CLINICAL TRIALS WITH PUBLIC HEALTH FOCUS

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What is public health focus?

- Public health is the science of protecting and improving the health of families and communities through promotion of healthy lifestyles, research for disease and injury prevention and detection and control of infectious diseases. Overall, public health is concerned with protecting the health of entire populations.

Controlling Hepatitis B – a Singapore success story

Long-standing veteran in epidemiological surveillance and research, Professor Goh Kee Tai works at the Ministry of Health and Saw Swee Hock School of Public Health, National University of Singapore. He has been a part of many a Singapore success story, including that of Hepatitis B.

Professor Goh Kee Tai

Singaporeans have faced many major health – related challenges from communicable diseases over the past five decades and beyond, notably epidemics of polio in the 1950s and 1960s, the high disease burden of Hepatitis B virus infection in the 1970s and 1980s, and the SARS pandemic in 2003 come to mind. While polio and SARS are no longer immediate threats, Hepatitis B virus infection has remained endemic. Chronic Hepatitis B virus infection is a precursor risk factor to liver cancer, one of the most common types of cancers in Singapore.

According to Professor Goh, the incidence of acute Hepatitis B and prevalence of Hepatitis B virus carriers in Singapore have fallen substantially, due to the inclusion of the Hepatitis B vaccine in the national childhood immunisation programme in the 1980s.

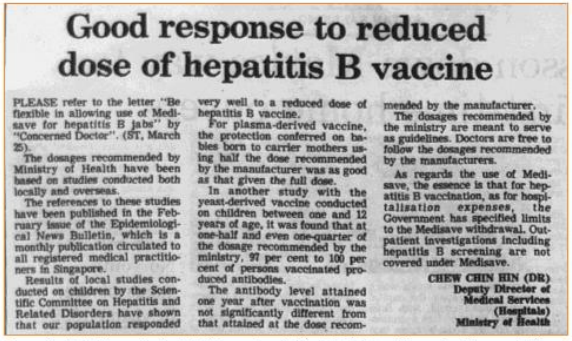
"The impact [of immunisation] has been tremendous. We know that vaccines are a very powerful public health tool. And the immunisation programme has been successfully implemented with effective results. Singapore has a good health infrastructure, and its people are committed [to protecting their families and getting themselves immunised]."

The Hepatitis B vaccine became available in the 1980s. By the early 1990s, the proportion of Singaporean children getting immunised was around 70-80 percent, and subsequently jumped to more than 95 percent from the mid-1990s onwards. (**Figure on page 11**)

Primary school children being tested for post Hepatitis B vacinnation immunity

This high, near universal Hepatitis B vaccination coverage rate in the 1990s may also be attributed to Singapore clinical research. When Hepatitis B vaccine first became commercially available, it was costly. As a result, the Ministry of Health funded a clinical trial evaluating the effectiveness of a lower dose in infants. Prof Goh and his colleagues conducted several trials, which involved children and adults. It was found that half the usual full dose of the vaccine recommended by the manufacturer was just as effective at preventing Hepatitis B virus infection as a usual dose. As a consequence of these clinical studies, a half-dose was initiated in Singapore, rather than the full dose. The cost of the vaccine was reduced substantially and as a result, more Singaporeans were able to be immunised.

More primary school children being tested for post Hepatitis B vacinnation immunitya



Good response to reduced dose of hepatitis B vaccine

PLEASE refer to the letter "Be flexible in allowing use of Medisave for hepatitis B jabs" by "Concerned Doctor" (ST, March 25).

The dosages recommended by Ministry of Health have been based on studies conducted both locally and overseas.

The references to these studies have been published in the February issue of the Epidemiological News Bulletin, which is a monthly publication circulated to all registered medical practitioners in Singapore.

Results of local studies conducted on children by the Scientific Committee on Hepatitis and Related Disorders have shown that our population responded very well to a reduced dose of hepatitis B vaccine.

