INA RESPOND
INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

INA-RESPOND Secretariat

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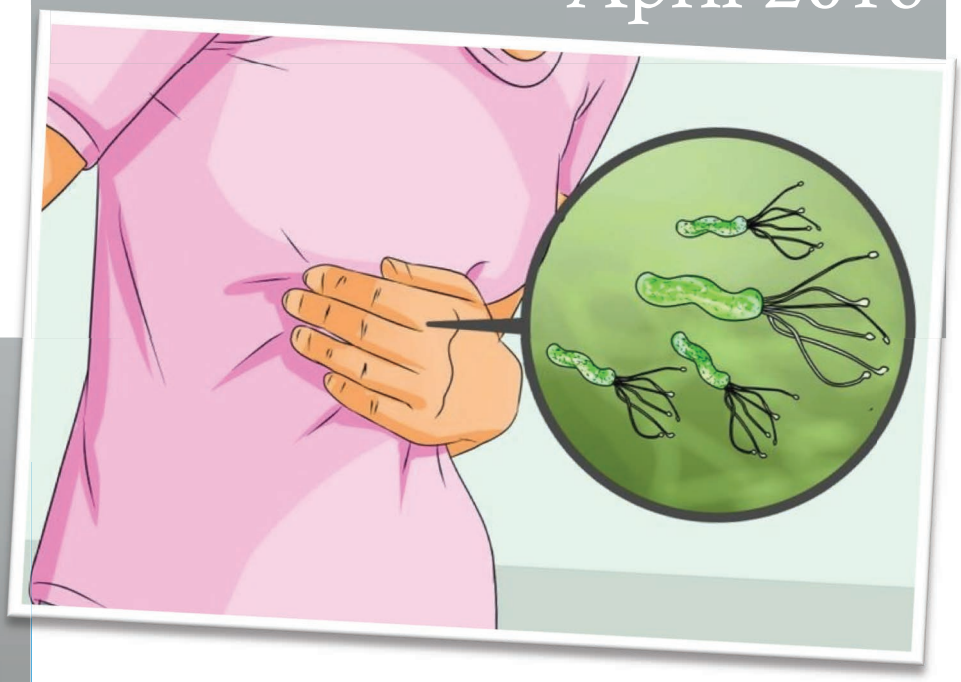
Newsletter
April 2016



In This Issue

Helicobacter Pylori, Gastritis, Ulcers, and Carcinoma

Helicobacter pylori (H. pylori) is a spiral-shaped bacterium that is found in the gastric mucous layer or adherent to the epithelial lining of the stomach. *H. pylori* causes more than 90% of duodenal ulcers and up to 80% of gastric ulcers.

Before 1982, when this bacterium was discovered, spicy food, acid, stress, and lifestyle were considered the major causes of ulcers. Since we now know that most ulcers are caused by *H. pylori*, appropriate antibiotic regimens can successfully eradicate the infection in most patients, with complete resolution of mucosal inflammation and a minimal chance for recurrence of ulcers.

Approximately two-thirds of the world's population is infected with *H. pylori*. Given this information, we should be well informed of what illnesses *H. Pylori* can cause and how we can reduce the spread of the disease using the right treatment and prevention measures. Find the information in this edition.

Page 5

The Mystery of Outlier

Do you still remember your statistics course when you were still in training to become a researcher? Know what outlier is? If you forget, find out what it is, here on

Page 4

Save The Date

We have had some important meetings since last month to talk about our network's activities and future studies.

This month, our network Steering Committee members gather once more to prepare for the audience with the Minister of Health, Republic of Indonesia.

