Letter to the Editor

No Role for Reintroducing OPV into the United States with Respect to Controlling COVID-19 [Response to the letter to the Editor by Chumakov et al.]

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1. OUR MOTIVATION

We appreciate the opportunity to respond to the points raised (Chumakov, Jamison, Aaby, Benn, & Gallo, 2021) about our health economic analysis (Thompson, Kalkowska, & Badizadegan, 2021), which we organize by theme. The letter (Chumakov, Jamison, Aaby, Benn, & Gallo, 2021) asserts that the “evident purpose of the paper was to attack the hypothesis that was recently published” by (Chumakov, Benn, Aaby, Kottilil, & Gallo, 2020). We respectfully disagree. A critical evaluation of a hypothesis does not constitute an “attack.” Consistent with the title and actual content of our study, we sought to objectively assess the health and economic impacts of reintroducing OPV into the United States to control COVID-19. In the context of updating (Thompson & Kalkowska, 2021b) a prior health economic analysis of the Global Polio Eradication Initiative (GPEI) (Duintjer Tebbens et al., 2011), we searched for evidence related to any externalities of GPEI investments. Our review of the published literature related to nonspecific effects of OPV (Thompson, Kalkowska, & Badizadegan, 2021, Section 3.4) concluded that the available studies “do not provide evidence suggestive of a measurable impact across the U.S. population” and that “for purposes of health economic analyses we do not see sufficient evidence of a benefit to model (i.e., no positive externalities relevant for potential inclusion in polio or COVID-19 health economic analyses).” Thus, we did not omit consideration of benefits. We explicitly stated that we could not find any available evidence sufficient to support any characterization of such benefits based on careful review. In contrast, based on our prior polio modeling relevant to the United States (Duintjer Tebbens et al., 2006; Thompson, 2015; Thompson et al., 2012; Thompson & Duintjer Tebbens, 2006; Thompson & Kalkowska, 2021a; Thompson, Kalkowska, & Duintjer Tebbens, 2015), we explicitly characterized the expected adverse health effects associated with administering OPV to the U.S. population in 2020 (Thompson et al., 2021, Section 3.3). In cost-effectiveness analysis, the intervention of delivering OPV to the U.S. population fits the characterization of “dominated” (i.e., it implies paying money to obtain net expected worse health outcomes), as implied by our conclusion that “health economic modeling suggests no role for reintroducing OPV into the U.S. with respect to controlling COVID-19.”

2. THE SCOPE OF OUR ANALYSIS

The letter (Chumakov et al., 2021) asserts that our analysis “addresses a straw man” and that the perspective by Chumakov et al. (2020) argued “the high value of randomized controlled trials to assess the existence and quantitative magnitude of this potential nonspecific effect of OPV.” The letter is correct that the original perspective by Chumakov et al. (2020) did not specifically propose to use OPV in the United States to control COVID-19. However, the perspective included multiple statements related to OPV use in the United States (e.g., “…in countries with sufficient vaccine coverage, the risk is minimal:
Over 35 years of OPV use in the United States has resulted in no documented case of cVDPV” (Chumakov et al., 2020). The perspective also stated that: “If the results of RCTs with OPV are positive, OPV could be used to protect the most vulnerable populations. However, OPV would be most effective if the entire population of a country or region is immunized synchronously” (Chumakov et al., 2020). More importantly, the letter (Chumakov et al., 2021) ignored quotes from the authors of the perspective reported in the mainstream media coverage of the perspective (some of which we cited in our study) (Cohn, 2020; Gallo & Arbess, 2020; Sullivan, 2020), which included very low cost estimates based on no actual economic analysis and furthered the concept of delivery to the entire U.S. population, possibly repeatedly (Gallo & Arbess, 2020). To date, we note no corrections or retractions of the cost estimates or discussions of repeated immunization for the entire U.S. population in these mainstream media pieces. Although we did not include this in our study, one article also stated: “The group is awaiting final federal approval for trials, which are planned in Maryland and New York among other sites using approximately 11,000 volunteers. They received donations of the vaccine but also are awaiting federal funding to conduct the studies.” (Cohn, 2020) We found and included mention of advanced planning for just such a clinical trial (NCT04540185) in our study (Thompson et al., 2021). Thus, although the letter (Chumakov et al., 2021) asserts that the perspective “did not even propose doing clinical trials in the United States: there are more than 140 countries with a total population of six billion people where this could be easily done,” our study provided evidence of plans to conduct such trials in the United States. We found and provided sufficient support of the consideration of widespread use of OPV in the United States to respond to COVID-19 to motivate our health economic study.

