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Newsletter

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In This Issue

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INA-RESPOND network is making its mark in the global health research communities with another release of online report in one of the BMC journals. Read about it here.

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Did you know that not getting enough sleep in one day makes you prone to infections? Read about the study conducted at University of California, inviting 164 healthy participants, aged 18 to 55 years in this edition.

World Rabies Day 2015

Rabies is a viral disease that is transmitted through the saliva or tissues from the nervous system from an infected mammal to another mammal. Since it is a zoonotic disease, it can pass between species (Bird flu and swine flu are examples of other zoonotic diseases.) Most human cases (90%) are caused by exposure from an infected dog. However bats, raccoons, skunks, foxes, and coyotes are also known to be important reservoirs of the disease.

The rabies virus attacks the central nervous system causing severely distressing neurological symptoms before causing the victim to die. Rabies is the deadliest disease on earth with a 99.9% fatality rate. Estimates suggest 3.3 billion people live with the daily risk of rabies. Best estimates are that 55,000 people die from the disease every year. Over half of the people who die are children.

In this edition, we are featuring a story of a fifteen-year-old girl who nearly died from rabies without receiving post exposure prophylaxis. How is this possible? Find out the story here.

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Steering Committee Member Profile

We are featuring our Steering Committee member, Dr. Sophia Siddiqui from the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda. Find out more about her here.

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Report: INA-RESPOND Making Its Mark in The Health Research Communities



**“Beijing Strain
Is Associated with
Resistance to First
Line Anti-TB Drugs.”**

Lisdawati et al. *BMC Infectious Diseases* (2015) 15:366
DOI 10.1186/s12879-015-1101-y

INA-RESPOND network is determined to improve the health of people in Indonesia and benefit the international community by conducting high-quality infectious disease research and disseminating its results.

The manuscript by INA-RESPOND, titled “Molecular epidemiology

study of *Mycobacterium tuberculosis* and its susceptibility to anti-tuberculosis drug in Indonesia,” in one of the BMC journals, “Infectious Diseases” has given way for the network to gain more support from researchers from various health and research institutions, national and international.

The manuscript talks about a way that can help researchers to understand the molecular epidemiology of tuberculosis and to address evolutionary questions about the disease spread and treatment. The study describes the first attempt to map the molecular epidemiology of TB in the Indonesian archipelago. The results show that drug susceptibility testing confirmed that the Beijing family of *M.tb* in Indonesia exhibited greater resistance to first line anti-TB drugs than other families.

For complete report, you can download the file at this link:
<http://www.biomedcentral.com/content/pdf/s12879-015-1101-y.pdf>
or you can visit our public website at <http://www.ina-respond.net/publication-list/>



RESEARCH ARTICLE

Open Access



Molecular epidemiology study of *Mycobacterium tuberculosis* and its susceptibility to anti-tuberculosis drugs in Indonesia

Vivi Lisdawati^{1*}, Nelly Puspandari², Lutfah Rifati², Triyani Soekarno², Melatiwati M², Syamsidar K², Lies Ratnasari³, Nur Izzatun³ and Ida Parwati³

Abstract

Background: Genotyping of *Mycobacterium tuberculosis* helps to understand the molecular epidemiology of tuberculosis and to address evolutionary questions about the disease spread. Certain genotypes also have implications for the spread of infection and treatment. Indonesia is a very diverse country with a population with multiple ethnicities and cultures and a history of many trade and tourism routes. This study describes the first attempt to map the molecular epidemiology of TB in the Indonesian archipelago.

Method: From 2008 to 2011, 404 clinical specimens from sputum-smear (SS+) TB patients, age ≥ 15 years, were collected from 16 TB referral primary health centers (PHC) in 16 provincial capitals in Indonesia. Susceptibility testing to first line drugs was conducted for 262 samples using the agar proportion method as per WHO guidelines. Spoligotyping was done on all samples.

