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INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

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Newsletter

TRIPOD, PROACTIVE, & ORCHID Study Updates

By: Eka Windari R., I Wayan Adi Pranata, Lois E. Bang, Melinda Setiyaningrum, Nur Latifa Hanum, Retna Mustika Indah, Riza Danu Dewantara

STUDY UPDATES

INA102

After the site closure in November, the TRIPOD team is finalizing the study report for NIHRD. Meanwhile, 2 manuscripts from baseline data are still being reviewed by the TRIPOD team and the US team. We are analyzing clinical and laboratory data for the 3rd manuscript on clinical TB and preparing concept plans to utilize specimens for further sub-studies.

Other ongoing activities regarding TRIPOD are summarized below:

1. Fifty-Two isolates sent to BSL 3 Facility, Central Lab Padjajaran University, Bandung for sub-cultured has grown, 3 isolates did not grow. The 49 isolates were extracted (DNA) and 32 isolates were done (DST). The next 30 isolates for subculture are in process.
2. Collaboration within the RePORT network on Epidemiology of TB Progression and Outcomes Study, using the TRIPOD data
3. Manuscripts writing: TRIPOD 1st manuscript will be finalized after getting feedback from the US author. 2nd manuscript that discusses the Performance comparison of AFB microscopy and Xpert compared to AFB culture is being prepared by the Manuscript writing team. The Author of 2nd manuscript has been confirmed from all sites.
4. Working on TRIPOD sub-study, using specimens from baseline to diagnose histoplasmosis.
5. Inviting the network to submit the Ideas on TRIPOD specimens used. Per protocol, there are 8 types of specimens collected on TRIPOD study for future use. Status for Repository specimens is provided in figure 1.

Site	Specimen Type	Whole blood (EDTA) - DNA	Whole blood (Heparin) - PBMCs	Whole blood (Heparin) – Plasma	Whole blood (PAXgene) - RNA	Urine	Saliva	Sputum	MTB Isolate
520 (n=32)	BL (32)	90	22	91	27	125	62	19	36
	M1 (24)	NA	18	64	21	99	NA	16	12
	M2 (24)	NA	22	68	24	93	NA	11	0
	EOT (15)	NA	28	45	15	60	30	2	0
560 (n=108)	BL (108)	382	204	328	102	440	216	131	272
	M1 (95)	NA	188	285	94	381	NA	107	60
	M2 (87)	NA	172	261	86	348	NA	91	20
	EOT (73)	NA	142	219	73	292	146	75	20
570 (n=128)	BL (128)	438	177	380	121	519	254	119	196
	M1 (104)	NA	162	311	103	416	NA	43	92
	M2 (97)	NA	162	294	98	392	NA	22	38
	EOT (80)	NA	162	243	81	320	160	4	12
580 (n=83)	BL (83)	235	130	210	67	308	147	26	42
	M1 (44)	NA	70	102	38	156	NA	18	6
	M2 (38)	NA	54	81	36	148	NA	16	0
	EOT (29)	NA	50	71	27	124	61	8	0
590 (n=89)	BL (89)	340	170	255	84	344	147	78	55
	M1 (59)	NA	98	147	49	196	NA	17	8
	M2 (56)	NA	80	120	41	164	NA	8	0
	EOT (40)	NA	46	72	24	96	46	9	0
600 (n=25)	BL (25)	100	50	75	25	100	50	50	30
	M1 (13)	NA	26	39	13	52	NA	26	4
	M2 (11)	NA	22	33	11	44	NA	22	4
	EOT (9)	NA	20	30	10	40	20	20	0
550 (n=25)	BL (25)	95	48	72	24	100	51	10	27
	M1 (20)	NA	36	54	19	68	NA	7	7
	M2 (20)	NA	36	54	17	72	NA	6	4
	EOT (15)	NA	26	39	13	52	25	0	2

INA104

Per 7 January 2022, from the 4,336 subjects enrolled, 1,356 subjects had ended their study due to these reasons: 1,028 subjects completed the study, 194 subjects died, 27 subjects moved away to a city where no PROACTIVE site is available, 30 subjects withdrew, 72 subjects were lost to follow up, and five subjects had negative HIV test result. The list of participants' end-of-study status based on all sites is shown in Table 1.

Table 1. List of participants' end of study status based on all sites

No	Site	*End of Study Duration*	Withdrew Consent	Participants with HIV negative	Moved	Death	Investigator Discretion	Lost to Follow Up	Total
1.	510 – RSUP Dr. Hasan Sadikin	1	1	0	2	4	0	0	8
2.	520 - RSUP Sanglah	1	0	0	0	1	0	0	2
3.	530 – RSUPN Dr. Cipto Mangunkusumo	135	0	0	0	17	0	4	156
4.	540 – RSPI Dr. Sulianti Saroso	0	0	0	2	5	0	0	7
5.	550 – RSUP Dr. Wahidin Sudirohusodo	118	0	0	5	18	0	30	171
6.	560 – RSUP Dr. Kariadi	60	1	3	0	11	0	1	76
7.	570 – RSUD Dr. Soetomo	128	13	0	3	19	0	5	168
8.	580 – RSUP Dr. Sardjito	20	0	0	3	4	0	0	27
9.	590 – RSUP Persahabatan	69	0	1	0	34	0	3	107
10.	600 – RSUP Dr. H. Adam Malik	126	3	0	2	20	0	19	170
11.	610 – RSU Kabupaten Tangerang	138	6	0	3	19	0	8	174
12.	630 – RSUD Dr. M. Ansari Saleh	89	1	0	1	7	0	2	100
13.	640 – RS St. Carolus	62	0	0	0	1	0	0	63
14.	650 – RSU Budi Kemuliaan Batam	65	3	0	5	8	0	0	81
15.	660 – RSU A. Wahab Sjahranie	16	0	0	2	4	0	0	22
16.	670 – RSUD Zainoel Abidin	0	0	0	0	11	0	0	11
17.	680 – RSUD Soedarso	0	0	0	0	10	0	0	10
18.	690 – RSUD Abepura	0	1	1	1	6	0	0	9
19.	700 – RSUD TC Hillers	0	1	0	0	11	0	0	12
Total		1028	30	5	29	210	0	72	1374

During December 2021, below SMV was conducted on:

- 15-16 December 2021, 5th onsite monitoring visit in site 680 Yos Sudarso Hospital, West Kalimantan.
- 29-30 Nov 2021 and 1 Dec 2021, 4th onsite monitoring visit in site 510 Hasan Sadikin, Bandung
- 15 Dec 2021, 3rd remote monitoring visit for site 700, dr. TC Hiller, Maumere, NTT

INA107 PARTICIPANT STATUS

Based on uploaded CRFs as of 6 January 2022, 153 participants were enrolled in the ORCHID-COVID-19 study, which consisted of 105 participants from site 610 (RSU Kabupaten Tangerang, Tangerang) and 48 participants from site 521 (RS Universitas Udayana, Denpasar). There were 146 participants (95%) who already completed this study, 2 participants passed away during the study caused by COVID-19 (in site 610) and suspect pulmonary thromboembolism (in site 521), and 5 participants decided not to continue the study categorized as other (figure 1).

