3 Safeguarding Health in Conflict Coalition. Violence on the front lines: attacks on health care in 2017. May, 2018. https://www.safeguardinghealth.org/sites/shcc/files/SHCC2018final.pdf (accessed May 8, 2019).
4 Buissonniere M, Woznick S, Rubenstein L. The criminalization of healthcare. June, 2018. https://www1.essex.ac.uk/hrc/documents/54198-criminalization-of-healthcare-web.pdf (accessed Sept 23, 2019).
5 Charny, JR. Counter-terrorism and humanitarian action: the perils of zero tolerance. March 20, 2019. https://warontherocks.com/2019/03/counter-terrorism-and-humanitarian-action-the-perils-of-zero-tolerance/ (accessed May 8, 2019).

Authors' reply

We thank Lisa Forman and colleagues, and Leonard S Rubenstein and Joseph J Amon, for commenting on our *Lancet* Commission report on the legal determinants of health.[1] Both letters raise key challenges in national and global health law and the vital importance of high-level leadership.

Forman and colleagues offer a compelling case for educating the health workforce on human rights law. Our Commission stressed the enhancement of legal capacities on the right to health, and we strongly support any actions to make human rights a core competency of health professionals—not only in formal education, but also in continued training. However, powerful structural barriers militate against the very idea of advancing the right to health. To change the political dynamics around human rights, we propose high-level guidance to states that encourages human rights training throughout the workforce. A transformative step would be if the UN High Commissioner for Human Rights, Michelle Bachelet, and WHO Director-General, Tedros Ghebreyesus, acted jointly to issue guidance to UN and WHO member states.

Advancing the human rights and health needs of people living in fragile and conflict-affected states is also vital, as articulated by Rubenstein and Amon. They rightly identify the rule of law as the foundational determinant of health: without it, questions surrounding sustainable development, good governance, effective institutions, and evidence-based interventions essentially have no practical relevance.

Armed conflict, political instability, and public distrust erode health systems, push people (especially the marginalised) further into poverty, and cause mass migrations. Complex humanitarian crises accelerate the spread of infectious diseases and other risks to health. The ongoing epidemic of Ebola virus disease in the Democratic Republic of the Congo provides perhaps the starkest illustration of a health emergency occurring under conditions of profound unrest.[2] Many states with a mean life expectancy younger than 60 years are conflict-ridden or post-conflict, fragile, or experiencing a breakdown in governance, such as the Central African Republic, Chad, the Democratic Republic of the Congo, Nigeria, and Somalia.[3] Ill-conceived sanctions can harm people and impede humanitarian assistance, including essential vaccines and medicines.

As Rubenstein and Amon aptly point out, a robust understanding of the interaction between health and the rule of law has particular importance in states experiencing conflict and lawlessness. Dealing with health emergencies during complex humanitarian crises—such as those in Afghanistan, Haiti, Syria, and Yemen—has sadly become the norm.[4] Our proposed, independent standing *Lancet* Commission on global health and the law could find new ways to advance the right to health in the world's most unstable regions.

LOG and JTM were co-chairs of the *Lancet* Commission on the legal determinants of health. All authors declare no competing interests.

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1 Gostin LO, Monahan JT, Kaldor J, et al. The legal determinants of health: harnessing the power of law for global health and sustainable development. *Lancet* 2019; **393:** 1857–910.
2 Gostin LO, Phelan A, Godwin Coutinho A, et al. Ebola in the Democratic Republic of the Congo: time to sound a global alert? *Lancet* 2019; **393:** 617–20.
3 WHO. World health statistics 2018: monitoring health for the SDGs. Geneva: World Health Organization, 2018.
4 Gostin LO, Sircar NR, Friedman EA. Fighting novel diseases amidst humanitarian crises. *Hastings Cent Rep* 2019: **49:** 6–9.

Clinical outcomes after ABO-incompatible renal transplantation

We read with interest the Article by Florian G Scurt and colleagues[1] on clinical outcomes after ABO-incompatible renal transplantation. Their interpretation that expanding the use of kidney paired donation instead of optimising the use of ABO blood group incompatible (ABOi) kidney transplantation should be moderated.

First, from their meta-analysis, Scurt and colleagues report an excessive increase in graft loss at 1 year (odds ratio [OR] 2·52 [95% CI 1·80–3·54]), at 3 years (1·59 [1·15–2·18]), and at 8 years (1·07 [0·64–1·80]) after ABOi kidney transplantation, with heterogeneities between studies (I^2) higher than 60%. However, the methodological standards in meta-analyses have shown that heterogeneity higher than 45–50% must be interpreted with extreme caution and requires further exploration through subgroup analyses.[2] Second, the authors reported higher survival in ABO-compatible kidney transplants than in ABOi kidney transplants until 5 years after transplantation; yet, the 8-year mortality data do not show the same difference between those groups. The 8-year mortality data are based on only three retrospective studies with 606 patients. The 0% heterogeneity reported between these three studies is difficult to understand, considering the discrepancy and heterogeneity between the populations.[3] Third, the use of ORs instead of hazard ratios for a time dependent event such as mortality

is not methodologically optimal, thereby restricting the interpretation of the observed effect and the validity of the overall conclusion.[4]

We do agree with the authors that given the widening worldwide organ shortage, kidney paired donation can facilitate live donor kidney transplantation for some incompatible pairs, but blood type O recipients have low match rates and ABOi renal transplant remains a crucial transplantation approach for many of these recipients.[5]

We declare no competing interests.