Results: Ninety-three of the 404 samples (23 %) were from the Beijing family, making it the predominant family in the country. However, the geographic distribution of the family varied by region with 86/294 (29.3 %) in the western region, 6/72 (8.3 %) in the central region, and 2/72 (2.8 %) in the eastern region ($p < 0.001$). The predominant genotype in the central and eastern regions was from the East-African-Indian (EAI) family, comprising 15.3 % (11/72), and 26.3 % (10/38) of the isolates, respectively. Drug susceptibility to first-line anti-TB drugs was tested in 262 isolates. 162 (61.8 %) isolates were susceptible to all TB drugs, 70 (26.7 %) were mono-resistant 16 (6.1 %) were poly-resistant, and 14 (5.4 %) were multi-drug resistant (MDR). The proportion of Beijing family isolates in the susceptible, mono-resistant, poly-resistant, and MDR groups was 33/162 (20.4 %), 28/70 (40.0 %), 6/16 (37.5 %), and 3/14 (21.4 %), respectively. Overall, resistance of the Beijing family isolates to any of the first line TB drugs was significantly higher than non-Beijing families [37/71 (52.1 %) vs. 63/191 (33.0 %) (p -value = 0.003)].

Conclusion: The distribution of *Mycobacterium tuberculosis* genotypes in Indonesia showed high genetic diversity and tended to vary by geographic regions. Drug susceptibility testing confirmed that the Beijing family of *M.tb* in Indonesia exhibited greater resistance to first line anti-TB drugs than did other families.

Profile: Insight to The Network's Steering Committee Members

If you have been invited to one of the network's Steering Committee meetings, you probably have had the pleasure of meeting this wonderful, energetic woman. Yes, we are talking about one of our Steering Committee members, Dr. Sophia Siddiqui.

A week ago, we made a request to Dr. Sophia to submit her profile. Seeing that she is a very busy woman with limited free time, we were not sure that we would get positive feedback from her. Imagine how excited we were when we received confirmation from her the following day!

Dr. Sophia Siddiqui was born and raised in Lahore, Pakistan. She graduated from the Allama Iqbal Medical College, University of the Punjab, Lahore in 1995. After completing her residency in Internal Medicine at the Illinois Masonic Medical Center in Chicago, Illinois, she was appointed and served as a Chief Resident before moving to Maryland to pursue a fellowship in Infectious Diseases at the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda in 2002.

During her fellowship she worked in the Laboratory of Immunoregulation, NIAID under Dr. Clifford Lane and was involved with research in HIV and Tuberculosis co-infection. It was during this time that she began

working in Mali, West Africa. The project was focused on research related to the immunology of HIV and Tuberculosis co-infection and developing research capacity in the context of clinical research.

During her fellowship she also completed her Masters in Public Health with a certification in International Health Policy and Finance from the Johns Hopkins University.

After completing her fellowship, she joined the Collaborative Clinical Research Branch (CCRB) in the Division of Clinical Research (DCR) in 2007 as a Medical Officer. The branch was engaged in multiple international collaborative projects including Mali, and this allowed her to continue her affiliation with the project.

"Collaborations in health research are a unique opportunity to appreciate the challenges we face as a global community and to find ways in which we can work together to address them."

Sophia Siddiqui, MD, MPH
Deputy Branch Chief,
Collaborative Clinical research Branch,
Division of Clinical Research, NIAID, NIH

Initially a Principal Investigator she eventually served as the DCR, Team Lead for the project until 2013.

In 2011 she became involved with the INA-RESPOND network and has been an active member of the Steering Committee of the network.

Dr. Siddiqui has a strong interest in international research. She feels that her work is a cross section of research and health diplomacy. The most rewarding aspect is finding ways of integrating sustainable capacity building while facilitating research that meets the needs and priorities of all partners.

She finds her work with INA-RESPOND very meaningful. The progress made in a short 5 years has been very impressive. Particularly inspiring is the dedication and commitment of the Indonesian researchers, steering committee members, and the secretariat staff.

Sophia Siddiqui, MD, MPH





Site Visit to RSUP, Dr. Kariadi,
Semarang



Meeting with Site team @ RSUP Dr.
Kariadi, Semarang



From left to right: dr. Venty, dr. Retna,
dr. Ena, dr. Dewi Lokida, Ms. Kanti L.,
dr. Annisa.