For plasma-derived vaccine, the protection conferred on babies born to carrier mothers using half the dose recommended by the manufacturer was as good as that given the full dose.

In another study with the yeast-derived vaccine conducted on children between one and 12 years of age, it was found that at one-half and even one-quarter of the dosage recommended by the ministry, 97 per cent to 100 per cent of persons vaccinated produced antibodies.

The antibody level attained one year after vaccination was not significantly different from that attained at the dose recommended by the manufacturer.

The dosages recommended by the ministry are meant to serve as guidelines. Doctors are free to follow the dosages recommended by the manufacturers.

As regards the use of Medisave, the essence is that for hepatitis B vaccination, as for hospitalisation expenses, the Government has specified limits to the Medisave withdrawal. Outpatient investigations including hepatitis B screening are not covered under Medisave.

CHEW CHIN HIN (DR)
Deputy Director of Medical Services (Hospitals)
Ministry of Health

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"As a consequence of these clinical studies, a half-dose was initiated in Singapore, rather than a full dose. The cost of the vaccine was reduced substantially and as a result, more Singaporeans were able to be immunised"

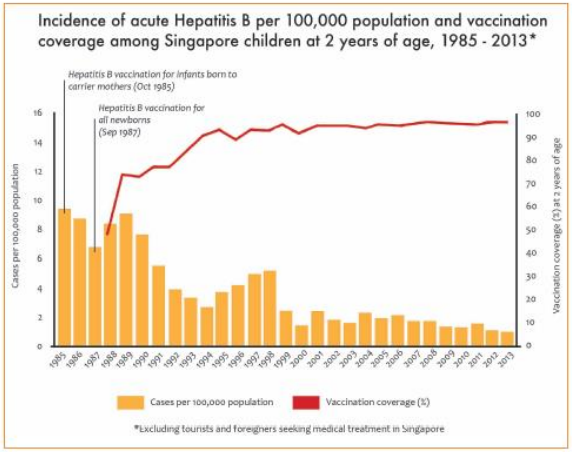

Figure: Incidence of Acute Hepatitis B per 100,000 population and vaccination coverage among Singapore children at 2 years of age, 1985-2013 (Source: Communicable Diseases Division, Ministry of Health)

ADEPT Dengue study

KEY PROJECTS

VI. ADEPT

"ADEPT marks the first step of a multi-centre investigator-initiated study in infectious diseases. It also marks the beginning of local collaboration between Infectious Disease Clinician Investigators and an academic research institute like SCRI. SCRI's operational support to run clinical studies is crucial in building up the synergy and capabilities necessary for quality clinical research."

Professor Leo Yee Sin
Principal Investigator
Clinical Director, Communicable Disease Centre
Director, Institute of Infectious Diseases & Epidemiology, Tan Tock Seng Hospital
Senior Consultant, Department of Infectious Diseases, Tan Tock Seng Hospital

(From left): Mr Liew Wei Ming (SCRI), Ms Wei Yuan (SCRI), Ms Cindy Seow (SCRI), Dr Limin Wijaya (SGH), Dr Cao Yang (SCRI), Professor Leo Yee Sin (TTSH)

Study of platelet transfusion in severe dengue cases in Singapore and Malaysia

Atropine to Treat Childhood Myopia

A drop a day keeps Nikhil's myopia at bay

PHOTO: LIANHE ZAOBAO

WHEN he was 10, Nikhil Angappan had myopia of 175 degrees in both eyes. Seven years on, the Anglo-Chinese School (Independent) student's prescription increased by just 25 degrees.

He was one of 400 children put on diluted atropine eyedrops by researchers at the Singapore National Eye Centre (SNEC) as part of a five-year trial.

And the results have been stunning, said SNEC. The research showed that the eyedrops, when given at ultra-low doses, slowed myopia by up to 60 per cent.

