.6 (10.8)	60.6 (11.1)	60.4 (9.7)	.74
Systolic blood pressure, mean (SD), mm Hg	2114	143.1 (30.6)	143.7 (30.5)	141.4 (30.9)	.15
Heart rate, mean (SD), bpm	2114	81.9 (19.7)	82.4 (20.2)	80.4 (18.0)	.04
Initial troponin, median (IQR), ng/mL	492	1.60 (0.48-6.09)	1.57 (0.47-5.70)	1.91 (0.69-8.71)	.16
LDL cholesterol, mean (SD), mg/dL	1587	121.0 (41.6)	120.7 (41.5)	122.1 (41.9)	.59
Triglycerides, median (IQR), mg/dL	1593	123 (93-174)	123 (95-175)	121 (90-173)	.51
Serum creatinine, median (IQR), mg/dL	980	1.1 (0.9-1.3)	1.1 (0.9-1.3)	1.0 (0.8-1.2)	.02
Fasting glucose, median (IQR), mg/dL	1394	130 (104-180)	133 (106-184)	120 (100-172)	.004
Hemoglobin, mean (SD), g/dL	2035	13.2 (2.1)	13.2 (2.1)	13.0 (2.1)	.15
ACS QUIK intervention, No. (%)	2114	1085 (51.3)	875 (54.7)	210 (40.9)	<.001
Socioeconomics, No. (%) ^c					
Married	2114	1751 (82.8)	1332 (83.3)	419 (81.5)	.36
Rural	2113	1595 (75.5)	1230 (76.9)	365 (71.2)	.009
Educational level, median (IQR), y	1941	9 (5-12)	10 (6-12)	8 (5-10)	<.001
Time to survey completion, median (IQR), d	1899	31 (30-34)	31 (30-33)	34 (30-49)	<.001
Unemployment, No. (%)	2114	(39.0)	584 (36.5)	240 (46.7)	<.001
Baseline monthly individual income, median (IQR)					
Rs	2074	9000 (2000-12 000)	10 000 (1500-12 000)	8000 (4000-10 000)	.56
International \$ ^d	2074	524.7 (116.6-699.6)	583.0 (87.5-699.6)	466.4 (233.2-583.0)	
Baseline monthly household income, median (IQR)					
Rs	2112	10 000 (8000-20 000)	15 000 (10 000-20 000)	7000 (4000-10 400)	<.001
International \$ ^d	2112	583.0 (466.4-1166.0)	874.5 (583.0-1166.0)	408.1 (233.2-606.3)	
Dependents, No. (%)					
<18 y	2114	1338 (63.3)	1056 (66.0)	282 (54.9)	<.001
>60 y	2114	1308 (61.9)	980 (61.3)	328 (63.8)	.30
Other individuals in household earning income, No. (%)	2114	1959 (92.7)	1494 (93.4)	465 (90.5)	.03

Abbreviations: ACS QUIK, Acute Coronary Syndrome Quality Improvement in Kerala; IQR, interquartile range; LDL, low-density lipoprotein; Rs, Indian rupees.

SI conversion factors: To convert troponin to micrograms per liter, multiple by 1.0; LDL cholesterol to millimoles per liter, by 0.0259; triglycerides to millimoles per liter, by 0.0113; serum creatinine to micromoles per liter, by 88.4; glucose to millimoles per liter, by 0.0555; and hemoglobin to grams per liter, by 10.0.

^a Unadjusted for differences.

^b Variables collected at hospital presentation among patients enrolled in the ACS QUIK study.

^c Variables collected from patients during follow-up at time of completion of the microeconomic assessment.

^d Uses 2015 conversion of 17152 Indian rupees to equal 1 international dollar:13

for clustering and temporal trends (adjusted risk difference, -0.09% [95% CI, -1.32% to 1.14%]; adjusted odds ratio, 0.98 [95% CI, 0.80-1.21]). Rates of reperfusion and in-hospital and discharge medication were higher in the intervention group compared with the control group, which persisted after adjustment. The present report adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies. The ACS QUIK trial and this substudy received institutional review board approval from local, national, and international bodies and was approved by the Indian Health Ministry Screening Committee. All participants or their delegates provided written informed consent.

Sample Identification

We performed age-stratified (<50 years; 50-70 years; and >70 years) and sex-stratified random sampling of a subset of participants who presented for 30-day follow-up to evaluate microeconomic (ie, individual- and household-level) costs associated with acute myocardial infarction hospitalization. The initial recruitment target was 2200 respondents, which provided 95% power to detect differences in catastrophic health spending across age and sex strata, assuming a baseline catastrophic health spending prevalence rate of 60%.² Recruitment for this substudy was planned to occur among sites and participants in the control period of the trial to minimize the potential influence of the toolkit intervention on costs, such as costs from higher rates of reperfusion and medications. However, slower-than-expected enrollment was identified during the first year of the trial owing to the length of the survey instrument and the time required from study personnel and participants. After consultation with the trial's data and safety monitoring board, we revised our sampling frame in November 2015 to an unselected population within the overall trial to achieve our recruitment target by June 2016. Among all individuals who completed the microeconomic survey, we excluded 10 individuals who reported hospitalization outside the date range of the ACS QUIK trial (from November 2014 to November 2016). The most recent hospitalization was used for primary analysis to minimize recall bias. When hospitalizations were reported in the same month and year, we used the longer hospitalization.

Assessment of Microeconomic Costs and Insurance Status

The instrument used to collect self-reported information on health care-associated expenditures, reimbursement, individual and household income, and household expenditures was developed in collaboration with experts from the World Bank and has been published.² Health insurance was defined by self-report of having in-

surance at ACS QUIK admission or by any self-report of reimbursed expenditures from an insurer at the 30-day follow-up visit. Trained study personnel administered the survey in person to the participants, their delegates, or both during the 30-day follow-up research visit in the Malayalam or English language based on the participant's preference. Costs were assessed in Indian rupees (Rs) and converted into 2015 international dollars based on purchasing power parities published by the World Bank (17.152=international \$)¹³; thus, unless otherwise indicated, all costs reported herein as "\$" represent international dollars.

Cardiovascular Hospitalization and Total Health Care Expenditures

Inpatient cardiovascular hospitalization costs were calculated as the sum of self-reported spending on hospital admission, diagnostic tests, emergency department, food, treatment, ambulance, surgery, medicine, attendants, travel, and other self-reported inpatient costs. Total health care costs additionally included posthospitalization expenses on physicians, rehabilitation, home care, diagnostic tests, food, medicine, transportation, and other self-reported post-hospitalization expenses. Out-of-pocket costs were calculated as the sum of all reported costs minus the total reimbursement by the insurance provider. A floor threshold of Rs 0 out-of-pocket costs was imposed where needed. Inpatient percentages were calculated only among patients with expenses reported.

Annual Household Expenses

Total annual household expenses were calculated as the sum of monthly expenses on rent, food, insurance, petrol, transportation, and educational expenses and annual expenses on goods, clothes, household fuel, health care, vehicle repair, property management, and any other self-reported household expenses. Nonfood expenses excluded monthly food expenses.

Proportionate Expenses

Cardiovascular disease expenditures as a proportion of annual household expenses were calculated as the out-of-pocket expenses on the most recent hospitalization as a proportion of the annual household expenditure. If Rs 0 total annual household expenditures were reported, then CVD expenses as a proportion of annual household expenditures were calculated as 100%.

Catastrophic Health Spending and Distress Financing

Among patients who had out-of-pocket expenses and reported total nonfood annual household expenditures, catastrophic health spending was calculated.

Table 2: Expenditures and Incomes From 2114 ACS QUIK Respondents Who Completed Microeconomic Questionnaires

Expenditure	Respondents, No.	Overall (N = 2114)	No Insurance (n = 1600)	Insurance (n = 514)	P Value ^a
CVD expenditures, median (IQR), international \$ ^{b,c}					
Total CVD expense	2114	480.4 (112.5-1733.0)	560.3 (134.1-1733.6)	161.4 (23.3-1726.9)	<.001
Inpatient CVD expense	2113	356.8 (96.8-1623.7)	448.9 (116.6-1638.0)	110.2 (14.6-1587.3)	<.001
Out-of-pocket CVD expense	2114	374.3 (104.9-1316.5)	536.4 (131.7-1564.0)	87.9 (17.5-492.7)	<.001
Inpatient expense/total CVD expense, median (IQR), % ^d	2106	93.5 (80.5-99.0)	93.5 (82.6-98.8)	93.2 (70.4-100)	.26
Annual household expenditures, median (IQR), international \$ ^{c,e}					
Expense	1523	3847.9 (2512.8-5597.0)	3827.5 (2448.7-5879.8)	3847.9 (2938.4-4780.8)	.50
Nonsubsistence expense	1196	1539.2 (1107.7-2976.3)	1612.1 (1107.7-3157.1)	1399.3 (1049.4-2110.5)	.01
Out-of-pocket CVD expense/annual household expense, median (IQR), % ^f	1523	12.4 (4.1-44.6)	13.3 (4.3-54.4)	9.6 (3.1-20.9)	<.001
Income effects					
Any decrease in individual income, No. (%)	2113	964 (46.0)	634 (39.6)	330 (64.3)	<.001
Any decrease in household income, No. (%)	2113	927 (44.0)	610 (38.1)	317 (61.8)	<.001
Decrease in individual monthly income since hospitalization, median (IQR), international \$ ^c	2058	0.0 (0.0-174.9)	0.0 (0.0-174.9)	58.3 (0.0-174.9)	<.001
Decrease in household monthly income since hospitalization, median (IQR), international \$ ^c	2111	0.0 (0.0-174.9)	0.0 (0.0-174.9)	58.3 (0.0-174.9)	.006
Catastrophic and distress spending, No. (%) ^g					
Catastrophic health spending	1196	644 (54.0)	533 (58.1)	111 (39.9)	<.001
Distress financing	2114	171 (8.0)	155 (9.7)	16 (3.1)	<.001
Catastrophic health spending or distress financing	1311	772 (59.0)	648 (63.4)	124 (42.9)	<.001

Abbreviations: ACS QUIK, Acute Coronary Syndrome Quality Improvement in Kerala; CVD, cardiovascular disease; IQR, interquartile range.

^a Unadjusted for differences.

^b Total CVD expenses include inpatient expenses on hospital admission, tests, emergency department, food, treatment, ambulance, surgery, other self-reported expenses, medicine, attendants, and travel as well as posthospitalization expenses for physicians' fees, rehabilitation, home care, other self-reported expenses, tests, food, medicines, and transportation. Out-of-pocket expense includes all CVD-related expenses minus any reimbursement for inpatient or posthospitalization services.

^c Uses 2015 conversion of 17,152 Indian rupees equal to 1 international dollar.¹³

^d Proportion is not calculated when total CVD expense is reported as zero or inpatient costs are missing.

^e Includes all expenses on food, gas, transportation, rent, insurance, educational level, goods, clothes, heating fuel, health care, vehicle repair, property management, and any other self-reported expenses. Nonsubsistence expenses exclude annual spending on food.

^f Proportion is not calculated when total household expense is missing.

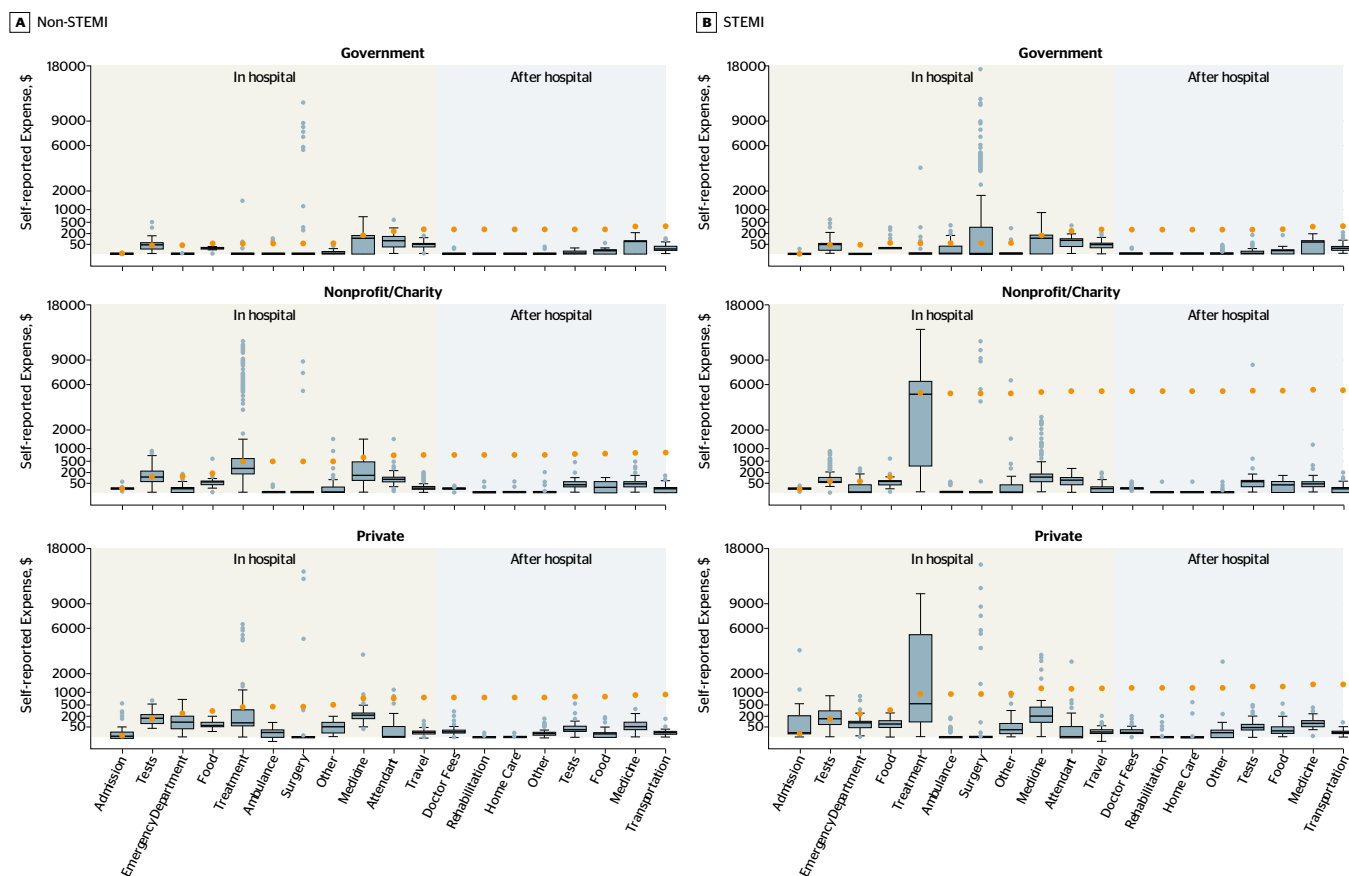
^g Defined by out-of-pocket CVD expenses meeting or exceeding 40% of annual nonsubsistence household expenses. Distress financing is defined by borrowing from friends, relatives, or bank, or by selling an asset to cover CVD-related expenses.

If out-of-pocket expenditures exceeded 40% of annual household expenditures minus food costs, then participants were considered to have experienced catastrophic health spending. Lower thresholds have been used to define catastrophic health spending (eg, 10% or 25%),¹⁴ but we reported results on the basis of our a priori conservative threshold that was based on previous reports.¹⁵ We also sought to compare prevalence rates in Kerala over time based on previous reports using the 40% threshold.² Among patients who reported how health care costs were covered, partici-

pants were considered to have experienced distress financing if they reported covering their health care costs by borrowing money from friends, relatives, or a bank or they sold or mortgaged an asset.

Statistical Analysis

We compared baseline demographic, clinical, and socioeconomic characteristics by insurance status using the t test for continuous, normally distributed covariates and the χ^2 test for categorical covariates. We used the Wilcoxon rank sum test and the Kruskal-Wallis test for nonparametric analyses. We similarly

Figure: Cumulative Cardiovascular Disease Hospitalization Costs

Costs are the sum of itemized medians for in-hospital and posthospitalization expenses among all 2114 Acute Coronary Syndrome Quality Improvement in Kerala trial respondents who completed microeconomic surveys, stratified by in-hospital and posthospital costs, ST-segment elevation myocardial infarction (STEMI) status, and hospital type. The top and bottom of the boxes

indicate 25th and 75th percentiles; bands in boxes, medians; whiskers, $1.5 \times$ (75th percentile – 50th percentile) and $1.5 \times$ (25th percentile – 50th percentile); gray circles, outliers; orange circles, cumulative costs by cost category; and \$, international dollars.

compared CVD expenditures, annual household expenditures, changes in income, and rates of catastrophic health spending and distress financing by insurance status. Similar analyses were performed by sex, hospital type (ie, government, nonprofit/charity, or private hospital), and ST-segment elevation myocardial infarction (STEMI) or non-STEMI status.

To evaluate the association between insurance status and catastrophic health spending and distress financing, we created hierarchical multivariable binomial regression models. We adjusted for patient-level factors, including Global Registry of Acute Coronary Events risk score variables (ie, age, sex, STEMI or non-STEMI status, baseline systolic blood pressure, and heart rate),¹⁶ and baseline household income. We did not include serum creatinine owing to the high frequency of missing data. We did not include in-hospital heart failure, cardiogenic shock, or cardiac ar-

rest in these models owing to collinearity and a small number of events (35 total). We further adjusted for hospital- and study-level factors by creating a random effect to adjust for hospital-level clustering and adjusting for ACS QUIK randomization group (intervention vs control groups). Finally, we sought to adjust for treatment-level factors, including reperfusion (eg, coronary artery bypass graft surgery, percutaneous coronary intervention, thrombolysis, or a combination thereof) and optimal in-hospital and discharge medications—defined as aspirin, second antiplatelet agent, anticoagulant (in-hospital only), β -blocker, and statin¹⁷—but the degree of missing data was too high. Complete case analysis was thus used for derivation of all variables and models. Data were analyzed from July through October 2018 and in March 2019. We used a 2-sided $P < .05$ to define statistical significance and Stata, version 15 (StataCorp), SAS, version 9.4

(SAS Institute Inc), and R, version 3.5.1 (R Foundation) to conduct statistical analyses. Code files used for generation of results can be downloaded from the internet.¹⁸

RESULTS

Baseline Characteristics

The flowchart of 2114 participants is given in eFigure 1 in the Supplement. Participant characteristics by insurance status are reported in Table 1 and by sex in eTable 1 in the Supplement. Mean (SD) age of participants was 62.3 (12.7) years, 1521 (71.9%) were men, and 1144 (54.1%) presented with STEMI. There were modest differences between 1600 uninsured participants (75.7%) and 514 insured participants (24.3%) in terms of mean (SD) age (62.9 [12.9] years vs 60.3 [11.7] years, respectively; $P < .001$), STEMI prevalence rates (838 of 1600 [52.4%] vs 306 of 514 [59.5%]; $P = .005$), ACS QUIK intervention group status (875 of 1600 [54.7%] vs 210 of 514 [40.9%]; $P < .001$), and educational level (median [interquartile range {IQR}] years of education, 10 [6-12] years for uninsured vs 8 [5-10] years for insured, $P < .001$). Of 2114 participants overall, most were married (1751, 82.8%) and from a rural setting (1595, 75.5%). The median (IQR) time to survey completion following hospitalization was 31 (30-33) days in the uninsured group compared with 34 (30-49) days in the insured group ($P < .001$).

Self-reported baseline monthly median (IQR) individual income was similar between uninsured and insured participants (uninsured, \$583.0 [\$87.5-\$699.6] vs insured, \$466.4 [\$233.2-\$583.0]; $P = .56$). By contrast, self-reported baseline monthly median (IQR) household income was higher among uninsured participants than insured participants (\$874.5 [\$583.0-\$1166.0] vs \$408.1 [\$233.2-\$606.3]; $P < .001$).

