Dear Editors of FrontiersIn,

We discovered that the study “Paediatric COVID-19: Report From Indonesian Paediatric Society Data Registry” is very thought-provoking [1]. Pudjiadi et al concluded that “The CFR of confirmed COVID-19 cases in children in Indonesia is high and should be a major public concern.” [1]. There is a premature closure on the conclusion because of a cognitive bias in the interpretation of the statistical data including confirmation bias, anchoring bias, and availability bias. These will lead to framing effects. response bias, overconfidence and sunk cost bias.

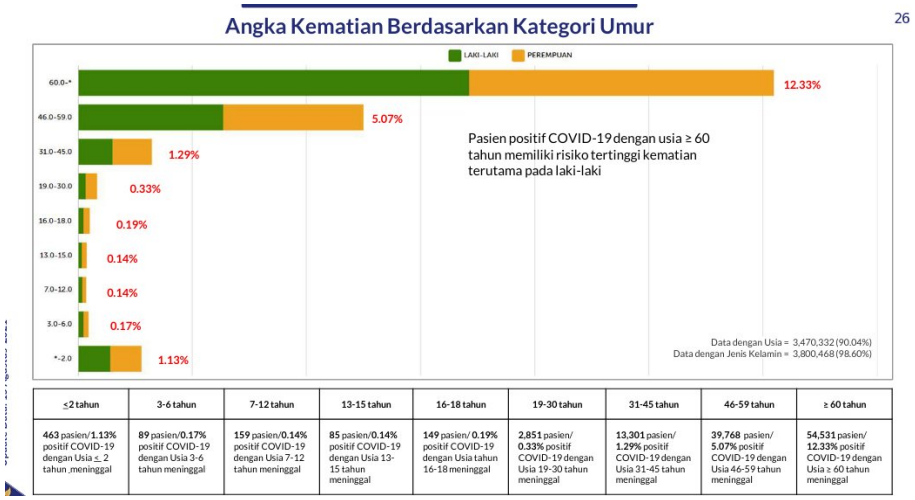
We criticise the methods of this study. We found inaccuracies in the data collected and the result because of:

1. In the method of sampling Pudjiadi et al said that the data only collected from March to December 2020, and the data did not represent the whole country's data as it reports individual paediatricians case findings. The age of data and missed interpretation can lead to the false conclusion to be used by the stakeholders at the time of publication.

The time gap between the data period (2020) and publication (September 2021) of the study is also rendering the conclusion of the study invalid. Official data from the Ministry of Health is available throughout 2021 and could have been used by the authors to provide an up-to-date analysis. The pandemic situation at time of publication is not comparable to the period analysed in the study, all parameters such as Sars-Cov2 variant in circulation, RT-PCR testing levels, levels of natural immunity (currently estimated to be at or over 80% [16]) in the population etc are very different. We have found additional examples of IPS (the authors of this study) using flawed and cherry picked data, which cannot even be verified, to make spectacular claims in the media seemingly to influence public perception and policy making: “Fatality Rate 3% - 5% [Figure 2]. This fact also needs to be considered in evaluating the reliability of the data / conclusions of the present study.

The data of this study (CFR 0.46%) is inconsistent with the official data from the Indonesian Ministry of Health, if we analyse within the following year of 2021 before the time of publication of the study. Even if we just consider the CFR, the real number as per the data from the Indonesian Health Ministry (from August 2021, in the midst of the "Delta Wave") is only 0.1%-0.2% for children aged 3-18 years. This is still based on the cause of death "with Covid" without proof of "from Covid", so the actual real number is most certainly even lower.[2]

Ministry of Health Covid19 report [2]:



≤2 tahun	3-6 tahun	7-12 tahun	13-15 tahun	16-18 tahun	19-30 tahun	31-45 tahun	46-59 tahun	≥ 60 tahun
463 pasien/**1.13%** positif COVID-19 dengan Usia ≤ 2 tahun ,meninggal	**89** pasien/**0.17%** positif COVID-19 dengan Usia 3-6 tahun meninggal	**159** pasien/**0.14%** positif COVID-19 dengan Usia 7-12 tahun meninggal	**85** pasien/**0.14%** positif COVID-19 dengan Usia 13-15 tahun meninggal	**149** pasien/ **0.19%** positif COVID-19 dengan Usia tahun 16-18 meninggal	**2,851** pasien/ **0.33%** positif COVID-19 dengan Usia 19-30 tahun meninggal	**13,301** pasien/ **1.29%** positif COVID-19 dengan Usia 31-45 tahun meninggal	**39,768** pasien/ **5.07%** positif COVID-19 dengan Usia 46-59 tahun meninggal	**54,531** pasien/ **12.33%** positif COVID-19 dengan Usia ≥ 60 tahun meninggal