Save the Date



1 Oct *

Teleconference with DSMB
Members

21 – 22 Oct

Riketsia & Dual Infections
Meeting @Jakarta

30 Oct

HIV Meeting @Makassar

9 – 10 Nov

INA-RESPOND Network
Steering Committee
Meeting @Jakarta

*Tentative

September Birthday

5 Sept	Drg. Tince	NIHRD
7 Sept	Ms. Ennycke Sary, S.Si	LT INA101 Site 550
10 Sept	Dr. Herman Kosasih	Secretariat
14 Sept	Ms. Ernawati	LT INA101 Site 510
17 Sept	Dr. Anis Karuniawati, SpMK, PhD	Co-PI INA101 Site 530
19 Sept	Dr. Fatmawati Ahmad	RA INA101 Site 550
	Dr. Munawir	RA INA101 Site 550
26 Sept	Ms. Tugur Ariyani, S.Si, DMM, MM	LT INA102 Site 590
	Ms. Kanti Laras, S.Si, M.Kes	Secretariat
28 Sept	Ms. Sri Hariastuti	LT INA101 Site 570



Rabies Patient Lives to Tell The Tale

By
Anandika Pawitri

What chance does a person have if he/she is too late to receive post exposure prophylaxis?

The story

Have you often heard stories of people who got bitten by rabid animal and lived to tell the story? Tens of thousands of people die each year from rabies. Once symptoms appear, it nearly always results in death. Here is the story of a fifteen-year-old girl who nearly died from rabies without receiving post exposure prophylaxis, making her the first person to survive rabies without being vaccinated. The million-dollar question is how did this girl survive?

One day in September 2004, Jeanna Giese picked up a bat outside her church in her hometown of Fond du Lac, Wisconsin without knowing that it was a rabid bat, and it bit her! Her parents cleaned the superficial wound, but they did not believe it was necessary to seek further medical treatment. It was a small bite, and they never thought of rabies. In the first three weeks, Giese displayed signs of rabies – fatigue, double vision, vomiting and tingling in her left arm. By that time, it was already too late for her to get the anti-rabies vaccine cocktail. Before we go on, let's talk the nature of this disease.

The Nature of Rabies

Rabies is a preventable viral disease of mammals most often transmitted through the bite of a rabid animal. Once it enters the body, the rabies virus multiplies before spreading into nerve endings. It then travels to the spinal cord and brain. Once the virus is in the central nervous system, it multiplies rapidly and spreads to the salivary glands, lungs, kidneys and other organs. All mammals, including monkeys, can carry the rabies virus, but the following species are more commonly infected: dogs, bats,

(continued)

TAKE ACTION:

PROVIDERS

Expand the application of existing technologies that could help more people at risk of rabies

FAMILIES

Protect your family by vaccinating your pets against rabies

EVERYONE

Recognize the signs and symptoms of rabies. Get yourself treated when exposed.

Protect us

Make sure we're
vaccinated against rabies



raccoons, foxes, jackals, cats, and mongooses.

Unfortunately, rabies can only be diagnosed once you have developed the disease and get the symptoms. Symptoms in humans can include: fever, hydrophobia, photophobia, aerophobia, confusion, or aggressive behavior. Rabies kills by compromising the brain's ability to regulate breathing, salivation and heartbeat. Ultimately, victims drown in their own spit or blood, and cannot breathe because of muscle spasms in their diaphragms.

Rabies is 100 percent preventable with vaccinations if patients receive them before the onset of symptoms. For people who have never been vaccinated against rabies previously, post exposure anti-rabies vaccination should always include administration of both passive antibody and vaccine. The combination of human rabies immune globulin (HRIG) and vaccine is recommended for both bite and non-bite exposures, regardless of the interval between exposure and initiation of treatment. People who have been previously vaccinated or are receiving pre exposure vaccination for rabies should receive only vaccine.

Rabies has an **incubation period of two weeks to three months** and **kills within a week** of the symptoms showing up.