Up to 6 January 2022, a total of 132 participants (86%) were identified as positive COVID-19, and only 21 participants (14%) identified as negative COVID-19. In site 610, the number of participants identified as positive COVID-19 was 95 participants (90%) and 10 participants (10%) as negative COVID-19. While in site 521, there were 37 participants (77%) identified as positive COVID-19, and 11 participants (23%) identified as negative COVID-19 (figure 2).

In site 521, SARS-CoV-2 was identified in 32 participants (67%) based on pathogen identification data. SARS-CoV-2 and influenza B (confirmed by RDT Antigen Influenza) co-infections were identified in 5 participants (10%). Influenza B infection (confirmed by RDT Antigen Influenza) was identified in 2 participants (4%). Dengue (confirmed by RDT Dengue NS-1) was also identified in 1 participant (2%). While in site 610, SARS-CoV-2 was identified in 94 participants (90%). SARS-CoV-2 and dengue (confirmed by RDT Dengue NS-1) co-infection were identified in 1 participant (1%). The pathogen cannot be identified within 18 participants (12%): 8 in Site 521 and 10 in site 610 (figure 3).

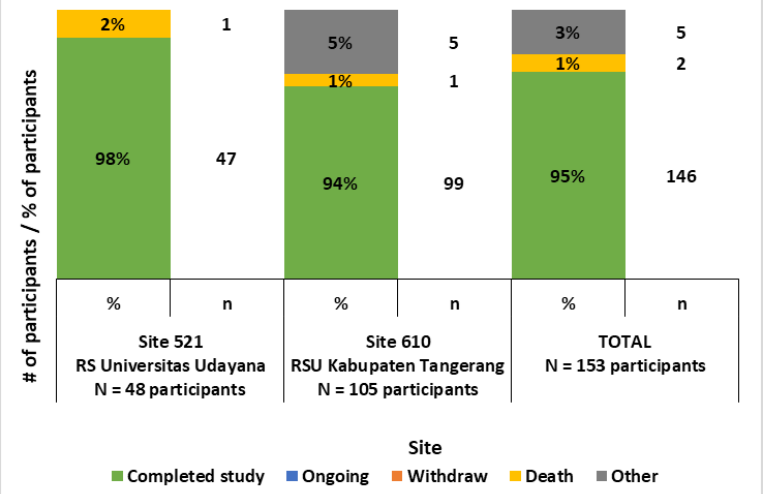


Figure 1. Participant status per site based on uploaded CRF as of 6 Jan 2022

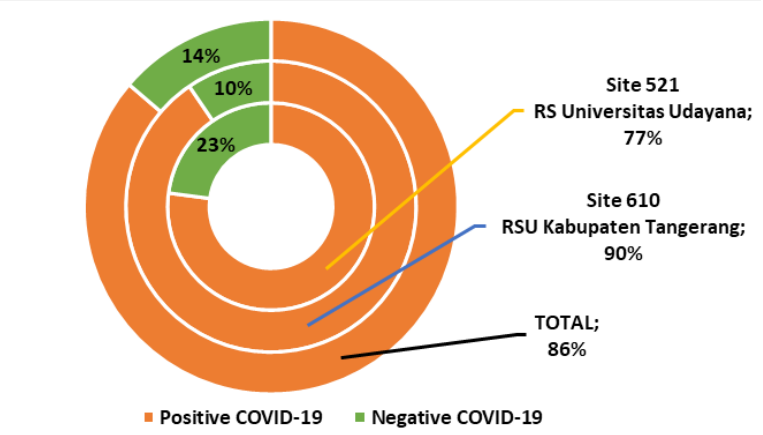


Figure 2. COVID-19 identification at enrolment based on uploaded CRF per 6 Jan 2022

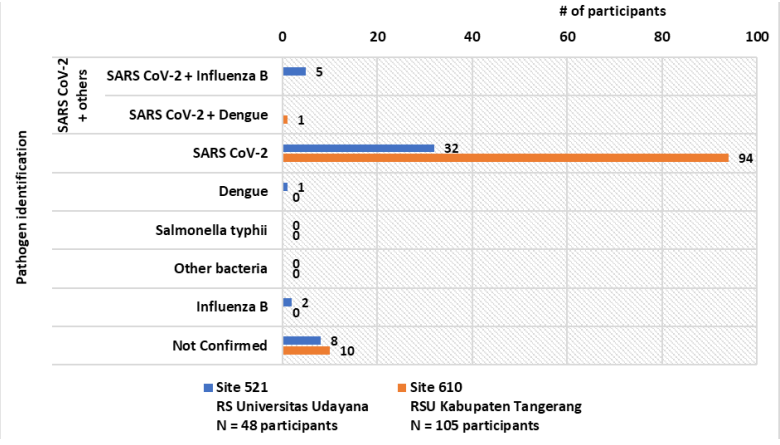


Figure 3. Pathogen identification based on uploaded CRF per 6 January 2022

INA-RESPOND Newsletter

SCIENCE CORNER

POTENTIAL ZOONOTIC BAT-BORNE DISEASE IN INDONESIA (PART 1)

By: Yan Mardian

Over the past 50 years, several viruses, including Ebola virus, Marburg virus, Nipah virus, Hendra virus, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory coronavirus (MERS-CoV), and SARS-CoV-2, have been linked back to various bat species. Bats, order Chiroptera, are the only mammals capable of powered flight and are among the most ancient of mammals and underwent extensive speciation for the last 100 million years. There are currently more than 1000 species of bats, making them the second most diverse mammalian group, after rodents, and representing 20% of extant mammalian species. It is increasingly accepted that bats are important reservoirs of many known and unknown viruses, many of which could spill over into animal and human populations, including RNA viruses such as Marburg virus, Hendra virus, Sosuga virus, and Nipah virus (1,2). Bats are reported to possess efficient and varied antiviral responses associated with adaptations in their immune system and their ability to evolve. The adaptive immune mechanism in bats can suppress the pathological effects of the inflammation caused by viral infection. However, various factors, such as stress, may contribute to unbalancing the mechanism, resulting in increased viral replication and shedding and potentially becoming a source of cross-species virus transmission, including human transmission (3,4).

In addition to direct isolation of these human pathogens from bats, accumulating evidence suggests that other emerging viruses, such as Ebola viruses, severe acute respiratory syndrome coronavirus (SARS-CoV), SARS-CoV-2, and Middle East respiratory coronavirus (MERS-CoV), also originated in bats, even if other hosts, such as civets for SARS-CoV and camels for MERS-CoV, are proximate reservoirs for human infection. A growing list of emergent coronaviruses, including the Swine acute diarrhea syndrome coronavirus, which emerged from horseshoe bats and killed >20,000 pigs, and the ongoing COVID-19 pandemic, further underscores the ongoing threat of bat-borne viral emergence (1,5). The rate of emergence of novel viruses appears to be increasing due to both increased spillover from their natural reservoirs and our improved ability in detection. To date, thousands of new bat-associated viral species have been discovered from at least 28 diverse viral families, the vast majority of which are likely host specific with limited zoonotic potential. Some bat-associated viral families, such as coronaviruses, henipaviruses, lyssaviruses, and filoviruses, are diverse and of great public and veterinary health concern because of their rapid evolutionary rate, pathogenicity in human or other hosts, and proven ability to emerge. Of note, large parts of the bat virus diversity remain uncharacterized, and discovery efforts have prioritized virus families with known zoonotic potential, such as the Coronaviridae (2).

