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REVIEW ARTICLE

APPROACHES AND CHALLENGES IN THE PREVENTION OF LEPROSY.

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INTRODUCTION

The case detection rate of leprosy has been declining very slowly for decades,(1) although with the steep rise in population over the last century, the actual number of cases has risen in some countries. Several possible causes for this long-term decline are suggested: firstly, an improvement in socio-economic conditions, as has occurred recently, especially in East Asia; secondly, the widespread use of BCG vaccine in infants, especially in the last few decades; and thirdly, better leprosy control measures. It is not easy, either to gauge the relative importance of these factors, or to boost their effectiveness through specific measures. There is now, however, a general desire to take a more proactive approach towards reducing the global burden of disease, including specific actions to reduce the transmission of infectious diseases such as leprosy (2).

Multi-drug therapy (MDT) has been surprisingly effective in treating individuals with leprosy.(3) Failures of treatment are rare, as are relapses and the development of drug resistance.(4) The management of reactions and neuritis remains a difficult clinical problem in many cases, but one of the best ways to reduce these complications is to get people started on MDT as early as possible, through early case-finding (5).

What is now proving to be another surprising aspect of MDT is that, despite very good global coverage, the rate of new case detection has hardly changed at all over the last decade, suggesting that effective treatment of individual cases of leprosy has a limited effect on transmission (6). There are at least two possible explanations for this. Firstly, and generally this is felt to be the most likely explanation, it seems very possible that people who are incubating the disease, especially those who will become multibacillary patients, become infectious before they develop clinical signs of the disease and present for diagnosis and treatment. We know that in measles, for example, the period of maximum infectivity is the one or two days before the rash appears, and by analogy leprosy, with its much longer timeframe could be infectious for a considerable period before the skin signs appear; we are also well aware of the fact that the early signs of leprosy are mild, and that many patients wait for months before seeking treatment (7). The second possible explanation for the lack of an effect of MDT on transmission could be the role of other reservoirs and routes of transmission – if an animal reservoir or the presence of *M leprae* in soil or water were important in maintaining leprosy transmission, treating individual cases would have little effect.

We know that leprosy in armadillos is important in the southern United States,(8) but it is not clear how important this may be in other parts of the Americas. Armadillos are not found outside the Americas and there is very little evidence to suggest an important animal reservoir elsewhere. While *M leprae* can be found in the environment near where people with leprosy live (9), it is difficult to prove whether this has any role in transmission or whether it is simply contamination from known cases. What we do know is that the risk of developing leprosy is higher in close contacts – people who are physically and/or genetically close to an index case (10) – although there are also many sporadic cases, without a history of contact.

Turning to the issue of prevention, we are learning from other Neglected Tropical Diseases (NTDs), many of which like leprosy tend to be very chronic in nature, that the burden of disease in the human population can often be reduced by treating the susceptible population intermittently with effective drugs, thus preventing disease from developing in some individuals as well as reducing the spread of the disease to others, whatever the mechanism of transmission may be (11). Combination with other strategies to disrupt known mechanisms of transmission, such as vector control or better sanitation, is valuable for certain specific diseases. This strategy is much less successful when an important and widespread animal reservoir exists, such as in leishmaniasis, for example.

In leprosy, discussions about prevention focus on people who may be incubating the disease – a stage that may take many years before clinical disease becomes apparent. There are two major problems to be addressed, namely identifying those people who are incubating the disease and then finding an effective and easily applicable method of managing that low-level infection, so that the person neither develops active disease nor becomes capable of transmitting the infection to others (12).

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New approaches to identifying people at risk

Traditionally, household contacts of new leprosy cases have been regarded as a high-risk group, and active case-finding has often been based on examining these people. They have a risk up to 8 times higher than average of developing leprosy over the next 4 to 5 years (13). Thus one approach to identifying people at risk of developing leprosy is to define segments of the population that are linked in some way to known cases. At a minimum, this would include household contacts of recently diagnosed new cases, but the definition could be widened to include people living nearby, or perhaps to whole communities where a number of new cases have been found. The rapid development of mapping technology, using geographical information systems (GIS), could allow one to calculate the population living within a certain radius of known cases, who could then be targeted for an intervention.

Another way of identifying people at high risk of developing leprosy is through the use of a diagnostic test. Currently no test is available with the requisite characteristics, namely the ability to detect leprosy infection as opposed to disease, with reasonably high sensitivity. If such a test became available, a major challenge would be how to utilize it on a large scale: would there be a need for pre-test counseling and informed consent, if it were to be used in the healthy population?