18 April	Preparation meeting for the audience with the Minister of Health, RI @ Double Tree, Cikini
20 April	Audience with the Minister of Health, RI @R. Cut Mutia Gd. A, Kemenkes, RI

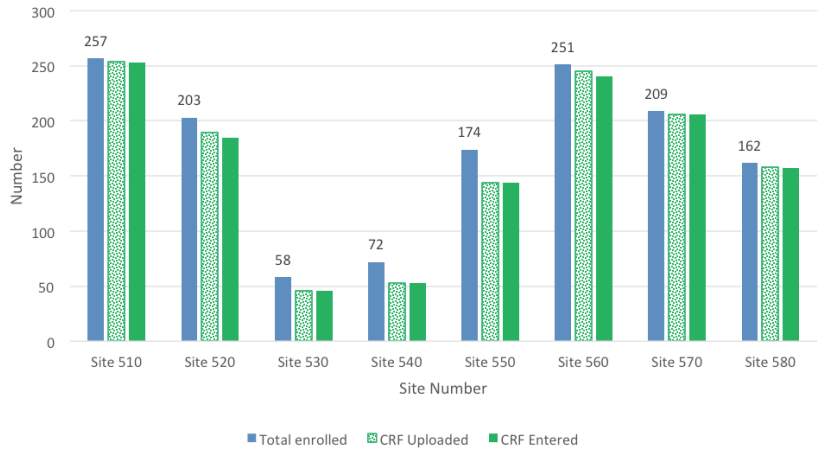
April Birthday

4 April	Ms. Hofiya Djauhari	Lab Tech Site 510
6 April	dr. Heni Kismayawati	NIHRD
13 April	dr. Haviv Muris Saputra	Research Assistant Site 570
15 April	dr. Rossa Avrina	NIHRD
20 April	dr. Annisa Rizki Afrilla	NIHRD
22 April	dr. M.M.D.E.A.H Hapsari	1st Co-PI Site 560
27 April	Prof. dr. Emiliana Tjitra	NIHRD

INA-RESPOND Study Updates

By dr. Anandika Pawitri,
dr. Nurhayati,
Ms. Novitasari

Graph 1. Enrolled Subjects and CRF Status at each site



510 – RSUP dr Hasan Sadikin, Bandung
520 – RSUP Sanglah, Denpasar
530 – RSUPN dr Cipto Mangunkusumo, Jakarta
540 – RSPI Prof Dr Sulianti Saroso, Jakarta
550 – RSUP dr Wahidin Sudirohusodo, Makassar
560 – RSUP dr Kariadi, Semarang
570 – RSUD dr Soetomo, Surabaya
580 – RSUP dr Sardjito, Yogyakarta

AFiRE Study (INA101) Updates

Up to April 3, the study has screened 4,824 patients. 1,386 subjects have been enrolled (806 adults and 580 children). The recruitment will end at the end of June 2016. We estimate the study will have recruited around 1,500 subjects by then.

The total enrollment and Case Report Form (CRF) status at each site is available in graph 1.

Detailed screening and enrollment progress is available in portal folder: Studies\INA101\Screening progress.pdf or go to the following link: https://ina-respond.s-3.com/EdmFile/getfile/797233

Sepsis Study (SEA050) Updates

There were 2 meetings last month to discuss the Sepsis study (SEA050) results. The first meeting was held on 17 March to discuss laboratory issues and research results, and the second was held on March 18, in which the results of the meeting on 17 March was brought up and further discussed with its meeting members.

On 17 March 2016, a laboratory meeting was conducted at NIHRD. Laboratory personnel from all INA-RESPOND reference laboratories were present on that day to discuss the study results. Laboratory representation are from NIHRD Center 1 and 2, *Universitas Indonesia*, Jakarta, *Universitas Padjadjaran*, Bandung, *Universitas Diponegoro*, Semarang, and *Universitas Gadjah Mada*, Yogyakarta. A valuable result was presented: there are pathogens, which never been found in hospital treatment Standard of Care (SoC), discovered by the study. This can be very prospective for future study since the pathogens are still underreported in Indonesia.

On 18 March, site PI, co-PI, and Research Assistants (RA) from all sepsis sites attended the adjudication meeting. The meeting was intended to decide final etiology diagnosis for each of the 79 subjects. There were 23 subjects with confirmed pathogen and unknown for the rest of the other subjects.