Expenditures, Catastrophic Health Spending, and Distress Financing

Health care expenditures and household expenditures are reported by insurance status in Table 2. The median (IQR) expenditure among respondents was \$480.4 (\$112.5-\$1733.0) per acute myocardial infarction encounter, largely driven by in-hospital expenditures. There was greater than 15-fold variability between the 25th and 75th percentiles. Total median (IQR) CVD-associated expenditures were higher among uninsured participants (\$560.3 [\$134.1-\$1733.6]) compared with insured participants (\$161.4 [\$23.3-\$1726.9]; $P < .001$), with an approximately 6-fold higher out-of-pocket, CVD-associated expenditures among individuals without insurance despite similar annual household expenditures. Catastrophic health spending was thus higher among individuals without insurance (533 of 1600 [58.1%] vs 111 of 514 [39.9%]; $P < .001$) as was distress financing (155 of 1600 [9.7%] vs 16 of 514

[3.1%]; $P < .001$). Expenditures are also reported by hospital type in eTable 2 in the Supplement and by STEMI status in eTable 3 in the Supplement. Costs are disaggregated as medians with corresponding IQRs for each cost subtype by STEMI vs non-STEMI status and hospital type in the Figure and by payment source in eFigure 2 in the Supplement.

Insurance, Catastrophic Health Spending, and Distress Financing

Table 3 reports the results of binomial regression models evaluating the associations between insurance and catastrophic health spending, distress financing, or both. In unadjusted analyses, lack of health insurance was associated with a 45% higher rate of catastrophic health spending (risk ratio [RR], 1.45; 95% CI, 1.25-1.70), which remained similar after adjustment for patient-level factors, including baseline income (adjusted RR, 1.49; 95% CI, 1.28-1.73), but was attenuated to 24% higher when adjusting for ACS QUIK intervention group and hospital cluster (adjusted RR, 1.24; 95% CI, 1.07-1.43). Similarly, lack of health insurance was associated with a 3-fold higher rate of distress financing (unadjusted RR, 3.11; 95% CI, 1.88-5.16), which was similarly attenuated after adjustment for patient-, study-, and hospital-level factors (adjusted RR, 3.05; 95% CI, 1.45-6.44).

DISCUSSION

Summary

In this study of 2114 survivors of acute myocardial infarction in Kerala, 24% of whom had baseline health insurance, we report detailed individual- and household-level income and expenditure data, including expenditures associated with hospitalization and subsequent cardiovascular care. Median expenditures were less than \$500 per episode, largely driven by in-hospital expenditures, but there was greater than 15-fold variability in expenditures between the 25th and 75th percentiles. We also quantified expected differences in expenditures by hospital type, with higher expenditures reported among respondents seeking care from nonprofit and private hospitals compared with public hospitals, which is concordant with previous reports from nationally representative samples.¹⁹ Individuals with or without health insurance had similar monthly incomes and similar annual household expenditures, yet individuals without baseline health insurance had approximately \$400 higher out-of-pocket cardiovascular health care costs, a 45% greater risk of catastrophic health spending, and a 3-fold higher risk of distress financing.

Figure: Cumulative Cardiovascular Disease Hospitalization Costs

Model	Catastrophic Health Spending			Distress Financing			Catastrophic Health Spending or Distress Financing ^a		
	Respondents, No./Total No.	RR (95% CI)		Respondents, No./Total No.	RR (95% CI)		Respondents, No./Total No.	RR (95% CI)	
		No Cluster Effect	Study Effect ^b		No Cluster Effect	Study Effect		No Cluster Effect	Study Effect
Unadjusted ^c	644/1196	1.45 (1.25-1.70)	1.22 (1.03-1.43)	171/2114	3.11 (1.88-5.16)	2.80 (1.50-5.22)	772/1311	1.48 (1.28-1.70)	1.23 (1.06-1.43)
Adjusted									
Model 1 ^d	644/1196	1.49 (1.28-1.74)	1.24 (1.07-1.43)	171/2114	3.14 (1.89-5.21)	2.87 (1.49-5.54)	772/1311	1.50 (1.31-1.73)	1.25 (1.09-1.44)
Model 2 ^e	644/1196	1.49 (1.28-1.73)	ND ^f	170/2112	3.36 (1.99-5.67)	3.05 (1.45-6.44)	771/1310	1.51 (1.31-1.74)	1.23 (1.11-1.36)

Abbreviations: ACS QUIK, Acute Coronary Syndrome Quality Improvement in Kerala; ND, not determinable; RR, risk ratio.

- a Among 918 participants who were missing information to calculate catastrophic health spending, 115 provided a response for distress financing.
 b Study-level effects included ACS QUIK intervention and a random effect for hospital cluster.
 c Unadjusted model reference is insurance.

d Adjusted model 1 is further adjusted for Global Registry of Acute Coronary Events risk score variables (age, sex, ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction status, systolic blood pressure, and heart rate). In-hospital heart failure, cardiogenic shock, and cardiac arrest were not included owing to collinearity and a small number of events.

e Adjusted model 2 is further adjusted for baseline household income.

f Binomial regression model did not converge.

Results in Context

Previous facility-based studies evaluating the costs of acute cardiovascular care in India have reported higher CVD expenditures and higher rates of catastrophic health spending than the present study.^{2,19,20} These differences may be attributable to sampling frames (by location, disease states, or both), definitions, or temporal changes in income, expenditures, or insurance or combinations thereof. Furthermore, one previous study used a lower threshold to define catastrophic health spending (30% of nonsubsistence spending vs 40% in the present report),²⁰ which also partially explains the lower prevalence rate observed in our study. Nevertheless, the rate of catastrophic health spending remains high, especially when compared with the incidence of catastrophic spending using global estimates aligned with the Sustainable Development Goals and other community-based reports of out-of-pocket spending from India.²¹ For example, using a health spending threshold of 10% of total consumption, global incidence was 9.7% in 2000 and rose to 11.7% in 2010,¹⁴ or approximately 5 times lower than in our study. However, distress financing was 3 to 6 times less common and lower than in previous reports, including in India,^{2,19} which may be driven by temporal increases in income, savings, or a combination thereof to better absorb health care-related cost shocks or greater wealth in Kerala compared with other states in India.¹⁹ Strategies to minimize the risk of “wealth shocks” will thus remain important not only to reduce the cycle of poverty from CVD but also to reduce associated mortality.²²

Beyond broader initiatives to increase income and reduce health care-related expenditures, expanding access and enrollment in health insurance programs appears to be a central strategy to provide such finan-

cial risk protection, especially given the consistent association between insurance status and catastrophic health spending. A 2018 systematic review of 66 studies demonstrated that lack of health insurance was associated with a 2.7-fold higher risk of catastrophic health expenditures across a range of noncommunicable diseases, including CVD.²³ Although health insurance should intuitively reduce out-of-pocket expenditures, not all studies show this association, especially among the lowest-income groups²⁴ and through insurance obtained from private or non-profit institutions.¹⁴ Incomplete insurance will not eliminate financial risk associated with health care and may counterintuitively increase financial risk when costs of treatment are not transparent. Within India, the effect of the central government's Rashtriya Swasthya Bima Yojana health insurance program on catastrophic inpatient spending appears limited based on the 2004 to 2012 survey data from the National Sample Survey Organization, but a longer time horizon for programmatic implementation may be needed.⁸ State-level government health insurance programs to provide financial support to low-income households, such as the lottery-based Kerala Karunya Benevolent Fund, could complement national programs but have not yet been evaluated. Decreasing point-of-care fees for accessing health services and increasing access to credit or to disability insurance may be additional complementary strategies to reduce financial risk associated with short-term care for cardiovascular or other conditions that warrant further research.⁶ India's March 2018 announcement of the Ayushman Bharat Pradhan Mantri Jan Arogya Yojana health insurance program, which would provide up to Rs 500 000 (approximately US \$7000) in coverage annually to 100 million families (500 million individuals), would be a major investment in health

that could substantially improve financial risk protection.²⁵

Strengths and Limitations

Our study has several strengths, including, to our knowledge, being the largest such study in India to report individual- and household-level detailed costs following hospitalization for an acute cardiovascular condition. Administrative claims data from government-sponsored programs, such as Rashtriya Swasthya Bima Yojana, have been shown to be insufficient for this level of granularity by condition or cost.²⁶ Thus, we also used infrastructure from the ACS QUIK trial to capture these complex data using trained personnel. However, our study also has potential limitations. First, data on expenditures and costs were self-reported, which raises the risk of recall or social desirability bias. However, there is no central database on costs from which we could otherwise obtain these data, and other national reports relied on recall that was much further out from the period of hospitalization than our study. Further, we used a previously published instrument developed in collaboration with economists from the World Bank to collect detailed data to minimize these risks. Second, we changed our sampling frame during the study from an age- and sex-stratified random sampling frame to an unselected sampling frame given the low initial recruitment rates, which highlights the challenge of collecting these data. While the sample may not be representative of Kerala or of India, our study had sufficient power to demonstrate associations between patient-, hospital-, study-, and treatment-level factors with catastrophic health spending or distress financing. Third, we collected data from individuals who survived acute myocardial infarction, and these individuals may have different incomes, expenditures, and coping strategies than those who did not survive. Fourth, data were missing from some participants, including variables such as household expenditures, which were needed to estimate the prevalence of catastrophic health spending and may have influenced our results.

CONCLUSIONS

The present results indicate that acute myocardial infarction carries substantial financial risk for patients in Kerala. Further expansion of health insurance access and coverage will be an important strategy for financial risk protection to disrupt the cycle of poverty from CVD in Kerala and in India.

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Acute Coronary Syndrome Quality Improvement in Kerala (ACS QUIK)

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Views & Reviews

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Organ transplantation stands out as an epitome of the potential of scientific progress in alleviating human suffering. In equal measure, it is also emblematic of the ethical challenges involved in the process of complex medical decision making.

Clinical Protocol to Manage the Nipah Virus Disease



Human Nipah virus (NiV) infection is an emerging zoonotic disease which was first recognized in a large outbreak of 276 reported cases in Malaysia and Singapore from September 1998 to May 1999.

In India, during 2001 and 2007 two outbreaks in human were reported from West Bengal and neighbouring Bangladesh. Large fruit bats of *Pteropus* genus are the natural reservoir of NiV. There is circumstantial evidence of human-to-human transmission in India in 2001.

Prepared by Nipah Advisory Group, Kerala Health Services and approved
by Additional Director of Health Services (Public Health Division)

During the outbreak in Siliguri, 33 health workers and hospital visitors became ill after exposure to patients hospitalized with Nipah virus illness, suggesting nosocomial infection. Nipah cases tend to occur in a cluster or as an outbreak.

EPIDEMIOLOGY

Agent: NiV is a highly pathogenic paramyxovirus

Natural Reservoir: Large fruit bats of *Pteropus* genus are the natural reservoir of NiV. Presumably, pig may become infected after consumption of partially eaten fruits that dropped in pigsty.

Seasonality was strongly implicated in NiV outbreaks in Bangladesh and India. All of the outbreaks occurred during the months of winter to spring (December-May).

Incubation period: varies from 4-21 days.

Mode of Transmission: Transmission of Nipah virus to humans may occur after direct contact with infected bats, infected pigs, or from other Nipah virus infected people. Another route of transmission of Nipah virus has also been identified from its natural reservoir to human: drinking of raw date palm sap contaminated with NiV.

DIAGNOSIS

Laboratory diagnosis of a patient with a clinical history of NiV can be made during the acute and convalescent phases of the disease by using a combination of tests. The designated Nipah virus testing facility for Kerala is MCVR Manipal. NIV Alappuzha also has the testing capacity, which may be utilised by Ernakulam/Alleppey/Idukki/Kottayam districts. DSO will decide destination of samples based on updated communication from DHS office.

CLINICAL FEATURES

Fever, Altered mental status, Severe weakness, Headache, Respiratory distress, Cough, Vomiting, Muscle pain, Convulsion, Diarrhoea.

In infected people, Nipah virus causes severe illness characterized by inflammation of the brain (encephalitis) or respiratory diseases.

In general, the case-fatality rate is estimated at 40-75%; however, this rate can vary by outbreak and can be upto 100%.

TREATMENT

- ▶ Currently there is no known treatment or vaccine available for either human or animals. Intensive supportive care with treatment of symptoms is the main approach to managing the infection in people.
- ▶ There is no proven treatment recommended for Nipah virus disease. Some observational data suggests that Ribavirin may be of use in reducing mortality among patients with encephalitis caused by Nipah virus disease. There is no data/evidence of its usefulness as a prophylactic drug
- ▶ Intensive supportive care with treatment of symptoms is the main approach to managing the infection in people.

CASE DEFINITIONS

Suspect Nipah Case

Person from a area/ locality affected by a Nipah virus disease outbreak who has:

- ▶ Acute Fever with new onset of altered mental status or seizure and/or
- ▶ Acute Fever with severe headache and/or
- ▶ Acute Fever with Cough or shortness of breath

Probable Nipah Case

Suspect case-patient/s who resided in the same village where suspect/confirmed case of NIPAH were living during the outbreak period and who died before complete diagnostic specimens could be collected.

OR

Suspect case-patients who came in direct contact with confirmed case-patients in a hospital setting during the outbreak period and who died before complete diagnostic specimens could be collected.

Confirmed Nipah Case

Suspected case who has laboratory confirmation of Nipah virus infection either by:

- ▶ Nipah virus RNA identified by PCR from respiratory secretions, urine, or cerebrospinal fluid.
- ▶ Isolation of Nipah virus from respiratory secretions, urine or cerebrospinal fluid.

Definition of a Contact

A Close contact is defined as a patient or a person who came in contact with a Nipah case (confirmed or probable cases) in at least one of the following ways.

- ▶ Was admitted simultaneously in a hospital ward/

shared room with a suspect/confirmed case of Nipah virus disease.

- ▶ Has had direct close contact with the suspect/confirmed case of Nipah virus disease during the illness including during transportation.
- ▶ Has had direct close contact with the (deceased) suspect/confirmed case of Nipah virus disease at a funeral or during burial preparation rituals.
- ▶ Has touched the blood or body fluids (saliva, urine, vomitus etc.) of a suspect/confirmed case of Nipah virus disease during their illness.
- ▶ Has touched the clothes or linens of a suspect/confirmed case of Nipah virus disease.

These contacts need to be followed up for appearance of symptoms of NiV for the longest incubation period (21 days), or preferably double incubation period, of 42 days.

Nipah virus disease: Guidelines for laboratory sample collection and diagnosis

Laboratory Diagnosis: Laboratory confirmation of a suspect/probable case can be made during the acute and convalescent phases of the disease by using a combination of tests. The designated Nipah virus testing facility for Kerala is MCVR Manipal.

Sample Collection and Transport Guidelines: Universal, standard droplet and bio-containment precautions should be followed during contact with excretions, secretions and body fluids of suspected patient for Nipah virus. Adequate bio-safety precautions should be adopted during collection/transport/ storage/ processing of suspected sample.

Sample collection: The samples should be collected as early as possible (preferably within 4 days) with all bio-safety precautions and accompanied with detailed history of patients on the proforma which can be obtained from the testing laboratory.

Sample collection should be done only after admission in an appropriately secure isolation facility, and ensuring that the staff member doing the collection is using adequate PPE.

During sample collection wear complete disposable Personal Protective Equipments (N 95 mask, double surgical gloves, gowns, goggles foot cover, etc). Wash hands with soap and water at least for 30 seconds and then clean hand using 1-2 ml alcohol based hand sanitizer before and after collection of samples.

The recommended samples are

- ▶ Throat swab in viral transport medium
- ▶ Urine 5 ml in universal sterile container
- ▶ Blood in red vacutainer (5ml)
- ▶ CSF (1-2 ml) in sterile container

Draft /interim guidelines document prepared by Nipah Advisory Group, Kerala Health Services and approved for issue by Additional Director of Health Services (Public Health Division), Kerala, dt 02.06.2018

This version takes precedence over all earlier versions of the State Guidelines wef 02.6.2018

As the situation is still evolving, the matter contained in this guideline is subject to modification at regular intervals

▶ Detailed reference documents to be read for addl information will be emailed to all DMOs and DSOs regularly

▶ All are advised to check DHS website or contact your DSO for updates, regularly

Transportation and Storage of samples:

Samples should be safely packed in triple container packing and should be transported securely under cold chain (2-8°C) to the testing laboratory with prior intimation.

Sample containing vials, tightly closed, should be kept in good quality zip-lock bags wrapped with sufficient absorbent cotton padding so that inside material should not come out of bag if it leaks. The plastic bag should be kept in another Zip-lock bag similarly, which should be sealed with adhesive tape. This carrier should be placed in a hard container sealed with impermeable tape or plaster and placed in thermocol box /vaccine carrier containing ice packs. The case sheets with complete information should be placed in plastic bag and should be pasted outside the container.

Nipah Virus Disease: Advisory for health care personnel

1. Wash hands thoroughly with soap and water for 20 seconds after contact with a sick patient.
2. Use appropriate mask and gloves during history-taking, physical examination, sample collection and other care-giving to suspected Nipah cases.
3. Follow Standard precautions for infection control at hospital settings:
 - ▶ Hand Hygiene.
 - ▶ Use of PPE.
 - ▶ Use disposable items (NG tube, ET tube, oxygen mask) while handling the patient.
 - ▶ Safe waste disposal for potentially infected material including used PPE, linen, clothing of patient.
4. All suspect cases should be admitted to the designated isolation ward/ facility in the hospital prior to any sample taking. Once the case is suspected of Nipah, bystanders should not be permitted in the ward.
5. Segregate all suspect cases of Nipah from all patients in the isolation ward/ facility.
6. Avoid unnecessary contact with suspected Nipah cases or use barrier nursing Maintain bed spacing of 2 metres at least
7. Any spillage of body fluids in the OP/Ward should be managed as per infection control guidelines.
8. Immediately report admission of a suspected Nipah case to State Surveillance Officer and CSU (IDSP) in the prescribed daily report formats
9. Mortuary staff should wear PPE while handling a dead body. Designated sealed bag should be used for transportation of the dead body.



The discovery of Nipah virus: A personal account

The outbreak was recorded as starting in September 1998 in the northern part of peninsular Malaysia, the virus had most likely spilled into the swine population as early as 1997.

by **Kaw Bing Chua**

THE INITIAL PREOCCUPATION WITH JAPANESE ENCEPHALITIS

The outbreak of Nipah virus was a tragic event for the people of Malaysia especially for those in the pig-farming industries.¹ Though, officially the outbreak was recorded as starting in September 1998 in the northern part of peninsular Malaysia, the virus had most likely spilled into the swine population as early as 1997.² This was substantiated with a finding of 6 encephalitis patients who were admitted to Ipoh General Hospital in 1997 and whose stored sera were found to have anti-Nipah virus IgG.³ The outbreak of febrile encephalitis in humans was preceded by the occurrence of respiratory illness and encephalitis in pigs in the same region. Unusual deaths in pig population were reported by pig farmers to veterinary officers in Veterinary Research Institute, but the cause of swine mortality was initially assumed to be due to classical swine fever (Personal communication, Dr Jasbir Singh, Veterinary Research Institute, Ipoh, Malaysia). Unfortunately, when human beings came down with encephalitis, a

label of Japanese encephalitis was put on it.

In the early period, acting on the opinion of experts and the country's senior consultant virologists, drastic control measures based on the control of Japanese encephalitis epidemic were proactively and intensively taken by the government to control the outbreak. Very intensive fogging of insecticides was carried out at the outbreak areas and other pig-farms. Thousands of doses of Japanese encephalitis vaccines were rushed in from Japan to vaccinate the farmers and those who stayed near the pig-farms.

