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EDITORIAL

Evidence, opportunity, ethics, and the allure of zero leprosy

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Summary After a decade in which the long-term downward trend in the number of people diagnosed with leprosy (also known as Hansen's disease) has stalled, there is new momentum toward a vision of zero leprosy. This has been facilitated by scientific advances, particularly related to post-exposure prophylaxis (PEP) for leprosy, and the coming together of the leprosy community in a new Global Partnership for Zero Leprosy. The World Health Organization is in the process of drawing up Guidelines for the use of PEP with single-dose rifampicin (SDR) for national leprosy programmes, although some investigators have expressed reservations regarding the robustness of evidence for its effectiveness; the potential for drug resistance; and ethical issues related to implementation of PEP, including informed consent and disclosure of leprosy diagnosis. Many of the same concerns have been raised and addressed in other neglected tropical disease (NTD) control and elimination programmes. I review features of these NTD control programmes, highlight benefits of the increasingly close relationship between the leprosy community and the larger NTD movement, and examine concerns regarding scaling up of PEP in light of the NTD experience. The fundamental question, "How much evidence is required to scale up a promising intervention?" is a perennial one in public health. In addition to drawing upon lessons from other NTD control and elimination programmes, I examine this question with reference to ethical principles in public health and suggest that the answer is not found in a yes/no dichotomy, but rather, in moving forward to scale up PEP within national leprosy programmes while incorporating 1) operational research to strengthen the evidence base; 2) robust monitoring for drug resistance; and 3) procedural safeguards as well as strong stakeholder engagement to protect human dignity and ensure adherence to the highest ethical standards.

Introduction

Hansen's disease, or leprosy, is an ancient, stigmatising disease caused by infection with *Mycobacterium leprae*. The introduction of multidrug therapy (MDT) in 1981, followed by a

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World Health Assembly resolution in 1991, which called for elimination of leprosy as a public health problem,[1] set the stage for a 90% decrease between 1985 and 2005 in the reported number of cases registered for treatment.[2,3] Significant advances also have been made in addressing stigma and discrimination and in preventing leprosy-related disability.[4,5] However, the number of people reported with newly-detected disease has not dropped below 200,000 per year, suggesting that current approaches to case detection and treatment have had limited impact on transmission.[2,4] It is now clear that the 2012 World Health Organization (WHO) Neglected Tropical Diseases (NTD) Roadmap was overly optimistic in its assessment that "vigorous case-finding and treatment would lead to global interruption of transmission by 2020."[3]

THE ALLURE OF ERADICATION

Leprosy is not unique in this regard. After the success of smallpox eradication in 1980, a wave of enthusiasm for disease eradication swept the public health world. The International Task Force for Disease Eradication (ITFDE) was established to bring some order to the rush to join the eradication bandwagon and to establish criteria, broadly based on scientific feasibility and political will.[6] In 1993, the ITFDE screened 94 diseases and concluded that six were potentially eradicable: dracunculiasis (Guinea worm disease), poliomyelitis, mumps, rubella, lymphatic filariasis, and taeniasis/cysticercosis (pork tapeworm). None of these diseases has yet been eradicated, although significant progress has been made towards eradication of dracunculiasis and poliomyelitis. The ITFDE considered leprosy and ruled it 'not now eradicable,' citing the need for improved diagnostic tests, the challenge of overcoming leprosy-related stigma, and the potential of transmission from non-human reservoirs, namely armadillos.[6]

The ITFDE's relatively short list of 'potentially eradicable' diseases did not deter enthusiasm for the concepts of eradication and elimination. Soon, encouraged by World Health Assembly resolutions and disease-specific advocates, dozens more diseases were targeted for 'regional elimination' (reducing transmission to zero in a defined geographic area, with ongoing need for surveillance) or the more nebulous 'elimination as a public health problem,'[7] which has been criticised as a hyperbolic and intentionally ambiguous synonym for control.[8] For example, the 2012 NTD Roadmap established the goals of eradicating yaws and global elimination of leprosy, blinding trachoma, lymphatic filariasis, and Human African trypanosomiasis by 2020. Five of the other 12 NTDs were targeted for regional or national-level elimination by 2020.[3]