Said Nikhil, now 17: "It may seem like a big inconvenience to put in the eyedrops every day. But after a while, it becomes routine. All it takes is a few seconds before you go to sleep." ■ TOP OF THE NEWS A6

'We are sure that we have a way to treat myopia'

By POON CHIAN HUI

FOR 16 years, doctors at the Singapore National Eye Centre (SNEC) have been trying to find a way to stop myopia in its tracks.

They say they finally have the answer: eyedrops with a concentration of 0.01 per cent atropine.

"We are at a stage where we are sure that we have a way to treat myopia," said SNEC medical director Donald Tan, adding that the eyedrops could be available for prescription in the next six months. "This is a breakthrough in the fight against myopia here."

With 80 per cent of people afflicted by the time they turn 18, Singapore is considered the myopia capital of the world.

The eyedrops do not cure myopia, but they seem to slow down its degenerative effects by up to 60 per cent. This means that a short-sighted child, whose eyesight would normally get worse by 100 degrees a year, will only experience a 40-degree increase.

For decades, it has been known that atropine, which is extracted from certain plants, can be used to counter myopia. The drug seems to stop the eyeball from growing longer, a hallmark of myopia. But it has not been widely used because of the side-effects caused by eyedrops with 1 per cent atropine, the normal available dose.

As the drug dilates the eye's pupil, letting in more light, children needed to wear sunglasses before going out in the day. Atropine also stops the eye muscles from working, making it harder to focus on near objects.

That meant that children needed to wear bifocal eyeglasses when reading. Several other studies also found that when the use of atropine stopped, the myopia "rebounded".

The answer was eyedrops with 0.01 per cent atropine.

In an SNEC study which began in 2006, 400 short-sighted children were put on daily eyedrops with three different concentrations: 0.5 per cent, 0.1 per cent and 0.01 per cent. The children were tracked for five years.

Results showed that side-effects were minimised for the most diluted eyedrops. Children did not need sunglasses or bifocals, but could go about their daily lives as usual. There was almost no rebound effect when the eyedrops were stopped for a year.

After five years, those on the 0.01 dose also fared the best, with the least decline in their eyesight.

The findings were presented at an international conference earlier this week.

Dr Lam Pin Min, an ophthalmologist at KK Women's and Children's Hospital, said he was "certainly looking forward" to the new eyedrops.

Currently, he prescribes regular (1 per cent) atropine to several young patients. But they have to use special spectacles due to the side-effects. With price tags of $400 to $1,000, the cost of the spectacles can be "prohibitive", said the MP for Sengkang West.

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Trial to test aspirin in colon cancer treatment

Past studies suggest the generic drug reduces risk of cancer returning

By Judith Tan

A SIMPLE aspirin pill might be the answer to the growing colon cancer headache.

The effect of aspirin on the world's third most common cancer has been of much debate in the past year.

Now, cancer doctors here are to start a multi-centre clinical trial across Asia to see how effective the off-the-counter painkiller is in reducing the risk of colon cancer recurring after surgery or chemotherapy.

It will involve a three-year treatment, administered along with the standard chemotherapy as part of the Phase III trial.

Dr Toh Han Chong, who heads the medical oncology department at the National Cancer Centre Singapore (NCCS), said: "Developing any new drug for cancer is a complex and expensive undertaking. Aspirin costs a mere three cents a tablet. Imagine its impact and the number of lives we could potentially save worldwide if the trial is proven beneficial."

Dr Toh and Dr John Chia, a fellow NCCS cancer specialist, will be leading the Phase III study involving 2,660 patients with Stages 2 and 3 colon cancer. They will be recruited from hospitals and medical centres here and in China, India, Indonesia, Malaysia and the Philippines.

"We already have 19 centres in our network and many more are lined up to join the study," Dr Chia said.

A million new cases of colorectal cancer are diagnosed in the world each year. In Singapore, colorectal cancer has overtaken lung cancer as the top killing cancer among men, and it is the second most common cancer among women, after breast cancer.

About 2,000 new cases are diagnosed in Singapore each year, a rate which is among the highest in the world.