With the failure to control the outbreak, a conference was initiated by the Ministry of Health, Malaysia and the Veterinary Research Institute to brainstorm issues regarding the outbreak. The meeting was held in Veterinary Research Institute on the 24th of February 1999. As I learned later from some physicians who attended the meeting, the unusual epidemiological features of the outbreak with involvement mainly adults, which was not the usual scenario of Japanese encephalitis outbreak in Malaysia

This article was originally published in *Neurology Asia*. When Dr Kaw Bing Chua discovered the Nipah Virus, he was a graduate student at the University of Malaya in Kuala Lumpur, Malaysia.

in the past, was brought up by some physicians. Unfortunately, this was interpreted as a different trend in Japanese encephalitis, as reported by the newsprint quoting Professor SK Lam, Head of Medical Microbiology Department, University of Malaya.⁴ At that time, there were some pig farmers who had already been given 2 and even 3 doses of mouse brain derived Biken Japanese encephalitis vaccines. They were told to be safe to go back to pig farms to work. Some later became infected with encephalitis and succumbed to the illness. This was interpreted by the Head as the possibility that the Biken mouse brain derived Japanese encephalitis vaccine was not effective. He initiated and liaised with Dr Hyunsoo Kim in Republic of South Korea to seek the import of live attenuated Japanese encephalitis (SA14-14-2) vaccine for field trial.

At that time, in our Department, the concern of the Head was just to confirm Japanese encephalitis. Thus, only measurement of Japanese encephalitis-specific IgM was carried out in the laboratory and

the cases was confirmed Japanese encephalitis. It was also mentioned that there was no necessity to confirm 100% during the Ministry of Health outbreak meeting.

THE DISCOVERY OF NIPAH VIRUS

I was officially involved in the outbreak investigation on 27th of February 1999 when a patient (PKL) from one of the outbreak farms in Bukit Pelandok was admitted to University Malaya Medical Centre with acute encephalitis. I isolated Nipah virus from his cerebrospinal fluid on the 9th day of inoculation into tissue cell culture, although his serum was also tested positive for Japanese encephalitis-IgM and Japanese encephalitis specific nucleic acids was apparently detected by RT-PCR on the third day of his admission. With the possibility that the outbreak was due to an unusual or even novel agent, I believed viral culture was necessary. I was wondering how to convince my Head of Department to give permission for virus isolation, as he believed then that the out-

I finally gave the reason that if it was a Japanese encephalitis outbreak, it could be from a different genotype of Japanese encephalitis virus, because of the unusual epidemiological features of the outbreak.

subsequently a post-doctorate scientist (Dr Brindha RN) was recruited to perform the Japanese encephalitis RT-PCR test on the same clinical samples. Probably because of asymptomatic endemic Japanese encephalitis infection⁵, low cut-off threshold positive value or cross-reactivity with other flavivirus group such as dengue which was hyperendemic in this country, a high rate of positive Japanese encephalitis-IgM serology was reported, although quite a proportion of patients' sera that were tested positive in the department were subsequently found to be of false positive by Division of Arbovirus Diseases, CDC, Fort Collins headed by Dr Duane Gubler (Personal communication). I also had reservations of the many positive RT-PCR, which I believed were false positive. This was communicated to the

Head of Medical Microbiology Department. To my disappointment, at the early March, the Head gave the feedback to the Ministry of Health that 40% of

break was due to Japanese encephalitis virus. I finally gave the reason that if it was a Japanese encephalitis outbreak, it could be from a different genotype of Japanese encephalitis virus, because of the unusual epidemiological features of the outbreak. With the isolated virus, we could sequence the complete virus genome. However, as soon as permission was granted, instead of inoculating the patient's cerebrospinal fluid and serum samples into C6/36 mosquito cell-line, which was the cells specifically used for isolation of Japanese encephalitis virus, I quietly inoculated the samples into a number of other continuous cell-lines seeded in 24-well cell culture plates at 105 cells per well. They were the MDCK cells from Madin-Darby canine kidney, Vero CCL-81 cells from African green monkey kidney, PS cells from pig spleen, Hep2 cells from human laryngeal carcinoma and MRC5 cells from human fibroblast. The culture plates were then carefully sealed and incubated at 37°C.

On 1st of March 1999, our Department received additional cerebrospinal fluid and serum samples of 5 patients admitted to Seremban General Hospital with similar illness. One hundred microlitres of each clinical sample was similarly inoculated into the respective cell-lines for virus isolation. By 5th of March, one of the patients' (EKK) cerebrospinal fluid sample gave a syncytial type of cytopathic effect in Vero cells that was quite similar to the type of cytopathic effect seen in Hep2 cells due to respiratory syncytial virus. I was so excited and anxious to see such an unusual cytopathic effect and showed it to the Head immediately. He took a look at the culture under the inverted microscope, turned to me and told me it was mostly some form of contamination. He told me to ignore it and discard it. At that point of time, I was stunned and could not believe my ears. I just could not describe my disappointment but would not dare to challenge him.

On 6th of March, 2 more of the original 5 cerebrospinal fluid samples from the Seremban General

around asking other academic staff to look at the cytopathic effect in the culture flask. I also caught hold of Professor CT Tan who was the physician in charge of the encephalitis patients in our Medical Centre. He did not think the outbreak was due to Japanese encephalitis, and favored an unusual or novel organism based on epidemiological reasons. He agreed with my finding but he was not an expert in laboratory virology. I also showed the findings to Dr Winnie Yeap, research assistant, and Dr Szazly Abu Bakar, another virologist in the Department.

On the 7th of March 1999 (Sunday), the remaining cells in the first cell culture flask with cytopathic effect (EKK) had shown complete cell death. I carefully harvested the infected cells, washed with sterile phosphate buffered saline, transferred them into wells of 24-well Teflon coated slides and subsequently inactivated them to be used as antigens for identification. At the same time, I carefully passed 0.5 ml of the culture supernatant into a 25 cm² flask of Vero cells to scale up the production of infected

He took a look at the culture under the inverted microscope, turned to me and told me it was mostly some form of contamination. He told me to ignore it and discard it.

Hospital patients (TCC, G) produced similar cytopathic effect in Vero cells. I immediately rushed to tell the Head about the findings. To my great disappointment, he did not even want to look at the cell culture and signaled to me to ignore it. On the 8th of March, the cerebrospinal fluid sample of PKL gave the same pattern of cytopathic effect. By then, his serum sample was also tested positive for Japanese encephalitis-specific IgM, and Japanese encephalitis nucleic acid was apparently detected by RT-PCR by the Arbovirus Unit of our Department. At that time, I could sense it was something new and deadly. Thus, I did not follow the instruction to ignore and throw away the virus cultures. During that period, it was also a great challenge to convince other staff in the department the possibility of something new. The only person who believed me, was my faithful medical laboratory technologist, Ms PS Hooi. I was so desperate to convince other colleagues that I went

Vero cells for electron microscopic study. I knew if the virus was new, existing typing reagents would not be able to identify the virus. But the morphology of the virus under electron microscope would at least be able to tell me which family the virus belonged to. That would be able to influence the control measures of the outbreak. There was a great temptation to perform negative staining of the virus for electron microscopy. I refrained from doing so as I sensed that the virus was highly deadly judging at the ways it replicated in culture flask, and patients were dying. In addition, the facility for such technique was not available in the department and the functioning electron microscope in campus was about a kilometer away.

I then managed to prepare 3 10-well Teflon coated antigen slides. I used one of the slides and began to carry out serological identification of the virus using whatever commercial typing monoclonal

antibodies against viruses that were known to cause syncytial cytopathic effect in tissue cultured cells. They were herpes simplex virus, respiratory syncytial virus, measles virus, mumps virus, and parainfluenza viruses. As expected, all turned out to be negative. Subsequently, I reasoned that if the patients were infected with the virus that I had isolated, they should have antibodies against the virus. Using another prepared Teflon slide, I carried out the detection of human antibodies against the isolated virus by indirect immunofluorescent assay using sera and cerebrospinal fluid derived from patients of Bukit Pelandok area and a patient from Ipoh (LKK) who was transferred to Tawakal Hospital in Kuala Lumpur. By 6.30 p.m. the stained slide was ready and when I looked at the finding, I could feel a chill going down my spine. All the patients' sera and cerebrospinal fluid included in the test had strong positive antibodies against the infected Vero cells. The infected syncytial cells lighted up as "bags of green fluorescence lanterns". I immediately called

with measles virus, mumps virus and human herpes simplex virus. We will pass these to him the following morning. He would re-code the serum samples and then pass to me for testing.

We did exactly as agreed on the following day. At noon of 8th March 1999, we met again to review my findings. The result was a 100% correct match. I was able to identify correctly the persons infected with the isolated virus. None of the serum samples from patients known to be infected with measles virus, mumps virus and human herpes simplex virus reacted with the isolated virus. I knew there was going to be a meeting with representatives from Ministry of Health and Veterinary Research Institute on the 9th of March 1999 in Institute of Medical Research down town. I persuaded him to release the finding in the meeting. I also managed to persuade him to include Professor CT Tan to the meeting despite earlier tension due to differences in opinion on the cause of encephalitis.

On the 9th of March, 2.00 pm, we met in the main

During that period, it was also a great challenge to convince other staff in the department the possibility of something new. The only person who believed me, was medical laboratory technologist, Ms PS Hooi.

up the Head of Department in his house and asked him to come to the laboratory. I can still remember vividly, he arrived at the laboratory at about 7.00 p.m. After looking at my finding in the UV-microscope, he looked up with his facial expression changed, turned to me and said, "Chua, why can't nature be more straightforward". At that time, the faithful medical laboratory technologist, Hooi was by the side and we just looked at each other. I felt like answering him, "Prof, nature was actually straightforward, it was you who thought otherwise". However, I did not have the courage and remained silent. Even then, he was still doubtful of the finding and told us that it could be cross-reactive antibodies. By then, it was almost 8 pm, and both myself and Hooi had not even taken our lunch. I suggested to him since I still had one more antigen slide, Hooi would pull out some patients' sera from the outbreak area and at the same time include some sera of patients known to be infected

meeting room of Institute of Medical Research and there was still a lot discussion about the outbreak as Japanese encephalitis. This was because the laboratory findings from the Arbovirus Unit, our Department had already confirmed 40% of the cases to be due to Japanese encephalitis. I was quite upset and worried that my Head of Department would back off and not release the finding. At that juncture, I decided that if he withheld the finding, I would disclose the result but prayed that I would not have to do so. I was relieved as towards the later part of the meeting, he finally mentioned the possibility of a new virus besides the Japanese encephalitis.

On our way home, it rained heavily and we were caught in a traffic jam. With Professor CT Tan sitting beside him, our neuropathologist Dr KT Wong and myself at the back, I told the Head that it was most likely a new virus and we needed international assistance urgently to identify the virus as quickly

as possible as the outbreak was getting out of hand. At that time, it was not easy to get courier company to ship consignment packed in dry ice overseas. I suggested to him to hand carry it out of the country after careful packing. To avoid being misunderstood that I liked to go overseas often as I just returned from Perth prior to this outbreak on work related to a chikungunya outbreak, I suggested to him to send a medical technologist. However, on reaching home at almost 8.00 pm, I told my wife to pack my clothing because I knew I would probably have to do the job personally. It was likely to be a very deadly virus.

True enough, on meeting the Head in the morning of 10th March, the first thing he told me was that should any one be needed to ship out the material for identification, it would be me. At that point, I did not have a USA visa and suggested to him to call up the Minister of Health for help. I was very impressed and touched by the Minister, the Honorable Dato' Mr. JM Chua, as he must have called the US embassy. I was given a 10- year US visa within 24 hours.

cell membrane under electron microscope suggesting viral morphogenesis at the membrane, a paramyxovirus seemed most likely.

On 12th of March 1999, I boarded the airplane and headed for the Division of Arbovirus-borne Diseases, Center for Disease Control and Prevention (CDC), Fort Collins, USA. I was sent to CDC in Fort Collins instead of CDC in Atlanta because the Head still held on to the idea that the outbreak was due to an arbovirus. I arrived at Denver Airport around 11.30 pm 13th of March, and took the Sambrock shuttle van service to Fort Collins. At 8.00 am 14th of March, Dr Nick Karabatsos picked me up from the hotel and took me to his laboratory. On arriving at the laboratory, he asked me whether I was familiar with immunofluorescence assay technique. I told him I had no problem and he immediately took out a whole panel of typing antibodies against known arboviruses and handed it to me. Using the antigens slides I brought along, 2 hours later, we found that none of the antibodies in the panel reacted with the virus infected cell. By then, Dr Bruce Cropp

At noon of 8th March 1999, we met again to review my findings. The result was a 100% correct match. I was able to identify correctly the persons infected with the isolated virus.

THE IDENTIFICATION OF NIPAH VIRUS

On 11th of March, after 3 days of fixation and embedding in epon, the inactivated Vero cells infected with the virus were ready for viewing under electron microscope. No functioning electron microscope was available in the Faculty of Medicine of the University. I took the ultra- thin sections of electron microscopy slides prepared by Ms Elsie Wong of Department of Pathology to the Institute of Higher Learning of the University. To my disappointment, the electron microscope in the Institute was not well maintained and only some blurred images of envelope viral particles ranging in size of 100+ to 200+ nanometer with thickening of infected cell membrane were visible. No conclusive information could be obtained. However, as the virus caused infected cells to fuse and lead to formation of syncytial giant cells in tissue culture Vero cells, with the finding of thickening of certain parts of

came in and led me to his electron microscope laboratory. On seeing his electron microscope (Philip EM410), which was an older version of the Institute of Higher Learning (University of Malaya)'s electron microscope (Philip CM12), my heart sank. The old scope still needed liquid nitrogen system for cooling. However, to my amazement, the old electron microscope was so well maintained that the moment he put the section that I brought along into the scope and turned on the screen, I could recognize the "concrete ring-like" structures of the paramyxovirus nucleocapsids cut in transverse section immediately. At that moment, a sense of great fear overwhelmed me. My God!!! it was truly a paramyxovirus. To my limited knowledge then, all paramyxoviruses known to me spread by close contact and droplet. No wonder all the Japanese encephalitis control measures intensively carried out by the Ministry of Health failed. I really felt very sorry for the poor pig farmers and workers who were given the Japanese

encephalitis vaccines, told they were protected and sent back to the farms and became infected.

I was so overcome by sadness, that as soon as we completed capturing the required electron micrograph images, I requested Dr Cropp to use the phone in CDC and called up my Head in Malaysia. I managed to get him at home. I still remember vividly what I told him over the phone; "Prof. Lam, Chua here, calling from CDC Fort Collins. Prof., listen! listen carefully! under the electron microscope, the virus has the morphology of a paramyxovirus. For God's sake, please do not talk about Japanese encephalitis anymore. I am quite sure now it's a paramyxovirus. Most likely it is a new paramyxovirus. The control measures for paramyxovirus are totally different from Japanese encephalitis virus. Please! I want you to urgently pass this message to the Ministry of Health to stop all the Japanese encephalitis control measures and switch over to the following control measures... Prof, listen carefully, you must pass the information of what I have just said to the Ministry of Health as soon as possible.... (I knew there will be a meeting in

ranging the flight schedule, there was a telephone call from Atlanta requesting me to go over. In brief, at CDC, Atlanta the virus was rapidly identified as a novel paramyxovirus by the wonderful team of experts working together. The moment the virus was identified, I made a special request to Dr Brain Mahy, who was the head of the Viral and Rickettsial Disease Division, to dispatch a team of experts to Malaysia to assist the control of this tragic outbreak, which I felt had already become too extensive for the local experts. He responded that CDC needed an invitation from the Ministry of Health of Malaysia. I phoned the Head about my request to Dr Brain Mahy, and the need for an official invitation. He subsequently called up the Minister of Health to send the required letter to Dr Brian Mahy.

In conclusion, epidemiology and clinical knowledge opened the mind to the possibility of other virus than Japanese encephalitis during the 1998/99 Malaysian viral encephalitis outbreak. Viral culture led to discovery of the novel infective agent which was not possible with serology and RT-PCR.

The moment the virus was identified, I made a special request to the head of the Viral and Rickettsial Disease Division, to dispatch a team of experts to Malaysia to assist the control of this tragic outbreak.

the Ministry of Health regarding the outbreak on the 17th of March)... I'll get Dr Bruce Cropp to process the electron microscopy photograph and fax it to you as soon as it is ready." There was a fairly long silence and he did not reply to my words.

On the following day, which was 15th March for USA, and 16th of March for Malaysia, the electron micrograph of Nipah virus was ready and I faxed it to him. On the same day, there was a teleconference between CDC at Fort Collins and CDC at Atlanta. A decision was made to transfer all the materials I brought along from Fort Collins to Atlanta. These were the virus isolates, patients' serum samples, antigen slides and fixed electron microscopy sections of infected Vero cells. Soon after the teleconference, I requested Dr Duane Gubler to help me confirm the earliest flight to return to Malaysia. All I could think of, at that time was the unfortunate pig farm workers, and wanted to rush back to assist the control of the outbreak. As Duane's secretary was ar-

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Counterfeit Drugs-Learning from the Past

Counterfeit medicine is a menacing problem in the health care sector of human beings. The possible counterfeit products may be available in human and veterinary drugs, medical devices, biological products, foods, dietary supplements or cosmetics.

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ABSTRACT

The large-scale prevalence of counterfeit medicine which was once thought to be in less developed nations is now alarming highly affluent ones. The reluctance of mighty drug companies to share the risk information is a major impediment in combating this menace added to this on-line drug purchase is compounding the problem. However, WHO has taken a number of proactive initiatives in monitoring the spread of SSFFC through task forces such as IMPACT and web based medical products rapid alert systems and also Interpol services. Trace and track surveillance methods of supply chains employing high

end technology viz., e-Pedigree, EPCIS and DPMS are yielding results. The grey areas in this serious health hazard scenario still are the lack of data on analytical reports and more so bio-analytical screening of the exposed population.

INTRODUCTION

Counterfeit medicine is a menacing problem in the health care sector of human beings. The possible counterfeit products may be available in human and veterinary drugs, medical devices, biological products, foods, dietary supplements or cosmetics. This review exclusively deals with counterfeit drugs in allopathic medicines. This medicine may be a fake medicine, contaminated or contain the wrong or no active ingredient. It may have the right active ingredient but improper dose.

