Global Health Cast 72

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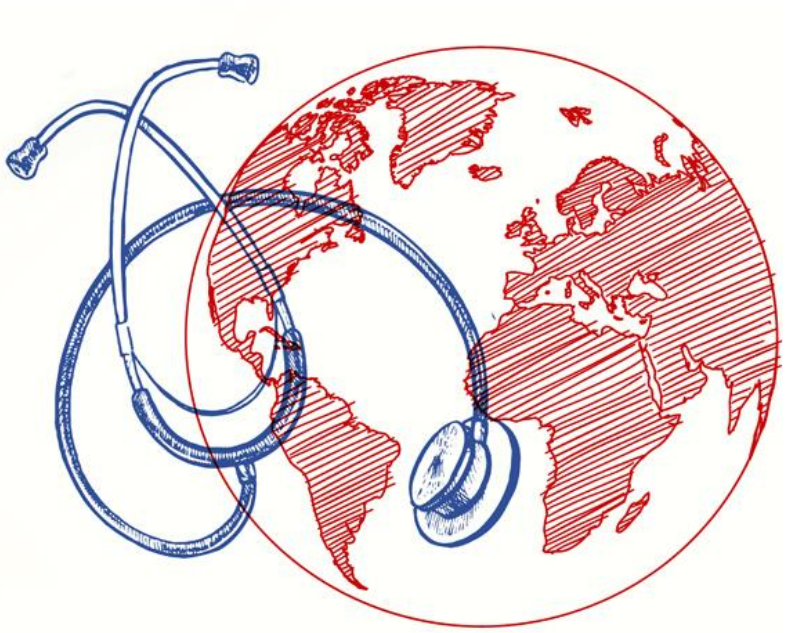

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What we talk about today

- Zika virus can have long-term consequences for the immune system
- Dengue infection linked to increased risk of COVID illness
- COVID infection can trigger changes to the immune system that may underlie persistent symptoms
- Do SARS-CoV-2 infection or vaccination cause birth defects?
- Burden of RSV in children <2 or ≥ 2 years of age
- Improved vaccines for the next pandemic
- Defining Long COVID

Zika virus can have long-term consequences for the immune system

Sustained chronic inflammation and altered childhood vaccine responses in children exposed to Zika virus

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Summary

Background Congenital Zika virus (ZIKV) infection leads to severe newborn abnormalities, but its long-term impact on childhood immunity is not well understood. This study aims to investigate the serum proteomics in children exposed to ZIKV during pregnancy to understand potential immunological consequences during early childhood.

Methods The study included ZIKV-exposed infants (ZEI) at birth (n = 42) and children exposed to ZIKV (ZEC) at two years of age (n = 20) exposed to ZIKV during pregnancy, as well as healthy controls. Serum proteomic analysis was performed on these groups to assess inflammation and immune profiles. Additionally, antibody titres against two common childhood vaccines, DTaP and MMR, were measured in healthy controls (n = 50) and ZEC (n = 92) to evaluate vaccine-induced immunity.

Findings Results showed elevated inflammation in ZEI with birth abnormalities. Among ZEC, despite most having normal clinical outcomes at two years, their serum proteomics indicated a bias towards Th1-mediated immune responses. Notably, ZEC displayed reduced anti-Diphtheria toxin and anti-*Clostridium tetani* IgG levels against DTaP and MMR vaccines. They also exhibited lower antibody titres particularly against Th2-biased DTaP vaccines, but not Th1-biased MMR vaccines.

The study highlights the long-term immunological consequences of congenital ZIKV exposure. Heightened inflammation was observed in ZEI with abnormalities at birth, while ZEC maintained a chronic Th1-biased immune profile.

The impaired response to Th2-biased vaccines raises concerns about lasting effects of ZIKV exposure on immune responses. Consequently, there is a need for continued longitudinal clinical monitoring to identify potential immune-related complications arising from prenatal exposure to ZIKV.

