1 Four points regarding reproducibility and external statistical validity: a
2 comment on Walter et al.

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10 SHORT COMMUNICATION

11 Walter et al. (2021) present phase 1–2–3 trial data that show two doses of the BNT162b2 (Pfizer–
12 BioN-Tech) Covid-19 vaccine were safe and effective in children aged 5–11 years. Given that
13 millions of children in this age group are receiving the paediatric Pfizer COVID-19 vaccine, that there
14 are potential risks, and that the balance of benefits over potential risks is more limited in children
15 compared to adults due to low rates of serious disease (ATAGI 2021), gold standards ought to be
16 applied to supporting data in terms of placebo-controlled disease endpoint efficacy trials, safety
17 databases large enough to detect adverse events, and appropriate data sharing to enable reproduction
18 and scrutiny of results. Four points are worthy of attention regarding the reproducibility and external
19 statistical validity of the analysis reported in Walter et al. (2021). ‘External validity’ refers to the
20 extent to which conclusions drawn from the data (and statistical tests thereof) are likely to correspond
21 to, or be generalisable to, the real world (Campbell 1957). ‘Reproducibility’ refers to the ability of
22 independent researchers to draw the same conclusions from the data (Kass et al. 2016).

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26 *1. Sample size of safety database*

27 2,268 participants received injections: 1,517 BNT162b2 and 751 placebo (Walter et al. 2021). No
28 myocarditis or pericarditis were reported, a finding Walter et al. state is consistent with low frequency
29 of these events in real-world data. The supporting citation (Cai et al. 2021) reports a rate of 2–3 cases
30 of myocarditis/pericarditis per million doses. Several other studies have found higher rates of these
31 events in young males, indeed their occurrence in this group has been stated to be approximately two
32 orders of magnitude higher, with estimates of 1.1 per 10,000 (ATAGI 2021; Witberg et al. 2021), 1
33 per 6,637 (Mevorach et al. 2021) or as high as 1 per 3,000 (Vogel & Couzin-Frankel 2021). Indeed,
34 a recent study of 301 13–18-year-old adolescents reported cardiovascular manifestations in 29% of
35 subjects following BNT162b2 vaccination, including seven cases of confirmed or suspected
36 myopericarditis (Mansanguan et al. 2022). Walter et al. report a low 0.14 probability of detecting an
37 event (of any nature) that has a real rate of 1 in 10,000 with 1,500 subjects (see Protocol document).
38 UK Government guidance suggests a "safety database of at least 3,000 study participants vaccinated"
39 (see [https://www.gov.uk/government/publications/access-consortium-alignment-with-icmra-](https://www.gov.uk/government/publications/access-consortium-alignment-with-icmra-consensus-on-immunobridging-for-authorising-new-covid-19-vaccines)
40 [consensus-on-immunobridging-for-authorising-new-covid-19-vaccines](https://www.gov.uk/government/publications/access-consortium-alignment-with-icmra-consensus-on-immunobridging-for-authorising-new-covid-19-vaccines), accessed 14 December
41 2021). While there are practical and ethical limits to the feasible size of safety databases in novel
42 trials (Nayak 2010), these limitations should be stated clearly in the context of previous assembly of
43 larger safety databases (e.g., Pellegrini et al. 2009 [>20,000 subjects]; Polack et al. 2020 [>40,000
44 subjects]).

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46 *2. Disease endpoint efficacy data do not demonstrate net benefit*

47 Walter et al. present data on the relative prevalence of symptomatic disease (i.e., Covid-19) in 5–
48 11-year-olds participating in the trial. The Protocol states that a minimum of 22 cases needed to be
49 detected in the surveillance period to achieve a power of 70%, below which hypothesis testing was
50 not to be conducted. The few cases of Covid-19 detected during the 5–11-year-old trial did not meet
51 this power criterion as just 16 cases of symptomatic Covid-19 were detected during the surveillance

52 period in the placebo group (~2% of subjects), compared to three in the vaccine group. These case
53 rates represent an absolute risk reduction of just 2%, which does not demonstrate a balance of
54 benefits over risks in terms of relative frequency and severity of disease symptoms versus adverse
55 events. Children usually have mild Covid-19 symptoms (Alsohime et al. 2020) while close to a
56 third of young vaccine recipients may experience cardiovascular events, with a report of 2%
57 showing elevated cardiac biomarkers or positive lab assessments (Mansanguan et al. 2022).
58 Additionally, the study addressed neither prevention of asymptomatic infection nor subsequent
59 transmission in children, as only symptomatic infection was recorded in the trial.