The committee is currently discussing how we are going to share our data with Thailand and Viet Nam. The country coordinator, dr Armaji Kamaludi, is keeping in contact with SEAICRN and Main PI, dr Direk, to decide this matter.

Photos of the meeting can be seen on page 11.

Mystery of Outlier

By:

dr. Aly Diana

Can you find something weird in this picture? If you can spot it easily, this article is probably not for you. However, if you have some doubts, I believe that you will benefit from spending a minute or two to continue reading this article.

Before I give you the answer. Please try to remember your statistics course a long time ago before you became an expert. Now, let's look at the explanations on standard deviation, normal distribution, and outlier. You will definitely be able to solve the mystery afterwards.

Standard deviation

Standard deviation is the most common measure of variation for numerical data in statistics. It measures how concentrated the data are around the mean. A smaller standard deviation represents that the data are distributed nearer to the mean. Looking at the mean and standard deviation of our data is very important to see how diverse our data are.

Normal distribution

Continuous random data of a population that fall into a smooth curve with a bell-shaped pattern will be said to have a normal distribution. Every normal standard distribution has certain properties: 1) the shape is symmetric; 2) the mean and median are the same and lie precisely in the middle of the distribution; 3) about 68%, 95%, and 99.7% of its values lie within 1, 2, and 3 standard deviation of the mean on both sides, respectively.

For example: If we are going to work in company X, we usually try to find out the estimation of the salary we will receive. In case the average salary/month is 6 million with standard deviation of 2 million, we can expect to get salary around 2 – 10 million (as 95% of all employees' salary lie within this amount). Looking at this statistics, it is not really informative, right? On the other hand, if the standard deviation is only 500 thousands, then you can get a better idea. The salary will lie within 5 – 7 million/month (for 95% of all employees).

Outlier

An outlier is any data point that fall very far from the average data pattern; it can be very small or very big. Most of it is caused by errors in measurement or data. Usually we define an outlier as a data which is below or above the value of 1.5 * IQR (interquartile range, the difference between the 75th percentile and the 25th percentile of the data).

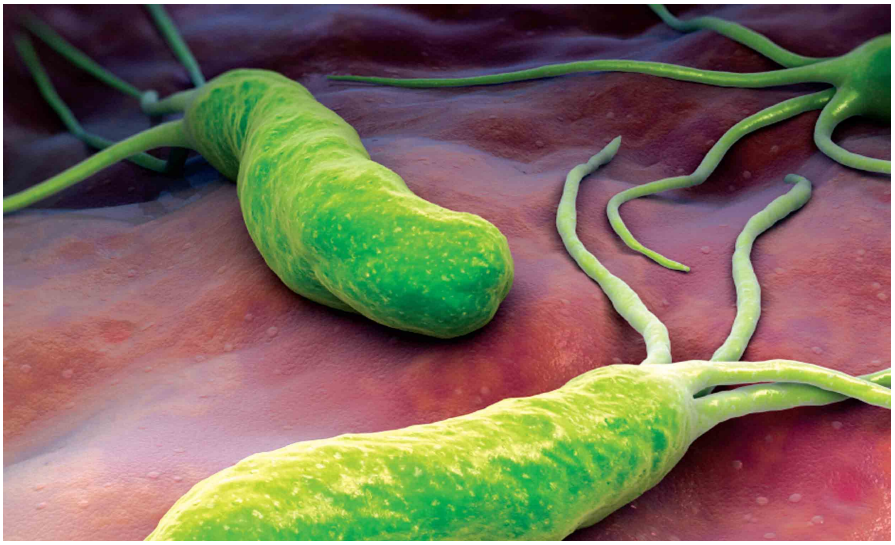
Now, let's look at Pistol Pete. If he is that notorious and lie well beyond our standard deviation, what do you think will happen to our normal distribution curve? Will the shape stay symmetric? Will the mean and median be the same and lie precisely in the middle of the distribution? Can you solve the mystery? What is your conclusion?