What we know about Zika virus

A mosquito-borne virus first identified in Uganda in 1947 in a Rhesus macaque monkey followed by evidence of infection and disease in humans in other African countries in the 1950s.

- Transmitted primarily by Aedes mosquitoes, which bite mostly during the day.
- Most people with Zika virus infection do not develop symptoms; those who do typically have symptoms including rash, fever, conjunctivitis, muscle and joint pain, malaise and headache that last for 2–7 days.
- Infection during pregnancy can cause infants to be born with microcephaly and other congenital malformations as well as preterm birth and miscarriage.
- Associated with Guillain-Barré syndrome, neuropathy and myelitis in adults and children.

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Dengue infection linked to increased risk of COVID infection + illness

Open Forum Infectious Diseases

MAJOR ARTICLE

Effects of recent prior dengue infection on risk and severity of subsequent SARS-CoV-2 infection: a retrospective cohort study

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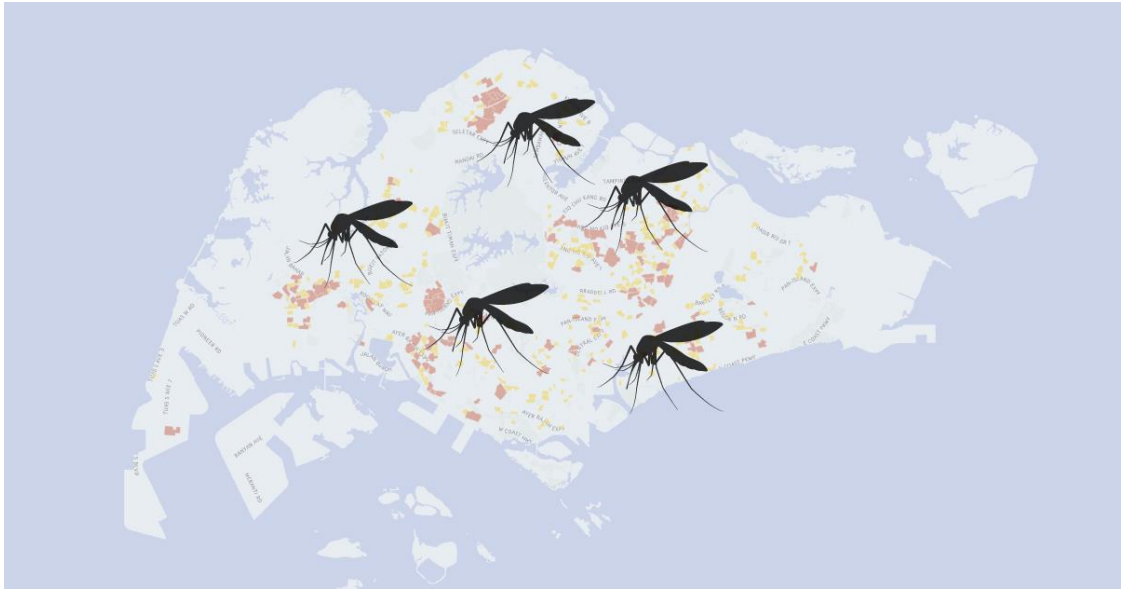
Background and Aims: Elucidating whether prior dengue potentially confers cross-protection against COVID-19 is of public health importance in tropical countries at-risk of overlapping dengue and COVID-19 epidemics. However, studies to-date have yielded conflicting results. We aimed to assess effects of recent prior dengue infection on risk and severity of subsequent SARS-CoV-2 infection amongst adult Singaporeans.



Conclusions

- Increased risk of SARS-CoV-2 infection and adverse COVID-19 outcomes were observed following preceding dengue infection in a national population-based cohort of adult Singaporeans.
- This observation is of significance in tropical countries with overlapping dengue and COVID-19 outbreaks.