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61 *3. Efficacy surveillance period*

62 Walter et al. calculate efficacy based on surveillance periods of 322 person-years (treatment) and 159
63 person-years (control), respectively, or the equivalent of approximately three months per participant,
64 and report VE of 90.7%. Antibody titres are expected to peak during this period (though correlates of
65 protection are unknown), following which there is a well-documented decline in BNT162b2 efficacy
66 (Eyre et al. 2021; Goldberg et al. 2021; Singanayagam et al. 2021). The reported VE, then, can only
67 be applied to this immediate post-vaccination period. Additionally, natural immunity conferred via
68 past infection is prolonged (Wu et al. 2021) and therefore absolute risk reduction and potential
69 benefits of vaccination decline over the course of the pandemic, while potential harms remain.

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71 *4. Reproducibility*

72 It is in the public interest that the analytical data used to support peer-reviewed publication of a
73 clinical trial are shared early (with appropriate protections; IOM 2015; Dron et al. 2021). Sharing
74 data allows findings to be independently reproduced, which is an important component of the
75 scientific process (Kass et al. 2016; Boeckhout et al. 2018), and supports integration of studies that
76 did not reach adequate power individually (Dron et al. 2021). The analytical data reported in Walter
77 et al. are available subject to vetted requests two years after the study ends (estimated completion

78 date May 2024; <https://clinicaltrials.gov/ct2/show/NCT04816643>, accessed 13 September 2022).
79 This embargo period represents an “unacceptable delay” (Doshi et al. 2022) and prevents independent
80 researchers from scrutinising or reproducing the conclusions made from the data in the meantime
81 (Krumholz & Peterson 2014).

82

83 *Conclusion*

84 The consequential findings of Walter et al. cannot be immediately independently reproduced because
85 supporting analytical data will not be released for 24 months following study completion. While
86 withholding data in this manner is not unusual, it prevents scrutiny that should be encouraged where
87 findings have consequences for millions of young children over the intervening period. The external
88 validity and generalisation of the findings may be limited by the relatively small size of the safety
89 database, the small number of recorded symptomatic cases in the RCT and the immediately post-
90 vaccination timeframe of the efficacy data, meaning that reported VE cannot be generalised through
91 time given observed waning of real-world efficacy. The emergence of the Omicron variant following
92 publication of this study casts further doubt on real-world vaccine efficacy given the variant has a
93 number of mutations linked to antibody escape and increased transmissibility (Karim & Karim 2021).

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95 *References*

- 96 Alsohime, F., Temsah, M. H., Al-Nemri, A. M., Somily, A. M. & Al-Subaie, S. (2020) COVID-19
97 infection prevalence in pediatric population: Etiology, clinical presentation, and outcome.
98 *Journal of Infection and Public Health*, 13, 1791-1796.
- 99 ATAGI (2021) ATAGI recommendations on the use of the paediatric Pfizer COVID-19 vaccine in
100 children aged 5 to 11 years in Australia. Australian Government, Department of Health.
- 101 Boeckhout, M., Zielhuis, G. A. & Bredenoord, A. L. (2018) The FAIR guiding principles for data
102 stewardship: fair enough? *European Journal of Human Genetics*, 26, 931-936.

103 Cai, C., Peng, Y., Shen, E., *et al.* (2021) A comprehensive analysis of the efficacy and safety of
 104 COVID-19 vaccines. *Molecular Therapy*, 29, 2794-2805.

105 Campbell, D. T. (1957) Factors relevant to the validity of experiments in social settings.
 106 *Psychological Bulletin*, 54, 297–312.

107 Doshi, P., Godlee, F. & Abbasi, K. (2022) Covid-19 vaccines and treatments: we must have raw
 108 data, now. *BMJ*, 376, o102.