World Health Organization in 2006 defined a "counterfeit" as "a medicine, which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both

branded and generic products and counterfeit products may include products with correct or wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.^{1,2}

The main types of counterfeit pharmaceuticals:

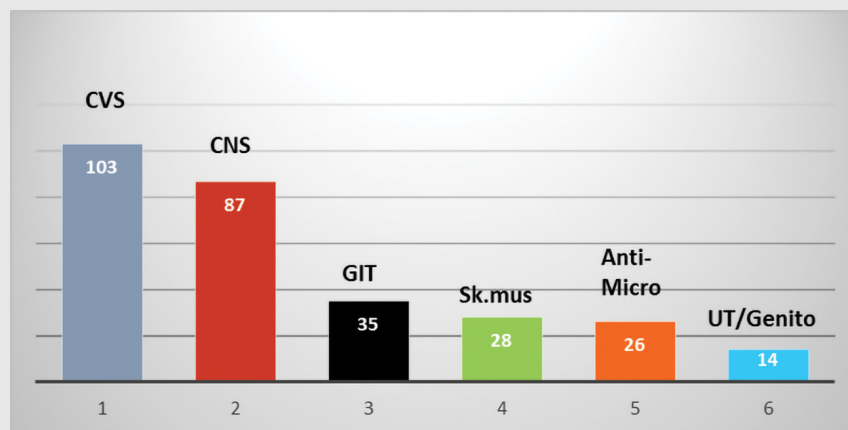
1. Incorrect Active Pharmaceutical Ingredient (API) or polymorph
2. Correct API but incorrect excipients
3. Re-packaged, out-of-date but genuine pharmaceuticals
4. Harmless but does not contain the active ingredient/s

World Alert

Many pharmaceutical companies and governments are reluctant to publicize the problem to health staff and the public, apparently motivated by the belief that the publicity will harm the sales of brand-name products in a fiercely competitive business. Publicly, at least, several industry sources say the justification for secrecy is to avoid any alarm that could prevent patients taking their genuine medicines. They argue that this secrecy, and the subsequent lack of public health warnings, is harming patients and that it is also not in the long-term interests of the legitimate pharmaceutical industry. The regulatory agencies advocate mandatory reporting to governmental authorities, which should also have a legal duty to investigate, issue appropriate public warnings, and share information across borders. This is not a role for the pharmaceutical industry, which has a serious conflict of interest.³⁻⁵

Although the major pharmaceutical manufacturers were aware of counterfeit medicines among their frontline products

Figure-1: Percentage of counterfeits in different lines of therapy



Source: <http://www.psi-inc.org/incidentTrends.cfm>

they were reluctant to share the information. Amongst them they formed a Non-profit Organization, Pharmaceutical Industry Survey (PSI) based in Virginia, USA. The PSI currently has the membership of 28 major pharmaceutical companies and has one of the most comprehensive and updated data bases on fake drug information but is not available in public domain. The veil of secrecy of its contents and investigation reports is so tight that even its member companies cannot share the contents, leave alone WHO, health workers or general public. However, after a public outcry and adverse publicity it has agreed to release information to national regulatory agencies on a "need to know basis". Most of the statistics are released through PSI Counterfeit Incident System (CIS) which are limited to instances of legitimate supply chain penetration. However, it should be noted that data from CIS is proprietary to its members and not made available to the public other than in yearly aggregate trend reporting on PSI's website.^{6,7}

The menace of counterfeit medicines was first alerted in late 1980's through newspaper articles, BBC talk shows etc. Most literature on fake drugs appears in public domain through investigative journalism with very little scientific enquiry through reputed scientific journals. This leads a situation of only a transient uproar. Therefore, their effects on consumers are difficult to follow up and mostly hidden from normal public through a maze of official health statistics. At the 1998 World Health Assembly this problem was extensively discussed and WHO decided to be taken up a more pro-active role. In 2006 it has launched International

Medical Products Anti-Counterfeiting Task Force (IMPACT).^{8,9}

WHO Member State Mechanism

In defining, tracking and tackling fake drugs the WHO proposed a Member State Mechanism under which some countries of UN/WHO system form a group. Due to differing patterns of legislations on crime and punishment amongst them, the nomenclature on Not Standard Quality (NSQ) and or even the word counterfeit does not address the definition. Therefore, at the 63rd World Health Assembly it was proposed that until a proper definition is framed they are referred as substandard, spurious, falsely-labeled, falsified counterfeit medical products or acronym SSFFC. The Member State Mechanism is a global format in which countries can deliberate to address the presence of SSFFC products. Global Surveillance and Monitoring System for SSFFC medical products was established in 2013 with 130 countries and about 20 high volume supply chain conglomerates. Network of about 500 personnel from the national regulatory agencies have been trained to use the system and over 950 SSFFC medical products are under scanner.^{10,11}

Contents of SSFFC medicine

Perhaps the best description of not only SSFFC contents but also NSQ was given in a publication by Rahul and Vasudha¹² have described the contents as

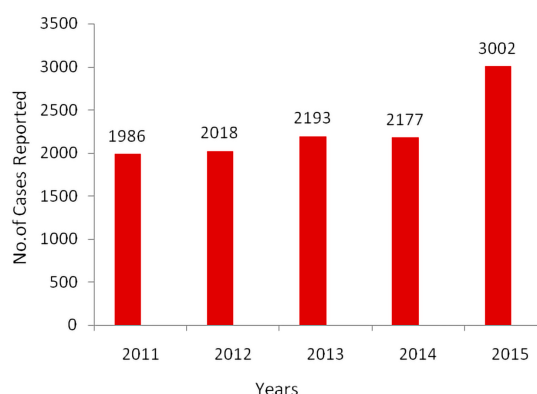
- 1) Falsified medical products may contain no active ingredient, wrong active ingredient or the wrong amount of active ingredient
- 2) They are found to contain corn starch, potato starch or chalk.
- 3) Some products have been toxic in nature with either fatal levels of wrong active ingredient or other toxic chemicals
- 4) SSFFC medical products are often produced in

very poor and unhygienic conditions by unqualified personnel, and contains unknown impurities and sometimes contaminated with bacteria.

- 5) Even if the active pharmaceutical ingredient (API) is correct or not in range of therapeutic dose the medicament is still dangerous or fatal.

Counterfeit medicines are part of the broader phenomenon of standard pharmaceuticals. The difference is that they are fraudulently mislabeled with respect to identity and or source. This product mostly has no therapeutic benefit; they can cause drug resistance and even death. Trade in counterfeit is extremely lucrative thus making it more attractive to criminal networks. A report released by the Centre of Medicine in the public interest in the United States, projects counterfeit drugs sales to reach US \$ 125 billion in 2020, a 110% increase from 2005. Counterfeit drugs can include life style drugs, lifesaving drugs, patent/generic drugs and even medical devices. Hence, the patient safety is at risk, as it permits substandard drug delivery to patients. Counterfeit drugs are fraudulently manufactured, where drug identity or its source

Figure-2: PSI collected data on counterfeiting, illegal diversion and theft incidents for fourteen consecutive years:



Source: <http://www.psi-inc.org/incidentTrends.cfm> source

is misrepresented to wrongly influence the judgment of patients and healthcare professionals. The Fig-1 indicates the percentage of counterfeit drugs available in different line of therapy.

A formulated drug such as tablet, capsule, syrup, etc, contains of two components. An API and the excipients which facilitate the administration, preservation and absorption of the drug molecule. The risk from these counterfeits can arise from any of these components. The bulk drug is imported or smuggled and formulated with cheap materials like corn starch, crude lactose or chalk which are susceptible to microbial contamination.^{13 & 14}

Counterfeit drugs can be introduced during any one of the following stages:

- Drug manufacturing of product by using the fake Active Pharmaceutical Ingredient (API).
- Packaging by inserting incorrect dosage
- Recycling by repacking used or expired drugs and
- Through internet by concealing address and other details.

2.1. Examples of counterfeit drugs

A few reported cases are presented to highlight the scale of the scourge

- Approximately one-third to one-half of packets of artesunate tablets, the pivotal, life-saving anti-malarial drug, purchased in Southeast Asia were fakes, containing no active ingredient at all. A nongovernmental organization in a Southeast Asian country bought 100,000 inexpensive "artesunate" tablets only to find that they were counterfeit. 15
- A total of 192,000 Chinese patients are reported to have

died in 2001 from fake drugs, and in the same year Chinese authorities "closed 1,300 factories while investigating 480,000 cases of counterfeit drugs worth 57 million USD". In 2004, Chinese authorities arrested manufacturers of grossly substandard infant milk powder and closed three factories after the death of over 50 infants.¹⁶⁻¹⁹

- In North America, counterfeit atorvastatin, erythropoietin, growth hormone, filgrastim, gemcitabine, and paclitaxel have been reported recently.²⁰
- Nigeria in 2001 threatened to ban the import of all drugs from India, a major supplier, because of the high prevalence of counterfeits amongst the imports.²¹
- In Haiti, Nigeria, Bangladesh, India, and Argentina, more than 500 patients, predominantly children, are known to have died from the use of the toxin diethylene glycol in the manufacture of fake paracetamol syrup.²²
- During the 1995 meningitis epidemic in Niger, the authorities received a donation of 88,000 Pasteur Merieux and SmithKline Beecham vaccines from neighboring Nigeria.²³ The drugs were found to be counterfeit, with no traces of active product. Some 60,000 people were inoculated with the fake vaccines.²⁴
- Counterfeit antiretrovirals (stavudine-lamivudine-nevirapine and lamivudine-zidovudine) in central Africa raises the prospect of a disastrous setback in the treatment of AIDS in sub-Saharan Africa, unless vigorous action is taken now.²⁵
- In Africa malarial deaths are estimated to be a million a year. About 60% are children below five years of age. Halofantine, paediatric syrup (Halfan)

a GSK product was faked and sold, which resulted in several deaths. This has alarmed health care professionals to the scale and range of distribution syndicates involved in the sale of fake syrup and adult tablets. The GSK group after relentless campaigns by BBC radio talks, has agreed to undertake a technical study of the seized fake Halfan.²⁶

- In 2013-2014 The seizure of large quantities of counterfeit prescription drugs containing fentanyl has thrown light on growth in overdose deaths in the United States, according to a report from the US-DEA which states global threat describes how "hundreds of thousands of counterfeit prescription pills, some containing deadly amounts of fentanyl have been introduced into U.S. drug markets." Center for Disease Control (CDC), Atlanta, reported that deaths from synthetic opioids (including fentanyl) upto 79%. A substantial portion of the synthetic opioid deaths appeared to be related to the influx of fentanyl.^{27,28}
- In 2015 FDA has alerted health care practitioners and the public that a counterfeit version of Botox was found in the United States and may have been sold to doctors and medical clinics all over the world. Botox is extensively used in cosmetic facial procedures.²⁹
- In May 2016, DEA was informed that counterfeit version of a FDA approved cancer drug, BiCNU (carmustine for injection) 100 mg, has been detected in some foreign countries.³⁰

Trace and Track Methods

It is now clearly understood that SSFFC products enter through supply chains which are porous

and not monitored. Added to these inadequacies are complex legal challenges which may differ between countries or between different regions within a country. After setting up of web-based system by the WHO on tracking the movement of counterfeit drugs on a trial basis in the western pacific region, it gradually expanded its activities to cover more WHO geographical regions. This network medical product the Rapid Alert System (RAS) alerts the authorities to take quick action.³¹

In an effort to counter this issue, countries and organizations are pursuing the need for serialization. The serialization process provides the complete scenario of a given product's chain of custody from the manufacturer to the point of dispensing. To support this number of trace and track procedures have been introduced. Some of them include existing methods like barcoding, Electronic Product Code (EPC) and a host of new technologies like Drug Pedigree Message Standard (DPMS).

The DPMS system calls for mass serialization which involves e-Pedigree method using Radio Frequency Identification (RFID), 2d-bar codes. These systems provide a window for recording and storing the complete movement of a product from entering the supply chain to the end-user. The e-pedigree regulation has a double advantage of not only tracking of counterfeit drugs but also diverted or smuggled genuine drugs gone beyond the use by date label. In India pioneering work in development and application of these software-based measures have been undertaken in big way by TCS Life Science and Health Care Unit.³²

E-Pedigree:³³⁻³⁵ E-Pedigree “means a record in electronic form containing information regarding each transaction resulting in a change of ownership of a given medical product from manufacturer, wholesalers until final sale to a pharmacy or health care professional furnishing, administering or dispensing product. It is therefore an interoperable electronic surveillance system for movement of medical products literally from “bench to bedside”.

Many anti-counterfeit technologies are available for manufacturers and brand owners, ranging from simple and effective to complex and sophisticated. The Global e-Pedigree software market and related features can be broadly segmented as following four types.

Visible features or overt features help end-users to verify the authenticity of the pack. These features are clearly visible, and it is hard to make any changes. A few visible features are holograms, OVD, color shifting security inks, security graphics, sequential numbering, and marking on the product.

Hidden features or covert features are used to enable brand owners to identify a fake product. General users will not be aware of their presence nor have the means to verify them. A few hidden features are invisible printing, embedded images, digital watermarks, hidden marks, anti-scan designs, laser coding and substrates.

Forensic techniques many high-end technology solutions are conducted in the laboratory and require testing to prove authenticity scientifically. These are a subset of hidden technologies, but the main difference is the scientific methodology required for authentication. A few such techniques are chemical taggants, biological taggants, DNA taggants, isotope ratios, and micro-taggants.

Track and trace technology serve a few important functions such as tracking items through the supply chain, providing traceability of the history of any item, and enabling authentication of the data at any time. Serialization, barcodes, RFID tagging, and topography or unique surface markings are a few of the techniques used in this technology.

Two Dimension Bar code

The label works like an ATM pin voucher. The user scratches off the cover and texts what is underneath to a free phone number, to find out if a product is genuine. Quick response (QR) codes are also being tested. These printed squares are an advanced version of the 2D barcodes. Anyone with a camera-enabled phone and web access can scan the code and be taken instantly to the pharma company website to

authenticate the drug. A committee set up by the Indian Ministry of Health has approved a proposal to put 2D barcodes and scratch-off labels on medicines and which also stipulated the compulsory implementation of a track and trace system from 1 January, 2012. According to the public notice issued by the Directorate General of Foreign Trade dated January 10th, 2011, exported pharmaceutical products should have track and trace capability using barcode technology as per GS1 global standards.³⁶

Radio Frequency Identification (RFID)

RFID uses the low-end of the electromagnetic spectrum. It is a generic term for technologies that use radio waves to automatically identify people or objects. By comparison these waves coming from radars are less dangerous than the waves coming FM radio. Radio frequency identification, or RFID There are several methods of identification, but the most common is to store a serial number that identifies a person or object, and perhaps other information, on a microchip that is attached to an antenna (the chip and the antenna together are called an RFID transponder or an RFID tag). The antenna enables the chip to transmit the identification information to a reader. The reader converts the radio waves reflected back from the RFID tag into digital information that can then be passed on to computers that can make use of it.³⁷

Initially many drug manufacturers were reluctant to tag their product due the additional cost and a lurking suspicion that technology may not be tamper proof. Despite these cutting edge software tools there should be a constant vigil to prevent tamper-

ing as counterfeiters have worked their way around this secure system and first instances of RFID tampering have surfaced. This has called for additional security features.³⁸

Hemalatha and Srinivasa Rao³⁹ have recently suggested electronic solution using the GSM/code division multiple access technology and internet which will be able to remove the gaps in the supply chain and a bio-metric based solutions at each step.

Analytical Tools

Analytical chemistry plays an important role in the assessment and maintenance of food quality and safety both in industry and for enforcement authorities at the national and international levels. Chemical analysis is a term used in a broader sense to encompass quality and utility of substances. During the past three decades, investigations on drug impurities and contaminants have made phenomenal advances, largely to the development of efficient separation techniques like column, paper, high performance thin layer chromatography (HPTLC), high pressure liquid chromatography (HPLC) and gas chromatography as well as sensitive methods of instrumental analysis such as ultraviolet (UV), infrared (IR), nuclear magnetic (NMR), electron spin resonance (ESR), optical rotatory dispersion (ORD), circular dichroism (CD) and mass spectroscopy. Some of the reported analytical protocols on purity and adulterants in drugs are cited here on a representative basis.^{40,41} HPTLC is the main screening method used today to decide if a drug product meets label specifications. There are simple, inexpensive, selective and semi-quantitative can be applied to detect steroid drugs in herbal

preparations.

Advanced techniques are playing a key role in identifying black sheeps in the pharmaceutical field. NIR measurements combined with chemo-metric data processing are an effect method. An example is Omcilon -A "M" in the paste is tested in the packaging condition and found adulteration containing triamcinolone acetone where Neomycin as active ingredients. NIR spectra Raman spectroscopy is non-destructive and can be used to asses both authenticity of the packaging as well as the pharmaceutical product. So, this method is particularly suited in the analysis of repackaged and out-of-date products. X-ray powder diffraction a reliable technique counterfeit control. Analysis of original Viagra tablets (sildenafil) & their imitations. This method is reliable and very fast and correctly predicts the presence or absence of active substance. Nuclear magnetic resonance (NMR) screening analysis involves solvent extraction and quantification using appropriate internal standards. Desorption electro spray-ionization linear ion-trap mass spectrometry for counterfeit anti-malarial tablets. pediatric syrups Halfan.⁴² Handheld devices are currently gaining more importance and numerous instruments are being developed. Mainly portable devices like the handheld Raman and IR spectrometers are being utilized owing to their non-destructive, rapid, and reliable properties. An increased demand for these is seen not only by the pharma companies, but also by health authorities, regulators, and law enforcement agencies.⁴³

There are very few attempts to evaluate the adverse reactions by bioanalytical methods in the patients exposed to fake drugs. This is a key area which may alert the medical profession to a hitherto unrecognized therapeutic risk.

CONCLUSIONS

Conclusions: WHO has dropped the term counterfeit and renamed as falsified to indicate the inferior quality drugs.⁴⁴ Counterfeit drugs are not only dangerous but also causes economic loss and declining faith of the public in the nation's health care system. Regulatory authorities should be motivated to promote the implementation of Good Manufacturing, Good Distribution and Good Pharmacy Practice guidelines and quality assurance systems to ensure supply chain integrity in addition they should improve the quality assurance, guidance on the role of quality control laboratories in combating counterfeit drugs. Mass serialization strategies must constantly upgrade. The governments need

to promote networking and collaboration among national and international drug regulatory authorities and to develop guidance for pharmacovigilance systems to include reporting and investigating suspected cases of counterfeit by making their foot prints less visible. The entry of on-line dispensation of drugs has compounded the situation. Newer security features must be incorporated and the existing safeguards must be re-looked and implemented mutatis mutandis. Therefore, all the genuine stake holders who are in hot pursuit after these mass killers must follow the adage "*if you want to stay where you are, you have to keep running*".

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Review Article

Ethics and living donor renal transplantation

Organ transplantation stands out as an epitome of the potential of scientific progress in alleviating human suffering. In equal measure, it is also emblematic of the ethical challenges involved in the process of complex medical decision making.

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Organ transplantation stands out as an epitome of the potential of scientific progress in alleviating human suffering. In equal measure, it is also emblematic of the ethical challenges involved in the process of complex medical decision making.

The guiding principles of medical ethics- autonomy, beneficence and non-maleficence find prominent expression in the area of living donor organ transplantation. Respect for autonomy dictates that health care professionals should yield to the decision making capabilities of individuals as autonomous agents, Beneficence prescribes that decisions taken after balancing the risks and benefits should always benefit the patient, and non-maleficence encodes the idea of primum non

nocere, that harm disproportionate to the benefit of treatment should be avoided¹.

Beneficence to the recipient is the foundation on which the entire edifice of transplantation stands. For patients with end stage renal disease (ESRD), living donor renal transplantation provides the best possible chance for superior outcomes.

Renal transplants account for up to 70% of the more than 1,00,000 solid transplants performed annually world wide, of which 46% are living donations². All decisions to sanction donation need to stand the scrutiny of the standard of non-maleficence to the potential donor, which is seemingly an impossible task because donor nephrectomy invariably has the potential to physical harm, albeit in varying degrees.

These evidently contrarian positions are balanced by autonomy as the primary ethical code which recognizes the informed donor's right to choose and to donate voluntarily, understanding and accepting the possibility for harm.

Assessment of the motivation for donation is critical in deciding whether transplant surgery could be considered ethically and morally acceptable. Although apologists for organ trade would stress the individual's right over his or her body including the right of sale of body products or parts, it is paramount to remember that a decision taken under the grinding yoke of poverty to sell an organ is never truly independent³. Poverty has been rightly identified as the worst form of coercion.

Legalizing payment for donation has been touted as the panacea for obviating exploitation of the poor, an experiment that has found application in only one country⁴. Poverty has been reported to be disproportionate among donors compared to recipients in Iran (84% vs 50.4%), implying possible systemic failures in ensuring that the ethical principle of justice is enforced⁵. In addition, the scarce data available from the country have suggested relatively poorer outcomes in paid compared to altruistic donors. Donor dissatisfaction has been documented with 76% of paid donors in a survey opining that kidney sale should be banned and that given a second chance they would prefer to beg (39%) or obtain a loan from usurers (60%) rather than vending a kidney⁶. The incidence of microalbuminuria has been found to be higher (35% vs. 0%, $p < 0.001$), and general health and social functioning Quality of Life (QOL) scores significantly lower ($p < 0.001$ and

$p = 0.02$, respectively) among paid unrelated donors than among related donors⁷. The demise of altruism and the decline in living related donations directly resulting from the paid donor program have been suggested as barriers to advancement of transplantation in Iran⁸.

A nuanced understanding of the prospective donor's socio-cultural milieu is as important to identifying coercion as is an assessment of economic realities. Patriarchy and gender inequality along with the established norms of the primacy of the needs of the family unit over those of its individual members are prevalent in several parts of the world. Resultant is an environment where non-empowered relatives of end stage kidney disease patients find themselves expected to donate, and transplantation becomes an entitlement, often reinforced by well-meaning physicians trying to help their patients.

Though organ donation has been depicted as a "gift of life", improved patient outcomes with adequately performed dialysis make a literal interpretation of this motto inaccurate in the setting of renal transplantation. While it is indisputable that renal transplantation is the treatment of choice for end stage kidney failure for the properly selected patient, portraying it as the only way to keep a near one alive to the prospective donor may be ethically unviable.