Figure 1. Mortality rate based on age (Ministry of Health, August 2021)

A serology survey conducted by University of Indonesia in Jakarta [3] determined that only 8.1% of cases were found by testing. Although this was only done for Jakarta, not the whole country, done during a different time frame than the data from this paediatric study and also not specific to children, the data from this serology survey is the only such data available and is still valuable to allow us to make a rough estimation that the actual infection fatality rate (IFR) is lower by a factor of around 10 compared to the CFR. We can apply this to both the flawed CFR from the paediatric study as well as the official MOH data and obtain the following actual IFR estimates:

IFR estimate of this study: 0.046%
IFR estimate of official MOH CFR: 0.01% - 0.02% depending on age group in 2-18 years cohort.

As per WHO guidance, CFR is a flawed metric which should not be used during an ongoing pandemic and IFR should be used instead [4]

2. The confirmation of death is inaccurate because they use only RT-PCR confirmed cases as reported by a certified laboratory to the MOH. The raw data does not even include information about the Ct value of RT-PCR test, which is critical to determine the probability of an actual infection vs. probable false positive. Because of that the analysis typically focuses on a positivity reported on the RT PCR certificate. Such analyses for example clinical autopsy are important in studying the cause of death and investigating relationships between conditions reported on the death. Because statistical data derived from RT PCR laboratory certificates alone can be no more accurate than the clinical autopsy finding. None of the deaths in the raw data can be considered as “confirmed”, they are at best “suspected” and are only showing a correlation between positive Covid test and death; there is no proof or even indication of causality.

3. Children with comorbidity or injuries who died with Covid 19 positive test and a cause of death not related to Covid 19 should not be included in the analysis. According to WHO definition for death due to the Covid 19 are as below:

"*A death due to COVID-19 is defined for surveillance purposes as a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g. cancer) and should be counted independently of preexisting conditions that are suspected of triggering a severe course of COVID-19." [5]*

To illustrate this point, we present 6 examples from the raw data which, from a pathology perspective, clearly fulfil the criteria set by WHO as "*there is a clear alternative cause of death that cannot be related to COVID disease".* These are just examples demonstrating the raw data used for this study is not suitable for reaching a conclusion related to Covid 19 and this should be sufficient grounds to question the suitability and reliability of the complete dataset. *1. Chronic kidney disease, diabetic ketoacidosis, 2. Space occupying lesion in the brain, hydrocephalus, 3. Obstructive ileus (post-operative), hypovolemic shock, 4. Imperforate anus without fistula, down syndrome, congenital heart disease (suspected), 5. Ensephalitis, frontal hematoma, 6. Burn injury 45% BSA ec fire, COVID 19 confirmed, hyperkalemia, hypoalbuminemia*

4. The study is not well designed, It is a descriptive study. They said that it is a cohort retrospective study but they didn't perform multivariate analysis. In descriptive research, the researcher does not have control over several variables to explain the phenomena.

5. There were multifactor confounding factors, which must be investigated. Most of the patients have disease that is related to gut dysbiosis for example ARDS, and Septic shock. Growing evidence reveals the role of hypersensitivity and gut-lung dysbiosis in the severe COVID 19 [6,7,8,9]. Gut dysbiosis may be caused by antibiotic treatment [8,9,10]. Such investigation is provided to uncover the treatment of the patients, determining immunopathology basis and the role of dysbiosis in all of the patients.

The official Indonesian Ministry of Health treatment protocols [11] for both self-isolating Covid19 patients at home as well in hospitals include several drugs which are proven as potential contributing factors to more severe Covid19 outcomes and deaths, for examples:

1. **Azithromycin**
   Zepa et al (2020) [10] reveal that the prescription of antibiotics to prevent/treat superinfections may further and profoundly affect COVID-19 patients' microbiota, especially broad spectrum agents. A special mention should however be made of **azithromycin**—a widely prescribed antibiotic for COVID-19 treatment—since it causes a very rapid reduction in bacterial richness (23%) and Shannon diversity (13%), with microbiota composition shifted primarily in the *Actinobacteria* phylum alongside reduction of abundance in the genus *Bifidobacterium*. Hence, **azithromycin**—more than other agents—has the potential to rapidly worsen the already weak microbiota status of elderly, comorbid COVID-19 patients."
   US NIH Covid-19 Treatment guidelines [12]: "The Panel recommends against the use of chloroquine or hydroxychloroquine and/or **azithromycin** for the treatment of COVID-19 in nonhospitalized patients"

