General discussion

In this thesis, we studied the health economic aspects of leprosy prevention through leprosy post-exposure prophylaxis with single-dose rifampicin in India. The thesis trajectory required defining the framework, set the baseline, explain the intervention, estimate the costs and determine the cost-effectiveness. This section contains a discussion of the research questions mentioned in the introduction section, strengths and limitations of the results, and recommendations for policy, practice and future research.

MAIN FINDINGS

Research Question 1

How do investment case concepts apply to leprosy elimination?

Answer

Based on an existing generic framework for a disease eradication investment case, we developed a 11-topic framework for leprosy elimination.

We selected the 'guide to prepare an eradication investment case' to develop an 11-topic framework for leprosy elimination [1]. The guide contains sections and sub-sections that describe the aspects necessary for an investment case. However, not all sub-sections of the guide were relevant to leprosy elimination or needed adjustment. After adjusting and finalising the framework, we identified the existing knowledge and information gaps for completing the investment case for leprosy. We synthesised available information through a systematic literature review under these topics and discussed the findings. Below, we highlight the main topics of the framework and discuss the overall scope of an investment case for leprosy elimination.

With regard to disease burden, the three decades long case detection trend (Figure 1) demonstrates the changes over time that can feed into the investment case. But the number of cases is a poor indicator for comparison across diseases which is desired for setting priorities and resource allocation. The other method to measure the burden is QALYs or DALYs. But before using DALYs widely in leprosy, the disability weights for grade I and II disabilities need revision to realistically reflect the suffering. Currently, the disability weights are low due to methodological challenges such as non-availability of data on sequelae, including grade I disability. In literature, the burden of leprosy is presented as either the number of new cases, registered prevalence rate, and proportion of grade-2 disability among new cases [2]. From the case trend, we observed that the global leprosy programme was not active enough in the recent past. In the last decade, the decline in the number of new cases was marginal in South-East Asia, which

indicates that the transmission is ongoing and that additional measures are required for further reduction [3]. By 2015, WHO pledged to reduce grade-2 disability by 35%, but the target was missed due to passiveness [4]. Now, WHO proposes to seriously follow its previous recommendation of contact tracing, but now combined with SDR [5]. These targets and evolving guidelines are important information for planning a realistic investment case for leprosy elimination.

Among elimination tools, SDR is most advanced due to a successful feasibility trial (LPEP) and its scientific documentation [6-11]. This information is ready to be part of the investment case. However, for comparison, similar information is also desired from other tools such as vaccines and rapid diagnostic tests. Vaccines still need to prove their feasibility, and rapid diagnostic test needs to be more accurate (sensitive and specific). The biological feasibility of eradication is doubtful because *M. leprae* and *M. lepromatosis* also have reservoirs in the environment and animals, and not only in humans. However, elimination of the disease is certainly achievable as seen before in Europe, therefore the investment case is focused on the elimination. Furthermore, genome sequencing studies can bring more clarity on the topic, which should also be proposed in the investment case. On the programmatic front, it is clear that vertical service delivery is not feasible and sustainable when elimination is close. Rather, integration of the national leprosy programmes with other programmes is a better strategy. The integration of a leprosy programme into the general health care is widely reported and these lessons can feed into the investment case. However, integration alone is not sufficient, but continuous awareness and training is also crucial to sustain and improve the services. The future requirement is to integrate leprosy services with other NTDs programmes and bring them all under a poverty alleviation agenda.

The investment case still needs more information than what is currently available and presented in the above paragraph. The current leprosy burden is an underestimation because many new cases and grade-2 disability cases are hidden, especially in India [12]. Further, leprosy consequences such as stigma, discrimination, and poor mental health are not seen as a burden, but are certainly important to calculate the economic burden of leprosy [13]. As a prominent finding of this thesis, health economic evidence on leprosy is limited and currently not sufficient to build an investment case; especially cost-effectiveness studies are very few. Cost-effectiveness studies are required under topics such as socioeconomic burden of leprosy, financing leprosy elimination, health systems and its capacity. The information on feasibility of new tools is also desired to interpret cost-effectiveness results. Certainly, leprosy elimination is in demand, and partnership is the way to meet that demand. An investment case document can help in advocacy, fund sharing and planning between stakeholders.