3. COST ESTIMATION AND THE VALUE OF INFORMATION

The letter (Chumakov et al., 2021) suggests that mass media coverage (Cohn, 2020; Sullivan, 2020) of the perspective either misquoted the authors of the perspective or misrepresented the costs by providing “(low) journalistic estimates.” We suggest that the authors of the letter should take up any issues of misquoting or misrepresentation with the authors of the mass media coverage. We note that a piece by one of the letter authors explicitly stated that: “Stimulating the innate immune system with OPV looks like a free and safe option for saving lives while we wait for an effective Covid-19 vaccine” (Gallo & Arbess, 2020), and we quoted this characterization of “free” in our health economic analysis (Thompson et al., 2021).

The letter (Chumakov et al., 2021) suggests that “Perhaps the key economic question to be addressed at this point concerns the value of the information clinical trials would provide on the magnitude and duration of an OPV effect.” Our health economic analysis suggests no expected benefits (Thompson et al., 2021, Section 3.4) and real expected financial costs (Thompson et al., 2021, Section 3.2) and health costs (Thompson et al., 2021, Section 3.3). Based on this health economic analysis and the inability to obtain OPV for use in the US in 2020 (Thompson et al., 2021, Section 3.1) and challenges associated with the logistics of its delivery (Thompson et al., 2021, Section 3.5), we expect the costs of using OPV in the US to respond to COVID-19 to far exceed the benefits. Given this outcome, the time delays associated with performing clinical trials, and our experience with performing value of information analyses (de Gourville, Sangrujee, Duintjer Tebbens, Pallansch, & Thompson, 2006; Thompson & Evans, 1997; Thompson & Graham, 1996; Yokota & Thompson, 2004a, 2004b), we did not anticipate any positive value of information for performing even the clinical trial in the US with respect to responding to COVID-19. The risks and costs of reintroducing OPV into the US differ from other countries, however, and as such, our analysis applies specifically to the US as we discussed (Thompson et al., 2021, Section 4). Any clinical trials using OPV in the US will need to consider the risks and costs of such use, including the potential liability for the vaccine manufacturer (Thompson et al., 2021).