The Story - Continued

When Giese arrived at the hospital, she was critically ill. She could not talk, sit or stand, and fell in and out of consciousness. Intubation was performed to help her breathe. The doctor even said that she looked as if she might die within the day. Instead of giving her up to the angel of death, an alternative technique by Rodney Willoughby, Giese's doctor, kept her alive. The doctor decided to "shut the brain down" by inducing a coma to give her own immune system time to build up antibodies against the virus. To add the element of surprise, this was the first time the therapy was attempted; doctors had no clue if it would work, and if it did, whether it would leave her brain damaged. Besides inducing coma, antivirals ribavirin and amantadine were administered. They tapered off the anesthetics after about a week, when the lab result showed Giese's immune system won the battle against the virus. After about six months she woke up from the coma, physicians also gave her a compound called tetrahydrobiopterin that is chemically similar to the B-complex vitamin folic acid, which may have improved her speech and ability to eat. Since then the treatment become known as Milwaukee protocol.

Remarkably, Giese survived. She recovered most of her cognitive functions within a few months, and other skills within a year. There are lingering signs of her illness: Giese,

once an avid athlete, says she now lists to one side when she runs and walks and no longer plays volleyball, basketball, and softball as she once did. She also speaks more slowly and sometimes not as clearly as before her illness, but Willoughby says these effects may fade over time.

Take-away Message

Rabies has an incubation period of two weeks to three months and kills within a week of the symptoms showing up. The vaccine series and other immune therapies are useless at this point and may even speed up and increase the severity of the symptoms. Usually, patients are made as comfortable as possible in the hospital or, in countries without sophisticated health care, sent home to die an agonizing death.

The Milwaukee protocol, although it remains controversial, if the technique is modified and enhanced, it might bring life to rabies victim.

Reference:

1. Jordan Lite (2008-10-08). "Medical Mystery: Only One Person Has Survived Rabies without Vaccine--But How?". Scientific American.
2. Johnson, Mark; Kwanza Newson (2006-05-11). "Hoping again for a miracle". Milwaukee Journal Sentinel.
3. Willoughby, RE; Tieves, KS; Hoffman, GM; Ghanayem, NS; Amie-Lefond, CM; Schwabe, MJ; Chusid, MJ; Rupprecht, CE (June 2005). "Survival after treatment of rabies with induction of coma" (PDF). *New England Journal of Medicine* **352** (24): 2508–14.
4. www.nhs.uk

Latest News: A Glance of Research Progress in the World



The use of whole genome sequencing (WGS) of *Mycobacterium tuberculosis*

As a result of new technologies, now DNA sequence of the whole bacterial genome can be determined fast at approximately US \$500. This technique, which is known as WGS, has commonly been used to investigate pathogenic bacteria, including *Mycobacterium tuberculosis* (*Mtb*). A review to evaluate the clinical value of WGS of *Mtb* has been published at the Lancet Infect Dis 2015 ([http://dx.doi.org/10.1016/S1473-3099\(15\)00071-7](http://dx.doi.org/10.1016/S1473-3099(15)00071-7)).

Several of them are:

1) To distinguish treatment failure from re-infection with a new strain, by comparing the isolates before and after treatment. In the relapse cases, the recurrent strains differed from the initial isolates by only a few nucleotides or single nucleotide polymorphisms (SNP) whereas strains from re-infections differed by at least 1306 SNPs from the initial isolates.

2) To trace the transmission by delineating the order of nucleotide changes. WGS can identify SNP differences in strains that were classed as identical by traditional strain-typing techniques. Figure below shows the evolution of nucleotide changes during a Dutch outbreak.

3) To better understand the molecular epidemiology of geographically diverse strains by analyzing SNP differences and deletions in the genomes. Based on that, human strains are divided into several lineages, lineage 1 (Indo-Oceanic), lineage 2 (East Asia), including the Beijing family,

lineage 3 (India and East Africa), lineage 4 (Euro-American), lineage 5-7 (Africa and Ethiopia), lineage 8 (animal) strains.

