Trends in population health and demography

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attributable to CYP2C19 metaboliser phenotypes.

For this brief reply, descriptive summaries are provided to evaluate efficacy (day 42 mortality), safety (treatment-related adverse events), and CYP2C19 metaboliser phenotypes. Given the small numbers, the effects of reduced enzyme activity (ie, results from the poor and intermediate metabolisers) and increased enzyme activity (ie, results from the rapid and ultrarapid metabolisers) were pooled. We found trends in the opposite direction than would be predicted if increased CYP2C19 activity adversely affected efficacy, as there were similar mortality rates between participants with reduced enzyme activity and extensive metabolisers, and lower mortality rates in participants with increased enzyme activity (appendix). Safety endpoints were also evaluated. For voriconazole, there was a weak trend in the opposite direction than would be predicted if reduced CYP2C19 activity had adversely affected safety, with higher rates of treatment-related adverse events seen in participants with increased enzyme activity. Hepatic safety showed a trend in the expected direction, with the highest rate of treatment-related adverse events among participants with reduced enzyme activity and the lowest among participants with increased enzyme activity (appendix). However, the relatively small number of participants and events decreased the precision of these observations.

In summary, there were no clear trends to support previous reports of an association between CYP2C19 phenotype and voriconazole efficacy or safety outcomes.[1] However, given the limitations of the small sample sizes within this dataset, we cannot convincingly conclude that such an association does not exist.

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1 Maertens JA, Rahav G, Lee D-G, et al. Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. *Lancet* 2021; **397:** 499–509.

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Stein Vollset and colleagues forecasted that population increase in sub-Saharan Africa will continue until 2100. Consequently, three of the region's countries will join Nigeria among the ten most populous countries globally: DR Congo, Ethiopia, and Tanzania.[1] Although we applaud the authors for including alternative scenarios based on change in educational attainment and access to contraception, the Article neglects safe childbirth as a co-driver of decreasing fertility rates.

According to Vollset and colleagues, educational attainment and contraceptive met need account for 80·5% of the variance in cohort fertility at age 50 years.[1] Including survival at birth as a covariate might be seen as a minor factor and difficult to predict; however, neglecting this driver throughout the Article risks presenting an unjustifiably simplified solution for overpopulation. Moreover, it could exacerbate the dangerous misconception that saving lives at birth leads to additional overpopulation and accelerated climate change.[2]

Across different cultures, when parents see their offspring survive childbirth and early childhood, they start planning for fewer children than originally intended and focusing on optimising their education and social circumstances. This dynamic, however, can take time and is interlinked with multiple other factors, such as a decline in the need for child labour and increased access to education and contraception.[3]

Although other causes of child mortality show promising declines, the epidemic of stillbirths and early neonatal deaths is underprioritised. In addition to a strong ethical and humanitarian imperative, ending this global burden of more than 5 million lost lives per year is forecasted to have a positive effect on demography and climate change.[4,5]

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1 Vollset SE, Goren E, Yuan C-W, et al. Fertility, mortality, migration, and population scenarios for 195 countries and territories from 2017 to 2100: a forecasting analysis for the Global Burden of Disease Study. *Lancet* 2020; **396:** 1285–306.
2 Rosling H, Rönnlund AR, Rosling O. Factfulness: ten reasons we're wrong about the world—and why things are better than you think. New York, NY: Flatiron Books, 2018.
3 Omran, A. The epidemiologic transition. A theory of the epidemiology of population change. *Milbank Mem Fund Q* 1971; **49:** 509–38.
4 You D, Hug L, Ejdemyr S, et al. Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Inter-agency Group for Child Mortality Estimation. *Lancet* 2015; **386:** 2275–86.

David Turnley/Corbis/VCG/Getty Images

5 Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet* 2016; **387:** 587–603.

Stein Vollset and colleagues concluded that the global population would most likely peak around 2064 with 9·7 billion people.[1] The media have focused on their claims of economic challenges from "inverted age pyramids". Both the projections and the prognosis are highly questionable and are doing a great disservice to women's reproductive rights and the global prospects for environmental security by undermining political will for eliminating unwanted births and ending population growth sooner rather than later.