2. **Redemsivir**
   WHO recommends against the use of remdesivir in COVID-19 patients [13]
   Remdesivir and Acute Renal Failure: A Potential Safety Signal From Disproportionality Analysis of the WHO Safety Database. [14]
   Kidney disorders as serious adverse drug reactions of remdesivir in coronavirus disease 2019: a retrospective case–noncase study. [15]

For cases in the raw data where an actual Covid19 infection was present (no actual infection is shown in the raw data, only RT-PCR based Covid19 positive test), it is thus reasonable to assume that those deaths may have actually been caused by administering the wrong medication rather than by the virus itself. For this reason, the deaths in the raw data are mislabelled as “confirmed” and should be labelled as “suspected” or “with Covid19 test”. The causality is not “confirmed”, it is “assumed” or “suspected” and alternative causes of death are not only possible but even probable.

Conclusion

Based on the above findings, the conclusion of the study should be rejected. It is based on a biassed CFR from the limited dataset of the authors of the study, contradicting the official MOH data and from a period which has no relevance to the pandemic situation at time of publication and also not in line with several WHO guidances on both classification of deaths as well as mortality rates. The raw data fails to demonstrate the causality between any death and Covid-19 yet falsely labels all deaths used for the conclusion as “confirmed”. The flawed conclusion of the study is used as a basis for public health policy by the Indonesian government [Figure 1], making the rejection or correction of this flawed study even more important. The official data from the Health Ministry of CFR 0.1-0.2% / IFR 0.01-0.02% combined with the data from this study about high percentage of comorbid children among the suspected deaths leads to a very different conclusion than the one presented in the study: Death among healthy children as a consequence of Covid19 is extremely rare, adequate measures to prevent and treat infections of children with certain comorbidities should be a priority.

PENGURUS PUSAT
IKATAN DOKTER ANAK INDONESIA
(Indonesian Pediatric Society)
Committed in Improving the Health of Indonesian Children

Rekomendasi Ikatan Dokter Anak Indonesia
Pemberian Vaksin COVID-19 (Coronavac®) pada anak usia 6 tahun ke atas
Pemutakhiran 2 November 2021

Perhatian khusus

Rekomendasi ini sifatnya dinamis dan dapat berubah sewaktu-waktu sesuai dengan perkembangan bukti-bukti ilmiah yang terbaru.

Dasar Pertimbangan

1. Sudah dikeluarkannya izin penggunaan dalam keadaan emergensi vaksin Coronavac® produksi Sinovac untuk anak berusia 6-11 tahun oleh Badan Pengawas Obat dan Makanan (BPOM)
2. Proporsi kasus anak terinfeksi COVID-19 13% (Data Satuan Tugas COVID-19 Nasional 1 November 2021)
3. Telah dimulainya pembelajaran tatap muka
4. Anak dapat tertular dan atau menularkan virus corona dari dan ke orang dewasa disekitarnya (orangtua, orang lain yang tinggal serumah, orang yang datang ke rumah, teman atau guru di sekolah pada pembelajaran tatap muka) walau tanpa gejala
5. Pentingnya mengontrol secara terus menerus penularan dan tranmisi COVID-19 di Indonesia
6. Pembelajaran dari beberapa negara dunia yang melaporkan peningkatan kasus rawat inap pasien anak dengan COVID-19.