The recognition of the role of bats in viral epidemics presents the risk of bats being responsible for them and thus of considering their eradication as a solution to the risk of infection. This reaction, which is unfortunately intuitive, would prove to be totally inappropriate and even prejudicial to human health. It has al-

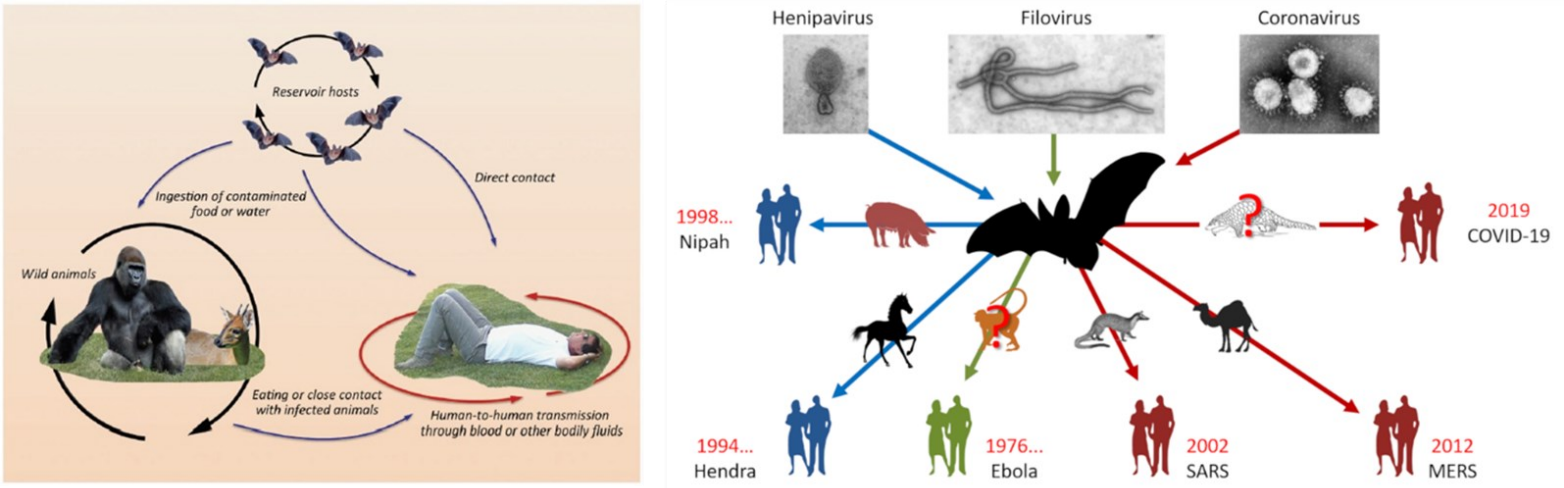


Figure 1. Schematic representation of virus transmission. Bats are the potential source of the virus. Infected bats can directly or through intermediate hosts spread the infection to humans. Human-to-human transmission can then result in epidemics (5)

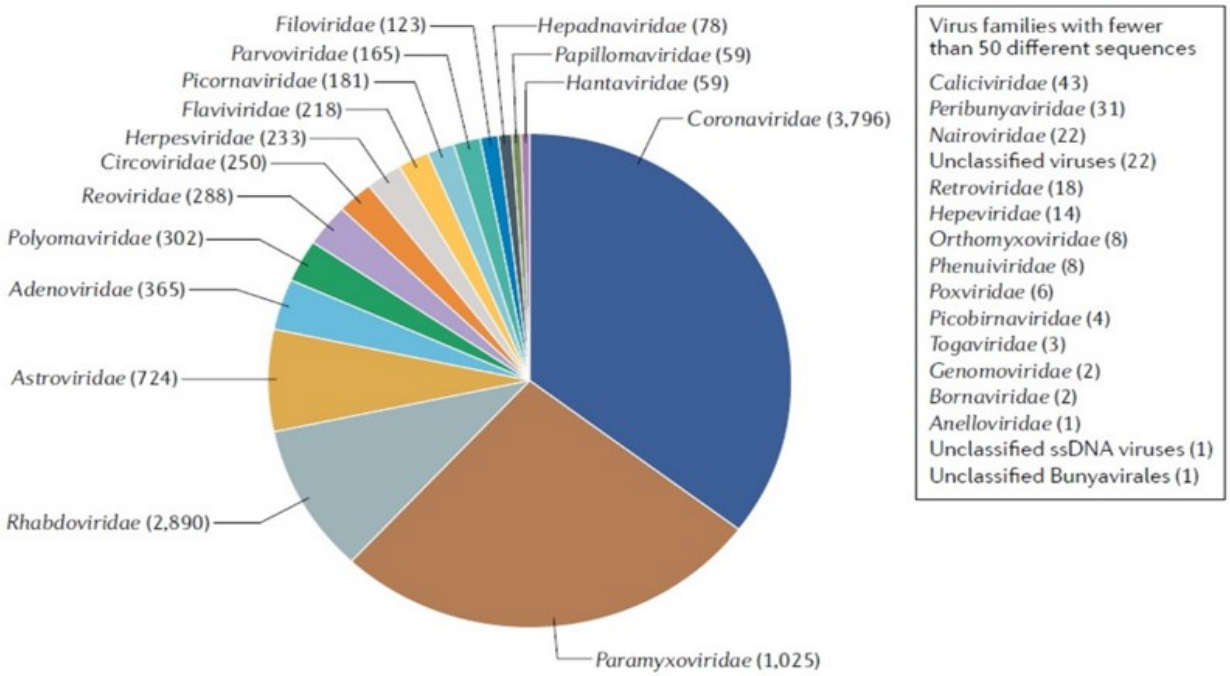


Figure 2. Currently described bat virus diversity (2)

ready been tested in Uganda, where, as part of campaigns to prevent Marburg virus infections, the destruction of fruit bats has been carried out in some mines (6,7). This has resulted in the re-invasion of these sites by susceptible bats and multiple reintroductions of the virus into newly connected populations. Reacting like this means forgetting that Chiropterans are key species in the functioning of ecosystems. In tropical environments, they play a significant role in the pollination of plants and the long-distance dissemination of seeds. As for insectivorous bats, they play a major role in regulating insect populations and thus reduce the use of pesticides. Very sensitive to changes in their environment, bats are excellent indicators of the health of our environment. The causes of epidemics are rather to be found in the disruption of natural ecosystems inflicted by human activities: intensification of agricultural practices leading to deforestation and habitat fragmentation, habitat degradation, and rapid urbanization (7).

Bats constitute a substantial portion of mammalian diversity throughout the Asian tropics. Indonesia supports high bat diversity which is at least 200 species. It is probable that Indonesia's abundant biodiversity of natural reservoir hosts (including bats), high tropical deforestation rates, thriving wildlife trade and hunting networks, and growing human population may increase the risk for zoonotic disease emergence (2,7–10). Therefore, this article will describe potential zoonosis spillover events in Indonesia of three viral family classes: coronaviridae, filoviridae, and paramyxoviridae.