One of many reasons for concern is that Vollset and colleagues' model shows an acceleration of fertility decline in sub-Saharan Africa starting from 2006.[1] This change is important in setting the trend for future decline. However, this trend is not seen with data from the UN or the Population Reference Bureau (appendix). This absence of evidence could suggest that the model is already overestimating the extent to which increases in educational attainment have reduced fertility. By modelling completed cohort fertility at age 50 years against average educational attainment at age 25 years, the 25-year lag misses the slowdown of fertility decline from the late 1990s,[2] which has been more strongly linked to waning family planning programmes than to educational attainment.[3,4]

More concerning is their unfounded claim that employment, and therefore gross domestic product, will depend on working-age proportion. The countries with the greatest extent of population ageing, such as Japan and Germany, have seen no such decline in employment, only an increase in workforce participation. When population decline offers so much benefit for minimising climate change, biodiversity loss, and food insecurity, it is irresponsible to use an untested assumption to advocate boosting growth, as Vollset and colleagues do.

I declare no competing interests.

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1 Vollset SE, Goren E, Yuan C-W, et al. Fertility, mortality, migration, and population scenarios for 195 countries and territories from 2017 to 2100: a forecasting analysis for the Global Burden of Disease Study. *Lancet* 2020; **396:** 1285–306.
2 Bongaarts J. Fertility transitions in developing countries: progress or stagnation? *Stud Fam Plan* 2008; **39:** 105–10.
3 de Silva T, Tenreyro S. Population control policies and fertility convergence. *J Econ Perspect* 2017; **31:** 205–28.
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As scientists and stakeholders in the field of population, we are concerned that the highly publicised population forecasts by Stein Vollset and colleagues,[1] and their models, data, and underlying assumptions, have not received enough critical scrutiny.

For example, some of the baseline data differ substantially from other available datasets derived from global (eg, the UN) and national or regional statistical offices (eg, Eurostat), and the migration scenarios deliver seemingly contradictory results. Observed data for completed cohort fertility of women at age 50 years who were born between 1955 and 1968 were used to partly project completed cohort fertility of women at age 50 years for younger cohorts who were born in 1969–2002 with incomplete fertility histories. These two datasets were jointly used to project future completed cohort fertility of women at age 50 years born in 2003–85, which can be found in the appendix.[1] We believe that the resulting fertility scenarios rest on highly uncertain estimates of the share of women with met need for contraception and its projected future trends. On the contrary, the mortality assumptions appear conservative in the context of research on the gains in longevity in the past century.[2] Problematic conceptions of the working-age population and measures of ageing were used, which do not account for changes in characteristics at either the individual or population level.

Vollset and colleagues adopt an overly simplistic approach to complex social processes, such as migration theory and policy, and the conceptual relationship between access to family planning and universal fertility outcomes. Simplistic views of the relationship between shifting population dynamics and climate change, the economy, and health systems are repeated in many of the authors' representations to the media.

The Article notes "A very real danger exists that, in the face of declining population, some states might consider adopting policies that restrict female reproductive health rights and access to services." It is for precisely this reason that projections of fast declines in fertility and population require greater critical scrutiny than ever before.

SG-B and TS have been involved in the development of the Wittgenstein Center for Demography and Global Human Capital forecasts. Signatories of this Correspondence are listed in the appendix.

Editorial note: the *Lancet* Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

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1 Vollset SE, Goren E, Yuan C-W, et al. Fertility, mortality, migration, and population scenarios for 195 countries and territories from 2017 to 2100: a forecasting analysis for the Global Burden of Disease Study. *Lancet* 2020; **396:** 1285–306.

For more about the **UN World Population Prospects 2019** see https://population.un.org/wpp

For more on the **Population Reference Bureau datasheets** see https://www.prb.org/datasheets

See **Online** for appendix

For more on the **Eurostat Population Database** see https://ec.europa.eu/eurostat/web/population-demography-migration-projections/data/database

See **Online** for appendix