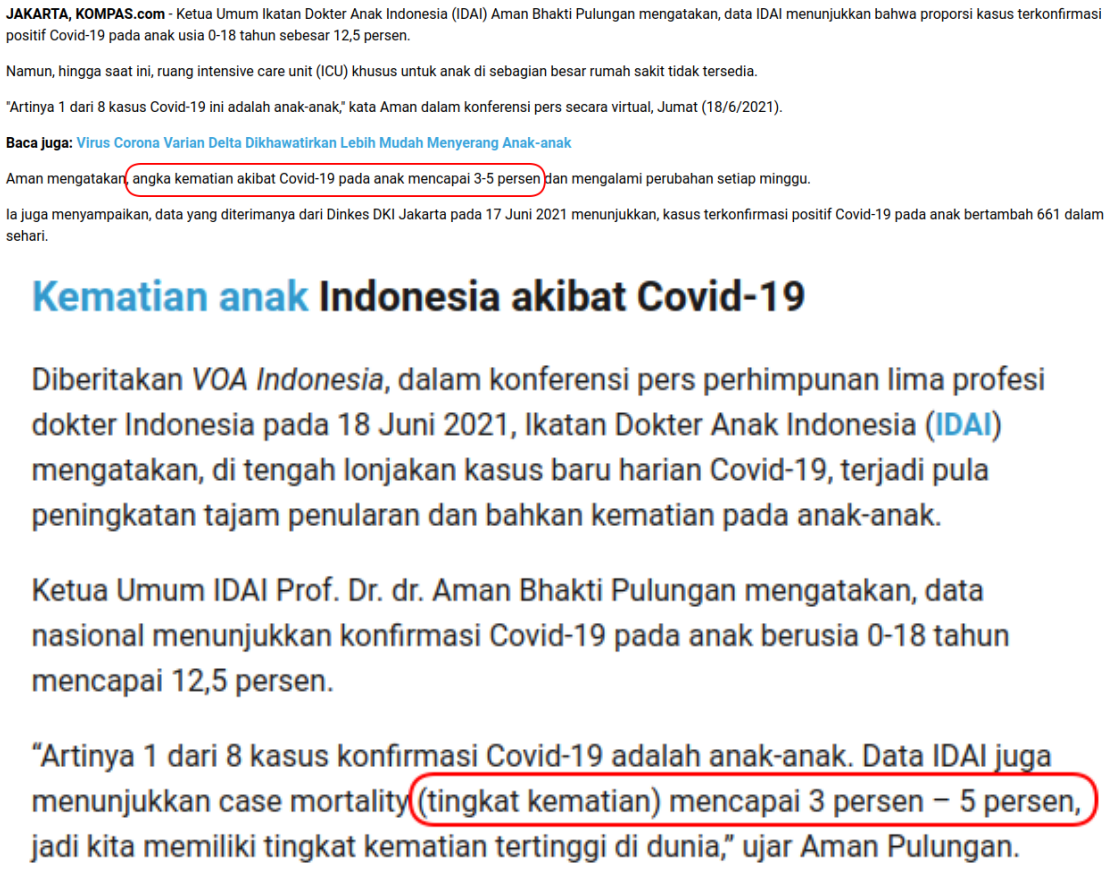
Maka Ikatan Dokter Anak Indonesia merekomendasikan sebagai berikut:

1. Pemberian imunisasi COVID-19 Coronavac ® pada anak golongan usia 6 tahun ke atas
2. Vaksin Coronovac ® diberikan secara intramuskular dengan dosis 3ug (0,5 ml) sebanyak dua kali pemberian dengan jarak dosis pertama ke dosis kedua yaitu 4 minggu
3. Kontraindikasi:
    a. Defisiensi imun primer, penyakit autoimun tidak terkontrol*
    b. Penyakit Sindrom Gullian Barre, mielitis transversa, acute demyelinating encephalomyelitis.
    c. Anak kanker yang sedang menjalani kemoterapi/radioterapi*

Sekretariat: Jl. Salemba 1 No. 5, Jakarta Pusat 10430
Tel. +62 21 314 8410, Email: ppidai@idai.or.id, website: www.idai.or.id

Figure 2. Recommendation letter from IPS (IDAI) for mass vaccination in Children.

Furthermore, this biassed publication has been used as a baseline to a framing effect. Media statements / claims about Fatality Rate 3%-5% from the authors of this study IPS (IDAI):



JAKARTA, KOMPAS.com - Ketua Umum Ikatan Dokter Anak Indonesia (IDAI) Aman Bhakti Pulungan mengatakan, data IDAI menunjukkan bahwa proporsi kasus terkonfirmasi positif Covid-19 pada anak usia 0-18 tahun sebesar 12,5 persen.

Namun, hingga saat ini, ruang intensive care unit (ICU) khusus untuk anak di sebagian besar rumah sakit tidak tersedia.

"Artinya 1 dari 8 kasus Covid-19 ini adalah anak-anak," kata Aman dalam konferensi pers secara virtual, Jumat (18/6/2021).

Baca juga: Virus Corona Varian Delta Dikhawatirkan Lebih Mudah Menyerang Anak-anak

Aman mengatakan, angka kematian akibat Covid-19 pada anak mencapai 3-5 persen dan mengalami perubahan setiap minggu.

Ia juga menyampaikan, data yang diterimanya dari Dinkes DKI Jakarta pada 17 Juni 2021 menunjukkan, kasus terkonfirmasi positif Covid-19 pada anak bertambah 661 dalam sehari.

Kematian anak Indonesia akibat Covid-19

Diberitakan *VOA Indonesia*, dalam konferensi pers perhimpunan lima profesi dokter Indonesia pada 18 Juni 2021, Ikatan Dokter Anak Indonesia (IDAI) mengatakan, di tengah lonjakan kasus baru harian Covid-19, terjadi pula peningkatan tajam penularan dan bahkan kematian pada anak-anak.