109 Dron, L., Dillman, A., Zoratti, M. J., Haggstrom, J., Mills, E. J. & Park, J. J. (2021) Clinical trial
 110 data sharing for COVID-19–related research. *Journal of Medical Internet Research*, 23,
 111 e26718.

112 Eyre, D. W., Taylor, D., Purver, M., *et al.* (2021) The impact of SARS-CoV-2 vaccination on Alpha
 113 and Delta variant transmission. *medRxiv*. DOI: <https://doi.org/10.1101/2021.09.28.21264260>

114 Goldberg, Y., Mandel, M., Bar-On, Y.M., *et al.* (2021) Waning immunity after the BNT162b2
 115 vaccine in Israel. *New England Journal of Medicine*, 385, e85. DOI:
 116 10.1056/NEJMoa2114228

117 Institute of Medicine (IOM) (2015) Sharing clinical trial data: Maximizing benefits, minimizing
 118 risk. The National Academies Press, Washington, DC.

119 Karim, S. S. A. & Karim, Q. A. (2021) Omicron SARS-CoV-2 variant: a new chapter in the
 120 COVID-19 pandemic. *The Lancet*, 398, 2126-2128.

121 Kass, R. E., Caffo, B. S., Davidian, M., Meng, X-L., Yu, B. & Reid, N. (2016) Ten simple rules for
 122 effective statistical practice. *PLoS Computational Biology*, 12, e1004961.

123 Krumholz, H. M. & Peterson, E. D. (2014) Open access to clinical trials data. *JAMA*, 312, 1002-
 124 1003.

125 Mansanguan, S., Charunwatthana, P., Piyaphanee, W., Dechkhajorn, W., Poolcharoen, A. &
 126 Mansanguan, C. (2022) Cardiovascular manifestation of the BNT162b2 mRNA COVID-19
 127 vaccine in adolescents. *Tropical Medicine and Infectious Disease*, 7, 196.

128 Mevorach, D., Anis, E., Cedar, N., *et al.* (2021) Myocarditis after BNT162b2 mRNA vaccine
 129 against Covid-19 in Israel. *New England Journal of Medicine*, 385, 2140-2149.

130 Nayak B. K. (2010) Understanding the relevance of sample size calculation. *Indian Journal of*
 131 *Ophthalmology*, 58, 469-470.

132 Pellegrini, M., Nicolay, U., Lindert, K., Groth, N. & Della Cioppa, G. (2009) MF59-adjuvanted
 133 versus non-adjuvanted influenza vaccines: integrated analysis from a large safety database.
 134 *Vaccine*, 27, 6959-6965.

135 Polack, F.P., Thomas, S.J., Kitchin, N., *et al.* (2020) Safety and efficacy of the BNT162b2 mRNA
 136 Covid-19 vaccine. *New England Journal of Medicine*, 383, 2603-2615.

137 Singanayagam, A., Hakki, S., Dunning, J., *et al.* (2021) Community transmission and viral load
 138 kinetics of the SARS-CoV-2 delta (B. 1.617. 2) variant in vaccinated and unvaccinated
 139 individuals in the UK: a prospective, longitudinal, cohort study. *The Lancet Infectious*
 140 *Diseases*. DOI: [https://doi.org/10.1016/S1473-3099\(21\)00648-4](https://doi.org/10.1016/S1473-3099(21)00648-4)

141 Vogel, G. & Couzin-Frankel, J. (2021) Israel reports link between rare cases of heart inflammation
 142 and COVID-19 vaccination in young men. *Science*.

143 Walter, E. B., Talaat, K. R., Sabharwal, C., *et al.* (2021) Evaluation of the BNT162b2 covid-19
 144 vaccine in children 5 to 11 years of age. *New England Journal of Medicine*. DOI:
 145 10.1056/NEJMoa2116298

146 Witberg, G., Barda, N., Hoss, S., *et al.* (2021) Myocarditis after Covid-19 vaccination in a large
 147 health care organization. *New England Journal of Medicine* 385, 2132-2139.

148 Wu, J., Liang, B., Chen, C., *et al.* (2021) SARS-CoV-2 infection induces sustained humoral
 149 immune responses in convalescent patients following symptomatic COVID-19. *Nature*
 150 *Communications*, 12, 1813.

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