COVID infection can trigger changes to the immune system that may underlie persistent symptoms

Differential decline of SARS-CoV-2-specific antibody levels, innate and adaptive immune cells, and shift of Th1/ inflammatory to Th2 serum cytokine levels long after first COVID-19

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Abstract

Background: SARS-CoV-2 has triggered a pandemic and contributes to long-lasting morbidity. Several studies have investigated immediate cellular and humoral immune responses during acute infection. However, little is known about long-term effects of COVID-19 on the immune system.

Methods: We performed a longitudinal investigation of cellular and humoral immune parameters in 106 non-vaccinated subjects ten weeks (10w) and ten months (10m) after their first SARS-CoV-2 infection. Peripheral blood immune cells were analyzed by multiparametric flow cytometry, serum cytokines were examined by multiplex technology. Antibodies specific for the Spike protein (S), the receptor-binding domain (RBD) and the nucleocapsid protein (NC) were determined. All parameters measured 10w and 10m after infection were compared with those of a matched, noninfected control group ($n=98$).

Results: Whole blood flow cytometric analyses revealed that 10m after COVID-19, convalescent patients compared to controls had reduced absolute granulocyte, monocyte, and lymphocyte counts, involving T, B, and NK cells, in particular $CD3^+CD45RA^+CD62L^+CD31^+$ recent thymic emigrant T cells and non-class-switched $CD19^+IgD^+CD27^+$ memory B cells. Cellular changes were associated with a reversal from Th1- to Th2-dominated serum cytokine patterns. Strong declines of NC- and

Results

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Conclusions

COVID-19 causes long-term reduction of innate and adaptive immune cells which is associated with a Th2 serum cytokine profile. This may provide an immunological mechanism for long-term sequelae after COVID-19.

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Are SARS-CoV2-infection or -vaccination cause birth defects?

- **Is there a risk for** major congenital anomalies after infection or vaccination against Vovid-19 during the first trimester of pregnancy.
- **Design** Prospective Nordic registry-based study.
- **Setting** Sweden, Denmark, and Norway.
- **Participants** 343 066 liveborn singleton infants in Sweden, Denmark, and Norway, with an estimated start of pregnancy between 1 March 2020 and 14 February 2022, identified using national health registries.
- **Main outcome measure** EUROCAT (European Surveillance of Congenital Anomalies) definitions. Risk assessment assessed by logistic regression, adjusting for maternal age, parity, education, income, country of origin, smoking, body mass index, chronic conditions, and estimated date of start of pregnancy.
- **Results** 17 704 (5.2%) infants had a major congenital anomaly.

Table 3 | Risk of congenital anomalies according to infection with covid-19 during the first trimester

EUROCAT categories of major congenital anomalies*	Without maternal infection (n=332 837)	With maternal infection (n=10 229)	Odds ratio adjusted for estimated start of pregnancy (95% CI)	Fully adjusted odds ratio (95% CI)†
Any	17210	494	0.94 (0.86 to 1.04)	0.96 (0.87 to 1.05)
Congenital heart defects	4707	161	1.08 (0.92 to 1.27)	1.08 (0.92 to 1.28)
Nervous system	435	8	0.65 (0.32 to 1.30)	0.68 (0.33 to 1.37)
Eye	600	16	0.86 (0.52 to 1.42)	0.84 (0.51 to 1.40)
Oro-facial clefts	481	17	1.08 (0.66 to 1.77)	1.12 (0.68 to 1.84)
Gastrointestinal	1164	27	0.88 (0.50 to 1.55)	0.92 (0.55 to 1.54)
Kidney and urinary	1585	44	0.94 (0.70 to 1.27)	0.96 (0.69 to 1.33)
Genital	1436	42	0.92 (0.67 to 1.26)	0.94 (0.68 to 1.29)
Limb				27)

Conclusions Covid-19 infection and vaccination during the first trimester of pregnancy were not associated with risk of congenital anomalies.

