Focusing on clarithromycin quadruple therapy and bismuth quadruple therapy, the investigators found only transient increases in antimicrobial resistance. On the other hand, they report sustained perturbation of the gut microbiome, even 1 year after treatment, as well as a small amount of weight gain, although without apparent metabolic consequences.

With this work, Liou and colleagues have made substantial inroads into understanding unintended consequences of screen-and-treat programmes. However, their results are only marginally reassuring; much more needs to be learned about the immunological, metabolic, and, particularly, microbiological consequences of *H pylori* treatment. Most importantly, the paper only scrapes the surface of antimicrobial resistance, looking at only faecal organisms and not organisms that might gain resistance to the antibiotics typically used for *H pylori* eradication (ie, metronidazole, tetracycline, and clarithromycin). In this era of rapidly increasing and life-threatening antimicrobial resistance, it is sobering to think that a macrolide—one of the few remaining alternatives for treating extremely drug-resistant typhoid[7]—might be widely used in healthy adults to prevent a disease that will only afflict a small percentage. In future studies, a metagenomic approach to resistance profiling could give more granular, actionable information on the effects of therapy on antimicrobial resistance.[8]

These remaining, hypothetical concerns, however important, need to be balanced with the incidence and lethality of gastric malignancy. For those million people who will acquire gastric cancer each year, we need to move forward cautiously but undaunted.

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1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68:** 394–424.
2 Liou JM, Chen CC, Chang CM, et al. Long-term changes of gut microbiota, antibiotic resistance, and metabolic parameters after *Helicobacter pylori* eradication: a multicentre, open label, randomised trial. *Lancet Infect Dis* 2019; **19:** 1109–20.
3 Parsonnet J, Harris RA, Hack HM, Owens DK. Modelling cost-effectiveness of *Helicobacter pylori* screening to prevent gastric cancer: a mandate for clinical trials. *Lancet* 1996; **348:** 150–54.
4 Rokkas T, Rokka A, Portincasa P. A systematic review and meta-analysis of the role of *Helicobacter pylori* eradication in preventing gastric cancer. *Ann Gastroenterol* 2017; **30:** 414–23.
5 Yeh JM, Kuntz KM, Ezzati M, Hur C, Kong CY, Goldie SJ. Development of an empirically calibrated model of gastric cancer in two high-risk countries. *Cancer Epidemiol Biomarkers Prev* 2008; **17:** 1179–87.
6 IARC *Helicobacter pylori* Working Group. *Helicobacter pylori* eradication as a strategy for preventing gastric cancer. Lyon, France: International Agency for Research on Cancer. 2014. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Working-Group-Reports/-Em-Helicobacter-Pylori-Em-Eradication-As-A-Strategy-For-Preventing-Gastric-Cancer-2014 (accessed Aug 9, 2019).
7 Andrews JR, Qamar FN, Charles RC, Ryan ET. Extensively drug-resistant typhoid—Are conjugate vaccines arriving just in time? *N Engl J Med* 2018; **379:** 1493–95.
8 Hu Y, Yang X, Qin J, et al. Metagenome-wide analysis of antibiotic resistance genes in a large cohort of human gut microbiota. *Nat Commun* 2013; **4:** 2151.

Complex task to estimate immune responses to various poliovirus vaccines and vaccination schedules

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Since licensing of the first poliovirus vaccine in 1955, multiple types of live attenuated oral poliovirus vaccines (OPVs) and inactivated poliovirus vaccines (IPVs) have been tested or licensed for routine childhood vaccination schedules. IPVs have been manufactured by inactivating the three serotypes of different poliovirus seed strains, either the wild or the Sabin polioviruses, the latter of which is used for manufacturing OPVs.[1] IPVs have also been used with different routes of administration and doses, and have been given at different ages.

WHO's Strategic Advisory Group of Experts (SAGE) on immunisation provides global recommendations for routine poliovirus vaccination. However, technical advisory committees of individual countries have often recommended alternative schedules with variations in the age of administration, number of doses, and combinations with other vaccines. Therefore, there is wide variation in routine poliovirus vaccination schedules.[2] This discrepancy has led to the need for trials that test the immunogenicity of poliovirus vaccines in different combinations and using different vaccination schedules. In low-income countries, where poliovirus transmission is largely faecal–oral, it is important for children to develop both robust intestinal immunity,

which prevents transmission of polioviruses, and humoral immunity, which protects them from paralytic poliomyelitis. Therefore, the review of poliovirus vaccines by Grace Macklin and colleagues[3] in *The Lancet Infectious Diseases* that reports on humoral and intestinal mucosal immunity is comprehensive.