Informed consent is pivotal to autonomous decision making and involves a full understanding of not just the immediate but also the long-term consequences of donor nephrectomy. The risk of immediate surgical mortality of living donation is small and the long-term risks of mortality and

end stage renal disease have not been to be shown to be increased in donors compared to the general population in most studies⁹. However, recent data from studies with longer term follow up have shown renal donors to be at an increased risk for both cardiovascular and all-cause mortality as well as end stage renal disease in comparison to equally healthy non donors who would have been eligible for donation¹⁰. The absolute rates remain reassuringly low in both groups and as yet there is no reconsideration of the belief that living donation is safe.

Expanding ESRD prevalence and better survival on dialysis have resulted in the creation of a large population of patients waiting for renal transplantation all over the world. Scarcity of data impedes the prediction of long term risks in the so called marginal living donors and makes informed choices difficult thereby adding another layer of ethical complexity¹¹. Deceased donor transplant programs exist in a rudimentary form, or not at all, in many geographic regions, a deficiency that needs urgent rectification. A black market for organ trafficking and trade thrives in this widening chasm. The elimination of transplant waiting lists and the promise of better outcomes for patients, however needy they may be, cannot be construed as a validation of the commodification of human beings. As the declaration of Istanbul unambiguously states-organ trafficking and transplant tourism violate the principles of equity, justice and respect for human dignity¹².

Ends do not always justify the means.

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Features

Going Viral

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India Fights Diabetic Retinopathy with AI

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South Korea's first patient was not diagnosed until he showed up at Samsung Medical Center in Seoul with MERS symptoms – **nine days after first showing signs of infection**, and after visiting a few other hospitals. That was bad enough.





Going Viral

In the age of social media, fears and rumours about outbreaks and epidemics can quickly spread out of control. How can health officials help contain the panic?

by **Mike Ives**

In the spring of 2014, Vietnam's state-controlled news media reported that dozens of children had died after turning up at hospitals in the capital, Hanoi, with rashes and high fevers. Doctors said the cause was a measles outbreak – the worst in Vietnamese history. Parents of victims rushed onto Facebook to share their grief and outrage. So did their friends and neighbours, who wanted to know how the outbreak was spreading, and whether it was even safe to take children to hospital. The authorities distributed information about the measles deaths via leaflets, loudspeaker bulletins and updates on the health ministry's website, recalls a nurse at a state-run hospital in Hanoi, who requested anonymity in order to speak frankly. "But there was so much information online that some people became panicked."

Vietnam is a one-party state that has responded efficiently to many natural disasters and health emergencies. During a 2005 outbreak of avian flu, for example, the Vietnamese agriculture minister famously ate chicken on national television in an effort to calm public fears about widespread poultry infections. But when the 2014 measles scandal broke, millions of Vietnamese were using Facebook, compared to almost none just a few years earlier. And the government, which sporadically blocks the network, was unable to extinguish a Facebook-fuelled bushfire of fear, anger and recrimination that swept the nation.

Much of the criticism landed at the feet of the health minister, Nguyen Thi Kim Tien, who refused to call the deaths an 'outbreak' even as the child death toll approached 130. Even before the measles crisis the health ministry had been on the defensive, following a string of previous scandals at public hospitals that had included mistaken diagnoses, faulty vaccinations and cases of bribery in surgery wards. So when Tien said that only 25 deaths were directly attributable to measles – while doctors at a Hanoi hospital said scores had died from measles-related complications – many ordinary Vietnamese viewed her comments as brazen obfuscation.

"The public saw a lot of people dying," recalls Dinh Duc Hoang, a contributing editor at VnExpress, a Vietnamese online newspaper. Ministry officials, he says, did publicly explain their epidemiological rationale for not declaring an outbreak, "but not enough, especially on social media," he says. "People didn't understand and thought the ministry was trying to hide the outbreak."

Since the turn of this century, the rise of online search engines and social media applications has allowed ordinary people around the world to find information during public health scares at an ever-faster pace. The change has been especially dramatic in the Asia-Pacific region, a global epicentre of internet users, smartphone sales and infectious-disease outbreaks.

This new environment presents a complex mix of opportunities and challenges for health officials. On one hand, increased public engagement during a health crisis can allow officials to communicate more directly with citizens. But every new online platform is also a conduit for spreading criticism or misinformation. The rise of social media makes it "harder for governments to shut down the flow of information, but the information itself may be unreliable," says Crawford Kilian, a Vancouver-based writer who covers the politics of public health.

Health officials are increasingly aware that online rumours and criticism during a health scare can fuel panic, undercut their credibility and weaken public confidence in the very healthcare systems that are meant to fight disease. And some of them are trying to close the digital gap by engaging their citizens – and critics – on social media. During the measles crisis in Vietnam, for example, senior health officials asked Hoang and around eight other well-known journalists to help improve the health ministry's social media presence and disseminate official updates to the public during health emergencies.

"Because of my job, I'm famous, and I know a lot of celebrities," Hoang explains. "I can contact people to get them to post correct information for people to read."

The premise – helping the ministry distribute 'correct' information through social media – was simple enough. But could, or should, a group of journalists and celebrities really help a one-party government restore public faith in a beleaguered health bureaucracy? And why did the ministry need their help in the first place?

Social media is only the latest digital 'disrupter' to change the public conversation around health scares; the first was the internet itself. And the first major health scare in which the internet played a decisive role in shaping public

opinion was the severe acute respiratory syndrome (SARS) outbreak – the first influenza pandemic of the 21st century.

SARS appeared in southern China in 2002 and created an international crisis in February 2003, after a 64-year-old medical professor from the Chinese city of Guangzhou checked into a Hong Kong hospital with respiratory failure. A guest staying at the same hotel as the professor then unwittingly infected more than 100 medical and nursing staff at a second Hong Kong hospital, and six other guests unknowingly spread SARS to Vietnam, Singapore and Canada. This was just the first phase of an outbreak that would spread to more than two dozen countries, infect 8,098 people and kill 774.

Within months of the first SARS infection, hundreds of thousands of ‘SARS’ searches had popped up on a newish platform called Google. Baidu, a popular Chinese search engine, also reported during the epidemic that ‘SARS’ was its top search item. Both sites were allowing ordinary people in China and beyond to instantly find information about the disease, rather than wait for updates from a local newspaper or television anchor.

“Back then, it was Web 1.0, where people go to a site and download information, and there’s no sort of participation,” says Randall N Hyer, a risk communications specialist who worked on a World Health Organization (WHO) risk-response team during the SARS crisis.

But not all the information that turned up in the search engines was accurate, and false rumours quickly went viral – faster, in fact, than the virus itself. One of the most damaging came from an unlikely source: a 14-year-old Hong Kong boy, who announced online that the city would soon be placed under quarantine and designated an “infected port”. His prank post gained attention and credibility because it mimicked a local newspaper’s website. It sparked a frenzy of panicked grocery shopping, which fed perceptions that Hong Kong was under siege.

According to *At the Epicentre*, a 2004 book coedited by Christine Loh (who is now Hong Kong’s undersecretary for the environment), the mood in the city felt “eerie”, in part

because there was widespread confusion around how the disease was spreading. Even a public disavowal of the teenager’s prank by Hong Kong’s then health director, the book states, did little to quell the eeriness.

But the internet wasn’t an entirely bad influence during SARS. For example, as infections piled up in Hong Kong, a group of concerned residents created a crowd-sourced website, sosick.org, showing a list of buildings with suspected or diagnosed SARS cases. Two weeks after the site appeared, the Hong Kong government began publishing the same information on its official website.

“The internet proved to be an invaluable tool for concerned citizens to use in challenging government secrecy,” Loh and her coauthors wrote.

Gabriel Leung, Hong Kong’s former undersecretary for food and health, says the SARS experience helped convince Hong Kong authorities of the need to be transparent with the public about the knowns and unknowns of an outbreak as it unfolds – well before a website such as sosick.org might challenge the government’s credibility. He applied the lesson during the city’s response to its next major public health emergency: an outbreak of H1N1, a deadly respiratory virus known as swine flu.

Swine flu was discovered in April 2009 in the USA, and at the time outbreaks had not been known to occur among humans. But as H1N1 quickly spread to Canada and Mexico, WHO declared it a Public Health Emergency of International Concern, and health officials on other continents braced themselves for its arrival.

It landed in Hong Kong in May 2009, when a 25-year-old Mexican tourist fell ill with swine flu in his hotel. Within hours, health officials had quarantined all of the hotel’s guests and deployed Leung to television stations to explain the rationale for a decision that was certain to make Hong Kong residents deeply anxious.

Internet-fuelled rumours about the disease proliferated, but Leung says he mostly stayed ahead of them by explaining the knowns and unknowns of the disease at daily press briefings, and by promising to show up every afternoon at the same time for as long as reporters had questions.

Within months of the first SARS infection, hundreds of thousands of ‘SARS’ searches had popped up in Google. Baidu, a popular Chinese search engine, also reported during the epidemic that ‘SARS’ was its top search item.

How Kerala Managed The Outbreak Communications

The 2018 Nipah outbreak in Kerala lasted hardly a month after the index case was reported on May 2. But galloping faster than the epidemic was misinformation, on social media platforms. Messages, a mix of fact and rumour, were forwarded multiple times every second, and public anxiety was rife. Some of the videos propagated unscientific information, saying the Nipah virus is transmitted through chicken meat popular in Kerala. Yet another false narrative, which did the rounds was about Kerala becoming a hub of diseases like dengue, H1N1 and chikungunya. Finally, when a much-circulated Nipah 101, ostensibly from a doctor of a famous Delhi hospital, was found fake, and a bogus warning to stop Keralans at Goa borders made the rounds, the government stepped in. The grapevine is as hard to manage as an epidemic, but how Kerala contained both the Nipah virus and social media was exemplary. By 2019, Kerala was better



prepared to deal with misinformation on social media! This is how they did it, in smart and sure measures!

► On social media, it was the Chief Minister Pinarayi Vijayan who led from the front. His Facebook post detailed the government moves to tackle the epidemic. He also said “The news of confirmation should not be a reason of panic. We request everyone to follow the instructions of the Health Department. Stringent action will be taken against those who spread misinformation. Together, we overcame the battle against Nipah in 2018. This time too, we are going to prevail in this battle.”

► The Minister for Health,

K.K. Shailaja, responding to some of the rumours about Kerala as a disease hub as false propaganda, said, “We have very efficient system and we are very vigilant about it. Here, all such cases, including the cases from private hospitals are being reported. So, we are able to tackle such issues in the first phase itself. We trace the reason and try to overcome it.” She too strictly warned the rumour mongers. In 2019, after confirming infection of the Nipah virus in a 23-year-old student in Ernakulam, the minister held a press conference to sensitise people against fake news on social media. She asked reporters to refrain from tracking the family

members or the patient's location. She specifically restricted visits to Nipah-affected areas to people who are specially trained.

► She also went on to arrange a medical bulletin by 11am every day and a press briefing by 5pm held either by the minister or by a senior official in the health department. Media was to provide information only from press briefings and medical bulletins. She assured that the health department would not hide any information from the media and requested the media to forgo exclusives at this point in time.

► After Nipah 2018, In addition to the government measures, a platform called ‘Arogya Jagratha’ (meaning Health Alert) was set up by the state for tackling misinformation and spreading health awareness.

From issuing warnings against fake news creators, setting up a public health awareness social media cell, regulating the flow of information in the news media and publicizing vigorously the official channels of information, getting top faces in the medical field to soothe public anxiety, Kerala has successfully managed to stop the spread of misinformation during a crisis.

“So long as you keep your promise, people will not be susceptible, or as susceptible, to the rumour mill, because they know the maximum time they have to wait is 24 hours before you will come out and give the facts again,” he says.

A daily press conference might have kept rumours and medical misinformation at bay during a health scare in the mid-2000s. But today, when fresh social media trends go viral every few minutes, a 24-hour information cycle can feel like an eternity. Social media can also challenge any official narrative that a health ministry tries to promote.

“Rumour mills will always be there... and social media by and large fuels that,” says Leung, now the dean of medicine

at the University of Hong Kong's School of Public Health. “It's not all negative, but social media is fast, it's furious.”

Swine flu, which killed between 150,000 and 575,000 people, was – according to a 2010 study in the journal PLOS ONE – the first global pandemic to occur in the age of Web 2.0, an era defined by ‘participatory’ web and social media. Since then, the dominance of social media has only increased, which has intensified the need for health officials to develop rapid online responses during health scares.

The challenge is now especially stark in countries, like Vietnam, where millions of people are flocking to Facebook or Twitter for the first time but health authorities are only just developing an online presence.

“The people still need it, and that’s the only source.”

In Vietnam, another public health scare bubbled up this spring, when WHO reported that an Australian tourist had been diagnosed with Zika virus after vacationing in the country. But as Facebook rumours began to swirl, the health ministry’s information chief, Nguyen Dinh Anh, began posting international news stories on his Facebook page and explaining what Vietnam was doing to prepare for a possible outbreak.

Hoang, of VnExpress, says the health minister’s Facebook page is still relatively sparse, and should be updated and managed by a professional. But the information chief’s response to Zika, he adds, seems to show that the ministry has at least recognised the importance of being trans-

parent about public health risks and engaging the Vietnamese public on social media.

This time around, “they’re posting on their own, without our help,” Hoang tells me between drags of a cigarette in a Hanoi café. “They won’t have the type of crisis they had with the measles outbreak.”

Ultimately, he adds, it would be difficult – if not impossible – for the health ministry to win the public’s complete trust, for the simple reason that Vietnamese bureaucracy is notoriously corrupt. But he says the ministry could perhaps work to become a more reliable conduit of information during future health crises.

“The people still need it, and that’s the only source.”

As late as the early 2000s, most Vietnamese found information about public health issues through state-controlled newspapers, television channels or a national network of public loudspeakers that broadcasts state-curated news in most towns and villages at daily intervals. All of those channels still exist, and the government still promotes them aggressively. The difference is that many urban Vietnamese now prefer to find information about health issues on health blogs or Facebook threads – and that some now hardly consult official news sources at all.

The new environment can feel liberating, but also scary, for Vietnamese who go online seeking authoritative information during a health crisis. “Vietnam, 10 years ago, was very poor,” says Nguyen Dieu Huong, an academic administrator in Hanoi and a member of Vietnam’s rising middle class. “We didn’t have the internet or ways to update people about, for example, epidemics. So people didn’t really feel anxious or afraid of epidemics, like they do now.”

During the 2014 measles outbreak, the anxiety bubbled up in a Facebook campaign called ‘Health minister, resign!’ that earned more than 100,000 ‘likes’ – a rare outpouring of public dissatisfaction in a one-party state that imprisons political dissidents. Thousands more Vietnamese logged on to discussion threads on Facebook and Webtretho, a popular web forum for parents. Among other questions, they debated whether the health benefits of bringing children to paediatric hospitals for vaccinations outweighed the ap-parent risks.

“We were scared to vaccinate our kids, and, at the same time, to not vaccinate them. So we were scared of everything,” says Thai Lan Anh, a Hanoi yoga teacher who par-

ticipated in those discussion threads.

Lan Anh says her first child, who was born in 2011, had already been fully vaccinated by the time the measles crisis hit. But she decided not to vaccinate her second child, who was born in 2014, out of an abundance of caution – and still hasn’t.

“I don’t think the Ministry of Health has been totally honest [about the risks of diseases and vaccinations],” she tells me between sips of fruit juice at a Hanoi café. “I don’t believe what they say.”

Even before the measles outbreak, health minister Nguyen Thi Kim Tien was among Vietnam’s most reviled public servants. An easy way to tell was the extensive focus on healthcare in Meeting Each Other at Year’s End, a hugely popular television satire that is performed once a year on Vietnamese state television. A 2013 skit, for example, showed a patient going to a Vietnamese hospital for a kidney operation, only to find that a doctor had removed the wrong kidney. A year later, a skit showed a health minister – widely assumed to be Tien – being placed on a machine that tested her ethical integrity. She failed miserably.

Against that backdrop, the health ministry quietly reached out to Hoang and other journalists in 2014 to solicit their ideas on improving the minister’s image and social media presence, according to Hoang. (A ministry spokesman, when reached for comment by telephone, asked for questions by email but did not answer them.)

Hoang, whose mother is a doctor, says he felt a duty to help.

“Ms Tien wanted to build an image of the doctors and herself as friendly and close to the public,” he says of his early exchanges with the ministry, which he insisted were informal and entirely pro bono.

Tien was setting up a Facebook page, and she asked if the journalists would mind ghost-writing some posts for her, according to Hoang. The journalists refused because they were too busy, he says. But, as a false rumour about Ebola spreading in Vietnam circulated on Facebook, they agreed to help staunch the flow of misinformation by using their Facebook pages to publicise the ministry’s Ebola updates.

Hoang says he also personally helped the minister improve her online image. First, he advised her to post a more friendly looking photo on her Facebook page. He also recommended that she interact more with ordinary people.

He saw an opportunity when a Vietnamese cancer patient wrote to a local newspaper to complain that a state-funded insurance programme was expiring, thus threatening to deprive her and other cancer patients of life-saving healthcare benefits. Hoang forwarded the patient’s letter to the minister, who drafted a reply that empathised with the patient’s predicament and explained the ministry’s insurance policy

in accessible language. Hoang then publicised the exchange on the VnExpress website and his Facebook account, which has more than 30,000 followers.

But even then, the exact effect of the intervention was unclear. “I made the two letters a campaign for the awareness of cancer and the image of the minister,” he says. “The campaign helped people understand the policy, but I can’t tell if it helped her image or not.”

Even so, health officials are still attempting to engage social media chatter in a way that keeps citizens informed about health scares in real time and tamps down misinformation, all without appearing to silence critics in a heavy-handed way or losing the public’s trust. That balance can be hard to strike, even in a rich country with a high rate of smartphone penetration and the highest internet speeds on earth.

That was clear in the spring of 2015, when the South Korean capital, Seoul, became ground zero for the largest outbreak outside the Middle East of Middle Eastern respiratory syndrome, or MERS.

MERS, which was discovered in 2012 in Saudi Arabia, was bound to cause anxiety wherever it landed because it kills 30 to 40 per cent of its victims. Moreover, because the disease’s inner workings are still poorly understood, it can be hard to detect if a doctor isn’t looking for it.

South Korea’s first patient was not diagnosed until he showed up at Samsung Medical Center in Seoul with MERS symptoms – nine days after first showing signs of infection, and after visiting a few other hospitals. That was bad enough. But for more than two weeks after South Korea’s initial MERS case was diagnosed, the government declined to publish the names of MERS-affected hospitals – just as the Hong Kong government had declined to publish basic information about SARS infections in 2003. And as health officials stalled, the outbreak spread to other hospitals.

Korean social media erupted with criticism, and on 4 June, a South Korean journalist published the list of affected hospitals on Pressian.com, an online news portal. The government, now in full damage-control mode, quickly followed suit, and a Samsung official later apologised for the hospital’s handling of the outbreak.

But the government’s and the hospital’s credibility was already tarnished. It didn’t help that, on the same day Pressian.com published the hospital list, South Korea’s Centers for Disease Control and Prevention made its Twitter account private, prompting a backlash from the scientific community and fuelling speculation that the government had something to hide – even if it didn’t.



Mike Ives Hong Kong-based journalist, a frequent contributor to the *New York Times*, and a former Vietnam correspondent for the *Economist* and AP

I visited Seoul during the crisis, and the city did not feel panicked. Perhaps the biggest visual reminders of the MERS virus, at least for non-native speakers, were the public health posters with images of a camel – the animals were the origin of the disease – that I saw in Seoul’s Incheon Airport. The camel didn’t look very scary. Yet on the streets and in the metros, many people were wearing face masks, reflecting the widespread public unease about the virus that was bubbling up on social media.

Over the course of a week, I asked South Korean journalists about the MERS situation, and many of them were highly critical of their government’s response to the outbreak. Officials should have released the names of affected hospitals more quickly, they said.

Lee Won-jae, a high school student, had a similar complaint. “Time has passed” since the first MERS infection, Lee told me, standing a few blocks from Samsung Medical Center in suburban Seoul on 12 June, at the height of the government’s MERS-news blackout. “Things should be wrapped up, but everything is still ongoing.”

