COR-NTD 2020
Virtual Meeting, November 12 – 14
Integrating for Impact

Leprosy Prevention in the Community: Exploring MDA strategies

Session Date: 11/12/20

Session Time: 11:00 AM - 2:00 PM EST

Session Description: The World Health Organization (WHO) recommends post-exposure prophylaxis with single-dose rifampicin (SDR-PEP) including contact tracing, screening for signs of leprosy, and administration of SDR as a tool to prevent leprosy among household, neighbor and social contacts. While this group is at highest risk of developing leprosy, many new patients are diagnosed in the community, with no known link to previous leprosy cases. The concept of focal mass drug administration (fMDA) with SDR aims to expand the target population of leprosy prevention activities to known clusters in the community and builds on the well-established concept of MDA and SDR-PEP.

A number of leprosy diagnoses above a threshold defined on a spatiotemporal scale would trigger an intervention targeting a defined community unit, e.g. a village or neighborhood. The intervention would target all resident community members and include modified screening for signs of leprosy and administration of PEP. As a new concept, a number of strategic and operational questions need to be considered before fMDA-SDR can be piloted. Strategically, fMDA can be deployed in highly endemic communities where traditional SDR-PEP strategies may either be too resource-intensive for national programs or miss a considerable proportion of the at-risk population. It might also be a tool to achieve transmission interruption under a Zero Leprosy/elimination agenda.

Operationally, the feasibility of screening the whole body for signs and symptoms at community scale is key. In addition, there are questions regarding more potent PEP regimens for contacts most at risk of developing leprosy, notably blood-related household contacts of multibacillary leprosy patients. Community engagement in fMDA also needs to be explored since standard leprosy control programs are not equipped to deliver MDA and community participation has traditionally focused on peer-support and self-help groups for leprosy patients. Lastly, careful consideration is needed regarding the risk of antibiotic resistance, both for M. leprae and other bacteria such as M. tuberculosis. In addition, practical issues related to the surveillance of drug resistance should be discussed.

The aim of the session is to present the concept of fMDA-SDR to a wider NTD community, learn from established MDA programs, and jointly find answers to key issues related to fMDA-SDR for leprosy control and elimination, which may inform planned proposals for pilot studies.

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Session Chairs: Peter Steinmann and Christa Kasang
Session Rapporteur: Liesbeth Mieras

KEY DISCUSSION POINTS

What key findings and data did the group identify via presentations?

A brief introduction was given by **Peter Steinmann** (Swiss TPH) on leprosy and chemoprophylaxis. Leprosy is an infectious disease, endemic in over 100 countries, more than 200,000 patients are diagnosed each year. Single dose of rifampicin (SDR) as post exposure prophylaxis (PEP) given contacts of leprosy patients reduces their risk of developing leprosy by 60%.

The LPEP Program was a three-year feasibility study during which >150,000 contacts received SDR-PEP in eight countries, after being screened for signs and symptoms of leprosy and eligibility criteria. It showed that the intervention is feasible and safe.

Christa Kasang (GLRA, Germany) presented the results of the LPEP study in Tanzania. She added that apart from SDR-PEP implementation being feasible, it also increased the attention of the national leprosy control programme to enhance efforts to control leprosy. Various studies are ongoing to find the most cost-effective ways of SDR-PEP implementation in various settings, as well as studies to overcome the risk of stigmatization after disclosing the disease status of the leprosy patient.

Epco Hasker (Institute of Tropical Medicine, Belgium) in his presentation, tried to answer the question: How to optimize targeting single dose rifampicin prophylaxis – individually or focal mass drug administration? Household contacts, but also neighbours and social contacts are known to be at increased risk. Apart from proximity to leprosy patients, there also are genetic factors; blood-related contacts are at higher risk.
In the PEOPLE project, a large, multi-partner clinical trial, testing four methods of preventive treatment in the Comoros and Madagascar, a clear gradient was seen in distance versus risk (see table below). However, almost 1 in 5 leprosy patients lived more than 100 meters from the nearest patient.
The acceptability of SDR-PEP is very high. There are hardly any refusals among household contacts. Among more distant contacts (in the community) up to 7% refusal is seen. However, door-to-door screening is very labour intensive, as was shown in a project in Bihar, India, were it took more than one year to screen a population of 33,000 and in the end only ¾ was screened. But, limiting the screening to close contacts, would have meant missing 75% of the patients.