Multiple reviews and meta-analyses[4,5] have studied the immunogenicity of different combinations of poliovirus vaccines and strains under different vaccination schedules. The review by Macklin and colleagues is a valuable addition to the scientific literature because it applies the innovative network meta-analysis methodology to estimate the immunogenicity of different OPV and IPV schedules. Network meta-analysis allows indirect comparisons of interventions that have not been included in head-to-head comparisons, and thus should be helpful to assess the immunogenicity of the wide variety of vaccines and schedules in the literature on poliovirus vaccines.

Overall, the results reported by Macklin and colleagues summarise those reported by others,[3] including the inability of IPVs to induce intestinal mucosal immunity in the absence of previous exposure to live poliovirus. The average proportion of individuals who developed intestinal mucosal immunity to type 2 poliovirus was similar following three doses of bivalent OPV (bOPV) with types 1 and 3 (30%) to that of three doses of bOPV with IPV (25%). Additional IPV doses did not enhance intestinal mucosal immunity. This finding is relevant for outbreak-response vaccination, particularly for outbreaks of type 2 vaccine-derived poliovirus. Type 2 OPV was withdrawn from routine vaccination in April, 2016, and is now maintained in a global stockpile for outbreak response. Although countries have used IPVs for responding to outbreaks of type 2 vaccine-derived poliovirus,[6] the use of IPVs should be planned considering possible previous vaccination with type 2 OPV, as IPV does not induce intestinal immunity, which is important for reducing faecal–oral transmission.

Macklin and colleagues also reported that a single IPV dose improves humoral immunity against serotype 2, with small additive value of a second IPV dose. The policy implications of this finding are unclear,[7,8] as other studies have reported opposing results.[9] After administration of one IPV dose, few participants show evidence of seroconversion, but more of them are primed to express a rapid immune response when challenged by another dose of poliovirus vaccine.[3] This effect mimics a possible scenario when a person vaccinated with a single dose of IPV is immunologically challenged by wild poliovirus.[7,8] However, it is not certain if IPV priming is protective; an investigation[9] done during a poliovirus outbreak showed a large difference in the effectiveness of one versus two IPV doses, which is not consistent with priming being immunologically equivalent to seroconversion. Furthermore, research in macaques has shown that the potential immunological effect of a single IPV dose might be time-limited.[10] Although both a single intramuscular full IPV dose and an intradermal one-fifth fractional IPV dose led to the formation of memory B cells, no circulating memory B cells could be detected after 5 months. Multiple IPV doses were essential to form memory B cells that could be detected for at least 16 months.

Macklin and colleagues reported that there are small differences in the immunogenicity of different types of IPVs, including those from alternative seed strains or that use different doses or routes of administration. This finding should be reassuring to countries that are considering two doses of fractional intradermal IPV instead of two full IPV doses. Uptake of fractional (one-fifth of the full dose) intradermal IPV has been slow and restricted to a few countries (eg, India, Bangladesh, Nepal, and Sri Lanka), despite a SAGE recommendation affirming the immunogenicity of two doses of fractional intradermal IPV. Unforeseen IPV production challenges lead to global IPV supply shortages. Intradermal IPV offers a much-needed alternative to stretch short IPV supplies to vaccinate more children.

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1 Shimizu H. Development and introduction of inactivated poliovirus vaccines derived from Sabin strains in Japan. *Vaccine* 2016; **34:** 1975–85.
2 Thompson KM, Pallansch MA, Duintjer Tebbens RJ, Wassilak SG, Kim JH, Cochi SL. Preeradication vaccine policy options for poliovirus infection and disease control. *Risk Anal* 2013; **33:** 516–43.
3 Macklin GR, Grassly NC, Sutter RW, et al. Vaccine schedules and the effect on humoral and intestinal immunity against poliovirus: a systematic review and network meta-analysis. *Lancet Infect Dis* 2019; published online July 23. http://dx.doi.org/10.1016/S1473-3099(19)30301-9.
4 Estivariz CF, Pallansch MA, Anand A, et al. Poliovirus vaccination options for achieving eradication and securing the endgame. *Curr Opin Virol* 2013; **3:** 309–15.
5 Hird TR, Grassly NC. Systematic review of mucosal immunity induced by oral and inactivated poliovirus vaccines against virus shedding following oral poliovirus challenge. *PLoS Pathog* 2012; **8:** e1002599.

6 Bahl S, Verma H, Bhatnagar P, et al. Fractional-dose inactivated poliovirus vaccine immunization campaign—Telangana state, India, June 2016. *MMWR Morb Mortal Wkly Rep* 2016; **65:** 859–63.

7 Resik S, Tejeda A, Sutter RW, et al. Priming after a fractional dose of inactivated poliovirus vaccine. *N Engl J Med* 2013; **368:** 416–24.