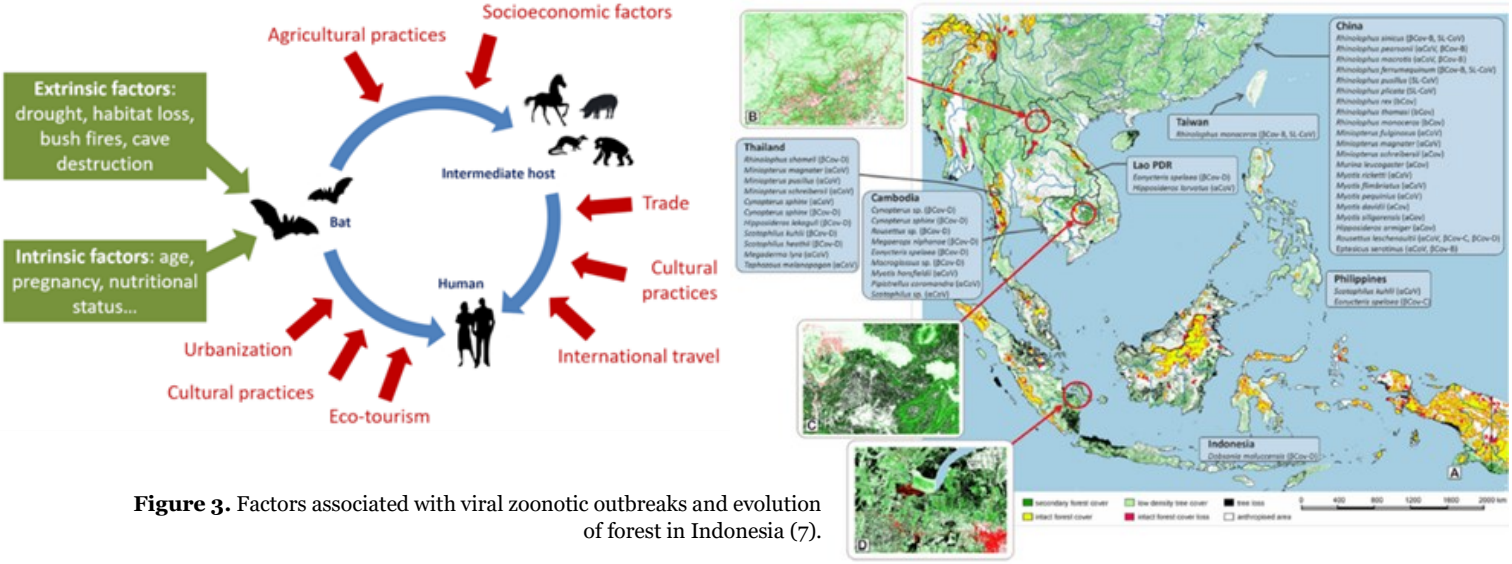
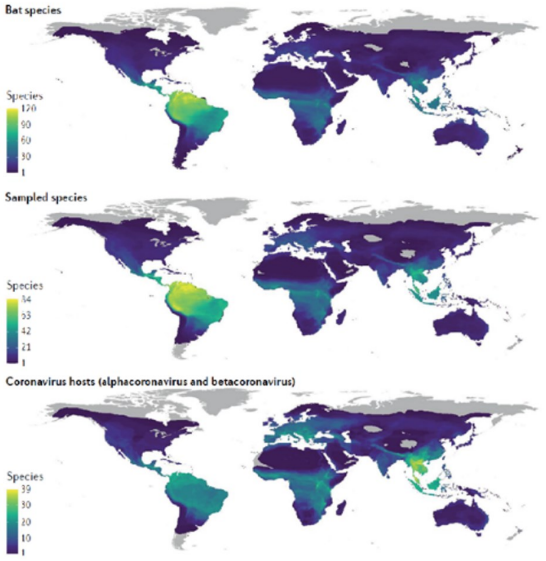
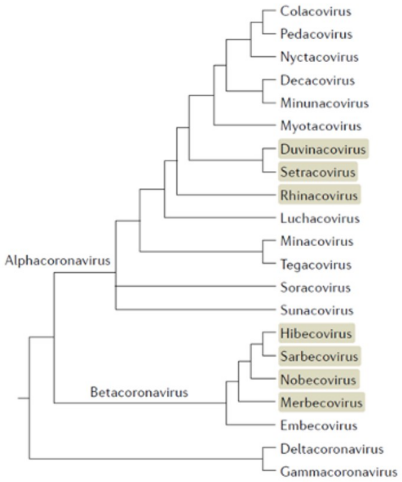


Figure 3. Factors associated with viral zoonotic outbreaks and evolution of forest in Indonesia (7).





Genus/subgenus	Notable virus species	Hosts species
Alphacoronavirus		
Colacovirus	Myl-CoV	Bats (Vespertilionidae)
Pedacovirus	PEDV	Bats (Vespertilionidae), pigs
Nyctacovirus		Bats (Vespertilionidae)
Decacovirus		Bats (Hipposideridae, Rhinolophidae)
Minunacovirus		Bats (Miniopteridae)
Myotacovirus		Bats (Vespertilionidae)
Duvinacovirus	HCoV-229E	Bats (Hipposideridae), dromedary camels, alpacas, humans
Setracovirus	HCoV-NL63	Bats (Rhinonycteridae), humans
Rhinacovirus	SADS-CoV	Bats (Rhinolophidae), pigs
Luchacovirus		Rodents (Muridae, Cricetidae)
Minacovirus		Ferrets, minks
Tegacovirus	CCoV, FCoV, TGEV	Cats, dogs, pigs
Soracovirus		Shrews (*Suncus murinus*)
Sunacovirus		Shrews (*Sorex araneus*)
Betacoronavirus		
Hibecovirus		Bats (Hipposideridae)
Sarbecovirus	SARS-CoV, SARS-CoV-2	Bats (Rhinolophidae), Malayan pangolins, carnivores (Canidae, Felidae, Mustelidae, Viverridae), humans
Nobecovirus		Bats (Pteropodidae)
Merbecovirus	MERS-CoV	Bats (Vespertilionidae), dromedary camels, humans
Embecovirus	BCoV, CRCoV, HCoV-OC43, HCoV-HKU1, MCoV	Rodents (Muridae, Cricetidae), dogs, rabbits, cattle, horses, pigs, sable antelopes, dromedary camels, giraffes, humans
Deltacoronavirus	PorCoV-HKU15	Birds, pigs
Gammacoronavirus	IBV	Birds, cetaceans

Figure 4. Coronavirus taxonomy and host distribution (8).