Table 4 | Risk

EUROCAT categ anomalies				odds ratio
Any				09)
Congenital heart				21)
Nervous system				31)
Eye				21)
Ear, face, and neck	57	6	0.44 (0.19 to 1.03)	0.44 (0.18 to 1.05)
Respiratory	72	9	0.68 (0.34 to 1.37)	0.67 (0.33 to 1.36)
Oro-facial clefts	179	46	1.12 (0.80 to 1.58)	1.03 (0.73 to 1.46)
Gastrointestinal	397	84	1.03 (0.74 to 1.44)	1.04 (0.74 to 1.46)
Abdominal wall defects	34	9	1.52 (0.69 to 3.33)	1.69 (0.76 to 3.78)
Kidney and urinary	593	134	1.03 (0.78 to 1.36)	1.01 (0.75 to 1.66)
Genital	322	72	0.95 (0.77 to 1.16)	1.00 (0.81 to 1.23)
Limb	1115	207	1.01 (0.88 to 1.16)	0.99 (0.86 to 1.14)

RSV in children < 2years and ≥2 years of age

- **Objective:** Describe RSV and RSV severity in children older than 2 years and to explore the potential extension of preventive strategies to this demographic group.
- **Methods:** observational retrospective study at Meyer Children's Hospital (from October 2019 to March 2023): Data from patients between 28 days and 18 years of age with RSV infection.
- **Results:** 584 infants and young children were hospitalized due to RSV infection. Epidemic seasons saw a rise in hospitalizations among children older than 2 years. Older children had higher comorbidity (41% versus 9% p=0.000) and prematurity (26% versus 14% p = 0.001) rates than those under 2 years.

RSV in <2 year and ≥2 year-old children

Group "under 2" and Group "2 and above" years of age of all RSV cases admitted from 2019 to 2023. Differences and significance.