The possible answer: As you can guess, the answer will depend on the sampling size and how extreme the outlier is. The lesson learned: it will be better to deal with the outlier first, before we start to plot a distribution curve.

The main point: normal distribution curve and outlier should not be put together, unless it is in a comic strip.

Reference:

Field A. (2009). *Discovering Statistics Using*



Helicobacter Pylori, Gastritis, Ulcers, and Carcinoma

By
Ms. Neneng Aini

What is *Helicobacter Pylori*?

Thanks to Marshall and Warren, who in 1984 discovered *Helicobacter pylori* (*H. pylori*) and disclose its role in gastritis and peptic ulcer, the two conditions are no longer considered chronic and frequently disabling conditions, but diseases that can be permanently cured.

H. pylori is a spiral shaped, gram-negative human pathogen that successfully colonizes gastric mucosa of most people. *H. pylori* has coexisted with humans for many thousands of years. Approximately two-thirds of the world's population harbors the bacterium, with infection rates much higher in developing countries, where a combination of untreated water, high-density population, and poor hygiene contributes to higher *H. pylori* prevalence. *H. pylori* infection is usually acquired in childhood and generally persists for life. Thus, infecting the majority of the world's population for as long as they live.

H. pylori Infection and transmission

H. pylori is commonly transmitted person-to-person by saliva. The bacteria can also be spread by fecal contamination of food or water. From the mouth, *H. pylori* moves through the digestive system and infects the stomach, or the first part of the small intestine. The spiral-shaped bacterium uses its tail-like flagella to move around and burrow into the stomach lining, which causes inflammation.

To survive in the acidic environment of the stomach, *H. pylori* secretes an enzyme called urease, which converts the urea to ammonia that neutralizes the acidity of the stomach, making it more hospitable for the bacterium, but toxic to human cells.

(continued)

TAKE ACTION:

GOVERNMENT

MUST CONTINUE TO CONDUCT NATIONAL EDUCATION CAMPAIGN TO INFORM HEALTH CARE PROVIDERS AND CONSUMERS OF THE LINK BETWEEN H. PYLORI AND STOMACH AND DUODENAL ULCER.

EVERYONE

MAKES SURE TO ALWAYS WASH HANDS THOROUGHLY, TO EAT FOOD THAT HAS BEEN PROPERLY PREPARED, AND TO DRINK WATER FROM A SAFE, CLEAN SOURCE.

Depending on where the infection occurs in the stomach, *H. pylori* can also cause overproduction of stomach acid.

Most people with *H. pylori* infection will never have any signs or symptoms, but some people may be born with sensitivity to the harmful effects of *H. pylori*. When signs or symptoms occur with *H. pylori* infection, they may include: an ache or burning pain in the abdomen, which is worse when the stomach is empty; nausea; loss of appetite; frequent burping; bloating; and unintentional weight loss.

When to check for *H. pylori*

People need to seek immediate medical help if they have any experience of:

- Severe or persistent abdominal pain
- Difficulty in swallowing
- Bloody or black tarry stools
- Bloody or black vomit or vomit that looks like coffee grounds

Diagnosis of *H. pylori* Infection

There are several methods for diagnosing *H. pylori* infection: noninvasive and invasive. The invasive tests are performed on specimens obtained at endoscopy. These include biopsy urease testing, histology and bacterial culture and sensitivity. In addition, there are non-invasive tests, including urea breath testing, stool antigen testing, and serology.

H. pylori infections as a risk factor for cancer and how *H. pylori* causes stomach/ gastric cancer

In 1994, *H. pylori* was recognized as definite carcinogen by International agency for research on cancer. *H. pylori* induced gastric cancer (GC) was accountable for 5.5% of global cancer burden. Since then, it has been increasingly accepted that colonization of the stomach with *H. pylori* is an important cause of gastric cancer and of gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

Gastric cancer (GC) is one of the most common carcinomas and the second leading cause of cancer-related deaths worldwide. *Helicobacter pylori* (*H. pylori*) infection causes a series of precancerous lesions like gastritis, atrophy, intestinal metaplasia and dysplasia; and it is the strongest known risk factor for GC, as supported by epidemiological, preclinical, and clinical studies. However, the mechanism of *H. pylori* developing gastric carcinoma has not been well defined.