Coronavirus

Coronaviruses that circulate in bat populations have spilled over into human populations several times, and most likely will continue to be a public health threat. The diversity and broad geographical distribution of bats, the ubiquitous shedding of coronaviruses from bat populations and the molecular interactions of coronaviruses facilitate their zoonotic capacity. Coronaviruses are a diverse group of viruses infecting many different animals, and they can cause mild to severe respiratory infections in humans. Coronaviridae is subdivided into four genera, viz., Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Bats are important natural hosts of alphacoronaviruses and betacoronaviruses. Little is known about the specific conditions of coronavirus spillovers, but human behaviours that may increase viral exposure include activities such as bat hunting and consumption, guano farming and wildlife trading. Coronavirus shedding in horseshoe bats was higher in human-dominated landscapes than in natural landscapes. In addition, the legal and illegal wildlife trade results in viruses being transported over longer distances within hosts maintained in stressful and unsanitary conditions, likely increasing shedding and transmission (8,11,12).

Combined ecological and epidemiological data with modeling of the spread of bats to map the risk of exposure to bat coronaviruses across China and Southeast Asia and estimate an average of 400,000 people are infected with a SARSr-CoV every year (unreported spillover events), which and suggest that human exposure to and spillover of SARSr-CoVs may be substantially underestimated, and is undetected by surveillance programs and clinical studies in the majority of cases. Their analysis identified regions in southern China, northeastern Myanmar, Lao PDR, and

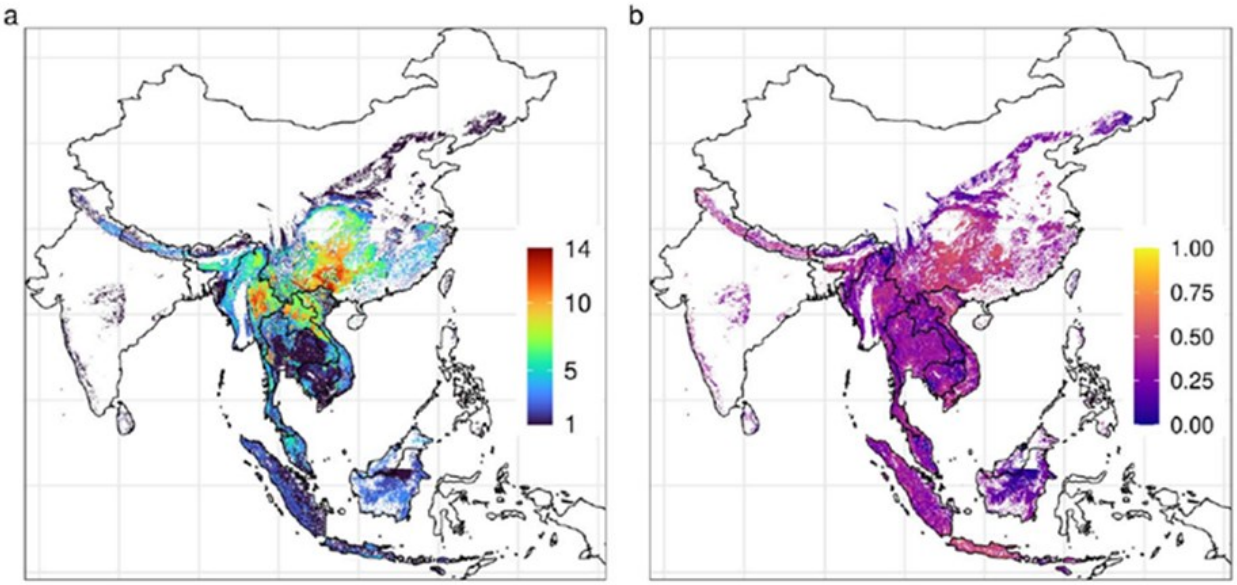


Figure 5. Hotspot maps of SARSr-CoV bat host species in Southeast Asia and relative spillover risk (10).

northern Vietnam as having the highest diversity of SARSr-CoV bat host species. These hotspots of SARSr-CoV bat reservoir host diversity may be particularly fruitful sites for viral discovery of novel SARSr-CoVs, assuming that viral diversity scales with host species diversity. While the data suggest significant levels of exposure, many of the diverse viral strains that infect people in the region each year may not be able to replicate well in people, cause illness, or be transmitted sufficiently among people to cause an outbreak. However, given the relatively large number of people likely to be infected each year with bat-CoVs, it is plausible that illnesses or clusters of cases due to novel bat-CoV infection occur regularly within the region, and are either not reported, or otherwise missed by clinical surveillance (10).

Among the many questions unanswered for the COVID-19 pandemic are the animal origin and cross-species infection route of SARS- CoV-2 are yet to be uncovered. Fundamental knowledge gaps remain about the understanding of mechanisms leading to successful spillover event. To date, the closest relatives to SARS-CoV-2 is RaTG13, sampled from a Rhinolophus affinis (horseshoe bat in Yunnan province), which shared a ~96% identical overall to SARS-CoV-2. However, its spike diverges in the RBD, which suggests that it may not bind efficiently to human ACE2. In contrast, some pangolin coronaviruses exhibit strong similarity to SARS-CoV-2 in the RBD, including all six key RBD residues. Neither the bat betacoronaviruses nor the pangolin betacoronaviruses sampled thus far have polybasic cleavage sites. A study reported molecular and serological evidence of SARS-CoV-2 related coronaviruses (SC2r-CoVs) actively circulating in bats in Southeast Asia. Whole genome sequences were obtained from five independent bats (Rhinolophus acuminatus) in a Thai cave yielding a single isolate (named RacCS203) which is most related to the RmYN02 isolate found in Rhinolophus malayanus in Yunnan, China (12–14).

Indonesia is reported to have 81 species of bats that belong to suborder Megachiroptera (fruit nectar-eating bats) and 158 species in the suborder Microchiroptera (non-fruit-nectar-eating bats). As many as 10 families of bats have been reported in Indonesia, including Pteropodidae, which belongs to the Megachiroptera suborder, and Rhinopomatidae, Emballonuridae, Nycteridae, Megadermatidae, Rhinolophidae, Hiposideridae, Vespertilionidae, Miniopterеridae, and Molossidae families that belong to the Microchiroptera suborder. As an archipelago country, Indonesia has the highest number of fruit- and nectar-eating bat species in the world. Fruit-nectar bats are very important for the process of pollination, fertilization, and seed dispersal. There are at least 21 genera and 81 species that belong to Pteropodidae family. The discovery of BatCoV in several species of bats in Indonesia suggests that bats are potential natural reservoir hosts for coronavirus and may transmit that virus to other species, such as occurred in previous infectious disease outbreaks such as SARS-CoV and MERS-CoV. Recent study in Indonesia collected a total of 182 rectal swab samples from 4 species of bats were acquired from bat collectors who were going to sell the bats to restaurants for consumption and from animal markets in several regencies/cities in Central Java Province (Surakarta City, Magelang Regency), Yogyakarta Province, and West Java Province (Bogor City, Cianjur Regency) in 2020 and 2021. They identified the presence of BatCoV on Cynopterus brachyotis, Macroglossus minimus, and Rousettus amplexicaudatus. The results showed that the BatCoV included in this study are from an unclassified coronavirus group. Notably, SARS-CoV-2 viral RNA and antibodies were not detected in the sampled bats (9). However, close contacts between humans, bats, and other animals have a high potential for transmitting zoonotic diseases. Further studies in Indonesia regarding coronaviruses carried by bats or other animals and the possible effects of environmental conditions are needed to identify possible novel virus transmission routes, particularly in live animal markets. Early detection of pathogen transmission and the application of appropriate control measures may minimize the destructive impacts on global health. Thus, more surveillance studies are needed to investigate the potentially important role of bats as natural reservoir hosts in the interspecies transmission of coronaviruses.