Would it be acceptable to give SDR-PEP to everyone in a high endemic village (= focal Mass Drug Administration [fMDA]), with minimal screening efforts, such as self-screening? What is the risk involved in treating some active patients with a single dose rifampicin? There would be case detection delay. However, the risk of stigma would be reduced, because the source patient would remain anonymous. The chances of inducing resistance in TB or leprosy are minimal if not negligible when using a single dose of a short-acting antibiotic. fMDA would have impact on transmission. This may be hard to measure because leprosy is a slowly developing disease, but the PGL-1 testing could help by either looking at seroconversion or recording sero-prevalence rates over the years in children. In the PEOPLE study it was found that ~30% of the contacts

and neighbours are positive; these were not only contacts of multibacillary leprosy (MB) but also of paucibacillary leprosy (PB).

MDA against intestinal schistosomiasis in Tanzania focusing on high-risk adult individuals was presented by **Humphrey Mazigo** (Catholic University of Health & Allied Science, Tanzania). The national prevalence is estimated at 52% (highest in Sub-Saharan Africa). Control strategies mostly focus on school children, but high risk adults are not included. Experience with community participation and including adults as a target group has demonstrated that community involvement in MDA activities is possible, the participation increasing over time with targeted information and a multi-sectorial approach contributes to the success.

Annemieke Geluk (LUMC, Netherlands) presented on the use of immuno-diagnostic point-of-care tests for leprosy surveillance and transmission assessment.
Biomarkers are produced by the immune system and can be found, even when the pathogen has been cleared. In order to stop transmission we need to identify individuals carrying the bacteriae because they are able to spread the infection. Anti-PGL-1 IgM can be used as a measure of (past) *M. leprae* infection:

1. There is a strong correlation between the Bacteriological Index and anti-PGL-1 IgM.
2. *M. leprae* PGL-1s are pathogen specified and have the strongest immunomodulatory capacity.
3. Anti-PGL-1 IgM levels decrease during MDT.

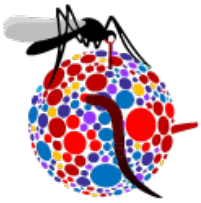
A quantitative (UCP-LFA), highly sensitive and stable, point-of-care test is available. Examples of use in field studies are: to measure the effect of prophylactic interventions on individual level; treatment with SDR-PEP based on anti PGL-1 IgM levels; assessment of *M. leprae* transmission in a population, by including children 5-10 years of age. It is now proposed for use in an fMDA study to measure the effect of SDR-PEP in a population.

Drug regimen and considerations around drug resistance were presented by **Charlotte Avanzi** (Colorado University, USA). The multidrug therapy (MDT) for leprosy consists of rifampicin and dapsone for paucibacillary (PB) leprosy. Clofazimine is included as third drug for multibacillary leprosy. Several drugs (such as fluoroquinolones) are available as second line drugs in case of resistance.

The detection of MDT component resistance is challenging because it cannot be cultured. The mouse footpad method is used, which is time consuming due to the slow growth of the pathogen. Genetic investigation has enabled molecular detection of mutations against some of the anti *M. leprae* drugs.

In 2008, a drug resistance surveillance network was set up with sentinel and reference labs. Most resistance cases are reported from Brazil and India. There is under sampling from many countries, this is due to the fact that a low priority is given to surveillance of drug resistance and the availability of resources is therefore limited.

There are scientific arguments that explain the low risk of drug resistance during SDR-PEP. However, no resistance surveillance was set up as part the (SDR-)PEP (research) projects that have been conducted or are ongoing.



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What issues were raised in discussions?