Among infected individuals, approximately 10% develop severe gastric lesions such as peptic ulcer disease, and 1%-3% of them progress to GC. The outcomes of *H. pylori* infection are determined by bacterial virulence, genetic polymorphism of hosts, as well as environmental factors. A high salt or a low fiber diet, exposure to *N*-nitroso compounds from diet or smoking, alcohol consumption, low socioeconomic status, high BMI, old age, and previous gastric surgery have all been linked to the increased rates of GC. The roles of environmental factors are suggested as sporadic genetic mutations are found more frequently than familial-acquired mutations (97-99%) in intestinal-type GC.

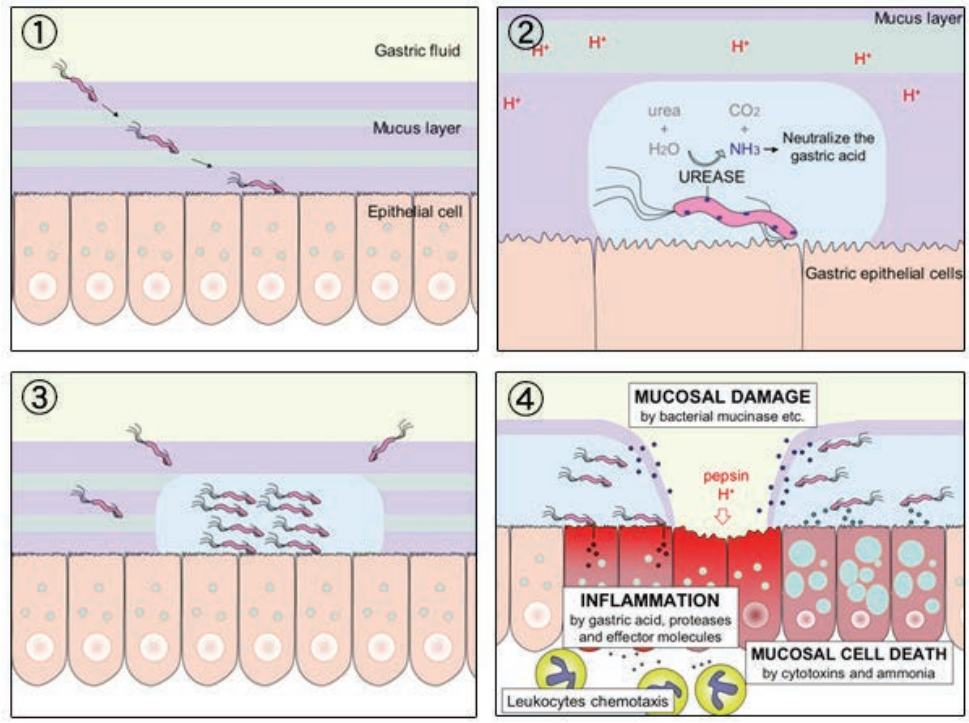


Figure 1. How H. Pylori survives the acidic environment and cause mucosal damage

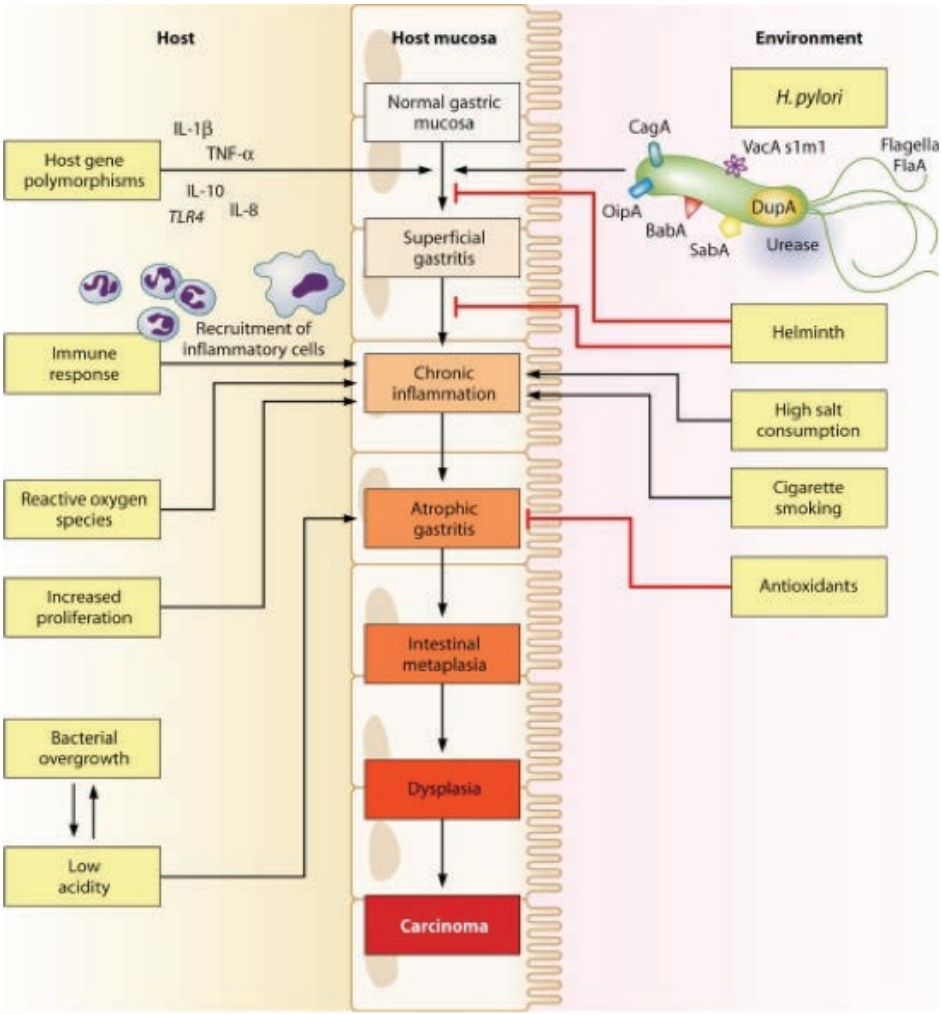


Figure 2. The process from normal gastric mucosa to carcinoma

Epidemiologic studies have shown that individuals infected with *H. pylori* have an increased risk of gastric adenocarcinoma. The risk increase appears to be restricted to non-cardia gastric cancer. For example, a 2001 combined analysis of 12 case–control studies of *H. pylori* and gastric cancer estimated that the risk of non-cardia gastric cancer was nearly six times higher for *H. pylori*-infected people than for uninfected people.

The association is stronger between *H. pylori* and gastric cancer involving the distal stomach or non-cardia, than that involving the proximal stomach or cardia. There is no information explaining why H pylori-related gastric cancer is mostly found in non-cardia cancer. Some studies have found a possible association between *H. pylori* infection and pancreatic cancer, but the evidence is conflicting.

Treatment of *H. pylori* Infection

According to several international guidelines, there are three lines of therapy that can be used in *H. pylori* eradication. The first-line therapy is a proton pump inhibitor (PPI) in combination with any of the antibiotics amoxicillin, clarithromycin or metronidazole, given for 7-14 days. However, even with these recommended regimens, failure in *H. pylori* eradication is still found in 20% of patients. The recommended second-line therapy is a quadruple regimen composed of PPI, bismuth subsalicylate, tetracycline, and metronidazole. For cases of failure from second-line therapy, European guideline recommends culture before starting the third-line treatment, and selection should be based on the microbial antibiotic sensitivity. The alternative candidates for third-line therapy are quinolones and rifabutin.