-Continued to part 2 in February 2022-

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INA-RESPOND Newsletter

FROM OUR PARTNER

ETHICAL CONSIDERATIONS IN CLINICAL TRIALS IMPORTANCE OF DIVERSITY IN CLINICAL TRIAL PARTICIPANTS (PART 2)

By: Louis Grue

Note: "minority" in this article refers specifically to the US minority populations.

Barriers and Solutions

Participant hesitancy and skepticism is one of the most significant barriers to increasing diversity in clinical research. Many patients, especially those who are members of racially or ethnically diverse groups, do not trust the research process and are wary of being used as a test subject. Unfortunately, there is precedent for this, as in the historical cases. The lack of diversity in medical trials has roots extending deep into U.S. history. Facing that ugly history is part of building trust and boosting participation in clinical trials by historically underrepresented communities, according to the PhRMA industry principles, which explicitly state that the Tuskegee experiment was unethical and featured serious mistakes. Still, the industry principles state that the horrible experiment became a conduit for "major changes in how clinical trials are conducted in order to protect the rights, safety, and well-being of clinical trial participants." Rather than lean into diversity and inclusion in medical trials, however, experts say the industry went in the other direction.

Increasing Diversity in Research

Regulators recognize the disparities inherent in clinical research populations, and they've attempted to implement guidelines to augment diversity in clinical trials. In 1993, the National Institutes of Health (NIH) implemented the NIH Revitalization Act, which required that Phase III clinical trials that received NIH funding conduct analyses to ensure that their findings took sex, gender, and race into consideration. An update to this, implemented in 2016 in the form of the 21st Century Cures Act, added increased accountability for researchers, if their trials did not adequately consider women and minority populations, it could jeopardize their future funding.

Barriers to Diversity in Clinical Research

Hesitance of Participants

Globally, hesitancy in clinical research spreads further by dishonorable researchers such as Andrew Wakefield, whose influential British study linking autism and the Measles, Mumps & Rubella Vaccine (MMR) vaccine, was retracted by The Lancet after discovering he did not consecutively recruit his participants as he had claimed. He demonstrated unethical behavior and showed, as described in the Canadian Medical Association Journal, "callous disregard" for the children in his study, upon whom invasive tests were performed.

Communication Barriers

As researchers attempt to recruit patients from diverse

communities, they must look internally at their recruitment practices. One significant barrier in reaching diverse participants is language-based, as providing translation services adds a layer to a discussion about risks and consent that is already sensitive. Researchers must ask themselves if they actively advertise their clinical trials to patients who primarily speak languages other than the local country language. Are they looking for patients in places that represent a wide swath of linguistic experience? The digital age provides new opportunities for researchers to extend their reach and communicate their clinical aims.

Costs of Participating

Participating in clinical research may impose a burden on a patient's personal resources, especially their time and money. For example, a rural patient who commits to a clinical trial may need to regularly drive to the nearest study site 100 miles away. This means hours of driving time and associated driving costs every time she travels to the study site. Additionally, participants may need to take time off work, arrange for childcare, and budget for parking and other expenses. Many patients cannot undertake the direct and indirect costs of participation, regardless of their level of interest in the trial process. Though there may be reimbursements available, patients may be unaware of them and may preclude their participation. By considering cost and transportation barriers, researchers can minimize in-person site visits and migrate more data collection into the digital sphere.

Lack of Clinical Trial Awareness

Lack of clinical trial awareness is one of the most common barriers to clinical trial recruitment. Some researchers describe patients as being stuck in a "pre-contemplation" stage of involvement, in which they have never heard of a clinical trial. For diverse groups to participate in clinical research, they must first have exposure to the concept. The healthcare community as a whole must do a better job at reaching out to patient communities and providing education on how clinical trials work and why patients may benefit from them. Sponsors that work with patient advocacy organizations (PAOs) or physicians and health communities that primarily support diverse populations can reach a wider, more inclusive pool of potential participants.

Promoting Diversity in Clinical Research

One of the most critical steps in expanding diversity profiles in clinical trials is increasing awareness of clinical research among diverse populations. Once achieving sufficient understanding, researchers can further promote diversity by:

- Reinforcing the notion of personal health.
- Ensuring participant safety.
- Providing clear information to participants so that they can make educated decisions.
- Demonstrating appreciation for subject participation.
- Advertising that support is available to participants.
- Strategic trial design can also help promote diversity in research. Researchers who studied recruitment of ethnic minorities for mental health trials noted that, unlike the US, many countries with a high amount of ethnic diversity do not have legal requirements in place that mandate inclusion of diverse populations in trial recruitment. These researchers suggest that designing trials that deliberately and proportionally recruit from a country's minority populations or focusing a research question on those minorities can help overcome these barriers.

Importance of Outreach and Community Engagement/ Good Participatory Practice (GPP)

Engaging the community is one opportunity among a multi-stakeholder approach that helps support clinical trial diversity. Protecting and promoting the health of diverse populations is central to the mission of the FDA Office of Minority Health and Health Equity (OMHHE). The OMHHE achieves this mission through efforts dedicated to advancing minority health focused research, and outreach and communication that works towards addressing health disparities and achieving health equity. Advancing diverse participation of minority populations in clinical trials is a key priority area for OMHHE. In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA), specifically section 907, emphasized the need for increased racial and ethnic minority participation in clinical trials. In response to FDASIA, OMHHE created the Diversity in Clinical Trials Initiative to raise awareness around minority participation in clinical trials. This initiative consists of an ongoing multi-media campaign to raise awareness on the importance of racial and ethnic minority participation in clinical trials, and includes multiple strategies:

- Educational materials in English and Spanish that highlight the value of clinical trial participation.
- Videos and Public Service Announcements including social media outreach that encourage different groups to participate in clinical trials.
- Ongoing outreach to engage different communities and health professionals to raise awareness about the need for diverse participation in clinical trials.
- Webinars, lectures, and podcasts.
- A dedicated webpage with all resources and materials, including a communications toolkit.

- Collaborations across government, professional associations, community-based organizations, academia, industry, and others to educate consumers and communities about the importance of minority participation in clinical trials.

What the COVID-19 Pandemic has Taught Us on this Subject

In 2020, as a high number of COVID-19 deaths were being reported in the news, some additional news was welcomed: Two American pharmaceutical companies racing to find a vaccine separately reported that human tests of their experimental drugs have shown highly promising results. Both companies reported that the pools of volunteers receiving the drugs included significant numbers of Black participants. Dr. Bill Gruber, Pfizer's senior vice president of vaccine clinical research and development, told Reuters last summer, describing a trial pool of 11,000 people for a vaccine being developed with German partner BioNTech that "Between Latinx and Black or African American populations, we're running at about 19%, and were trying to push even higher than that." Pfizer now reports that 30% of U.S. trial participants had "diverse" backgrounds, with Black people and those identified as either Hispanic or by the gender-neutral term Latinx accounting for approximately 10% and 13% shares, respectively.