At the time, President Park Geun-hye was still recovering from handling a ferry accident that had happened in April 2014, in which 304 South Koreans – mostly teenage students – were killed. The government had faced criticism over its rescue efforts. Because of the MERS scandal, Lee said, “there’s a bigger distrust of the government now than before”.

A few months later, as South Korea’s MERS epidemic was tapering off, a team of researchers from Hong Kong and the USA published a briefing about it in the *Western Pacific Surveillance and Response Journal*. The South Korean government’s response to MERS, they concluded, was “reminiscent” of the Chinese government’s response to SARS in 2003.

Gabriel Leung, the former Hong Kong official, agrees. He says one lesson may be that having a prosperous economy does not necessarily prepare health officials to respond smoothly to a 21st-century outbreak in real time and in a way that doesn’t damage the government’s credibility.

“Despite the high-income nature of the setting, despite excellent medical care, there are some lessons that societies generally need to learn experientially rather than just from a theoretical perspective,” he says of the MERS crisis.

India Fights Diabetic Blindness with Help from Artificial Intelligence



Photography By Atul Loke/The New York Times

MADURAI, India — The Aravind Eye Hospital will treat anyone who comes through the door, with or without money. Each day, more than 2,000 people arrive from across India and sometimes other parts of the world, crowding into the hallways and waiting rooms of this 43-year-old hospital at the southern end of the country.

On a recent morning, Vt Muthusamy Ramalingamm, a local resident, walked into a room on the second floor, sat down and rested his chin on a small desktop device that pointed a camera into his eyes.

A technician tapped on a screen at the back of an eye scanner, and within seconds a diagnosis appeared on a computer against the wall. Both eyes showed signs of diabetic retinopathy, a condition that can cause blindness if untreated.

In most hospitals and clinics around the

world, trained physicians make this diagnosis, examining a patient's eyes and identifying the tiny lesions, hemorrhages and discoloration that anticipate diabetic blindness. But Aravind is trying to automate the process. Working with a team of Google artificial intelligence researchers based in California, the hospital is testing a system that can recognize the condition on its own.

Google and its sister company Verily targeted this type of blindness because of its prevalence and because it is the sort of illness that an A.I. system can detect early. Google is not charging the hospital while it tests the technology.

Researchers hope this A.I. system will help doctors screen more patients in a country where diabetic retinopathy is increasingly prevalent. Nearly 70 million Indians are diabetic, according to the World Health Organization, and all are at risk of blindness. But the country does not train enough doctors to properly screen them all. For every one million people in India, there are only 11 eye doctors, according to the International Council of Ophthalmology.

The project is part of a widespread effort to build and deploy systems that can automatically detect signs of illness and disease in medical scans. Hospitals in the United States, Britain and Singapore have also run clinical trials with systems that detect signs of diabetic blindness. Researchers across the globe are exploring technologies that detect cancer, stroke, heart disease and other conditions in X-rays and in M.R.I. and CT scans.

Last month, regulators certified the eye system for use in Europe under the Verily name. And the Food and Drug Administration recently approved a similar system in the United States. But hospitals are treading lightly as they consider deploying systems that are vastly different from technology traditionally used for health care.

Aravind's founder, Govindappa Venkataswamy, an iconic figure in India who was known as "Dr. V" and died in 2006, envisioned a network of hospitals and vision centers that operate like McDonald's franchises, systematically reproducing inexpensive forms of eye care for people across the country. There are more than 40 of the vision centers around India.

In addition to screening patients in Madurai — one of the largest cities in southern India —



The technology still faces regulatory hurdles in India. Google's eye system is certified for use in Europe but awaiting approval in the United States.

the hospital plans to install Google's technology in surrounding villages where few if any eye doctors are available. The new A.I. system could radically expand the number of people who can be screened.

"Right now, there is a bottleneck when it comes to just screening patients," said Dr. R. Kim, a nephew of Dr. V's who now serves as chief medical officer at Aravind.

Behind the new screening methods are neural networks, complex mathematical systems that can learn tasks by analyzing vast amounts of data. By analyzing millions of retinal scans showing signs of diabetic blindness, a neural network can learn to identify the condition on its own.

A neural network is the same technology that is rapidly improving face recognition services, talking digital assistants, driverless cars and instant translation services like Google Translate.

Because these systems learn from enormous amounts of information, researchers are still struggling to completely understand how they work — and how they will ultimately behave. But some experts believe that once they are honed, tested and properly deployed, they can fundamentally improve health care.

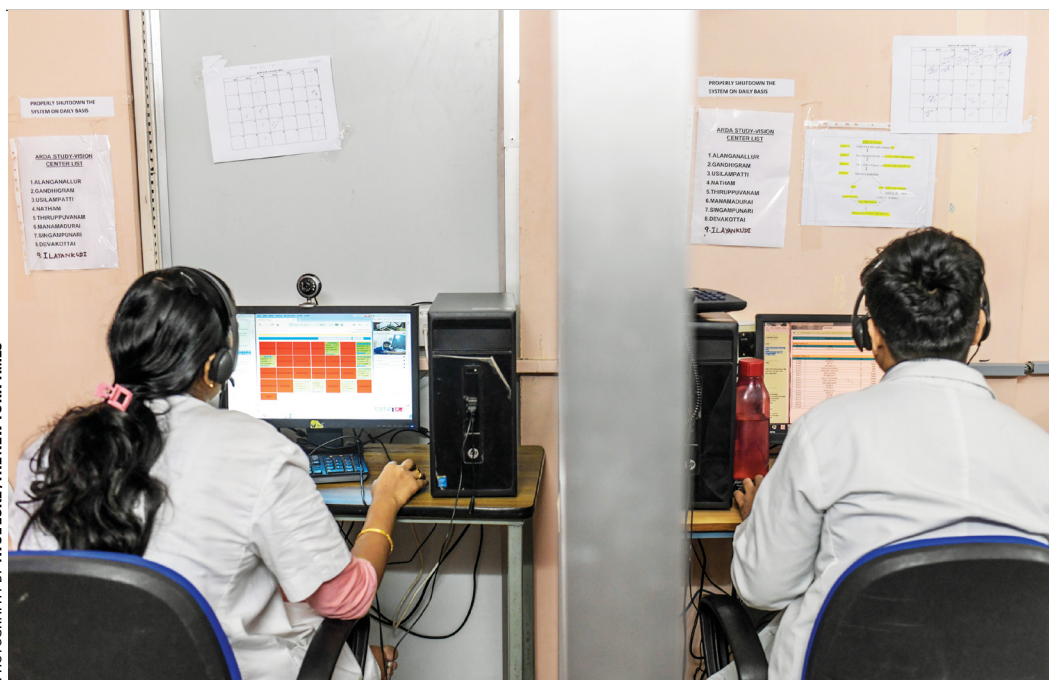
At Aravind, computer screens mounted on the walls of the waiting rooms translate information into the myriad languages spoken in the hospital.

During his exam, Mr. Ramalingamm, 60, spoke Tamil, the ancient language of southern India and Sri Lanka. He said he was comfortable with a machine diagnosing his eye condition, in part because it happened so quickly. After the initial screening by the A.I. system, doctors could treat the eyes, perhaps with laser surgery, to stave off blindness.

The system performs on a par with trained

Doctors at Aravind communicating with one of the small vision centers that the hospital runs in many of the cities and villages surrounding Madurai.

PHOTOGRAPHY BY ATUL LOKE / THE NEW YORK TIMES



ophthalmologists, according to a study published in *The Journal of the American Medical Association*. But it is far from completely replacing a doctor.

Earlier in the day, Pambaiyan Balusamy, 55, sat in the same room. The Google system diagnosed “proliferative” retinopathy in his left eye — the most serious form of the condition — but it could not read the scan of his right eye, most likely because the eye had developed a cataract.

Doctors can sometimes make a diagnosis when faced with cataracts and blurry eye scans. The Google system still struggles to do this. It is trained largely on clear, unobstructed images of the retina, though Google is exploring the use of lower-quality images.

Even with this limitation, Dr. Kim said, the system can augment what doctors can do on their own. Aravind already operates small vision centers in many of the cities and villages surrounding Madurai. The hope is that the Google system can make eye screening easier in these facilities and perhaps other locations across southern India.

Today, in these vision centers, technicians take eye scans and send them to doctors in Madurai for review. Automated diagnosis can streamline and expand the process, reaching more people in more places — the kind of “McDonaldization”

espoused by Dr. V.

The technology still faces regulatory hurdles in India, in part because of the difficulty of navigating the country’s bureaucracy. And though Google’s eye system is now certified for use in Europe, it is still awaiting approval in the United States.

Luke Oakden-Rayner, the director of medical imaging research at the Royal Adelaide Hospital in Australia, said these systems might even need new regulatory frameworks because existing rules weren’t always sufficient.

“I am not convinced that people care enough about the safety of these systems,” he said.

Though these deep-learning systems are new, they are hardly the first effort to aid diagnosis through computer technology. As Dr. Oakden-Rayner pointed out, software called breast CAD — approved by the Food and Drug Administration in 1998 — has been widely adopted in the United States to help with the detection of breast cancer, in part because Medicaid provides a rebate when the technology is used. But studies have shown that patient outcomes did not improve and in some cases declined.

“On paper, the Google system performs very well,” Dr. Oakden-Rayner said. “But when you roll it out to a huge population, there can be problems that do not show up for years.”



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Case Reports

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A novel technique in the use of endoscopically retrieved saphenous veins for femoropopliteal artery bypass

Dr George Varghese Kurien, Dr Manoj Padmanabhan Nair, Bineesh Sukumaran Pillai, Aster Medcity, Kochi

INTRODUCTION

Saphenous vein grafts have been established as the gold standard conduit for lower extremity bypass grafting¹. Conventionally, the great saphenous vein (GSV) is typically harvested via a long continuous or “skip” incisions that may extend from the groin to the ankle, before its use as an arterial conduit. This approach, however, is associated with significant morbidities, including surgical site infections, ischemic skin flaps, fat necrosis, lymph leaks, increased postoperative pain, and longer hospital length of stay (LOS) for as many as 24% to 43% of patients.² Endoscopic vein harvest (EVH) has been demonstrated to improve early morbidity when compared with the conventional open harvest technique (OVH) for infrainguinal bypass surgery. The aim of this article is to report a simple but unique technique to tunnel the vein graft without injury in the usage of reverse saphenous vein grafts in infrainguinal bypass surgeries.

CASE REPORT

A 50 year old male labourer by occupation, was admitted with a non-healing ulcer of the anterior aspect of the tibia with rest pain. He was a chronic smoker with a pack

year of 32 and a history of intermittent claudication and rest pain. The peripheral pulse was not palpable infrapopliteally on the left leg. The systemic examinations were within normal limits. Clinical evaluation was suggestive of a Rutherford grade 2, category 4. The patient was maintained on medical management with standard regimens, however he was not symptomatically relieved. He had a claudication distance of 100 metres. Two months later, he sustained a left tibial fracture following a fall at his workplace. He underwent an open reduction and internal fixation of the left tibia at an outside hospital and was referred to us with a non-healing wound over the anterior aspect of the left shin. Doppler evaluation revealed a monophasic flow in the infrapopliteal vessels. He was evaluated with a peripheral CT aortogram, which revealed a completely occluded superficial artery with a two vessel run-off infrapopliteally (Figure 1). The lesion was categorised as TASC II TYPE D, and infra popliteal revascularisation was planned after discussion with the patient and family. We performed a femoropopliteal bypass using autologous reverse saphenous vein grafts, which were harvested by the endoscopic venous harvesting technique.

SURGICAL TECHNIQUE

For EVH, the patient was placed in a supine position and a transverse stab incision was made at the medial tibial condyle. Sharp dissection was carried out to identify the GSV, which was then elevated with a vessel loop. Another stab incision was made in the groin to disconnect the saphenous vein from the saphenofemoral junction. The calf portion of the vein was

also harvested by redirecting the catheter caudally, and a separate stab incision was made at the medial calf to disconnect and ligate the vein distally. An ankle incision was not used. EVH was performed with the disposable VASOVIEW 7 EVH System (MaquetInc, Wayne, NJ), using a carbon dioxide insufflation technique (flow set at 5, and pressure of 12 mm Hg) in the perivenous tunnel created by the camera dissector. Bipolar electrocautery (set at 25 V) was employed to divide side branches in situ, with silk ties applied prior to grafting. During blunt tip dissection, a regular sequence of short gentle motions is performed, allowing the CO₂ to promoted dissection and ensuring that side branches are dissected thoroughly to allow adequate length for branch division. By providing an adequate margin and keeping electrocautery energy settings on the lowest possible settings, the risk of thermal injury is minimized.

Once removed, the great saphenous vein was dilated with plasmalyte. The side branches were ligated and clipped. For tunnelling the saphenous vein through the submuscular plane we improvised a new technique. We introduced an autoclaved 5Fr Fogarty catheter cover for threading across the tunnel (figure 3). A standard atrium tunnel set was used in the sub sartorial muscular plane. The 5Fr Fogarty cover was threaded along the tunnel. An Ethicon Ethisteel™ no 6 – 75 cm (MNV-9494) straight tip was used to thread along the Fogarty cover. The end was made into a loop. The reversed end of the vein was attached to the loop end of the Ethisteel™, and the vein was threaded along the whole length of the tunnel. Once the vein reached the desired length for the distal anastomosis, the Fogarty cover was removed. Our remaining attention focused on the construction of proximal and distal anastomoses, as in a standard femoropopliteal bypass.

DISCUSSION

Arterial bypass is a classic, yet very efficient surgical method of treatment for peripheral arterial obstructive disease in critical ischemia patients, with good results for limb salvage and improvement

Figures

of quality of life. This method of reconstruction has been utilized in preference to prosthetic bypass on the basis that experimental and clinical studies¹⁻⁴ have shown a poor long-term patency rate when synthetic material was utilized to bypass the occluded superficial femoral artery. Minimally invasive vein harvesting techniques were initially introduced in 1994 and have been developed to reduce the wound morbidity associated with open vein harvest (OVH)⁵. Since its introduction in the mid-1990s, EVH has undergone many transformations, with both refinements in harvesting technique and vessel handling, in addition to technological advancements towards more practical and protective features. New-generation EVH systems have been developed to minimize endothelial cell damage secondary to "thermal spread." They use a bipolar radiofrequency energy source designed to keep thermal spread to a minimum (less than 1 mm), potentially minimizing graft injury.

Although studies shows that EVH may be associated with a decreased rate of wound complications, it is also associated with inferior graft patency in patients treated for critical limb ischaemia, with an increased incidence of severe stenosis within the body of the graft requiring reintervention. Limb salvage and secondary patency rates are similar for OVH and EVH.

To date, despite widespread acceptance of the in situ bypass technique, there is not a scintilla of evidence that use of the in situ bypass is associated with a patency rate superior to that of concurrently performed reversed vein bypass (in situ versus reverse graft). Various explanations have been advanced in an effort to explain the presumed improved results noted with the in situ bypass, including

improved endothelial preservation, preservation of intact vasa vasorum, and improved arterial hemodynamics resulting from an improved size match between the anastomosed proximal and distal vessels. Recent objective studies comparing in situ and reversed grafts have failed to confirm these presumed differences when the requisite critical analyses were performed⁶⁻⁸. In addition, numerous recent reports describing methods of recognizing and treating postoperative arteriovenous fistulas and valve site stenosis attest to a disturbing incidence of second operations required to maintain patency of in situ grafts of saphenous vein. The use of in situ grafts in the anatomical position can lead to kinking and angulation while entering the deeper anastomotic sites as already described in the literature.

CONCLUSION

We at our centre routinely use reverse saphenous vein grafting for femoropopliteal bypass operations. We have quite commonly encountered the technical problems of vein avulsion and internal bleeding while tunnelling the reverse saphenous vein graft through the subsartorial tunnel. Technical complications encountered while tunnelling the saphenous vein have not been well described in the literature. Though people have tried a soft mouldable tunneler, use of the Fogarty catheter hard cover has never been reported in the literature. Although the tunnel created by the endoscopic dissector can be used for the purpose of threading the vein, small intimal tears and stretching on the side branches while tunnelling can lead to disastrous consequences, sometimes resulting in sacrificing the only conduit remaining for the patient. The subsartorial tunnel is superior to the tunnel created by the EVH dissector. This necessitates the use of a tunneler. The use of a Fogarty catheter cover as described can reduce the risk of intimal damage during traction while tunnelling, side branch avulsion, and slipping of ligatures which can result in disastrous consequences of internal bleeding, which forces conversion to an open wound exploration, or resorting to the use of prosthetic grafts which have reportedly lower graft primary, primary assisted and secondary patencies.

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Figure 1: He was evaluated with a peripheral ctaortogram which revealed a completely occluded superficial artery with a two vessel run off infrapopliteally.

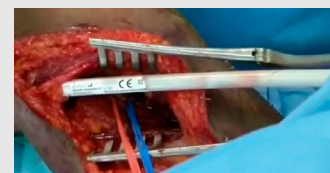


Figure 2: We performed a femoropopliteal bypass using autologous reverse saphenous vein grafts which was harvested by the endoscopic venous harvesting technique.



Figure 3: We introduced an auto-claved 5 fr fogarty cover for threading across the tunnel.

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Penetrating Abdominal Injury with Rupture at DJ

The rare case of rupture at the Duodeno-jejunal Junction. Associated injuries were large anteroposterior perforation of the stomach and burst fracture of the lumbar vertebrae in a young male due to bullet injury. The management and review of literature are discussed.

Dr Fawaz, Aster Sanad, Saudi Arabia

INTRODUCTION

We report the first case of rupture at the Duodeno-jejunal Junction. Only one case of perforation at the DJ has been reported which was a spontaneous perforation in an 8 month old infant reported by L limi et al.¹

Duodenal, especially Duodeno-jejunal Junction (DJ) perforation is rare. Commonly, gastrointestinal perforation is seen as a result of trauma (blunt or penetrating), infection, volvulus, adhesions, intussusception or strangulated hernia. The most common site of gastrointestinal perforation is the ileum followed by colon, stomach and oesophagus. Diagnosis of duodenal perforation poses a challenge, as its presentation is subtle, especially in those without trauma. Our patient was a victim of bullet injury, clinically he had abdominal pain and tenderness on palpation, associ-

ated CT findings of free air and free fluid in the abdomen [fig 1]. He was timely operated and we discovered his injuries intraoperatively. We confirm that double layer repair at the DJ with effective closure can ensure adequate management option for injuries to the DJ.

CASE REPORT

A young 38 years old male came to the emergency of our hospital with history of gun shot injury with an entry wound of about 1 cm over his left side of the chest just 1.5 cm below and lateral to the xiphoid process. There was no exit wound. The patient was not very ill looking but was in a lot of pain mainly over his abdomen & lower back. His initial BP was around 110/70 and Pulse was about 98 bpm with a good oxygen saturation. His chest examination revealed a normal air entry on both sides, abdominal

examination revealed mild tenderness all over the abdomen with severe pain in the lower back. We report this case as the first case of Duodeno-jejunal Junction rupture after bullet injury as in literature only one case has been reported of spontaneous DJ perforation in an 8 month old infant .

We did Chest and abdomen CT scan, which revealed normal chest scan , but free air and free fluid in the abdomen, and the bullet at the level of L2, vertebra with comminuted fracture of the said vertebrae [Fig 2,3].