Despite impressive progress on many fronts, it appears that few of the WHO 2020 targets for these diseases will be fully achieved. As virtually all campaigns to eradicate or eliminate diseases have shown, success is rarely realised as quickly, easily, or inexpensively as anticipated. Further, the failed effort to eradicate malaria during the decade between 1955 and 1965 underscored the risks of overpromising: donors abandoned the effort, the disease rebounded, and the entire concept of eradication was thrown into disfavour.[6]

In light of the persistent technical challenges raised by the ITFDE in 1993, as well as the predictable yet unfortunate scaling back of leprosy control after national programmes reached their targets for 'elimination of leprosy as a public health problem' (which left significant pockets of transmission), and the collapse of the Global Alliance for the Elimination of Leprosy in the early 2000s,[9] it may seem an unusual moment for the leprosy community to be organising under the banner of 'zero leprosy.' But both the WHO and the International Federation of Anti-Leprosy Associations (ILEP) have embraced a strategic vision of zero leprosy, which includes zero transmission, zero disability, and zero discrimination.[10,11] In

addition, a new Global Partnership for Zero Leprosy was launched just before World Leprosy Day in January 2018.[12] What factors contribute to this renewed resolve and momentum? I wish to explore three convergent influences.

RENEWED MOMENTUM

First, as noted above, during the past decade, as the annual number of people reported with leprosy stagnated above 200,000, hope began to fade that enhanced case-finding and MDT alone would substantially reduce transmission. In response, there has been renewed interest in developing and evaluating new tools and approaches, including diagnostic tests, vaccines, and chemoprophylaxis.[13] Progress along these lines has rekindled hope and inspired new possibilities.

The clinical diagnosis of leprosy is notoriously difficult. We currently lack adequate assays for point-of-care diagnosis as well as serologic tests to identify foci of transmission, but serologic, PCR, and T-cell based assays are now being developed and evaluated.[14,15] There is also renewed interest in the potential of vaccination, including greater appreciation for the preventive role of BCG vaccine,[16,17] expanded field evaluation of leprosy vaccines in India,[18] and completion of Phase I human trials of LepVax, a synthetically-produced leprosy vaccine.[19] In the short term, the most promising innovation for reducing transmission of *M. leprae* is enhanced case-detection and MDT treatment for those diagnosed with leprosy, along with chemoprophylaxis for their contacts and their communities.[20] This approach, known as post-exposure prophylaxis (PEP), will be further discussed below.

The second factor contributing to renewed momentum for zero leprosy is the increasingly close relationship between the leprosy community and the larger NTD community. In the mid-2000s, advocates for control of a disparate group of 13 tropical diseases successfully made the case for grouping them together under the rubric of NTDs.[21] This rubric, which the WHO adopted, raised the profile of these 'diseases of neglected people,' facilitated more effective advocacy for resources, and enabled greater programmatic coordination and integration. A watershed moment for the NTD movement came in 2012, at a meeting in London supported by the Bill & Melinda Gates Foundation and attended by leaders from the WHO, the pharmaceutical industry, national governments, and global health. In the London Declaration, they committed to the "control or elimination of 10 NTDs in line with targets set by the WHO."[22] The London Declaration established an *uber*-partnership that, in addition to representation from industry and the engagement of the WHO, catalysed the development of disease-specific alliances or coalitions, which among other things were responsible for monitoring progress toward the 2020 WHO goals and reporting to the London Declaration "scorecard."[22]