New approaches to preventive treatment for those at risk

In 2018, WHO published new Guidelines for the Diagnosis, Treatment and Prevention of Leprosy(14), based on a rigorous review of the available literature. These Guidelines recommend the use of single-dose rifampicin (SDR) as preventive treatment for adult and child (2 years of age and above) contacts of leprosy patients, after excluding leprosy and TB disease and in the absence of other contraindications.

This recommendation is largely based on the COLEP study, carried out in Bangladesh (12). One of the interesting findings of that study was that the contacts who were closest to the index case, obtained less protection from SDR than the contacts who were more distant. This is taken to suggest that some of those who are close to the index case may have already progressed to a heavier infection with *M leprae* by the time SDR was given, so that in those cases it was an inadequate dose and unable to clear the infection. This naturally led on to the idea that if these already infected people could be identified, a stronger prophylactic regimen may be much more effective in preventing leprosy in that special group. This is the basis of the PEP++ study, which uses a 3-dose regimen of rifampicin and moxifloxacin over an 8-week period (15). The main challenge in this study has been to find a way of identifying the group which needs the stronger regimen.

While these developments in chemoprophylaxis have been taking place, a parallel development has occurred in producing a vaccine for leprosy. While BCG and related whole organism vaccines, such as *M w*, now known as *M indicus pranii* (Mip) are being tested in various situations, a protein sub-unit vaccine has been developed by the Infectious Diseases Research Institute in Seattle, USA. LepVax as it is known, has completed Phase I trials in the USA and will begin further trials shortly (16). In this context, the question is whether any of these vaccines will effectively prevent leprosy in contacts, perhaps in combination with chemoprophylaxis. LepVax and killed organism vaccines, such as Mip, could be given at the same time as antibiotics, whereas BCG, a live vaccine, could not.

One possible issue with the whole organism vaccines is the precipitation of active leprosy in a small fraction of contacts. A recent study in Bangladesh indicated that 0.4% of contacts developed leprosy lesions within 3 months of receiving BCG (17); although this seems a small proportion, if the vaccine were used on a large scale this could become a major problem. It remains to be seen whether this problem will occur with LepVax, but animal studies have suggested it would be safer than BCG in those already infected, and may even be beneficial when given to those with active leprosy (18).

If LepVax does prove to be effective and without important adverse effects, even in people with active leprosy, it may be easier to implement on a wide scale than chemoprophylaxis. This is because recipients of chemoprophylaxis must be examined to exclude leprosy and TB, whereas a safe vaccine could be given to anyone, in the same way as other vaccines.

Counter-arguments

There are several potential arguments used against the strategy outlined here (19), although the use of chemoprophylaxis has been robustly defended as a worthwhile public health measure (20). Firstly, the risk of inducing resistance to rifampicin in either *M leprae* or *M tb* has been shown to be extremely low (21), on the basis that a single dose will not induce resistance, and that everyone receiving the prophylaxis is examined to exclude clinical signs of either leprosy or TB. It is important that drug resistance surveillance is continued and the results in areas where chemoprophylaxis has been used can be monitored.

A second argument relates to the effectiveness or otherwise of the prophylactic regimen. Certainly there could be improvements in the regimen given to contacts and this is being tested in a number of studies; one study uses a double dose of rifampicin, while another uses a 3-dose regimen (15). It is hoped that in future, LepVax will bring additional efficacy to the prophylactic regimen, as well as providing a much longer duration of protection.

The possibility of increased stigma towards people revealed as index cases is a third objection to this strategy. Up to now this has not been a problem in most areas where post-exposure-prophylaxis (PEP) has been tested (22). There are, however, alternative approaches that could be used in areas where stigma is a major concern, such as covering a larger group of people living in an endemic area, without identifying the index cases.

CONCLUSION

In conclusion, the new Guidelines from WHO represent a milestone for leprosy control, in that a new method for preventing leprosy has been recommended for widespread use. Much research is needed to strengthen this approach, increasing its use as widely as possible, and taking note of improvements that may be developed in the coming years, in particular, the approval of new vaccines in the fight against leprosy.

Conflict of interest*:* American Leprosy Missions has been the main donor behind the development of LepVax by the Infectious Diseases Research Institute.

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