The patient was taken to the Operating theatre where he underwent Laparotomy, which revealed large amount of recently eaten food material, on further inspecting we found a perforation in the anterior wall of stomach around 2 cm x 1.5 cm which was repaired in two layers after freshening the edges, we mobilized the greater omentum and opened the lesser sac to look for any other injury and we found posterior gastric perforation around 3 cm x 4 cm which was repaired in a similar manner. There was no pancreatic injury noticed. There was a rent in the mesentery and after following the same we found a near complete transaction at the DJ involving the around 70-75 % of the circumference as seen in Figure (4 & 5). There was a non expanding retroperitoneal hematoma but all the other viscera was normal. The DJ was repaired primarily in two layers, and after that a leak test was done with methylene blue to confirm the integrity of repair which showed a minor leak at the corner, so 2-3 sutures were reinforced and again a leak test did not reveal any leak, a nasogastric tube was inserted as low as the D2 and the abdomen was closed over two drains one at the site of DJ repair and other in the pelvis. On day

Figures

3 we removed the lesser sac drain. Patient remained in the ICU he was nil by mouth for 4 days we delayed orals until we assured that there are no signs of leak. On 5th day we did CT abdomen with oral contrast did not reveal any leak with distal run off of the contrast to the small bowel and no collection noticed as in. So he was started on oral fluid then progressively increased to soft diet, on 6th day the drains were removed subsequently. Later on the 10th day he was operated by neurosurgery, the patient was discharged, he has come for follow up once and is doing fine [fig 6].

DISCUSSION

The incidence of duodenal injuries varies from 3% to 5% of all trauma laparotomies². Most (80%) of these injuries are caused by penetrating trauma, with gunshot, stab, and shotgun injuries responsible for 75%, 20%, and 5%, respectively. Duodenal injuries cause morbidity in up to 65%, and an overall mortality rate was between 5.3% and 30%, but injuries to the duodenum itself are responsible for a mortality rate of approximately 10% [3-5]. Throughout the years, surgeons have developed several innovative and temporizing procedures to both repair the wounded duodenum and prevent fistulization from repair breakdown. The first method of suture line protection was the “triple tube ostomy” described by Stone and Fabian.⁶ Despite its technical simplicity and encouraging initial results, reports from others have failed to show improved outcomes with this technique. Ivatury et al.^{7,8} found an increased incidence of duodenal fistula and complications when duodenal decompression was used (Stone and Fabian’s “triple ostomy”), and their current preference was to avoid them.³



Figure 1: MD Contrast Ct Abdomen indicating free air in the peritoneal cavity.

Figure 2: MD Contrast CT abdomen, indicating the bullet at the level of vertebra with burst fracture. **Figure 3:** MD Contrast CT abdomen, indicating the bullet at the level of vertebra with burst fracture.

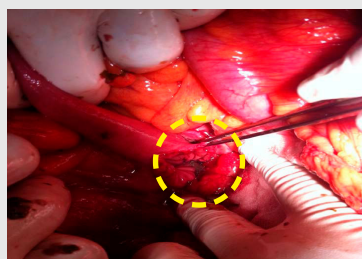
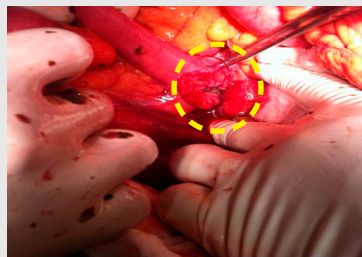


Figure 4: Intraoperative photo , arrow indicating the rupture site at the DJ. **Figure 5:** Intraoperative photo , arrow indicating the rupture site at the DJ. **Figure 6:** Follow up picture of the patient , arrow shows the site of entry wound.

Procedures for complete diversion of the gastrointestinal stream were soon developed. Berne et al.⁹ excluded repairs by “diverticulizing” the duodenum. Although effective in diverting enzymatic secretions, the procedure is complex,

is time consuming, and resects normal tissue in young, often healthy patients. Today, diverticulization is seldom performed.⁷

Vaughan et al.¹⁰ in 1977 described the first pyloric exclusion, but despite its technical simplicity

and swiftness, the procedure entails a permanent alteration of the gastrointestinal tract with the construction of the gastrojejunostomy. Pyloric exclusion offers minimal advantage over adequate nasogastric drainage when primary duodenal repair is performed and is associated with increased operative time, an extra intestinal anastomosis, and gastric suture line ulcers.¹¹⁻¹³ Postpyloric exclusion marginal ulceration occurred in approximately 10% of patients who underwent postoperative surveillance endoscopy.¹⁴

Significant controversy exists regarding the best surgical treatment for complex penetrating duodenal injuries. Debridement and primary repair or resection and anastomosis are suitable for the majority of duodenal injuries, especially for penetrating injuries.³ The physiologic presentation of the patient is the most important factor in predicting mortality in patients with traumatic duodenal injuries.^{15,16} Ivatury et al.

classified treatment according to the hemodynamic status of the patients and pointed out that in the hemodynamically unstable patient, a damage-control approach consisting of hemorrhage control, rapid sealing or resection of gastrointestinal perforations without establishing continuity, temporary abdominal closure, and ICU resuscitation should initially be performed and gastrointestinal tract integrity restoration should be accomplished in a second operation. In hemodynamically stable patients, lower-grade lesions of the duodenum, low-velocity penetrating wounds with no delay in diagnosis and treatment, simple primary repair is an adequate treatment for the majority of duodenal injuries.^{3,7,8} As seen in our patient optimal management was primary repair and was associated with shorter operative time and with simple and fast damage-control surgery and good postoperative recovery. The surgeon should be aware that treatment with a minimalistic approach, with only primary repair, may be ideal.⁴

Duodenal injuries are often associated

with multiple major intra-abdominal vascular and solid organ injury. These associated injuries compromise the patient's hemodynamic status and quickly descend them into the triad of acidosis, hypothermia, and coagulopathy. Lengthy, complex procedures in these cases inevitably lead to poor outcomes. For these reasons, the principles of damage-control surgery come into play to manage organ-specific injuries. The management philosophy is the avoidance of complex reconstructive procedures but at the same time advocating necessary debridement and adequate drainage.¹⁷

The traditional treatment of a post-operative duodenal fistula is adequate drainage and control via an anterior laparotomy with or without drain placement and with or without an open abdomen/temporary abdominal closure system. The retroperitoneal approach that has been previously described by Van Vyve et al.¹⁸ coined retroperitoneal laparoscopy has also been used as an alternative drainage method for the management of postoperative blunt duodenal trauma complications. This approach allows a total exploration and drainage of the duodenum and permits reexploration and removal of necrotic retroperitoneal secretions without the risk of intra-peritoneal cross-contamination.

CONCLUSION

Application of basic damage-control techniques for Penetrating Duodenal Trauma leads to improve survival and an acceptable incidence, primary repair of the perforation at the DJ is adequate enough surgical management in a fresh case of trauma.

Furthermore, the management of possible subsequent complications of initial damage-control management can be managed with the same philosophy of simplicity with acceptable outcomes. Retroperitoneal laparoscopy is an effective means for treating a duodenal leak and associated extensive retroperitoneal abscess and should be performed sooner than later. On the basis of our findings,

we believe that the general rule that "less is better" should be adopted for the management of all penetrating duodenal injuries.

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Case Report

Amniotic Band Syndrome in 20 Weeks Foetus Associated With Limb Defects

Amniotic band syndrome has been studied since the time of Hippocrates and Aristotle. Amniotic band syndrome is a group of sporadic congenital anomalies of varying severity involving limbs, craniofacial region or trunk.

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ABSTRACT

Amniotic Band Syndrome is a series of congenital malformations ranging from minor constriction rings to complex multiple congenital anomalies, that are attributed to amniotic bands that entangle and disrupt foetal parts. While mild variants have a good prognosis with normal life expectancy, severe cases may be incompatible with life. We report a case of a 20 week old foetus with an amniotic band around the right upper limb, entanglement around the neck and a Congenital Talipes Equinovarus deformity of the right foot, delivered from a 31 year old female

patient, who came for a routine check up to the Department of Obstetrics and Gynecology at DM Wayanad Institute of Medical Sciences, Meppadi post, Kerala. Early prenatal diagnosis of this defect by Ultrasonography is a boon to Obstetricians, Pediatricians and Surgeons.

INTRODUCTION

Amniotic Band Syndrome (ABS) has been studied since the time of Hippocrates and Aristotle.^{BS} is a group of sporadic congenital anomalies of varying severity involving limbs, the craniofacial region or trunk.² Reported incidence

ranges widely, from 1 in 1200 to 1 in 15000, depending on the criteria used.² Amongst women pregnant with ABS foetuses, spontaneous abortion is a common outcome and incidence can be as high as 178/10000.¹

The case discussed here is a presentation with simultaneous amniotic band constriction around the right upper limb, entanglement around the neck, and congenital Talipes Equinovarus deformity of the right foot, as seen in a fetus delivered from a 31 year old woman at 20 weeks gestation. This case offers important insights for gynaecologists, radiologists and pediatricians for early prenatal diagnosis and treatment.

CASE REPORT

A 31 year old woman in a non-consanguineous marriage who had conceived naturally presented at 20 week gestation to the Department of Obstetrics and Gynecology OPD at DM Wayanad Institute of Medical Sciences, Meppadi, Kerala for a routine check-up. The patient's past two pregnancies had been uneventful. She was taking regular antenatal care with folic acid supplementation for the present pregnancy and the first trimester scan had been normal. There was no past history of trauma, drug intake or amniocentesis.

P/A examination of the uterus at 18-20 weeks showed this to be relaxed, with no foetal heart sound (FHS). On ultrasonographic examination, the foetus showed no cardiac activity and indicated oligohydramnios. Hence the pregnancy was terminated with consent of the patient by extra-amniotic Foley's induction.

A foetal examination after the termination of pregnancy showed a constriction band around the right upper limb and an entangle-

Figure 1. Showing constriction band around the right arm and neck of the foetus.



ment around the neck.

There was a right lower limb deformity with similar presentation to Congenital Talipes Equinovarus deformity.

DISCUSSION

Amniotic band syndrome (ABS) comprises of a spectrum of anomalies which vary in severity.² The triad of ABS includes amnion-denudation of the placenta; foetal attachment or entanglement by amniotic remnants; and foetal deformation, malformation and disruption.² In the present case, we report an amniotic band around the right shoulder, entanglement around the neck and Congenital Talipes Equinovarus Deformity.

Embryological basis of TA

In 1930, Streeter's intrinsic hypothesis proposed disruption in embryogenesis at the time of formation of the germ disk as a cause for ABS.³ In 1965 Torpin's extrinsic hypothesis suggested that the birth defects are instead caused by the primary rupture of the amnion early in gestation.³ In 1992, Moerman .et.al proposed that ABS is a collection of three distinct lesions-constrictive tissue bands, amniotic adhesions and the more complex limb-body wall complex.⁴

Kalousek .et.al divided the amnion defects into the Limb Body Wall Complex (LBWC), caused by an early defect of the amniotic sac, and the amnion rupture sequence, caused by amniotic bands.⁵ They also reported that the incidence of amnion rupture sequence is much higher in pre-viable spontaneous abortions than in term fetuses, indicating that most cases are spontaneously aborted.⁵

Etiological factors for Amniotic Band Syndrome:

Various studies point to different etiological factors, including

maternal drug abuse, cigarette smoking, unplanned pregnancy, anorexia, hyperthermia, young maternal/paternal age, dietary glycaemic index, abdominal trauma, infections, amniocentesis etc. which have been implicated in the causation of ABS.² A human homologue of the mouse Disorganisation gene (Ds) has been proposed as a cause of some cases of amnion disruption by a two-hit mechanism (the gene is yet to be identified). Some cases of ABS-like anomalies associated with cleft lip and palate may result from mutations in the genes Disorganization p63 or IRF6.⁶

There have been reported associations with underlying diseases including Ehler Danlos Syndrome and osteogenesis imperfecta. The malformations of ABS should be distinguished from others occurring in a syndromic setting by the fact that the clefts do not follow anatomic lines of closure and the lesions are asymmetrical.⁷ This is important since most cases of Amniotic band syndrome are sporadic and there is no risk of recurrence in subsequent pregnancies. 2In the

present case, an exact etiology was not found.

The accepted modality of treatment for amniotic band syndrome in utero is by foetoscopic laser surgery before the bands begin to compress the fetal parts.¹

CONCLUSION

An awareness of Amniotic Band Syndrome helps the obstetrician in identifying foetal anomalies, prognosticating about them to expectant parents, terminating pregnancy in appropriate situations and counseling the parents on the possibility of recurrence of the anomaly in subsequent pregnancies. Radiologists should be aware of Amniotic Band Syndrome as one of the causes for intrauterine fetal demise during prenatal ultrasound examination. Early detection of this will help to deliver appropriate treatment.

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case report

Index case of Nipah -2.0 in Kerala; A case report

A 23 year old man presented to the emergency department with a high grade fever of 8 days duration. He had visited Trissur, from where he came back home after 2 days with fever.

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INTRODUCTION

Nipah virus (NiV) is a Paramyxovirus that has recently been responsible for outbreaks in India. In 2018, it caused an outbreak in Kozhikode that resulted in 17 deaths. This year, it has again resurfaced in Kerala. The index case was identified in the Department of Neurology at Aster Medcity, Kochi, Kerala. Due to early detection, isolation and containment measures initiated by all of the involved departments, there were no further cases identified. A number of close family members, close contacts and nursing personnel were placed under observation or isolation in the nearby Cochin Medical College, Nipah isolation ward. Repeated sampling of suspected cases did not disclose any further infections and the infection was contained at 'Patient Zero'. In this article, we discuss the clinical presentation of the index case.

CASE REPORT

A 23 year old man presented to the emergency department with a high grade fever of 8 days dura-

tion. After visiting multiple hospitals, he had been referred to us. He was from Thodupuzha [Idukki district], 60 kilometers from Kochi. He had visited Trissur, from where he came back home after 2 days with fever.

On day 8, in the ED, he was febrile, delirious and had tremors of his limbs as well as spontaneous myoclonus and dysarthria. His mother denied any history of similar illness among his friends, any significant past medical history or recreational drug abuse. He underwent an MRI brain scan, which showed numerous similar sized small infarcts scattered in the subcortex and cerebellum as well as the ponto-mesencephalon. These lesions were visible only on the diffusion weighted MRI (DWMRI) images and did not enhance with contrast. The initial differential diagnosis was that of multiple septic emboli. An urgent Echo cardiogram was performed at the bedside and did not disclose any valvular lesions indicative of infective endocarditis.

Blood cultures were sent and

common endemic infections such as leptospirosis, scrub typhus, dengue and malaria were ruled out. A chest x-ray was also normal. The patient was started on injections of Ceftriaxone and Vancomycin at meningitic doses and transferred to the ward. The next morning, as he was still delirious, a lumbar puncture was performed and a cerebrospinal fluid (CSF) sample was sent for an encephalitic test panel (including DNA and RNA viruses). The patient was started on Acyclovir injections at 10mg/kg Q8H. CSF testing showed around 50 cells, predominantly lymphocytic, with normal sugar and protein levels. The encephalitic panel was positive for Nipah virus the next evening.

The patient was noted to have dysautonomic features such as tachycardia, volatile blood pressures and unexplained tachypnea. He was immediately transferred to the medial ICU and isolation precautions were initiated. The next morning, he was started on 2g solid dose Ribavirin, followed

by 1.2g on days 2-10. The CSF, blood, urine and throat swabs were further tested with Real-time PCR, nested RT-PCR and anti-Nipah human IgM and IgG antibodies via the enzyme-linked immunosorbent assay (ELISA). By day 10, further dysautonomia in the form of urinary retention developed, and an indwelling Foley's catheter was placed. The urine and CSF were positive for Nipah Viral RNA, IgM and IgG antibodies on day 8.

The patient was noted to be persistently delirious (hyperactive delirium) and was agitated. He was intermittently sedated with fentanyl. By the end of the second week, the indwelling catheter could be removed and he was gradually ambulated. As

Ivabradine for tachycardia, both of which improved. His arterial blood gases remained normal throughout his clinical course and he did not require any ventilatory support.

DISCUSSION

As the first reported patient, our patient was the index case of Nipah virus in 2019 in Kerala. The infection was contained at Aster Medcity. NiV has been well known to cause outbreaks in various south east Asian countries, starting with Malaysia in September 1998, followed by Singapore in 1999. Subsequent outbreaks have occurred every year in Bangladesh from 2001 onwards. In 2001, NiV was detected in India (West Bengal, 2001 & 2007). In May

turn-around time from XCYTON Diagnostics in Bengaluru. The turn-around time of 36 hours enabled us to immediately diagnose NiV and rapidly initiate isolation measures.

Of the 10 cases reported from Kozhikode, 7 of them developed encephalitis. 2 patients survived and 1 died of ARDS. Even among the cases of encephalitis, mortality was predominantly due to acute respiratory distress syndrome (ARDS). However, in all mortalities, the duration from onset to death was quite rapid, and there was no time to complete adequate neuroimaging. Most of these patients also had dysautonomia (tachycardia and fluctuating blood pressures). In view of the severity of the encephalitis, a neurogenic pulmonary edema is also a possibility, however this could not be proven in any of the cases and ARDS was considered more likely. Myocarditis was also considered in some of the patients. As NiV primarily causes a small vessel vasculitis, this could explain the small infarct-like lesions in the brain on the MRI. The two survivors had a milder form of the disease and could also complete a course of oral Ribavirin for up to 14 days. None of the patients received NiV monoclonal antibody therapy. The survivors also did not suffer any sequelae of NiV infection.

In common with our patient, most of the NiV encephalitis patients had fever, altered sensorium and dysautonomic features. The dysautonomia probably occurred due to brainstem involvement. The rapid progression, high mortality rate and brainstem involvement further underscores the similarity of NiV to 'Rabies' which is albeit uncommonly also acquired from bats.

Of the 10 cases reported from Kozhikode, 7 of them developed encephalitis. 2 patients survived and 1 died of ARDS. Even among the cases of encephalitis, mortality was predominantly due to acute respiratory distress syndrome (ARDS).

NiV urine PCR remained positive on day 16, he remained in isolation. By day 20 all samples tested negative and he was transferred out of isolation. All indwelling catheters and lines were removed. A new MRI did not show any new lesions. However the patient remained febrile and had persistent tachycardia. Repeated blood and urine cultures, CRP, ProCalcitonin, Chest xray and blood counts were normal. After all sources of infection had been ruled out, the possibility of a central fever with dysautonomia was considered. He was started on symptomatic treatment with Naproxen for fever and

2018, a NiV outbreak was noted in north Kerala (Kozhikode). The infection was traced to fruit bats and coincided with the bat breeding season which runs from December to May.

A number of methods can be used to diagnose NiV infection. These include serum neutralization tests such as ELISA, viral PCR, viral isolation or immunohistochemistry on biopsy specimens. These tests are run at a number of Virology laboratories including The National Institute of Virology (NIV), Pune, NIV Alleppey and the Manipal Institute of Virology. However, we could also obtain a prompt and rapid

Regulars

**One Nephrologist
1000 + kidney
Transplants**
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**Penicillin's
First Patient**
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“It is very important to propagate the concept of organ donation from brain-dead persons, so that several people who are suffering end stage renal disease can have a second lease of life. The quality of life after a successful kidney transplant is much superior to the life on dialysis.”

- **Dr V Narayanan Unni**, Senior Consultant, Nephrology has performed more than 1100+ kidney transplants during his career



One Nephrologist 1100+ kidney Transplants

A VETERAN OF ASTER MEDCITY, KOCHI, DR V NARAYANAN UNNI, SENIOR CONSULTANT, NEPHROLOGY HAS PERFORMED MORE THAN 1100+ KIDNEY TRANSPLANTS DURING HIS CAREER AND HAS MORE THAN 34-YEARS OF EXPERIENCE IN TREATING PATIENTS OF ALL AGES WITH KIDNEY DISEASES.

L

ike many nephrologists, Dr Unni was drawn to nephrology by a duty of patient care after four years of general practise, on seeing “the difficulties faced by patients on dialysis”. There can be few transformations more dramatic than that of patient recovery following transplant, of which Dr Narayanan has witnessed many, having conducted more than 1100 transplant procedures over the course of a 34 year career.

Prior to specialising in transplantation, Dr Unni's career pathway began in India, leading him to the Christian Medical College, Vellore and to the P.G.I. Chandigarh, both centres of excellence for renal transplantation in India; here, he lectured students as well as dealt with the demands of the busy casualty and intensive care units. Dr Unni was an exceptional student, and was awarded both the Gold Medal awarded by Malabar Christian College, Calicut for the First Rank in the University in 1973 and the Gold Medal for the Best outgoing student of Calicut Medical College in 1978.