Third, human and ethical considerations have long been central to leprosy control and to care for affected people. As the leprosy community develops more effective tools to reduce transmission and draws closer to the broader NTD movement, its underlying humanitarian impulse cannot help but be influenced by the 'audacious goal' of disease eradication.[23] Citing three fundamental 'ACE principles,' Frank Richards argues that the allure of disease eradication is inevitable.[24] Eradication represents a supreme human Accomplishment; it achieves Closure in a struggle against a formidable adversary; and it advances Equity, a core value and goal of global health.[25,26] The moral case for NTD elimination is reinforced by the terrible toll of physical, emotional, social, and economic suffering that these diseases inflict on affected people and their communities. Both as causes and consequences of social

suffering, NTDs are inextricably linked to poverty, exploitation, and discrimination. In making the ethical case for elimination of lymphatic filariasis and onchocerciasis, Bailey and colleagues argue that these diseases undermine human agency, freedom of affiliation, and respect for affected people, thereby creating intractable 'clusters of disadvantage' that are ethically untenable.[27] If this argument holds for lymphatic filariasis and onchocerciasis – and I believe it does – it must certainly also be true for leprosy. When faced with the enormity of human suffering caused by leprosy, the moral imagination is inclined toward eradication.

LEPROSY AND NTDS

Although leprosy was included in the initial list of NTDs, it has a unique history. Distinguishing features include the centuries-old involvement of, and support from, communities of religious faith; a strong emphasis on the human rights approach to fight discrimination, as evidenced by the recent appointment of a UN Special Rapporteur for discrimination against people affected by leprosy;[28] years of experience addressing issues of stigma as well as mental health and well-being of affected people;[29] and meticulous attention to clinical care and disability prevention. The priority given to compassionate clinical care contrasts sharply with the primary emphasis on interrupting transmission for most other NTDs, especially for those addressed through periodic mass drug treatment, known as preventive chemotherapy. For example, the WHO strategy to eliminate lymphatic filariasis as a public health problem includes two pillars: interrupting transmission and providing care for affected people.[30] However, virtually all the attention and resources have gone into scaling up preventive chemotherapy rather than providing care to those who continue to suffer from the 'public health problem.'[31] In its deepening dialogue and involvement with the broader NTD coalition, the leprosy community has contributed important insights and skills, particularly in the areas of human rights, disability prevention, and care for affected people. Human rights are increasingly part of the NTD discourse[32] and recent experience in Nepal highlights the feasibility and potential synergies of integrating services and training in self-care for people whose limbs are affected by leprosy or lymphatic filariasis.[33]

In return, the leprosy community has been influenced by its association with the larger NTD community in three important ways. First, leprosy control now finds itself imbedded within the broader NTD effort, in which shared experience and programme integration are key themes. Leprosy is now well-represented in major NTD gatherings, such as the annual meetings of the NTD NGO Network and the Coalition for Operational Research on NTDs. Synergies appear particularly promising in the areas of mental health and well-being, tropical dermatology or skin health (which includes not only leprosy but also Buruli ulcer, cutaneous leishmaniasis, yaws, mycoses, and other conditions), integrated clinical care, advocacy, surveillance, and programme coordination.

Second, the leprosy community is increasingly influenced by concepts and approaches related to interrupting transmission that have been worked out for other NTDs over a period of several years. For example, as programmes for NTDs such as lymphatic filariasis near the 'end game' of elimination, the need to identify and treat residual 'hot spots' of ongoing transmission and disease has become clear. Methods to do this are under development and are likely to be applicable to case-detection and PEP for leprosy. Similarly, concepts and methods that the NTD community has adopted for planning, monitoring, and executing NTD elimination programmes are now available for adaptation by leprosy. Since actual transmission of these pathogens is rarely, if ever, directly observed, interruption of

transmission is inferred from epidemiologic data concerning incidence of infection; prevalence of serologic markers for exposure, particularly in children; and, when relevant, monitoring of infection in vectors or non-human reservoirs, all in the context of sustained, enhanced surveillance. Several features of leprosy, including the long incubation period of *M. leprae* and the lack of reliable indicators of early infection, make it difficult to draw quantitative inferences regarding transmission from observations of disease incidence. Clearly, the impact of PEP on *M. leprae* transmission will depend on many factors, including the intensity and effectiveness of case finding.