To fill the information gaps, we conducted health economic studies, which are included in this thesis. In chapter 3, we selected SDR as the new tool and explored its operational alignment with the health system. This has provided more information on how to roll-out SDR and in which circumstances we can expect effectiveness. SDR is feasible to implement in most endemic countries along with their national programmes. It is, however, less effective in countries where a contact tracing system is not in place. Further in chapter 4, we focused on the economic burden of leprosy on society by estimating the household expenditure on leprosy. This was high, and as a result, the health-seeking behaviour of patients was poor. If we invest in prevention, this economic burden can be lessened substantially. In chapter 5, we focused on the economic burden of leprosy on the health systems. We found that the prevention of leprosy by SDR is financially feasible if implemented as an additional activity under ongoing contact tracing. In chapter 6, we estimated the cost-effectiveness of SDR in different disability burden situations, and showed that it can realistically be scaled-up in India.

We only conducted studies in India, which is not sufficient to complete an investment case at the global level, but we demonstrated how to systematically collect the information. We conclude that the investment case for leprosy elimination is an important and relevant concept. We already have much information to complete the investment case, including the results of this thesis. More health economic information on the new tools of prevention is desired from other endemic countries. For completion of the global investment case with SDR, we require similar cost-effectiveness estimates from Indonesia and Brazil, which together with India constitute 80% of the global caseload. The information should be collected in a planned and collaborative manner as described in chapter 3. We recommend completing the global investment case for leprosy elimination with SDR in other leprosy endemic countries to contribute to the WHO guidelines for 2021-2025.

Research Question 2

Can post-exposure prophylaxis with SDR be implemented into a national leprosy control programme?

Answer

SDR is feasible to implement along with the national leprosy control programmes in endemic countries without many structural and human resource changes.

The implementation feasibility of SDR was demonstrated by the LPEP program in seven countries within their respective national leprosy control programmes. The LPEP program explored the feasibility and impact of combining three key interventions, i.e.,

contact tracing, contact screening, and administration of SDR. The activities were implemented through established structures of the national leprosy programmes. The aim was to explore the feasibility of the intervention package to improve early case detection, prevent leprosy and integrate with the national leprosy programmes.

The LPEP program was implemented in countries that were different with regard to the level of endemicity, national programme activity, and health system capacity. The programme ran for several years (2015-18) without any country dropout, which is in itself evidence of feasibility. However, due to health system differences, one fixed approach was not suitable to implement the programme. Therefore, countries were consulted to define their functional parameters and targets. However, it was ensured that these changes and adjustments were documented to interpret the results correctly. Another indication of feasibility is the high coverage of the LPEP program, which enrolled 9,186 index patients and listed 179,769 contacts, of which 174,782 (97.2%) were traced and screened. Further, SDR as an intervention was well accepted by the community, contacts and health staff as only 0.7% (n=1,182) contacts refused the SDR, which was otherwise administered to 86.9% (n= 151,928) of the screened contacts. LPEP also demonstrated that high coverage is feasible without compromising on the quality of screening. Out of those screened, only 13.1% (n=22,854) were excluded from SDR for various reasons. LPEP also increased the case detection by finding 1,300 persons suspected for leprosy, and confirming 810 (62.3%) of them as new leprosy patients. The countries that had some level of contact tracing in place had better coverage than those without any previous contact tracing. Next, rifampicin was yet again proven to be a safe drug as no adverse events were reported from any country. The challenge was to cover neighbour and social contacts, because the availability of health staff was limited, the area to cover was large, and contacts were often absent during the house visits. This resulted in extra workload for the health staff, but their high level of motivation led to success [9].

SDR distribution is still ongoing in 4 out of 6 LPEP countries after completion of the LPEP program. The WHO recommendation in the recent leprosy guidelines played an important role to adopt it as a policy in countries [5]. Another factor for SDR sustainability was a planned exit policy of the LPEP program. In the last year of LPEP and a year after completion, countries received some funds and technical support to carry on the SDR work independently. Two examples of technical support are delivery of an SDR tool kit and minimal data set recommendation for recording and reporting [7, 10]. We conclude that SDR is feasible and safe to implement in different epidemic and programmatic situations. Sustainability is high when the local public health staff own the intervention.