4. RISK OF VACCINE-ASSOCIATED PARALYTIC POLIO (VAPP)

The letter (Chumakov et al., 2021) asserts that we “erroneously claim that more than 10% of U.S. population is ‘fully susceptible’ to poliomyelitis. This contradicts the very conclusion of the seroprevalence study they cite and ignores waning of antibody levels that occurs with age, without making people susceptible to poliomyelitis.” As we discussed (Thompson et al., 2021, Section 3.3), we performed modeling that accounts for actual historical OPV and IPV vaccine coverage in the United States as well as historical transmission and we compare our results
to measurements from serological studies. Our estimates of VAPP reflect the reality that for over 20 years, the entire annual birth cohort received only IPV vaccine, which occurred with less than 100% coverage and induces immunological protection at a less than 100% take rate. Thus, every year for the past 20 years, the population of fully susceptible Americans with no exposure to live poliovirus transmission and that did not receive or did not take IPV continued to accumulate. The estimates from our model suggest a lower fraction of fully susceptible individuals than would be implied by direct use of the serological study results as we discussed (Thompson et al., 2021, Section 3.3). During the past 20 years, efforts by the Pan American Health Organization and the GPEI substantially reduced the risks of importation of wild polioviruses into the United States, and high IPV coverage inhibited the risk of transmission of OPV-related viruses. These conditions support the accumulation of a group of fully susceptible (mostly young) Americans, who would be at risk of VAPP in the event of OPV vaccine administration to all Americans (at least without delivery of an IPV dose first), with known differences for the three poliovirus serotypes. Prior to the United States shifting from OPV to IPV, the United States reported approximately 10 cases of VAPP annually (Thompson & Duintjer Tebbens, 2006) (one to seven of these annually captured through adverse event reporting systems in the 1990s (Thompson, 2015). Thus, the cumulative build-up of fully susceptible Americans, which would also include some older adults who by chance escaped exposure to live polioviruses and never received polio vaccines, leads to our estimates. As discussed, these estimates fully account for prior immunization with IPV and OPV. In addition, the experience in Israel (1) included the identification and vaccination of fully susceptible individuals with IPV prior to reintroducing OPV, (2) occurred after a shorter period of time of accumulation (i.e., between the national OPV use cessation in 2005 and resumption in 2014), and (3) involved a much smaller national population (Kalkowska et al., 2015). Delivery of an IPV dose to all Americans prior to delivery of an OPV dose would substantially increase the costs and did not appear as a consideration in the original perspective (Chumakov et al., 2020).

5. INSUFFICIENT CARE IN OUR REVIEW

The letter (Chumakov et al., 2021) suggests that we dismissed “the solid body of literature indicating that OPV (and other live attenuated vaccines) produce nonspecific protective effects.” Contrary to this statement, we did in fact cite and analyze the referenced body of work as well as all other available studies in detail (Thompson et al., 2021, Section 3.4). Our objective consideration of the overall body of literature, including two independent systematic reviews commissioned by the World Health Organization, still leaves considerable doubt about nonspecific effects of live attenuated vaccines as targeted therapies for any disease (Higgins et al., 2016; Kandasamy et al., 2016).

6. THE VALUE OF SCIENTIFIC DISCOURSE

Remarkably, the letter concludes with the opinion that our analysis is “deeply flawed” and “stifles medical research at the potential costs of hundreds or thousands of lives.” We do not believe that the letter demonstrates flaws in our analysis or provides its own analysis to support the claim that our paper implies potential costs of hundreds or thousands of lives. We appreciate that journals recognize their responsibility for maintaining a degree of accuracy and balance, that we feel our paper introduced into policy discussions more realistic cost estimates and potential health risks than provided by the authors of the hypothesis that using OPV could help with the response to COVID-19 (Chumakov et al., 2020; Cohn, 2020; Gallo & Arbess, 2020; Sullivan, 2020).

We sympathize with the sentiments of the letter in desperately seeking a cure for COVID-19. However, promising nonspecific positive benefits at low (or no) implied costs, can lead to misperceptions about what the public can expect. As experts in risk analysis, pathology, poliovirus transmission modeling, and health economics, we are uniquely in a position to quantitatively evaluate the health and economic outcomes of reintroducing OPV in the United States. We hope that our work will encourage readers to fully engage in the scientific discourse, evaluate the evidence carefully for themselves, and demand that scientific journals and media coverage related to journal publications provide realistic and well-supported evidence as a basis for any claims.

We suggest that any reintroduction of OPV into the United States should follow active discussion by public health leaders about the risks, costs, and benefits of such use, and hope that future dialogue continues in peer-reviewed channels rather than solely
in viewpoints, tweets, or the lay press. We continue to see no role for reintroducing OPV into the US with respect to controlling COVID-19, particularly with the recent encouraging results related to late-stage trials of specific vaccines for COVID-19. The likely introduction of COVID-19 specific vaccines for widespread use prior to the start of a clinical trial to explore the benefits of OPV to respond to COVID-19 adds further evidence of little or no value of information expected from the clinical trial and saved trial costs and avoided OPV-related risks.

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