Third, and perhaps most importantly, as a disease-specific group under the Uniting to Combat NTDs umbrella, the leprosy community has learned from the challenges and successes of other NTD alliances and coalitions, which have played a crucial role in advancing the NTD agenda. For example, the Global Alliance to Eliminate Lymphatic Filariasis (GAELF) was established in 2000 to align a wide range of public and private partners in support of the WHO-led Global Programme to Eliminate Lymphatic Filariasis (GPELF). A particularly important contribution of the GAELF was its engagement in convening a forum to develop a comprehensive research agenda. Ninety scientists and filariasis experts from more than 20 countries participated in this process, resulting in recommendations and priorities that attracted significant funding for operational research.[34] The research forum played a crucial role in demonstrating to donors that the lymphatic filariasis community was unified, organised, and serious about reaching the WHO targets for elimination. In another example, the International Coalition for Trachoma Control (ICTC), through a visionary and highly collaborative process, developed a strategic roadmap for global elimination of trachoma as a public health problem. This document, which described the resources needed for success and articulated how those resources would be used, was central in attracting more than $150 million to support national trachoma elimination programmes.[35]

These and other examples provided encouragement and clarity to the leprosy community as it began to consider a new Global Partnership for Zero Leprosy. Two key intended outputs for the Global Partnership in 2018 are a comprehensive research agenda and a roadmap for operational excellence, following a process of broad participation across the leprosy community.[12] With the formation of its Global Partnership, the leprosy community will be more fully represented within the Uniting to Combat NTDs framework.

ZERO LEPROSY – QUO VADIS?

I wish now to turn to the prospects for zero leprosy and to an emerging debate about a promising innovation that may help move us toward that goal, namely PEP. Early experience with multiple doses of dapsone demonstrated a significant protective effect when given to contacts of those diagnosed with leprosy.[36,37] This was followed by a trial in Indonesia using post-exposure rifampicin in two doses separated by 3–4 months. The study had three arms: a ‘blanket’ group comprised of all eligible people living on three small islands; a ‘contact group’ on another island, where rifampicin was given to household and neighbour contacts; and an untreated control group. Incidence of leprosy was significantly lower in the population that received ‘blanket’ prophylaxis (a 75% reduction) compared to the control group. The incidence in the ‘contact group’ was not significantly different from that in the control group,[38] suggesting that limiting PEP to close contacts would have limited impact on *M. leprae* transmission.

The most influential research on PEP to date is the COLEP study, a cluster-randomised, double-blind, placebo-controlled trial involving 21,711 contacts of 1037 leprosy patients in Bangladesh, 2002–2007. Overall, contacts who received single-dose rifampicin (SDR) experienced a 57% reduction in the risk of leprosy after 2 years and 30% after 5–6 years.[39] These findings, consistent with previous studies of PEP, were promising enough for the Novartis Foundation, along with Netherlands Leprosy Relief, American Leprosy Missions, FAIRMED, and the German Leprosy and Tuberculosis Relief Association to collaborate with Ministries of Health in Brazil, Tanzania, Nepal, India, Sri Lanka, Myanmar, Cambodia, and Indonesia to evaluate the feasibility of implementing PEP with SDR on a broader scale. Preliminary findings of this effort, known as the LPEP program, are summarised by Steinmann *et al.* in this issue of *Leprosy Review*.[40]

Several additional countries have implemented PEP with SDR,[24] and further studies are underway to examine whether the effectiveness of the PEP approach can be optimised by combining BCG and PEP (the MALTALEP trial),[41] or, in addition to other modifications, by providing more than one dose of rifampicin (PEP++).

As a strategy to decrease the incidence of *M. leprae* infection, PEP holds promise for the goal of zero leprosy. While momentum builds to scale up PEP in leprosy-endemic countries, Professor Diana Lockwood and colleagues have raised a note of caution, if not objection.[42] Their reservations, which deserve careful consideration, include concern about 1) the strength of evidence regarding the effectiveness of PEP; 2) the potential for PEP with SDR to lead to drug resistance; and 3) ethical challenges with implementing the strategy. The global NTD programs that currently rely on preventive chemotherapy as a major strategy have wrestled with these same issues. Therefore, it may be helpful to examine the concerns of Lockwood and colleagues through the NTD lens.