Moderna said its 30,000-person phase three vaccine study included more than 11,000 people from communities of color, including more than 6,000 Hispanic or Latinx people and more than 3,000 Black or African American participants. Yet while the industry insists it is moving with deliberate speed toward diversity and inclusion in experimental drug trials, some say it's taking baby steps and has a long way to go toward building trust with African Americans and other minority communities. Jonathan Jackson, a cognitive neuroscientist and director of the Community Access, Recruitment, and Engagement Research Center at Massachusetts General Hospital in Boston, whose center investigates the effects of diversity and inclusion on human subject research says "There are a lot of outstanding questions". Jackson notes that "A lot of people who have been running the COVID-19 vaccine studies have been really excited because they have recruited a more diverse population, compared to what they're used to". However, he suggests "The bar that you're trying to clear shouldn't be a study that you ran last year," but the goal should be to mirror the population most affected by the targeted disease.

Now, a renewed focus on health inequities has sparked hope among health advocates for a structural change that has been a long time coming: more diversity in clinical trials.

Back to 1994, when the NIH released the guidelines for including women and minorities in clinical studies. Women now make up roughly half of study participants in NIH-funded clinical trials, but people from historically excluded racial and ethnic groups still lack representation.

Experts say the recent racial and social justice movement in the US and globally has strengthened the conversation about the root causes of health disparities and lasting solutions. This includes clinical trial participation. What is clear is it is important to have the right people at the table. That is what is really going to drive trust, when people understand the whole process and can attest to their involvement in it. Clinical researchers have had a great teaching moment during the pandemic to build on what the entire population saw in the development of the COVID vaccines and treatments.

To remove this hurdle, researchers have embraced the rise of technology to help conduct clinical trials. Offering patients the option to conduct trials at home via video conference and track their experiences online blows open the boundaries we once faced as researchers. This embrace of technology has decentralized trials, and can increase diversity and open up a new way of doing things.

The COVID-19 pandemic also showed how quickly science can change day to day, as well as the necessity of organized oversight of trial procedures and results to avoid public confusion and medical research retractions.

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INA-RESPOND Newsletter

A NEW YEAR, A NEW START, A NEW RESOLUTION

By: Monica Surjanto

The new year is an opportunity to make a new resolution. This resolution could be to have a healthier and more active lifestyle for most people. A healthy and active lifestyle is a long-term commitment with comprehensive health benefits for your body. A healthy lifestyle is a way of living that lowers the risk of being seriously ill or dying early. Not all diseases are preventable, but many deaths, particularly those from coronary heart disease and lung cancer, can be avoided. Health is not just about preventing disease but also about physical, mental, and social wellbeing. A more positive, healthy lifestyle role model will influence people, family, office, school, and children.

How do we start?

1. Stop smoking

Smoking is the most significant single self-imposed risk to the health of all. It can cause respiratory illness, coronary heart disease, cancer. Half of all people who regularly smoke will be killed by cigarettes, half in middle age and half in their senior years.[1]

Step action plan:

⇒ Monitor your current pattern of tobacco use - when do you use it and why?

⇒ Decide to give up tobacco now – whatever your age, it will lower your risk.

⇒ Choose alternative things to do when you are tempted to use tobacco.

⇒ Practice ways of saying "NO" to help you

⇒ Ask your friends, family to give you support.

2. Get active

Regular physical activity is proven to help prevent and treat noncommunicable diseases (NCDs) such as heart disease, stroke, diabetes, and breast and colon cancer. It also helps prevent hypertension, overweight, and obesity and improves mental health, quality of life, and well-being.[2]

Physical activity can and should be integrated into the settings where people live, work, and play. It is essential that adults can be physically active and less sedentary at work. Sedentary behavior is defined as any behavior characterized by an energy expenditure ≤1,5 metabolic equivalents, such as: sitting, reclining, or lying down. Recent evidence indicates that high levels of continuous sedentary behavior (such as sitting for long periods) are associated with abnormal glucose metabolism and cardiometabolic morbidity, as well as overall mortality. Reducing sedentary behavior through the promotion of incidental physical activity (for example, standing, climbing stairs, short walks) can support individuals to increase their levels of physical activity incrementally towards achieving the recommended levels for optimal health.[2]

Step action plan:[1]

⇒ If you are not physically active, identify **WHEN** you could be more physically active and **HOW**. Examples: put more physical effort into housework, brisk walk, get off the bus or train one stop earlier, choose to climb the stairs rather than an elevator.

⇒ Set daily step target, Get more than 10000 steps/day.

⇒ steps/day); and 5) 'highly active' (>12,500 steps/day)

⇒ Do exercise in moderate to vigorous intensity in the duration of a minimum of 150-300 minutes/week. The activities consist of aerobic exercise, strengthening exercise, stretching routine, and balance exercise for the elderly.

⇒ Determine your goals, find a workout that you love, and develop a plan and commitment.

⇒ Start slowly. Listen to your body: you are doing too much too soon if you experience dizziness, nausea, pain, and extreme tiredness.

3. Healthy eating

People are now consuming more foods high in energy, fats, free sugars, and salt/sodium. However, many people do not eat enough fruit, vegetables, and other dietary fiber such as whole grains.

A healthy diet helps protect against malnutrition in all its forms and noncommunicable diseases, including diabetes, heart disease, stroke, and cancer.

Step action plan:

⇒ Eating at least 400 g of fruit and vegetables per day.[3]

⇒ Reducing the amount of total fat intake to less than 30% of total energy intake helps prevent unhealthy weight gain.[3]

⇒ Reducing saturated fat (fatty meat, butter, palm and coconut oil, cream, cheese, lard) to less than 10% of total energy intake.[3]

⇒ Reducing the use of trans fat (found in baked and fried foods, and pre-packaged snacks and foods, such as frozen pizza, pies, cookies, biscuits, wafers, and cooking oils and spreads) to less than 1 % of total energy intake[3]

⇒ Replacing saturated fats and trans-fats with unsaturated fats (fish, avocado, nuts, sunflower, soybean, canola, and olive oils).[3]

⇒ The Recommended Dietary Allowance of protein for a healthy adult with minimal physical activity is currently 0.8 g protein per kg body weight (BW) per day. To meet the functional needs such as promoting skeletal-muscle protein accretion and physical strength, dietary intake of 1.0, 1.3, and 1.6 g protein per kg BW per day is recommended for individuals with minimal, moderate, and intense physical activity.[4]

⇒ Reducing salt intake to the recommended level of less than 5 g per day.[3]

⇒ Limiting the consumption of foods and drinks containing high amounts of sugars, such as sugary snacks, candies, and sugar-sweetened beverages (i.e., all types of beverages containing free sugars – these include carbonated or non-carbonated soft drinks, fruit or vegetable juices and drinks, liquid and powder concentrates, flavored water, energy, and sports drinks, ready-to-drink tea, ready-to-drink coffee, and flavored milk drinks).[3]

Finally, improving your health in this new year is a big goal and should be taken seriously. A New Year's resolution is a promise to change a few things in your life. It can be anything - stopping an undesirable habit permanently, doing something new and positive from the first day of the year, or accomplishing a goal. Focus on being persistent, make your goals specific and realistic and turn your resolutions into long-term habits. Happy new year, happy new you!