8 Anand A, Zaman K, Estivariz CF, et al. Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: a randomized controlled trial. *Vaccine* 2015; **33:** 6816–22.

9 Robertson SE, Traverso HP, Drucker JA, et al. Clinical efficacy of a new, enhanced-potency, inactivated poliovirus vaccine. *Lancet* 1988; **1:** 897–99.

10 Bhaumik SK, Kulkarni RR, Weldon WC, et al. Immune priming and long-term persistence of memory B cells after inactivated poliovirus vaccine in macaque models: support for at least 2 doses. *Clin Infect Dis* 2018; **67** (suppl 1)**:** S66–77.

Healthy survival after tuberculosis

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WHO estimates that 1·6 million people die each year before or during tuberculosis treatment. In *The Lancet Infectious Diseases*, Kamila Romanowski and colleagues'[1] meta-analysis showed that tuberculosis survivors have approximately three-times to four-times greater mortality than their local populations, including among younger adults. These transformative findings show that tuberculosis, already the most frequent cause of death from a single infectious agent, is associated with even greater mortality than current estimates. This excessive tuberculosis-associated mortality and the proposed pathways that might explain it are summarised in the figure.

Each year, millions of tuberculosis cases are believed to be missed and, globally, 18% of tuberculosis treatments are unsuccessful, explaining some of the tuberculosis-associated deaths.[2] Tuberculosis recurrence is a potential pathway to mortality after tuberculosis, regardless of apparent treatment success or whether recurrence is diagnosed and treated. Recurrence due to relapse is especially probable when treatment is inadequate because of non-completion, intermittent adherence, or inappropriate treatment with drugs to which a patient's tuberculosis is resistant.[3] Recurrence might also be caused by reinfection in households, communities, or health-care facilities.[4] These issues emphasise the importance of global efforts to increase case-finding, treatment success, rapid drug-susceptibility testing, and infection control.[2–5]

Although tuberculosis diagnosis and assessment of cause of death are notoriously unreliable in the resource-constrained settings where most tuberculosis cases occur,[6] the available data suggest that most deaths after tuberculosis are not caused by recurrence.[1] Sequelae of tuberculosis, such as residual or secondary lung diseases, might cause death[7,8] independently of apparent treatment success. These deaths could occur either directly through respiratory failure, indirectly through cardiovascular effects (such as pulmonary hypertension),[9] or through as-yet uncharacterised mechanisms that might explain increased ischaemic heart disease and cancers after tuberculosis.[10]

Comorbidities and social determinants (eg, HIV infection, smoking, and poor living conditions) predispose to tuberculosis recurrence and sequelae,[11] and also often cause death by mechanisms completely unrelated to tuberculosis, potentially explaining much of the excess mortality during and after tuberculosis.[12] Furthermore, comorbidities and social determinants are often worsened by the psychosocial and economic challenges of tuberculosis illness, treatment, and associated catastrophic costs, constituting a vicious cycle leading to, and being worsened by, tuberculosis.[13]

Tuberculosis treatment has saved millions of lives,[2] but drug toxicity also contributes to excess mortality after treatment, as evidenced by the harmful effects of months of multidrug treatment on liver, kidney,

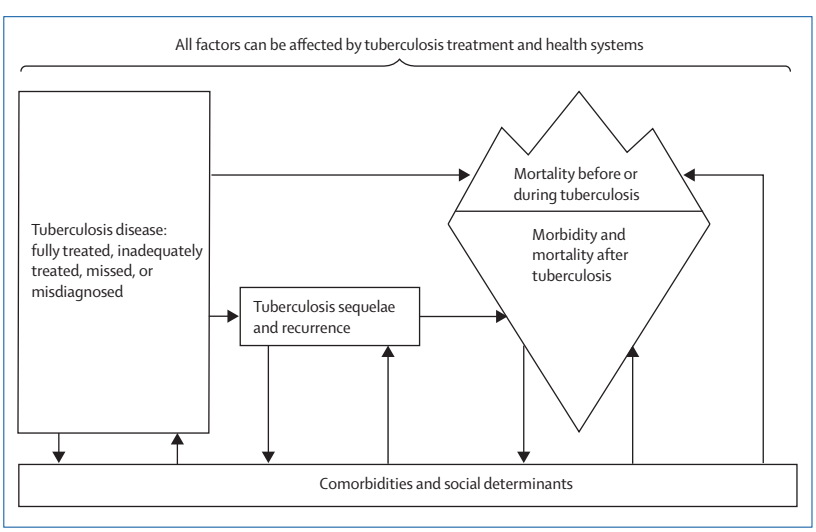

Figure: **Schematic indicating potential pathways explaining tuberculosis-associated mortality**