INADEQUATE EVIDENCE OF BENEFIT

Although household contacts of those with leprosy are at greatest risk of developing the disease, SDR appears to be less effective in reducing risk among household contacts,[38,39] and is therefore also less cost-effective for this group.[43] Consequently, it can be argued that SDR does not adequately protect those who need it most – a clear limitation of the approach. However, the intent of SDR in the current context is to reduce the incidence of leprosy overall, not only for household contacts. The proportion of cases that occur in people who are not household contacts of those with known leprosy varies, ranging from 40% to 74%, suggesting either multiple sources or unrecognised exposure.[44] These findings would argue for a community-level or 'blanket' approach to SDR in national leprosy programmes rather than limiting it to household contacts.

Second, in the COLEP study, the protective effect of SDR against all forms of leprosy was statistically significant, with a 56.6% reduction in incidence (CI 32·9%–71·9%) during the first 2 years. For multibacillary (MB) leprosy alone, the reduction in risk was similar in magnitude (four cases in 9,951 people receiving SDR and nine cases in 10,006 people receiving placebo), but not statistically significant.[39] One interpretation of these data is that they provide evidence that SDR has no prophylactic effect on MB leprosy. However, as Richardus and Smith point out in this issue of *Leprosy Review*,[45] the study was not powered to detect as significant the observed level of effect against MB leprosy. An alternate interpretation, supported by the direction and magnitude of the point estimate of effect against MB leprosy, is that such an effect is very likely, but the evidence to date is inadequate to prove it as statistically significant.

Similarly, among contacts of those with paucibacillary leprosy in the COLEP study, SDR prophylaxis significantly reduced the 2-year risk of developing leprosy (OR 0·38, CI 0·16–0·87 and OR 0·42, 0·20–0·89 for contacts of those with 2–5 lesions and single-lesion leprosy, respectively). Among contacts of people with MB leprosy, those who received SDR had roughly half the incidence of leprosy during the 2-year follow-up as did those who received placebo (OR 0·52, CI 0·22–1·19). The difference was not statistically significant, but here again, the study was not sufficiently powered.[45]

All of the global NTD programmes that rely on preventive chemotherapy as a key strategy have faced the question of whether the scientific evidence of effectiveness at the community level was adequate to scale up the interventions to the national and global level. In most cases, the decision to scale up the programme provided opportunities not only to deliver much-needed benefits to at-risk populations, but also, in the process, to collect additional evidence regarding effectiveness, cost-effectiveness, and improved implementation practices. However, once the benefits of drug treatment are established at the individual level and feasibility of preventive chemotherapy is shown at the community level, it becomes ethically untenable to conduct large-scale randomised clinical trials (RCTs). This has been a particular problem for soil-transmitted helminthiasis (STH) control.[46] The most dramatic effects of de-worming on health outcomes are seen in people with intense worm burdens, and these represent a small proportion of most populations. Many community-based studies, however, assessed outcomes across the entire population, including lightly-infected and uninfected people. Consequently, systemic reviews and meta-analyses using the Cochrane or Campbell Review methodologies, which privilege RCTs, showed limited overall effect.[46–48] The orchestrated and highly publicised disparagement of mass de-worming by groups using these methods has been detrimental to de-worming programmes.[49–52]

The fact that the COLEP study did not demonstrate a statistically significant effect of SDR against MB leprosy does not negate the fact that it showed a significant effect on PB leprosy, which generally contributes a higher proportion of cases to the total number reported. And as noted previously, the COLEP study did not rule out an effect against MB leprosy. Thus, wide-scale implementation of SDR could significantly reduce incidence of leprosy overall. However, the leprosy community should heed the reservations of Lockwood and colleagues. To avoid the sensationalised charges of inadequate evidence that have plagued the STH community, it will be important to further assess the effectiveness of PEP in various sub-groups, whether using SDR or other forms of chemoprophylaxis, as it is scaled up in national leprosy programmes. Data from the ongoing LPEP programme and other PEP-related research should provide additional insights.