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1 Scurt FG, Ewert L, Mertens PR, Haller H, Schmidt BMW, Chatzikyrkou C. Clinical outcomes after ABO-incompatible renal transplantation: a systematic review and meta-analysis. *Lancet* 2019; **393:** 2059–72.
2 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21:** 1539–58.
3 Ioannidis JPA, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. *BMJ* 2007; **335:** 914–16.
4 Tudur C, Williamson PR, Khan S, Best LY. The value of the aggregate data approach in meta-analysis with time-to-event outcomes. *J R Stat Soc* 2001; **164:** 357–70.
5 Opelz G, Morath C, Süsal C, Tran TH, Zeier M, Döhler B. Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction: results from 101 centers. *Transplantation* 2015; **99:** 400–04.

We read with interest the Article by Florian G Scurt and colleagues[1] on clinical results after ABO-incompatible kidney transplantation from living donors. Regrettably, we feel obliged to point out a serious technical problem with this meta-analysis.[2] The authors included multiple publications from the same authors that were based on overlapping patient populations. They also included data from review articles and registry analyses that contained data from patients already reported in individual studies (appendix). For example, patients who received ABO-incompatible kidney transplants in 2004–06 at Freiburg University Hospital, Freiburg, Germany, were counted four times, with Scurt and colleagues citing the initial analysis (reference 67),[1] a later extended analysis (reference 69),[1] a three-centre analysis (reference 66),[1] and a review article from the Collaborative Transplant Study (reference 52).[1] Patients from the Tokyo Women's Medical University, Tokyo, Japan, might have been counted up to seven times (appendix). Another meta-analysis by de Weerd and colleagues[3] on the same topic identified only 1346 unique ABO-incompatible patients compared with the much larger 7098 patient sample that formed the basis for Scurt and colleagues' meta-analysis.[1] Readers should be aware that the meta-analysis reported by Scurt and colleagues is technically quite problematic and does not validate previous reports in a much larger population of more than 7000 patients.

We declare no competing interests.

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1 Scurt FG, Ewert L, Mertens PR, Haller H, Schmidt BMW, Chatzikyrkou C. Clinical outcomes after ABO-incompatible renal transplantation: a systematic review and meta-analysis. *Lancet* 2019; **393:** 2059–72.
2 Felson DT. Bias in meta-analytic research. *J Clin Epidemiol* 1992; **45:** 885–92.
3 de Weerd AE, Betjes MGH. ABO-incompatible kidney transplant outcomes: a meta-analysis. *Clin J Am Soc Nephrol* 2018; **13:** 1234–43.

Authors' reply

Alexandre Loupy and colleagues emphasise issues deserving special consideration. In the Discussion section of our Article,[1] we have outlined shortcomings associated with the use of a meta-analysis for this purpose. Our considerations include the problem of high heterogeneity (I^2) in the studies reporting different outcomes. The high between-study variation of the included reports is mostly from differences—eg, in study protocols, populations, and approaches to measurement. Therefore, in our meta-analysis we first used the random-effects approach instead of the fixed-effects model. We did sensitivity testing to assess the influence of each individual study on the pooled effect size or to identify one or more outliers included in the review by omitting each individual study.[2] From this testing we saw no change in I^2.


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See **Online** for appendix

We used meta-regression to explore the reasons for high I^2 and thereafter decided to adjust effect sizes on the covariates of recruitment period (data not shown) and rituximab-based or non-rituximab-based desensitisation protocols (data are in the appendix of our Article[1]). However, I^2 across these groups remained over 40%. Subdivision of the studies into two or more groups on the basis of sex, age, antibody titre before transplantation (donor specific antibodies, plasma reactive antibodies, and human leukocyte antigen), and allocation of blood group type was not feasible because of insufficient data.

See **Online** for appendix

A disadvantage of I^2 statistics is that I^2 increases with patient number.[3,4] We present another subgroup analysis in which studies with the largest cohorts (Axelrod, Bentall, Ko, Morath, Montgomery, and Takahashi) are omitted (appendix). ABO-incompatible renal transplantation (ABOi-rTx) remains significantly associated with increased risk of death and graft loss after the first 3 years, and the heterogeneity across studies decreases considerably.[5]

We agree with Loupy and colleagues that the results of the 8-year mortality and graft-survival data should be interpreted with caution.

Our search identified only three published studies with possible publication bias and inconclusive trial sequential analysis (more details