Participants:

1. Annemieke Geluk
2. Christa Kasang
3. Peter Steinmann
4. Epco Hasker
5. Roderick hay
6. Jessica Fairley
7. Paul Emerson
8. Charlotte Avanzi
9. Wim van Brakel
10. Patrick Lammie
11. Catherine Mukopfa
12. Heather Kilgore
13. Nienke Veldhuijzen
14. Ria Snijders
15. Chandrakant Revankar
16. David Blok
17. PJ Hooper
18. Bill Gallo
19. Michael Marks
20. Chelsea Toledo
21. Liesbeth Mieras

Mass **skin screening** to rule out giving SDR-PEP to leprosy patients instead of contacts without signs and symptoms of leprosy is laborious. A balance needs to be found between what is practically feasible and the benefits of skin screening. Could this be replaced by community education about (early) signs and symptoms of the disease and/or self-screening?

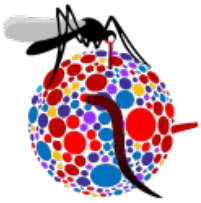
There is a lot to learn from the experience with **other PC-NTDs**, such as from the trachoma programme with MDA. An important difference with other PC-NTDs is that leprosy is a relatively rare disease, though there are high-endemic leprosy pockets that can be targeting with fMDA. There are other PC-NTDs that are also gradually moving towards a more focalized implementation of MDA because of ongoing transmission in pockets.

There are multiple projects that show the feasibility and effectiveness of **community involvement** in MDA.

Point-o- Care (POC) tests to find infection are especially useful in the context of leprosy, because it has such a long incubation time. Waiting for effects in the number of newly detected patients, takes a long time. A POC test would give a much quicker result. Cross-sectional samples can be taken before and after an intervention. Sero-prevalence in children is a proxy indicator for transmission. Whether this affects the acceptability of SDR-PEP is to be determined, but it would provide evidence on the effect of the intervention.

Mapping is very useful in determining the target areas for fMDA. When using GPS coordinates the confidentiality of these data should be taken into account; they should only be used as aggregated data.

It is highly recommendable to seek **collaboration with other MDA programmes** and work in an integrated manner to use synergy effects and increase cost-effectiveness. The main costs driver for MDA programmes is reaching the community.



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KNOWLEDGE GAPS IDENTIFIED

What data and tools need to be generated to address the issues raised by the group?

It is important to agree on the last mile, to determine **when to start and when to stop** MDA and to have a clear understanding of the target groups. Mapping and testing can both be used to define what the end point will be. Once important stakeholders are aligned on what needs to be achieved, it becomes easier to define the necessary steps towards the endpoint. Having a lab measure to detect transmission would be very helpful.
For MDA programmes the following is required:

- A clear trigger point to start
- A defined point to end
- A monitor system to determine whether the right points were chosen

Making rifampicin available for SDR-PEP implementation is and urgent next step. If any more information is needed for the pharmaceutical industry to make this happen, this needs to be given priority.
Options to use other or additional drugs for a leprosy chemoprophylaxis regimen were discussed. A combination of two or more drugs could overcome discussions around resistance. However, some concerns were raised about the use of critical TB drugs and feasibility issues when it comes to drug combinations or repeated administration.

RECOMMENDED NEXT STEPS

What operational research and other actions need to be taken to address the knowledge gaps identified by the group?

There is extensive experience with MDA but not much experience with the use of MDA for a disease with a relatively low prevalence. fMDA for leprosy is a new idea that has not been used anywhere in the world.
A randomized control trial can help demonstrate the effectiveness of fMDA for leprosy.

Operational research is needed to gain experience with the implementation of fMDA for leprosy, in terms of feasibility, acceptability and cost effectiveness.

Define start and end point as specified above.

Experience needs to be gained with integrated approaches, in combination with MDA for other PC-NTDs, because these are generally preferred over single disease approaches.

Mapping will be needed to target fMDA. There is only limited experience with the identification of clusters.

Surveillance for resistance needs to be setup in areas where chemoprophylaxis for leprosy is being / will be implemented, starting with the collection of baseline data.