TUBERCULOSIS

Response to Comment on "Community-Wide Isoniazid Preventive Therapy Drives Drug-Resistant Tuberculosis: A Model-Based Analysis"

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Our modeling work suggests that isoniazid preventive therapy (IPT) can be effective in reducing drug-sensitive tuberculosis (TB) and that the risk of IPT driving resistance can be reduced by improving the detection and rapid treatment of individuals with drug-resistant disease and by limiting IPT to those in whom the intervention will have the largest benefit.

We thank Dr. Kingsley N. Ukwaja for his response to our recent paper (*1*), and we welcome the opportunity to clarify what we believe are the primary policy implications of our work. There are challenges that dampen current enthusiasm for expansion of community-wide isoniazid preventive therapy (IPT).

These include issues alluded to by Dr. Ukwaja: little evidence that these programs can help alleviate disease burden at the population level (*2*), concerns that individuals with active tuberculosis (TB) may inadvertently receive monotherapy in programs where screening has suboptimal negative predictive value (*3*), limited evidence of the individual benefits of IPT among individuals without positive tuberculin skin test (TST) responses (*4*), and concerns about the resource needs associated with expanding IPT in resource-constrained settings (*5*).

Although these issues deserve full discussion, our modeling work addresses a more circumscribed issue related to the potential for community-wide IPT to act as a selective pressure favoring the emergence of drug resistance over relatively long time horizons. This work was motivated by claims, based on a limited number of studies of the risk of resistance among individuals receiving IPT, that community-wide IPT would not drive increasing drug resistance (*6*) because it apparently did not increase the risk of resistance among those individuals (*7*, *8*). To explore whether the individual-level effects on resistance could be extrapolated to the population level, we modeled IPT as being effective among individuals treated, despite variable reports on the role of IPT in controlling TB at the population level. Our model demonstrates that the direct (that is, among individuals treated with IPT) and the indirect (that is, among all individuals in the community) effects of IPT need not be the same: IPT can select for resistance at the population level even if it does not directly increase the risk of resistance among exposed individuals.

In turn, different population-level dynamics may account for some of the differences in apparent effectiveness of IPT in different settings, for example, because in a high-burden setting, reinfection may well occur very shortly after IPT treatment ceases, decreasing the effective duration of protection from IPT. Although one would not expect individual-level (that is, within-host natural history) effects of IPT to differ strongly from one setting to another, one would expect that different epidemics would give rise to different risks of reinfection after IPT (*9*) and different implications for the role of IPT in TB control.

We do not believe that this work should serve as "nail in the coffin" for IPT, and certainly not for the more general idea of expanding preventive therapy to mitigate the risk of TB among immunocompromised individuals. As with any antibiotic, increased use can be expected to increase selective pressure in favor of resistant strains. Selective pressure is directly related to the effectiveness of an intervention; only through IPT's considerable potential to help control drug-sensitive TB does the selective pressure arise. Even if community-wide IPT does act as a selective pressure in favor of drug resistance, it does so over the course of decades, and our models (as well as others) suggest a potential role of preventive therapy for mitigating the overall burden of TB. Understanding the exact reasons that Thibela failed to show these expected improvements in community control remains a major priority (*2*).

Our modeling work suggests that IPT can be effective in reducing drug-sensitive TB and that the risk of IPT driving resistance can be reduced by improving the detection and rapid treatment of individuals with drug-resistant disease and by limiting IPT to those in whom the intervention will have the largest benefit (that is, those with positive TST) (*10*). Preventive therapy that includes multiple drugs and drugs that are not used for treatment of active disease may also help to circumvent the risk that widespread use of preventive therapy will undermine the effectiveness of treatment of active disease.

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