INADEQUATE EVIDENCE OF LACK OF HARM – DRUG RESISTANCE

Lockwood and colleagues also raise the important question as to whether broad-scale use of SDR will accelerate drug resistance.[42] Rifampicin is a cornerstone of multidrug therapy both for leprosy and tuberculosis. The potential for accelerating drug resistance has been a major issue for – and an objection to – all NTD programmes that rely on preventive chemotherapy. Indeed, monitoring for drug resistance in NTD programmes has been criticised as inadequate, and these criticisms persist.[53] Relative to other NTD programmes, the level of awareness and commitment to monitoring drug resistance is arguably greater for leprosy; the WHO has issued guidelines for monitoring drug resistance and periodically publishes findings of ongoing surveillance in the Weekly Epidemiologic Record.[54,55] Available evidence indicates

that *M. leprae* resistance to rifampicin is relatively low.[56,57] As Lockwood and colleagues note, however, widespread development of high-level resistance to rifampicin would pose a grave threat both to leprosy and tuberculosis control programmes.

In this regard, the central question for leprosy, as for other NTD programmes, is whether potential drug resistance should be regarded as an absolute contraindication to scaling up programmes that have the potential to significantly improve human health. In weighing risks and benefits, public health officials, who are given responsibility for the health of populations, are generally more disposed than research scientists to accept the longer-term risk of drug resistance in order to alleviate current suffering. The problems arise when budget restrictions and the push to achieve programmatic goals override valid concerns about drug resistance. When this happens, as it often does, adequate resources are not invested in monitoring for drug resistance or exploring alternative approaches that would reduce this risk. It will be important for the leprosy community to invest accordingly while scaling up PEP in national programmes. National programmes should also take precautions to restrict the availability of rifampicin in order to limit inappropriate multiple dosing among those seeking to protect themselves from leprosy.

ETHICAL BARRIERS TO IMPLEMENTATION

Within the field of bioethics, Principlism is the dominant framework. The four principles – beneficence, non-maleficence, autonomy, and justice – serve as guardrails for weighing competing claims and guiding ethical decision-making.[58] In practice, using the principles to balance the claims of different stakeholders is easier said than done. Each of us, individually and as societies, accord priority to the four principles differently.[59] This influences our decision-making when faced with ethical dilemmas in which opposing claims are staked to competing principles.

Further, in public health, scientific evidence for the efficacy of an intervention – its potential for beneficence – is just the starting point for a conversation about the ethics of programmatic implementation.[60,61] Public health officials must ask: Are there alternatives that yield equivalent health benefits while infringing less on autonomy or non-maleficence? Has the intervention been explained and justified to the public with honesty, trust, and transparency? Has the public – particularly stakeholders who will be affected by the intervention – been involved in the decision to deploy the intervention? These questions address the ethical principles of autonomy and justice. The key point here is that while an intervention may, in itself, be beneficial, it can be deployed in a manner that violates the principles of justice or autonomy and therefore will be difficult to justify on ethical grounds.

The concern of Lockwood and colleagues related to the efficacy of PEP with SDR is essentially related to the issue of beneficence: is the evidence adequate to demonstrate that PEP with SDR will deliver real (and enough) benefit? Their cautionary note about drug resistance can be framed in terms of the ethical principle of non-maleficence. We turn now to two additional concerns related to the principles of autonomy and justice.

First, how will PEP be explained to community members and people who are being offered SDR? Informed consent requires a message that is readily understood but adequately nuanced to avoid misinterpretation. Based on available data, it would be overreaching to convey the impression that SDR will absolutely prevent leprosy in those who receive it.

Risk communication is an inexact science – and a frequent challenge – in public health. During the 2017–2018 influenza season, public health officials faced similar difficulties in

convincing the public to be immunised with a vaccine that had a 36% efficacy against influenza A and influenza B virus infection.[62] How best to obtain informed consent for SDR with PEP is not clear in all situations, and requires further investigation by social science and communication researchers, with full involvement of those in leprosy-endemic communities.