"In the past 20 years, many drugs have been evaluated in an attempt to improve the survival rate of colorectal cancer patients. Only one chemotherapy drug has shown to have done that, by only 2.5 per cent," Dr Chia said.

But in the past year, interest in aspirin was piqued with several observational studies in journals suggesting that colon cancer patients who were given aspirin had significantly less risk of the cancer returning.

"The chances were as high as 50 per cent, hence we decided to carry out the Phase III clinical trial," Dr Chia added.

Phase III studies are randomised, controlled multi-centre trials on large groups – ranging from 300 to 3,000 each.

They are definitive tests of how effective a drug is, in comparison with current standard treatment.

The study will be funded by the National Medical Research Council, SingHealth Foundation and non-profit Grameen Foundation. Proceeds from this year's Run for Hope will also be channelled to the project.

Nobel Peace Prize winner Muhammad Yunus, who is committed to affordable health care, said that if such a study proved successful, it could "save the lives of millions of colon cancer sufferers worldwide and save billions in health-care dollars".

But both Dr Toh and Dr Chia warned against patients jumping the gun and taking aspirin outside the clinical trial.

"Aspirin reduces inflammation in the blood, thinning it to allow blood to flow more easily. Taking aspirin without proper or strict medical advice or supervision can increase one's risk of bleeding," Dr Chia said.

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Study on pre-hospitalization resuscitation to improve outcome of cardiac arrest

TRIAL SPONSOR & OTHERS: STUDY BUDGET MANAGEMENT

KEY PROJECT: PAROS2

Clockwise from top left: Ms Jane Yeo (SCRI), Dr Fahad Javaid Siddiqui (SCRI), Dr Pryseley Assam (SCRI), Ms Nur Shahidah Bte Ahmad (SGH), Ms Jolyn Chuah (SCRI), A/Prof Edwin Chan (SCRI), A/Prof Marcus Ong (SGH), Dr Nurun Nisa De Souza (SCRI) and Ms Maeve Pek (SGH)

The Pan Asian Resuscitation Outcomes Study (PAROS) Phase II is a follow-up to the PAROS Phase I (2010 to early 2013). The objectives of both Studies is to increase the survival rate for Out-of-Hospital Cardiac Arrests (OHCA) in Singapore and the Asia Pacific. PAROS 2 assesses the clinical impact of a low-cost, community-level EMS intervention and looks at how EMS intervention can be widely disseminated in order to lead to significant improvement in OHCA survival rates.

SCRI's support for the contracts administration for the Study ranges from drafting to execution of contracts with both sponsors and participating EMS sites from developing countries. Besides being responsible for the mitigation of contractual and financial issues with sites and Sponsors, SCRI helps to SCRI helps to provide budget oversight and manages administratively the multiple grants received.

"SCRI has been a great help in running a multi-centre, international trial. The Study budgeting team helps to ease the burden of dealing with legal and financial issues (e.g. drafting and execution of contracts, management of grants) related to the Study, thus allowing my team and me to focus on our research work.

SCRI's expertise in the areas of statistical support, protocol design and manuscript drafting has also been critical to the PAROS network. SCRI is truly a convenient one-stop hub for the busy researcher."

Associate Professor Marcus Ong Eng Hock
Senior Consultant, Clinician Scientist and Director of Research, Department of Emergency Medicine
Director, Health Services Research and Biostatistics Unit, Division of Research and Director, Unit for Pre-hospital Emergency Care (UPEC), Singapore General Hospital
Associate Director, Health Services and Systems Research (HSSR), Duke-NUS Graduate Medical School
Senior Consultant, Ministry of Health, Hospital Services Division

Ms Jolyn Chuah
Bsc
Business Operations Associate, SCRI

Jolyn's oversight of project funds and mitigation of contractual issues with the multiple sites of the PAROS2 Study made her a critical resource for the Study. Her ability to meet the challenges of the multiple sites and Sponsors has made Jolyn a vital member in the Business Operations Team.