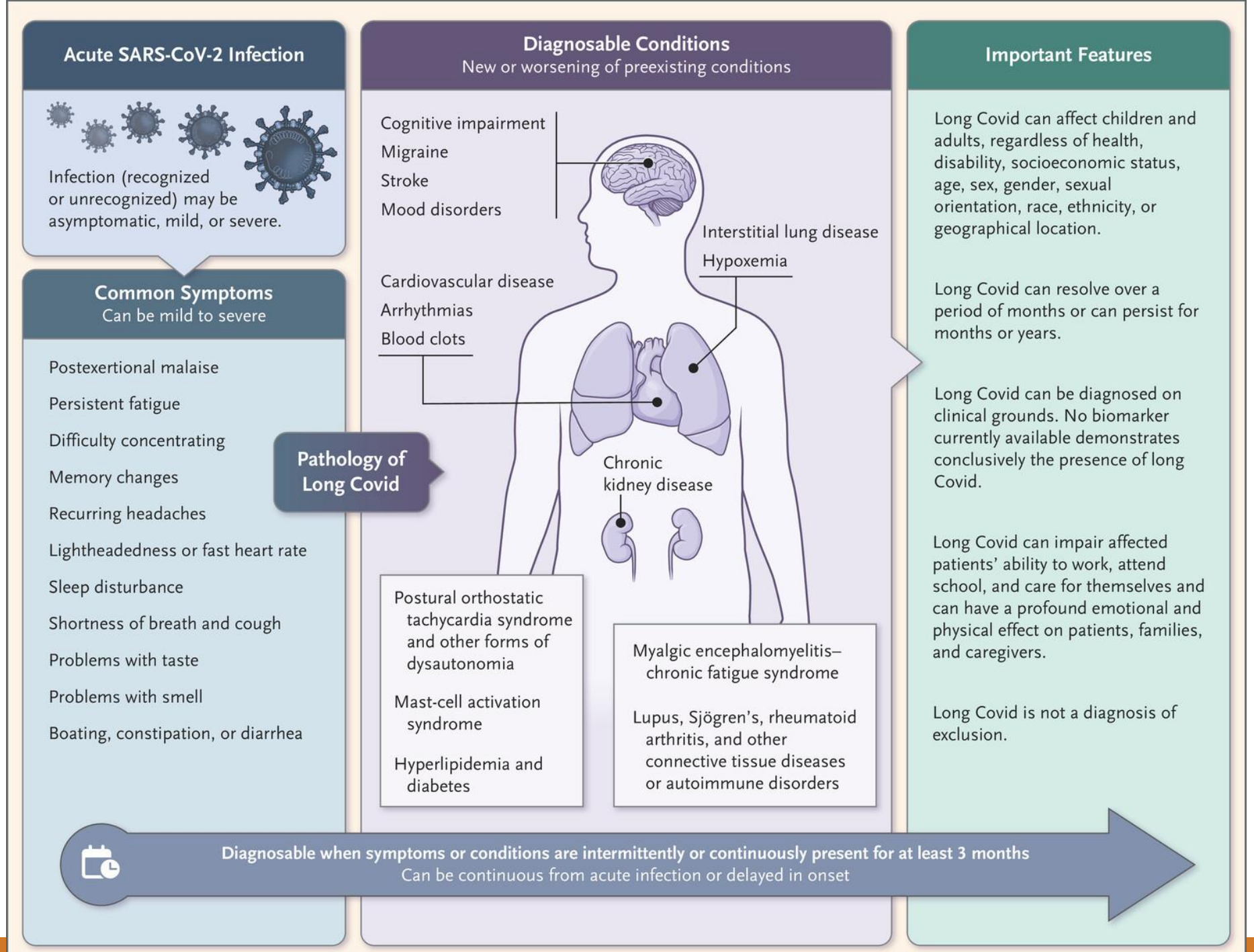
	<2 years	≥2 years	<2 years	≥2 years	Chi- square	p value	OR	CI (95 %)	
								Inf	Sup
	455	**129**	**%**	**%**					
Gender					0.001	0.974	1.01	0.68	1.49
Male	230	65	50.55	50.39					
Female	225	64	49.45	49.61					
PICU Admiss									
Yes									
No									
Oxygen ther									
Yes									
No									
Prematurity					10,402	0.001	0.47	0.29	0.75
Yes	65	34	14.29	26.36					
No	390	95	85.71	73.64					
Coinfection					2,102	0.147	0.72	0.46	1.13
Yes	96	35	21.10	27.13					
No	359	94	78.90	72.87					
Comorbidity					73,224	0.000	0.15	0.09	0.24
Yes	43	53	9.45	41.09					
No	412	76	90.55	58.91					

Conclusion: There is an increased risk of severe RSV LRTIs in children ≥2 years with prematurity or comorbidity.

… Objectives for the next Pandemic?

Objectives for Next-Generation Covid-19 Vaccines.	
Objective	**Justification**
Establishment of a correlate of protection	Reduce the need for large, expensive clinical trials to assess vaccine efficacy
Broader protection	Prevent pan-sarbecovirus transmission and infection, including for SARS-CoV-2 variants and seasonal coronaviruses
Greater duration of immunity	More effectively induce innate and adaptive immunity, with less need for booster dosing
Prevention of infection (sterilizing immunity)	Reduce the risk of transmission and asymptomatic infection
Alternative routes of administration	Permit needle-free administration, such as mucosal or transcutaneous administration
Sustainable manufacturing approaches	Promote simplicity in production; reduce costs and the need for ultrarefrigeration
Improved safety profile	Reduce the risk of local and systemic reactions
Platform plasticity	Permit scalability and rapid production; facilitate targeting of new antigens for new variants and pathogens
Increased trust and acceptance	Enhance vaccine uptake