Second, despite significant progress, challenges remain in addressing the stigma and human rights violations to which affected people are subjected. A major potential barrier to implementation of PEP is that explaining to potential recipients the need for SDR may reveal the leprosy status of affected people who rightly fear stigmatisation if that information is shared.[63] Indeed, this is a key ethical issue that distinguishes leprosy, as stigma tends to be more pronounced with leprosy than with other NTDs. In addition, preventive chemotherapy for other NTDs is typically based on district-level population-based assessments rather than on index cases.

Focus group discussions in Bangladesh recently suggested that disclosure of one's leprosy status to neighbourhood members caused greater concern than disclosure to household and family members,[64] a pattern that has been observed elsewhere.[63] The ongoing LPEP and PEP++ studies are measuring public opinion and gathering important information related to willingness to disclose.[40] While the need to address stigma complicates the challenge of interrupting transmission of *M. leprae*, it also means that the twin goals of 'zero discrimination' and 'zero transmission'[10,11] are inextricably linked. This linkage will guard against the kind of dissociation observed in lymphatic filariasis elimination programmes between efforts to interrupt transmission and the provision of care to affected people.[31] It augurs well for a more holistic approach. Successfully attending to the difficult issue of stigma and respecting the fundamental human and ethical issues around disclosure will likely be the crux for successful implementation and scale-up of PEP at the national level. Clearly, more research is needed, imbedded within programmes. Based on the preliminary experience with LPEP, Steinmann and colleagues recommend exploration of alternative approaches to contact tracing that don't require individual disclosure.[40] Broader 'blanket' coverage with PEP may be one such approach.

Conclusion

After a decade of relative stagnation in the downward trend in the number of people diagnosed with leprosy, there is new momentum toward a vision of zero leprosy. Two major influences have generated this new optimism. First, significant scientific advances have been made in understanding and refining PEP, and there are also promising developments in vaccines and diagnostic tests. Second, the leprosy community has come together in a new Global Partnership for Zero Leprosy, as full partners in the larger NTD community. The increasingly close relationship between the leprosy and the larger NTD communities has yielded fruitful exchanges of insights, know-how, and approaches.

Wisely, the Global Partnership for Zero Leprosy has not promised to achieve elimination of leprosy by a specific date. Rather, at this point, the Partnership represents a coming together of the community, a collective setting of intention to work, dream, and achieve together. Without this foundation, scientific advances cannot be deployed in a coordinated manner to realise their full global potential.

In the short term, PEP, combined with enhanced case detection, represents the most promising approach to reduce transmission of *M. leprae* and bring us closer to the goal of zero

leprosy. At the same time, important concerns have been raised by several investigators regarding the effectiveness of this intervention; the potential for drug resistance; and ethical issues related to implementation, including informed consent and disclosure of leprosy diagnosis.

This current tension is, in many ways, a classic one for public health. Typically, scientists, physicians, and university-based researchers are cautious, arguing that data are inadequate to justify broad-scale implementation. On the other side, public health officials and programme managers feel compelled to do what is possible now to address suffering, even with imperfect tools. The first group fears the violation of the principle of non-maleficence through action; the second, through inaction. Collectively, we must wrestle with the question, "How much evidence is required?" At its foundation, this is an ethical question, one that involves a weighing of risks and benefits. As with all ethical questions, each of us brings our own personal values and emotions into the mix. These debates, which require that all voices be heard, represent our insurance against unforeseen ethical blind spots and unintended consequences as we move forward. The debates are both crucial and healthy, especially at this moment of inflection for the leprosy community.

We tend to frame the answer to this question in dichotomous terms: either "hold the presses" or "full steam ahead with our eyes closed." But there is a middle way, which strives to relieve suffering with current tools, while acknowledging the need to learn as we go – and investing in the necessary operational research and technical excellence. When taken seriously, the voices of caution serve to improve the quality, effectiveness, and ethical profile of our programmes.

In general, the NTD community has emphasised the beneficence of its programmes, which is, in fact, impressive. In my view, we have not always been as systematic and intentional in addressing non-maleficence.[65] The leprosy community can do better. We can move forward with PEP and do so with adequate monitoring for drug resistance, appropriate investments in operational research to address ethical issues of informed consent, and robust promotion of best practices for maximising the effectiveness of the PEP platform.

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