Alternative Therapies for *H. pylori* Infection

While antibiotics are the main agents used in the therapy of *H. pylori* infection, the development of resistance has limited their application. Also, administration of antibiotics perturbs the microbiota, the microorganisms that colonize the human gastrointestinal tract, and thus causes side effects, such as diarrhea. Because of this, alternative therapies, including the use of probiotics such as *Saccharomyces boulardii* (*S. boulardii*) and *Lactobacillus* strains, have been combined with antibiotics.

Photodynamic therapy has been used for the treatment of *H. pylori* infection. Photodynamic therapy (PDT) is a treatment that uses a photosensitizer or photosensitizing agent, and a particular type of light (blue light). When photosensitizers are exposed to a specific wavelength of light (300-500 nm), they produce a form of oxygen that kills nearby *H. pylori*. Blue light phototherapy may represent a novel approach to eradication of *H. pylori*, particularly, in patients

who have failed standard antibiotic treatment.

Barry Marshall (left) and Robin Warren (right)

How can *H. pylori* infection be prevented?

Different vaccine formulations with different antigens, adjuvants, and application routes have been tested. The most promising vaccine-induced immune reaction seems to be achieved by mucosal priming and a systemic boost. Recently, a reverse vaccinology approach was employed to predict the potential vaccine candidates against *H. pylori* and search novel antigens using computational methods or bioinformatics.

As stated previously, *H. pylori* is commonly transmitted person-to-person by saliva. The bacteria can also be spread by fecal contamination of food or water. To reduce the chances of infection, health care providers generally advise people to:

- ✓ Wash their hands thoroughly with soap and water after using the bathroom and before eating
- ✓ Make sure that the people who prepare food have washed and cooked the ingredients properly
- ✓ Drink water from a clean and safe source
- ✓ Maintain oral hygiene; people with poor oral hygiene have a higher prevalence of *H pylori* in dental plaque and in the stomach.
- ✓ Stop interacting (kissing) with those infected; if a family member has *H. pylori*, you should be very careful when you kiss them. Also keep their toothbrush, cups, and utensils in a different area so the bacteria cannot be transmitted through saliva.
- ✓ If a family member gets sick with positive *H. pylori* infection, other family members need to get checked as well.

Further Reading:

- Khatoon, 2016; Safavi , 2016; Zhang 2016; Ishaq, 2015; Malnick, 2014; Yang, 2014; Anderl, 2014; Ayala, 2014; Koshiol , 2012;
- http://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/h-pylori-fact-sheet
- https://publichealth.arizona.edu/outreach/health-literacy-awareness/hpylori/transmission
- http://dx.doi.org/10.3978/j.issn.2305-5839.2014.11.03

Report: IT and Data Management Infrastructure Assessment

By

Michael Holdsworth
Brian K. Moyer

On Monday, 21 March, the INA-RESPOND Secretariat office in Jakarta received two visitors from the National Institute of Allergy and Infectious Diseases, NIH, Brian K. Moyer and Michael Holdsworth.

Brian Moyer and Michael Holdsworth performed an IT and Data Management infrastructure assessment at the INA-RESPOND offices in Jakarta, Indonesia from Monday the 21st to Thursday the 24th of March. The purpose of the visit was to evaluate IT and Data Management infrastructure in relation to international standards. The word "infrastructure", as used in this context, not only refers to hardware/software systems, but also refers to staff availability, staff expertise, procedures, training, support resources and required documentation.

Both Brian and Michael are subject matter experts, in IT and clinical research data management, respectively, who work for the National Institutes of Health/National Institute of Allergy and Infectious Diseases/Office of Cyber Infrastructure and Computational Biology (NIH/NIAID/OCICB), which manages technologies for international biomedical research programs.

Brian Moyer is currently the International Deputy Program Manager. Over the past 9 years he has designed, managed, and implemented IT and data management projects for infectious diseases studies being run in multiple countries throughout Africa and Asia. He uses technology to facilitate the exchange and processing of information within the research community and to improve the quality of global public health research.