Ketua Umum IDAI Prof. Dr. dr. Aman Bhakti Pulungan mengatakan, data nasional menunjukkan konfirmasi Covid-19 pada anak berusia 0-18 tahun mencapai 12,5 persen.

"Artinya 1 dari 8 kasus konfirmasi Covid-19 adalah anak-anak. Data IDAI juga menunjukkan case mortality (tingkat kematian) mencapai 3 persen – 5 persen, jadi kita memiliki tingkat kematian tertinggi di dunia," ujar Aman Pulungan.

Figure 3. An example of framing effects.

Reference

1. Pudjiadi et al. Pediatric COVID-19: Report From Indonesian Pediatric Society Data Registry. Front. Pediatr., 23 September 2021. https://doi.org/10.3389/fped.2021.716898

2. Indonesian Ministry of Health. 2021. https://covid19.go.id/storage/app/media/Analisis%20Data%20COVID-19%20Indonesia/2021/Agustus/Analisis%20Data%20COVID-19%20Mingguan%20Satuan%20Tugas%20per%2015%20Agustus%202021-compressed.pdf

3. Result of Jakarta serology survey: https://www.cnnindonesia.com/nasional/20210719093557-20-669361/anies-separuh-warga-jakarta-pernah-terinfeksi-virus-corona

4. **WHO Scientific Brief**

5. WHO. International Guidelines For Certification And Classification (Coding) Of Covid-19 As Cause Of Death.2020. P3

6. Sanchez-Gonzalez M.A , Moskowitz D , Issuree P.D, Yatzkan G , Rizvi S.A.A, and Day K. A Pathophysiological Perspective on COVID-19's Lethal Complication: From Viremia to Hypersensitivity Pneumonitis-like Immune Dysregulation. Infect Chemother. 2020 Sep;52(3):335-344 https://doi.org/10.3947/ic.2020.52.3.335 pISSN 2093-2340·eISSN 2092-6448.

7. Aktas B and Aslim B. Gut-lung axis and dysbiosis in COVID-19. Turk J Biol (2020) 44: 265-272.

8. Yeoh YK, Zuo T, Lui GC-Y, et al. Gut 2021;70:698–706.

9. Bozkurt H.S. Intestinal Dysbiosis Might Contribute To Poor Prognosis In Covid-19.2020. ResearchGate

10. Donati Zeppa S, Agostini D, Piccoli G, Stocchi V and Sestili P.Gut Microbiota Status in COVID-19: An Unrecognised Player? Front. Cell. Infect. Microbiol. 2020: 10:576551. doi: 10.3389/fcimb.2020.576551 10.3389/fcimb.2020.576551.

11. MOH Covid19 Treatment protocol original Indonesian language: KEPUTUSAN MENTERI KESEHATAN REPUBLIK INDONESIA NOMOR HK.01.07/MENKES/5671/2021 TENTANG MANAJEMEN KLINIS TATA LAKSANA CORONA VIRU

12. US NIH Covid-19 Treatment guidelines : https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/chloroquine-or-hydroxychloroquine-and-or-azithromycin/

13. https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients

14. https://pubmed.ncbi.nlm.nih.gov/33340409/

15. https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7907730/

16. Herd Immunity estimation of 80% by Epidemiologist from Universitas Gajah Mada, November 2021 Pakar UGM Sebut 80% Penduduk RI Kena COVID Varian Delta, Ini Untung Ruginya
Statement from Indonesian Health Minister that Indonesia is estimated to have 80% herd immunity:
https://kumparan.com/kumparannews/menkes-soal-corona-turun-80-populasi-sudah-imun-nanti-dibuktikan-survei-1wtcgE8MZO1

Authors and reviewers of this letter:

Dr.Susilorini, MD.,MSi.Med.,SpPA, Departement Pathology Anatomy, Faculty of Medicine, University Islam Sultan Agung, susilorinidr@gmail.com

Dr. Puji Rianti, pujirianti@apps.ipb.ac.id

Ted Hilbert, Science and Data Coordinator, Majelis Penderitaan Rakyat (MPR, officially registered foundation “Yayasan Raudhatul Akhyar Karawang), tedhilbert@gmail.com

Ali Ridhok (Babeh Aldo), Founder, Majelis Penderitaan Rakyat (MPR, officially registered foundation “Yayasan Raudhatul Akhyar Karawang), Raudhatulakhyar135@gmail.com