4) To determine resistance conferring mutations by identifying mutations in a single strain before and after

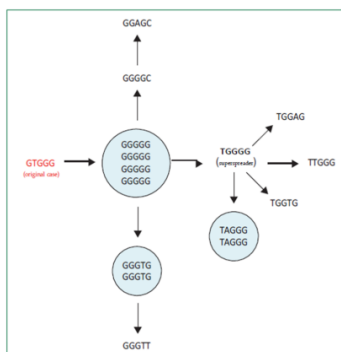
the development of resistance, and to have a better understanding on the occurrence of resistance inconsistency such as strains with identical mutations have varying levels of resistance, some resistance strains are not transmitted while others cause large outbreaks, or no known mutations associated with resistance in some strains that are resistant to an antibiotic. Sequencing resistant strains are very important to analyze the active compound during drug discovery.

Despite all the benefits described above, WGS is still not able to explain several issues, for example, the differences in transmissibility between strains or why some strains tend to be more virulent or more prone to the development of multidrug resistance.

Sleeping Well Keeps Infections Away

If you only sleep less than 6 hours at night, please try to add more, because a recent study demonstrates that statistically short sleep may be associated with an increased risk of infection, regardless of age, stress levels, race, education, body mass index, or smoking habit. This study was conducted at the University of California, inviting 164 healthy participants, aged 18 to 55 years. These people were given nasal drops that contained an infectious dose of rhinovirus (RV) 39 and then quarantined and monitored for 5 days. Sleep duration and continuity were measured for 7 consecutive night using wrist actigraphy devices and self-reported sleep diaries, whereas RV infection was assessed by culturing the daily nasal samples. Approximately 75% of the participants were infected, and 29.3% were both infected and sick. The illness was associated with shorter of sleep duration. The odds ratios among those who slept between 6-7 hours, 5-6 hours and <5 hours, compared to those who slept >7 hours were 1.66, 95% CI 0.40-6.95; 4.24, 95% CI 1.08-16.71; and 4.50; 95% CI 1.08-18.69 respectively. The results of this study suggest that sleep is critical to our well-being.

Further reading: Prather AA, et al. Behaviorally Assessed Sleep and Susceptibility to the Common Cold. *Sleep*. 2015;



Tracing single nucleotide polymorphism changes from genomic sequencing data to infer transmission routes in a hypothetical outbreak

INA-RESPOND Study Updates

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



AFire Study (INA101) Updates

Up to 6 September, sites had screened 3,812 patients and enrolled 1,119 subjects (641 adults and 478 children). See chart for detailed information on the enrollment.

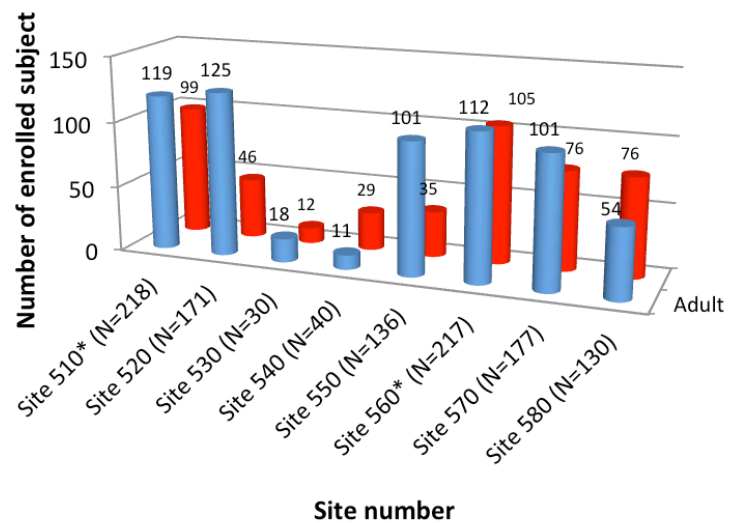
Currently, the top recruiters are still held by site 510 (RSUP. Dr. Hasan Sadikin, Bandung) and site 560 (RSUP. Dr. Kariadi, Semarang)

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>

For further information about this study please go to: <http://www.ina-respond.net/afire-study/>

Enrollment Progress per site



*510 – RSUP dr Hasan Sadikin
520 – RSUP Sanglah
530 – RSUPN dr Cipto Mangunkusumo
540 – RSPI Prof Dr Sulianti Saroso
550 – RSUP dr Wahidin Sudirohusodo