Michael Holdsworth has worked in clinical research data management for 15 years. He has specialized in implementing validated data management systems that meet regulatory requirements and adhere to international standards. Currently, Michael is a Senior Data Analyst working on various infectious diseases studies being conducted in Africa and Asia.

Increasingly, regulatory agencies are recognizing the importance of IT and database infrastructure in maintaining data integrity, data security and data privacy. The Food and Drug Administration (FDA) was one of the first regulatory agencies to publish regulations governing how electronic systems should be implemented and maintained. Other regulatory agencies have, subsequently, published similar regulations. More and more, government agencies, non-profit health organizations and private

Brian K. Moyer (Contractor)
Project Manager
International Biomedical Research Support Program (IBRSP)
Office of Cyber Infrastructure and Computational Biology (OCICB)
National Institute of Allergy and Infectious Disease (NIAID)

Michael Holdsworth (contractor)
DataFax and Data Management Support
Office of CyberInfrastructure and Computational Biology
National Institute of Allergy and Infectious Diseases, NIH

sector companies are collaborating, on mattes involving health and research. Global health, particularly infectious diseases, has become an international focus since the 1990s.

Similarly, regulatory agencies have started to work together and adopt similar regulations, with the realization that shared international standards are essential to support collaborative research. For example, Good Clinical Data Management Practices (GCDMP), which is a comprehensive manual of clinical data management standards published by the Society for Clinical Data Management (SCDM), has quickly been adopted as a global standard. GCDMP standards are now recognized and utilized in most countries of the world.

The results and recommendations of the IT/Data Management Infrastructure assessment have been published in a comprehensive report, which is still to be reviewed by senior management. As such, the specifics of the assessment/recommendations cannot be discussed in this article. However, generally, the assessors are very impressed with the expertise of the existing INA-RESPOND staff members, who have done a good job with the existing infrastructure. Certain aspects of the IT/Data Management infrastructure are missing (in the form of expertise, hardware/software systems, procedures, training, support resources and documentation).

Previously, the INA-RESPOND program relied on the services of a United States (US)-based Contract Research Organization (CRO) and, for a variety of reasons, this resulted in some of the infrastructure being held with the CRO in the US, instead of being centered locally in Jakarta with the INA-RESPOND program. Generally, the assessors believe that it would be beneficial to build up local INA-RESPOND infrastructure so that all staff expertise, hardware/software systems, procedures, training and documentation are centered with the local offices in Jakarta.

Michael Holdsworth
Brian K. Moyer

Brian K. Moyer and Michael Holdsworth with the INA-RESPOND Secretariat team.

From left to right (back): Meity Siahaan, Yayu Nuzulurrahmah, Kanti Laras, Brian K. Moyer, Anandika Pawitri, Michael Holdsworth, Antonius Pradana, Agus Noviardhi, Dedy Hidayat.

From left to right (front): Nurhayati, Neneng Aini, Herman Kosasih, Salfia Lastari, Novitasari, Yanti Triswan, Dwi Arie Pramanto

Sepsis Lab Meeting – 17 March @NIHRD

Back row (left to right):

Novitasari, Deni Pepy, Silvita, Nana, Gustiani, Armaji, Sri Fatmawati, Nurul, Ririn, Herman, Nawang, Kanti, Pat

Front row (left to right):

Hera, Ungke, Purnomo, Dewi Lokida, Andi Yasmon

Adjudication Meeting – 18 March 2016 @ Double Tree, Cikini

INA-RESPOND Newsletter

Advisors	: dr. M. Karyana, M.Kes, dr. Herman Kosasih
Art & Language	: Dedy Hidayat S, S.Kom, Dona Arlinda, MD
Columnists	: dr. Anandika Pawitri, dr. Nurhayati, Ms. Novitasari, dr. Aly Diana, Ms. Neneng Aini, Mr. Michael Holdsworth, Mr. Brian K. Moyer
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