Research Question 3

What is the cost-effectiveness of SDR?

Answer

SDR is cost-effective when assuming that disability could be prevented, i.e., US$ 443 per DALY averted over 25 years.

The result of our cost-effectiveness analysis for SDR in India was below the GDP per capita (2017) of India, and therefore SDR can be said to be very cost-effective. The cost-effectiveness was mainly due to the intensified supporting activities such as contact screening and awareness, which translated into high coverage. These results apply to areas where some form of contact tracing is already part of the routine programme. The SDR cost (USD 2.9; 95% CI: 2.5–3.7) used in the analysis pertains to only SDR activities such as contact listing, screening and administering the rifampicin. A fresh introduction of contact tracing with SDR will surely be expensive as existing contact tracing reduces the cost of training and infrastructure. Furthermore, motivation and skills of health staff are better if they are already familiar with contact tracing, leading to better effectiveness.

The presented cost-effectiveness results are based on the health system perspective. If the patient's perspective is also added, SDR will certainly yield more benefit. Precisely, if we prevent a leprosy case then we also prevent US$ 9.5-12.4 per health care visit by the patient, resulting in cost savings. During the treatment, there are at least 12 visits for a MB patient and 6 visits for a PB patient. The majority of the patient's expenditure is contributed by the indirect expenditure such as wage loss, which is often hidden, but a factor for delay in detection. The affected person avoids the diagnosis due to wage loss, spreads infection, and increases the chance of disability. In addition, we recommend that high endemic areas with high disability rates should be prioritised first to secure larger impact. In summary, each case prevented will contribute manifold in reduction of the economic burden due to leprosy. We conclude that SDR is a cost-effective strategy and its scale-up is recommended in India, prioritizing high endemic areas first.

STRENGTHS AND LIMITATIONS

A wide range of methodologies were applied in this thesis. We conducted a systematic literature review (**chapter 2**), a mixed method study with qualitative research (**chapter 4**), two costing studies (**chapter 5 and 6**) and a cost-effectiveness analysis with simulation modelling (**chapter 7**).

The systematic literature provided detailed information on the topic of investment case and comprehensively arranged the available evidence. The review followed a strict criterion-based search and selection, which ensured the validity of results. Generally, literature review results dilute quickly due to inflow of new information from new publications, therefore the results of our review from 2016 would need an update. In 2019, a report on the proceedings of an expert consultation on the leprosy elimination investment case was published [14] and summarized developments, providing updated information.

The mixed method study provided a comprehensive overview of the baseline situation before the intervention. Particularly, the qualitative analysis provided critical explanations about the quantitative data. However, as a limitation, qualitative results are difficult to generalize to another country or population, therefore, caution is warranted when extrapolating results. However, the qualitative information will provide a base to design future studies. Finally, we used a widely accepted and simple WHO framework on health systems, which provided consistency for data collection and analysis in the multicentre nature of the mixed method study.

The costing studies were part of following-up the recommendation of chapter 2 and covered the health systems and societal perspective. The health system cost was addressed by estimating the public expenditure, whereas the societal aspect was addressed by estimating the expenditure by the patients. This provided a complete overview of the economic burden of leprosy. We used deterministic and stochastic methodology to generalize the costing results. Generally, cost data are skewed, requiring a suitable distribution to build a deterministic model. We accounted for such situations by performing a detailed diagnostic and model fitting exercise. We used different sampling methods suitable for health systems (purposive) and societal (random) costing because the unit of analysis was different. However, random sampling is the gold standard, but due to a large number of health facilities and financial constraints, it was not feasible for health system costing. The cost alone does not inform on the long-term efficiency or decision to scale-up, therefore we performed cost-effectiveness analysis by utilizing the SDR costing results.