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Hepatobiliary Malignancies

Cost-effectiveness analysis of liver resection versus transplantation for early hepatocellular carcinoma within the Milan criteria

Kheng Choon Lim, Vivian W. Wang, Fahad J. Siddiqui, Luming Shi, Edwin S.Y. Chan, Hong Choon Oh, Say Beng Tan, Pierce K.H. Chow ✉

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Cited by: 7 articles Refresh Citing literature

Am score 3

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Regional liver cancer registry to be set up

Linette Lai

In a bid to collect more data on liver cancer, the National Cancer Centre Singapore (NCCS) has inked a deal with two partners to set up a regional cancer registry over the next few years.

This will involve monitoring some 2,000 liver cancer patients from seven to eight countries – including Singapore – and finding out which treatments work best.

Experts will also look at issues such as when patients are diagnosed, and if cost is an issue when patients choose between different forms of treatment.

The centre will work with the Singapore Clinical Research Institute (SCRI) and healthcare technology firm IMS Health Asia. They signed a memorandum of understanding on Friday at the Asia-Pacific Hepatocellular Carcinoma Trials Group Scientific Forum.

"(Liver cancer) is... very relevant to us," said Associate Professor Teoh Yee Long, chief executive of SCRI. More than 80 per cent of liver cancer cases are in the Asia-Pacific, he added. In Singapore, it is the fourth-most common cancer among men. It is also among the top five most common cancer deaths for both genders.

The first phase of the project will involve countries such as Japan, China and South Korea, and could be extended as more partners come on board.

"Even setting up a single registry in a single country is difficult, so this is a big challenge," Prof Teoh said.

The available data on liver cancer varies from country to country, said Professor Pierce Chow, a senior consultant surgeon at NCCS. The registry will help to overcome this, he said, and provide a big-picture overview of the disease and what happens to those who have it. The hope is that their findings will be able to inform government policy here and abroad.

For example, Prof Chow said, the study could find data suggesting that screening for liver cancer early – though costly – works out to be cheaper overall than picking up the disease at a late stage.

"Having this kind of information allows policy agencies to allocate their resources accordingly in a way that benefits patients the most," he said.

At Friday's forum, NCCS also signed a separate agreement with local bioanalytics firm InvitroCue.

They will be working on a study of 100 patients from at least five countries to try and better understand cancer disease patterns and how they relate to an individual person's genetic data.

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Bill and Melinda Gates Foundation

Funders for HIV, TB and Malaria clinical research

Aeras TB Vaccine Candidates in Clinical Trials *Potential Boost Vaccines*

SSI HyVac4 / AERAS-404 Status: Phase I

- Recombinant protein vaccine intended to be a booster vaccine
- Phase I clinical trials being conducted in Europe and Africa

GSK M72 Status: Phase II

- Recombinant protein vaccine intended to be a booster vaccine
- Phase I and II trials conducted in Europe, Africa and Asia, including a Phase I trial in HIV+ in Europe

AERAS-402 / Crucell Ad35 Status: Phase IIb

- Viral vectored vaccine utilizing adenovirus 35; intended to be a booster vaccine
- Phase I and II trials conducted in North America and Africa; Phase IIb recently initiated in HIV+ in S. Africa

MVA85A / AERAS-485 Status: Phase IIb

- Viral vectored vaccine utilizing modified vaccinia Ankara; intended to be a booster vaccine
- The most clinically-advanced booster vaccine for tuberculosis with an ongoing proof-of-concept Phase IIb trial in infants
- Previous clinical trials in the UK and Africa, including in HIV+
- Awarded orphan drug status by EMEA

AERAS-422 rBCG Status: Phase I

- Recombinant BCG
- Phase I conducted in the US

Conclusions

- Unlike pharmaceutical companies led clinical trials which aim to develop new drugs to a selected population, clinical trials with public health focus looks into cost-effective treatment to benefit the public

- Funding is also available from philanthropic foundations

- Sometimes pharmaceutical companies may also conduct public health focus clinical trials for products which could benefit large populations

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Thank You