560 – RSUP dr Kariadi
570 – RSUD dr Soetomo
580 – RSUP dr Sardjito

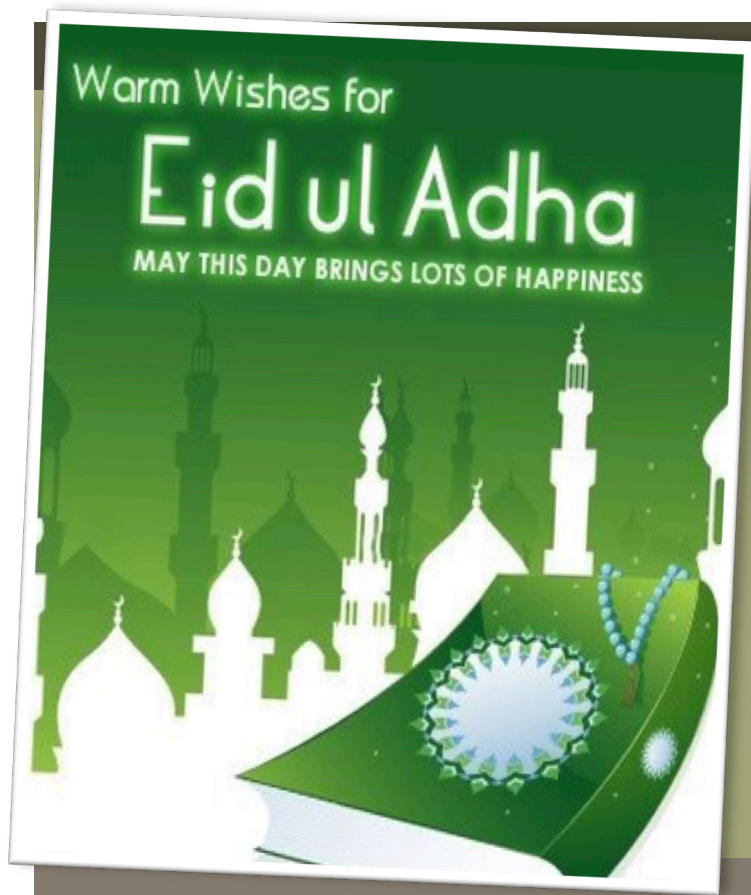
Sepsis Study (SEA050) Updates

Viet Nam and Thailand, the 2 other countries participating in this study, will stop enrollment in November 2015. Indonesia is currently enrolling as many subjects as possible before the end of the enrollment period, December 2015.

PCR RNA 16s optimization and validation testing is currently being performed in Tangerang Hospital. The results are satisfactory. We are expecting them to finish in 1-2 months

**Screening and Enrollment Progress
up to 8 September 2015**

	Site 41 – RS dr. Cipto Mangunkusumo	Site 42 – RS dr. Wahidin Sudirohusodo	Site 43 – RS Sardjito
Number of Screened Patients	Adult : 18 Pediatric : 5 Total : 23	Adult : 39 Pediatric : 25 Total : 64	Adult : 113 Pediatric : 83 Total : 196
Number of Enrolled Patients	Adult : 4 Pediatric : 0 Total : 4	Adult : 10 Pediatric : 3 Total : 131	Adult : 15 Pediatric : 5 Total : 20
Enrollment Expectation	Adult : 15 Pediatric : 15	Adult : 25 Pediatric : 25	Adult : 20 Pediatric : 20
Number of days after enrollment	Day 33 (activation date: 6 August 2015)	Day 194 (activation date: 26 February 2015)	Day 138 (activation date: 23 April 2015)



SELAMAT HARI RAYA IDUL ADHA 2015

*Semangat dalam berkorban,
untaian harapan untuk ampunan,
dan keteguhan dalam beriman,
itulah makna Idul Adha.*

INA-RESPOND Newsletter

Advisors

Art & Language

Columnists

Thanks to

Disclaimer

: dr. M. Karyana, dr. Herman Kosasih

: Dedy Hidayat S, S.Kom

: dr. Anandika Pawitri, dr. Nurhayati,
Ms. Novitasari, dr. Sophia Siddiqui

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