NASEM Definition of Long COVID



Ely EW et al., NEJM 2024:
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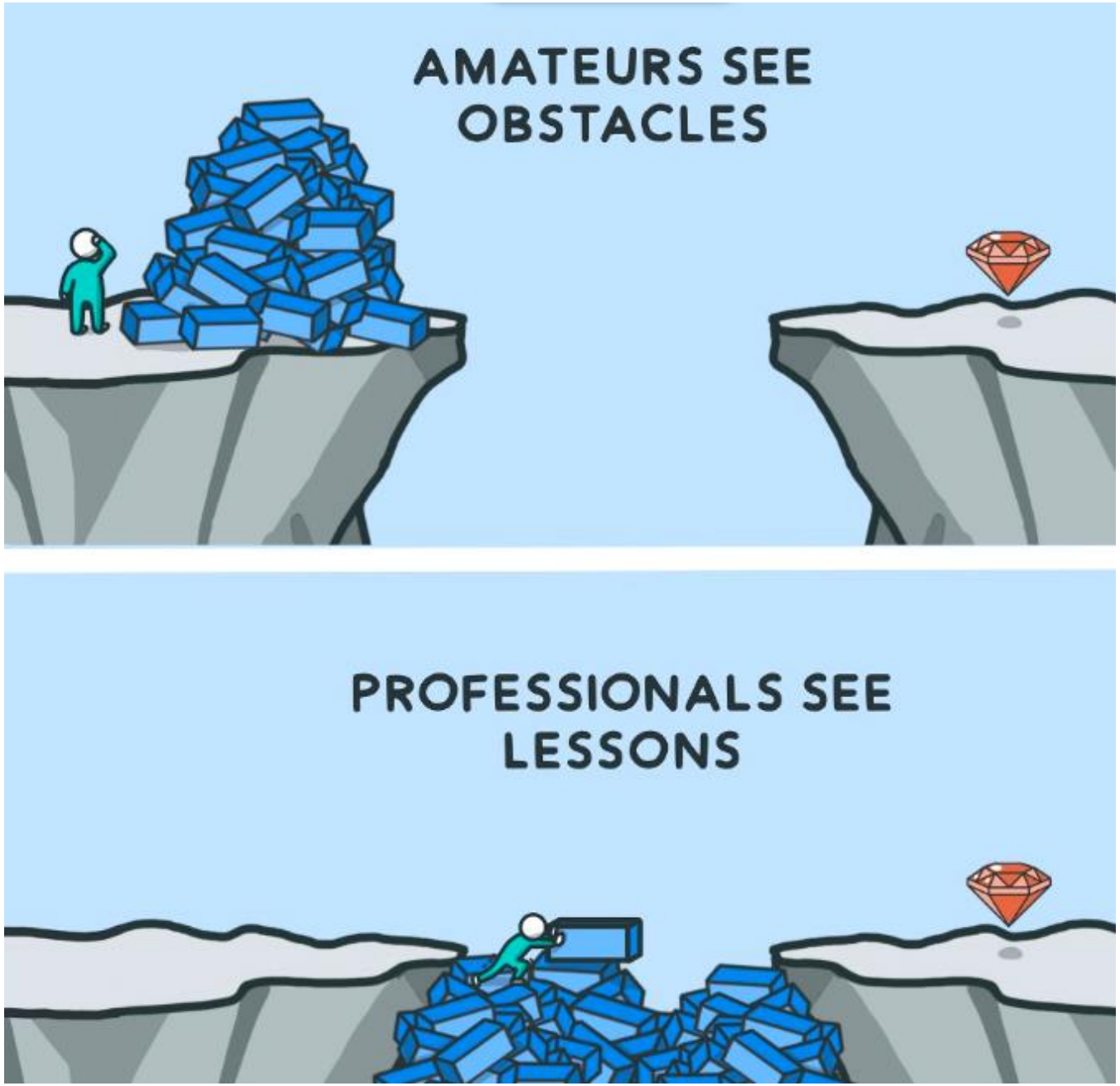
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