Dr Unni still recalls his first transplant at Dammam Central Hospital, Saudi Arabia. The 25-year-old patient received a kidney from her brother, and involved some of the most challenging procedures of his career. "Kidney transplantation in children is very challenging; however, it is extremely rewarding. Results of kidney transplantation in children are even better than those in adults, if this is done by an experienced team." The youngest child for which Dr Unni's team has performed a transplant was below 2 years of age at the time of transplant, and he often meets his former patients; "The longest survival in my experience is 34-years (kidney donated by the patient's sister); both donor and recipient have a normal kidney function even now, and come to me for regular follow up."

Many developments in techniques have occurred since Dr Unni's first transplant, and Dr Unni has been at the forefront of surgical methods development, writing a number of papers detailing the outcomes of case studies employ-

ing new robotics procedures, as well as detailing unusual cases and their outcomes, such as procedures in patients with congenital abnormalities of the kidney and urinary tract. Although Dr Unni is familiar with reports of the development of an Implantable Artificial Kidney, he cautions that "The artificial kidney is still in the experimental stage; this would need more refinements before it can be widely used in patients."

There are ongoing difficulties in India in encouraging living donors to come forwards despite first degree blood relatives typically providing optimal matches, and

quality of life to those undergoing dialysis, but he considers it "our duty as medical personnel to educate people about the benefits to the society by promoting and encouraging deceased donor kidney transplantations."

Dr Unni emphasises the importance of adherence to lifestyle and post-operative care advice following transplantation; "If the patient (recipient) is not careful with his medications, follow up and his lifestyle, the results may not be good." His advice to patients and early career nephrologists is as follows:

Diet and exercise - It is

extremely important for the patient to have a disciplined life style

Immuno-suppressant medicines

- These need to be taken

regularly as advised by the Nephrologist

Anxiety, depression and mental health - this is usually not a problem, as long as the kidney is working well.

Kidney rejection - The incidence is very low, if the donor is a first degree blood relative.

Lifestyle changes - It is very essential to ensure that body weight does not increase. Smoking is to be avoided, and regular exercise is essential.

Dr Narayanan Unni is currently the Lead Senior Consultant in Nephrology and Urology at Aster MedCity, Kochi, where he initiated the kidney transplant programme and established the DNB programme in Nephrology.

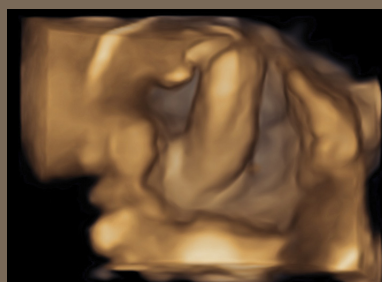
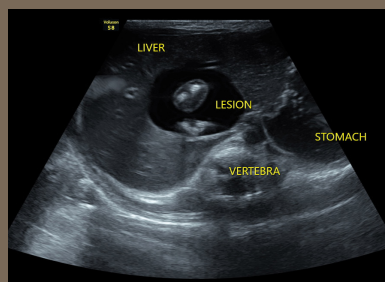
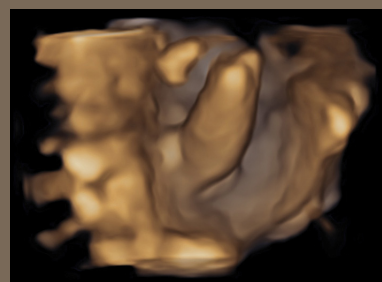
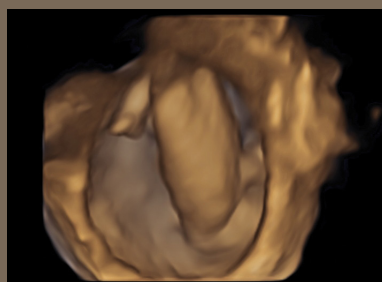
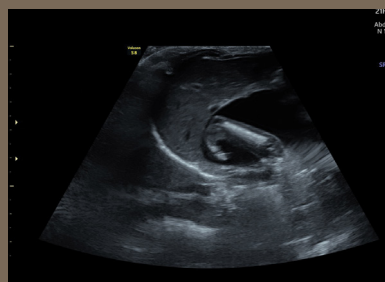
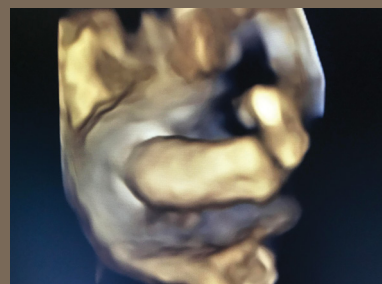
"It is very important to propagate the concept of organ donation from brain-dead persons, so that several people who are suffering end stage renal disease can have a second lease of life. The quality of life after a successful kidney transplant is much superior to the life on dialysis."

the number of deceased donor kidney transplantations in India is unfortunately too small to meet the demand. Dr Unni has been an outspoken advocate of both living and deceased donor organ donation within The International Transplantation Society and at international conferences around the world;

"It is very important to propagate the concept of organ donation from brain-dead persons, so that several people who are suffering end stage renal disease can have a second lease of life. The quality of life after a successful kidney transplant is much superior to the life on dialysis." Not only does Dr Unni have a passion for improving patient outcomes and returning



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Fetus-in-fetu (FIF) - Is it a baby inside the baby?

Fetus-in-fetu (FIF) is an extremely rare developmental abnormality with an incidence of 1 in 500 000 births. It was first reported in 1808 by George Young. Since then, less than 200 cases have been reported worldwide. FIF is characterized by the incorporation of one or more partially-developed fetuses into the body of an otherwise normally developed fetus and most commonly presents with a mass in the abdomen.

In this case, a 5 days old infant was referred from a neighbouring hospital to Aster MIMS Kottakkal, Kerala, India for scanning of an abdominal mass. During the ultrasound, a cystic structure with calcified limb-like structures within it was found. It resembled a fetal limb, near to the liver and kidneys of the

neonate. Further, a 3D & 4D scan was performed, and the diagnosis of Fetus in fetu was confirmed. The malformed Fetus was excised in Kozhikode Medical College on the 45th day after birth. Postoperatively the patient recovered well without any complications. Sonographic reports of such a case are nominal. However, the 3D images of Fetus in fetu limb has not been acquired anywhere else.

Multiple theories are proposed regarding the embryogenesis of Fetus-in-fetu (FIF). Most recent literature review suggests that it is a diamniotic, monochorionic, monozygotic twin in the body of the host twin after anastomosis of the vitelline circulation. Other theories include demised multiple pregnancies and a variant of teratoma.



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Penicillin's first patient

Uncovering the truth behind the first man treated with the world's first antibiotic.

by **Mike Barrett**



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their task to trying to fill a bath with the plug out. It also explains the need for frequent repeat doses.

The patient's urine was collected and rushed to the penicillin production unit at the Sir William Dunn School of Pathology, where Chain desperately purified excreted drug for reuse. But he couldn't recover enough. Alexander relapsed and eventually died.

His temporary reprieve, however, helped convince the penicillin team that curing him would have been possible, if only enough of the drug could have been made.

With Heatley, Florey left for the USA. There, Florey persuaded several large pharmaceutical companies (including Merck, E R Squibb & Sons, Charles Pfizer & Co. and Lederle Laboratories) to scale up production. This meant that by the end of World War II thousands

of Allied soldiers were surviving battlefield wounds and being treated for sexually transmitted infections, including gonorrhoea. The work sparked the antibiotic revolution.

Recently, an elderly aunt of mine told me a story of an old friend of hers, Sheila LeBlanc. Sheila is the daughter of Constable Alexander. What's more, she is still alive and living in California. I emailed Sheila with some questions. She explained how, when her father died in 1941.

The discovery of penicillin by Alexander Fleming in 1928 is often portrayed as a stroke of serendipity falling upon a sloppy worker who had left a bacterial culture plate open on his bench while taking a holiday. The fungus that landed there killed the bacteria – and the lucky Fleming could claim to have saved the world.

It was no simple fluke. The Scottish doctor had, in fact, been leading research into the quest for antimicrobial agents for many years by this time. Fleming, however, failed to develop the drug, finding it too difficult to purify. This was left to Howard Florey, Ernst Chain and Norman Heatley in Oxford over a decade later – work catalysed by the necessity of war.

The first patient to be treated with penicillin was a policeman, Constable Albert Alexander. According to popular legend, Alexander developed sepsis after pricking himself while pruning roses in the garden of the police house in the pretty hamlet of Wootton in Oxfordshire in the early autumn of 1940.

By the time the researchers felt they could test penicillin in humans – having cured infections in mice and proven its safety in a terminally ill human volunteer – Alexander was deteriorating fast. Now in the Radcliffe Infirmary in Oxford, he was covered in abscesses and had already lost an eye.

He received an initial dose of 200 mg of penicillin, followed by another 300 mg every three hours over five days. His short-term recovery was remarkable. However, the original penicillin formulation was excreted from the body so rapidly that Florey likened

The first patient to be treated with penicillin was a policeman, Constable Albert Alexander.



JAMA Neurology
May 20th 2019

Association Between Unrecognized Myocardial Infarction and Cerebral Infarction on Magnetic Resonance Imaging

This is a cross-sectional sub-cohort study involving 925 patients from the ICELAND MI registry to determine whether unrecognized MI detected by cardiac magnetic resonance imaging (MRI) is associated with cerebral infarction.

Five enrolled participants had nondiagnostic brain MRI studies and were excluded. Among 925 participants, 480 (51.9%) were women; the mean (SD) age was 75.9 (5.3) years. There were 221 participants (23.9%) with cardiac MRI evidence of MI, of whom 68 had recognized MI and 153 unrecognized MI. There were 308 participants (33.3%) with brain MRI evidence of cerebral infarction; 93 (10.0%) had embolic infarcts of undetermined source. After adjustment for demographic factors and vascular risk factors, the likelihood (odds ratio) of having cerebral infarction was 2.0 (95% CI, 1.2-3.4; $P=.01$) for recognized MI and 1.5 (95% CI, 1.02-2.2; $P=.04$) for unrecognized

MI. After adjustment for demographics and vascular risk factors, unrecognized MI was also associated with embolic infarcts of undetermined source (odds ratio, 2.0 [95% CI, 1.1-3.5]; $P=.02$).

In a population-based sample, we found an association between unrecognized MI and cerebral infarction. These findings suggest that unrecognized MI may be a novel risk factor for cardiac embolism and cerebral infarction. Limitations include small sample size and limited demographics.



JACC: Heart Failure
Volume 7, Issue 7

Burden and Causes of Hospital Admissions in Heart Failure During the Last Year of Life

Congestive heart failure (CHF) is a chronic medical condition with a high morbidity and mortality. Despite increases in multidisciplinary team approaches for heart failure management, care of patients towards the end of life is often not prioritized. Efforts to improve care for heart failure patients at the end of life will need to understand the common issues faced by this patient population. This

study sought to evaluate the causes of medical decompensation in patients with heart failure in the last year of life. The retrospective analysis found that heart failure and cardiovascular disease were common reasons for hospital admission, but the majority of admissions were for non-cardiac issues. While hospitalization frequency increased towards the time of death, the proportion of admissions for cardiac and non-cardiac causes remained unchanged.

The findings of this study underscore the importance of recognizing non-cardiac issues in patients with end-stage CHF. The main strength of this study is the large cohort of heart failure patients in their final year of life. The limitations of the study include the lack of information on functional class, ejection fraction, and reliance on diagnostic codes for establishing cause of admission.



Journal of Clinical Oncology
June 19, 2019

Treatment Outcomes of Immune-Related Cutaneous Adverse Events

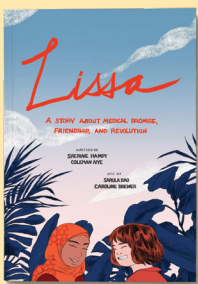
The aim of this study was to report the efficacy of topical and systemic treatments for

immune-related cutaneous adverse events (irCAEs) attributed to checkpoint inhibitors in an uncontrolled cohort of patients referred to onco dermatology clinics. A retrospective analysis of patients with irCAEs evaluated by dermatologists from January 1, 2014, to December 31, 2017, at three tertiary care hospitals and cancer centers were identified through electronic medical records. Clinicopathologic characteristics, dermatologic therapy outcome, and laboratory data were analyzed.

In this retrospective analysis, 285 patients with 427 irCAEs related to ICIs were studied to assess the efficacy of topical and systemic treatments prescribed by dermatologists. The most common irCAEs were pruritus (32%) and maculopapular rash (28%). Researchers found that irCAE phenotype was not associated with primary cancer diagnosis, but was associated with ICI class ($p=0.007$), in that maculopapular rash was predominant in patients who received combination therapy. Furthermore, dermatologic interventions such as topical corticosteroids, oral anti-pruritics, and systemic immunomodulators significantly reduced the severity of irCAEs (mean Common Terminology Criteria for Adverse Events grade 1.74 at diagnosis vs. 0.71 at follow-up, $p=0.001$). The largest improvement was observed in maculopapular rashes (mean grade reduction -1.40). Treatment patterns did not differ significantly between dermatologists ($p=0.06$). In all seven patients with corticosteroid-refractory irCAEs, targeted biologic immunomodulatory therapies improved symptoms.

How social contexts shape Medical Decisions – Story of Anna & Layla

Lissa is a graphic novel written by academics Sherine Hamdy and Coleman Nye and illustrated by artists Sarula Bao and Caroline Brewer. The complete graphic novel was released as the debut title in the ethnoGRAPHIC series published by the University of Toronto Press.



Lissa: A Story About Medical Promise, Friendship, And Revolution

Written By:
Sherine Hamdy & Coleman Nye
Art By:
Sarula Bao & Caroline Brewer



As young girls in Cairo, Anna and Layla strike up a friendship that crosses class, cultural, and religious divides. Years later, Anna learns that she may carry the hereditary cancer gene responsible for her mother's death. Meanwhile, Layla's family is faced with a difficult decision about kidney transplantation. Their friendship is put to the test when these medical crises reveal stark differences in their perspectives.

Anna is the daughter of an expat American oil family living in Cairo, and Layla, her Egyptian friend, is the daughter of the apartment building's bawab, or caretaker. The book opens with Anna's mother, is diagnosed with, battles against, and succumbs to breast cancer. Five years and thousands of miles later, Anna learns that she, too, may carry the hereditary cancer gene respon-

sible for her mother's death. Meanwhile, Layla's family back in Egypt is faced with a difficult decision about kidney transplantation for her ailing father who, due to his faith, staunchly opposes Kidney Transplant. Yet, Layla's hard-won education as a young doctor places her at a distance from her parents' traditional views as well as Anna's medical preferences.

As a medical student doing rounds at the Cairo University Hospital, Layla witnesses a case of advanced cancer. The professor complains, "These ignorant peasants always wait until the last minute to come and get treatment." Layla boldly responds: "Most people don't get good treatment even if they do come early! And why should people come to see doctors who think they are 'ignorant peasants'?"

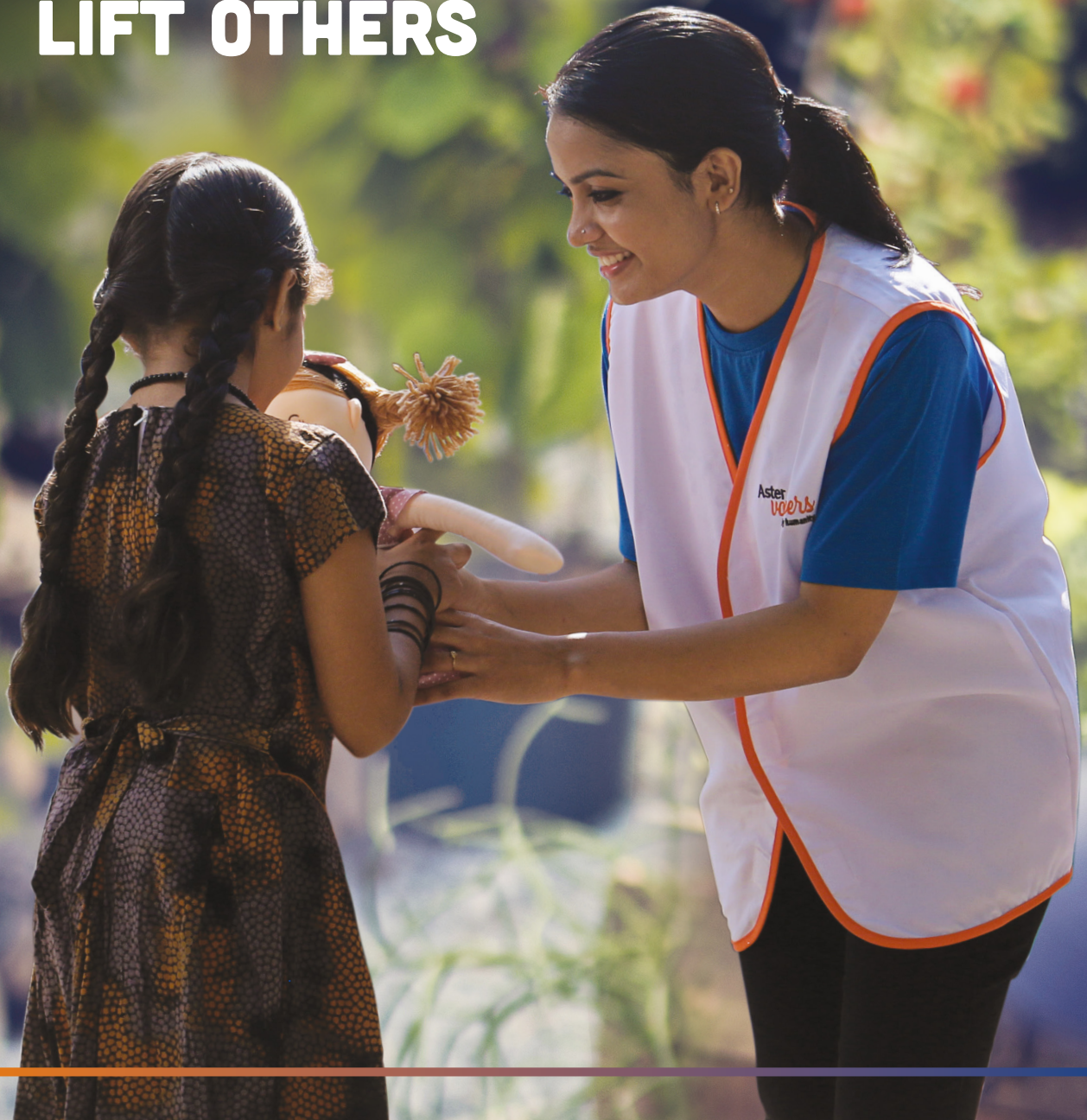
At the same time, back in the

United States, Anna attends a college lecture on genetics, learns that she may carry a gene, BRCA, that would put her at a higher risk of getting cancer. This leads her to consider her own testing options.

The Book showcases an extraordinary contrast between Layla's father's unwillingness to receive a kidney transplant either from a paid donor or from his offspring in Egypt and Anna's continued research into prophylactic mastectomy in the U.S. As Anna goes under anaesthesia for her prophylactic mastectomy in the US, a revolution breaks out in Cairo.

This book brings anthropological research to life in comic form. Artfully combines scholarly insights in visually-rich storytelling to foster a greater understanding of global politics, inequalities, and solidarity and leaves the reader to think how social contexts shape medical decisions.

WE ONLY RISE WHEN WE LIFT OTHERS



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*dated as on 31st May 2019

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The collective goodwill and positive energy that this generates is amazing -
and I think this definitely helped me recover faster."*

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This is our simple promise. And this promise sums up why we exist. This promise is what fosters our culture, our way of life. This promise is what we strive to honour every day, every moment. It is this promise that inspires us to work seamlessly to ensure that no patient, no doctor, no nurse, no stakeholder turns around to ask, "is this how you treat me well?" It is this promise that binds together the very fabric of our existence and our future.

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