For the cost-effectiveness analysis, a long term perspective was needed because interventions that include contact tracing and screening will initially increase the number of new cases due to the existing backlog of cases [15]. Also, effects of leprosy interventions are known to only be visible after years due to the long incubation time [16]. We therefore applied modelling to analyse the long term impact of SDR. Mathematical modeling is the only tool for predicting future leprosy trends and the potential im-

pact of interventions [17]. However, results are only valid on the assumption that the deployment of the intervention remains unchanged over the forecasted period. Also the modelling was limited because of lack of data about disability, which is a problem in general. Cost-effectiveness studies for leprosy would improve generally, if more detailed data would be collected on different types of disability. The costing results are also time-bound and the decision is dependent on the applied willingness-to-pay threshold. We provided detailed information in our study on factors or assumptions that can influence the results, also with regard to the setting. The costing results are difficult to apply to other economic regions, therefore more such evidence is needed in a reasonable time frame to complete the global investment case for leprosy elimination.

RECOMMENDATIONS FOR POLICY AND PRACTICE

From the above discussion, we summarize the following recommendations for leprosy control policy and practice:

1. We recommend completing a global investment case for leprosy elimination with SDR in other leprosy endemic countries to contribute to the WHO guidelines for 2021-2025. For this purpose a roadmap can be developed including (at least) the following steps:
    - Estimate health system cost of SDR for other endemic countries, particularly Indonesia and Brazil
    - Estimate patient's expenditure on leprosy care and opportunity cost to receive SDR
    - Estimate the fund required globally to cover contacts - family and neighbours - of leprosy patients in different programmatic situations
    - Estimate the cost-effectiveness of SDR globally with revised disability weights for leprosy
2. We showed SDR to be a cost-effective strategy in India and for that reason recommend its scale-up in that country.
3. SDR is a cost-effective intervention with a return of investment after 5 years and onwards. For a larger benefit, we recommend long term implementation of SDR.
4. The best results of SDR can be expected in moderate to high disability burden areas, as there will more chance for SDR to prevent disabilities. We recommend to prioritize these areas for implementation of SDR-PEP.
5. The leprosy burden estimates need revision by accounting for hidden cases. We recommend active case surveys as part of routine leprosy control programmes in endemic countries with standardized monitoring and reporting.

6. The leprosy programme performance was better and the patient expenditure was low under the enhanced health system of DNH in India. We recommend that in India the state leprosy programmes that are part of the general health care system should be enhanced as well to reduce the economic burden of leprosy patients.

RECOMMENDATIONS FOR FUTURE RESEARCH

The studies in this thesis are among the first to contribute to the development of an investment case for leprosy elimination. It is important that research in leprosy continues to focus on leprosy elimination and its economic aspects. Factors that have an indirect effect on policy and planning should also be considered for future research. Based on studies in this thesis, we formulate the following set of recommendations for further research:

1. Future studies should include cost and cost-effectiveness analysis of SDR and other preventive interventions to feed into the global leprosy elimination investment case.
2. Better health system capacity leads to better implementation of SDR, which also determines its cost-effectiveness. We therefore recommend the collection of information on the health system together with costing studies to interpret the effects of preventive interventions such as SDR accurately.
3. Health system studies should focus on the financial sustainability of integration of leprosy health services with other co-existing NTDs.
4. We found that human resource is an important factor from the point of view of health financing and operational research. Health systems research should also focus on enhancing human resource (HR) capacity.
5. We recommend economic studies in areas with no leprosy contact tracing to enable cost-effective implementation of contact tracing in their health system and prepare for the implementation of SDR.
6. We recommend to systematically study the lessons learnt from the experience of other infectious diseases that have been eliminated or at the verge of elimination in order to apply these where possible to the leprosy elimination investment case.

CONCLUSION

An investment case is applicable to plan and advocate the investment in leprosy elimination, but is as yet far from complete. Completion of a leprosy elimination investment case is the collective responsibility of all stakeholders working in the field of leprosy, and their data collection and research for an investment case needs to be coordinated and aligned. Sustainability of an intervention is high when the local public health staff own the intervention. Other than the level of leprosy endemicity, the health system capacity for contact tracing is important for the cost-effectiveness of implementing SDR-PEP in a leprosy control programme. In this thesis we conclude that post-exposure prophylaxis with SDR is feasible, safe, cost-effective, and compatible with most national leprosy programmes, including that of India, the focus country of this thesis.

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