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INA-RESPOND Newsletter

COMIC CORNER

CRISPR-CAS9 SYSTEMS: HAVE OUR DREAM FINALLY COME TRUE?

By: Aly Diana

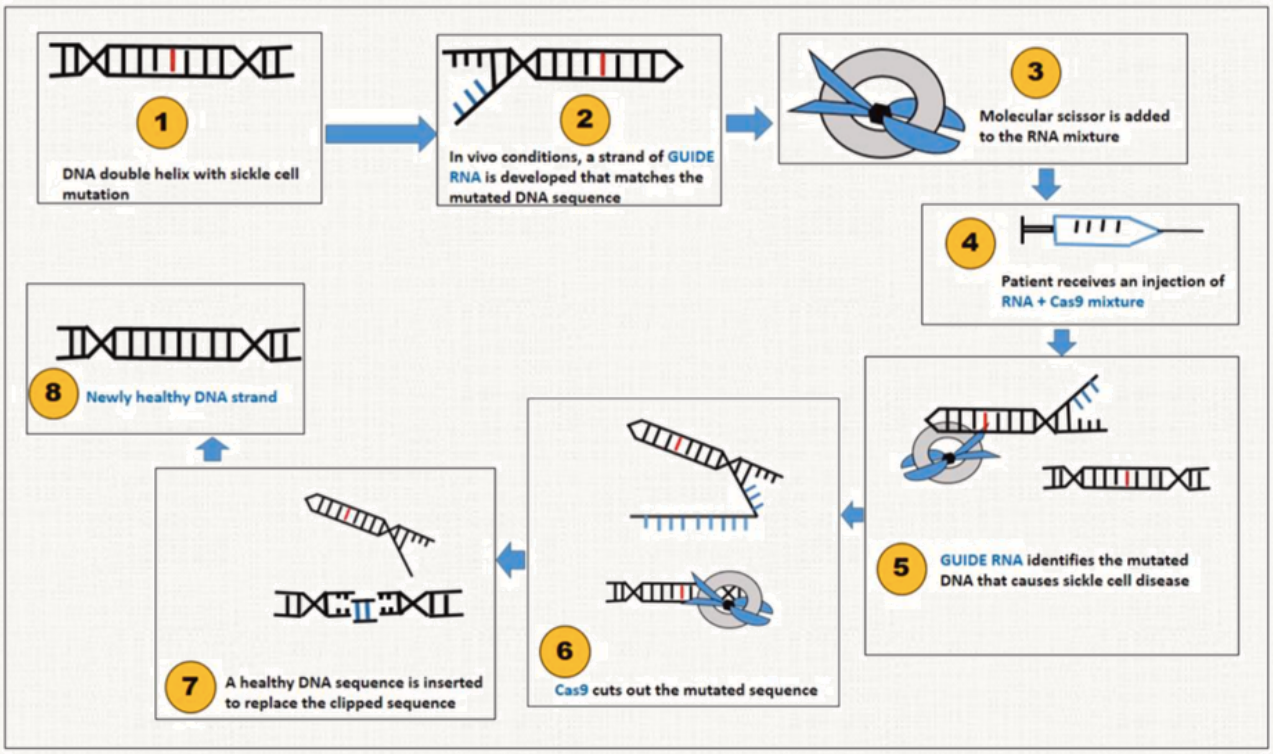

Illustration of CRISPR Cas9 system to create a potential therapy for Sickle cell disease (Source: https://doi.org/10.1016/j.gene.2021.145615)

Disclaimer: This topic is beyond me, but I hope that the science world will finally invent a magic bullet to cure uncured diseases and create a better world. Here I present a brief explanation of CRISPR-Cas 9, how it works, and the challenges in applying the technology in humans. I avoid discussing the ethical issues and the controversies around them.

CRISPR stands for **clustered regularly interspaced short palindromic repeat DNA sequences**. The bacterial CRISPR locus was first described by Mojica et al. (published in 1993) and later identified as a key element in the adaptive immune system in prokaryotes (published in 2000). The locus consists of snippets of viral or plasmid DNA that previously infected the microbe (later termed "spacers"), which were found between an array of short palindromic repeat sequences. Later, Bolotin et al. discovered the Cas9 protein in Streptococcus thermophilus, which unlike other known Cas genes, Cas9 was a large gene that encoded for a single-effector protein with nuclease activity (published in 2005). They further noted a common sequence in the target DNA adjacent to the spacer, later known as the protospacer adjacent motif (PAM)—the sequence needed for Cas9 to recognize and bind its target DNA. Later studies reported that spacers were transcribed to CRISPR RNAs (crRNAs).

A critical discovery demonstrated that a CRISPR system from one bacterium was transferable to different bacterial strains. The crucial work, which arguably marked the beginning of CRISPR as a biotechnology tool, has demonstrated that Cas9 enzymes can be reprogrammed to target the desired DNA sequence in bacteria. These studies also simplified the CRISPR system by using a single short RNA. The endogenous CRISPR system requires two short RNAs: the mature crRNA and a trans-activating crRNA (tracrRNA). The crRNA is composed of the part that serves as a guiding sequence and another part base

that pairs with the tracrRNA. Both crRNA and tracrRNAs are required to form the Cas9 protein–RNA complex that cleaves DNA with double-stranded breaks (DSBs) at target sites. Notably, Jinek et al. showed that CRISPR-Cas9 could also be guided by a single chimeric RNA formed by the fusion of tracrRNA and crRNA, called single guide RNA (sgRNA). These studies were immediately followed by ground-breaking publications showing that CRISPR can be adapted for in vivo genome editing in eukaryotic cells.

For the first time ever, researchers had an extremely flexible tool that could be easily guided to target nearly any location in the genome by simply designing a short sgRNA. Due to high editing efficiency and ease of use, researchers from diverse fields quickly adopted CRISPR technology as a method of choice for various genome-targeting purposes. Notably, since its inception as a genome-editing tool in late 2012 to 2018, more than 9000 research articles have been published about it, and the number of publications seems to continue to increase each year.

A major limitation is the production of off-target effects in host cells, especially in mice embryos and adult human cells. That is, despite attempting to edit a certain gene, other genes become altered. The primary reason behind the off-target effects is that Cas9 fails to recognize the target sequences. A higher proportion of off-target mutations occur in humans than in lower animals. The delivery of sgRNA and Cas9 to the host cell is a constant challenge to the scientific community. Scientists have used plasmids, viruses, and ribonucleoproteins for delivery purposes, but the process also suffers from limitations.

CRISPR–Cas9 tools should be precisely and safely designed for long-term use in therapeutics. Some studies have shown that CRISPR–Cas9 activates overexpression of the TP53 gene through double-stranded breaks and leads to cell death. Inactivation of TP53 through CRISPR–Cas9 can decrease cell death but will increase off-targets and carcinogenicity. Nevertheless, the FDA approved CRISPR testing in humans to correct genetic defects causing sickle cell disease in March 2021. Hopefully, in 4-5 years, we can hear good news about this study. Let's keep our fingers crossed; probably a magic bullet may exist one day after all.

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