Effectiveness of Rifampicin Chemoprophylaxis in Preventing Leprosy in Close Contacts: A Systematic Review

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Abstract.

Leprosy (Hansen's disease) remains a major public health problem in endemic countries, where the decline in new-case detection has been slow, suggesting ongoing transmission, particularly among household members and other close contacts who face a higher risk of disease. This study aimed to evaluate the effectiveness of rifampicin as post-exposure prophylaxis (PEP) for preventing leprosy among contacts of index cases, while also describing variations in prophylactic regimens. The review was conducted in accordance with PRISMA guidelines through literature searches in PubMed and Google Scholar using combinations of terms related to leprosy/Mycobacterium leprae and rifampicin. Study selection involved title/abstract screening followed by full-text assessment based on predefined inclusion and exclusion criteria. Six studies met the eligibility criteria; these were predominantly randomized trials and evaluated diverse interventions, including single-dose rifampicin (SDR), double-dose rifampicin PEP at 20 mg/kg (SDDR-PEP), SDR plus BCG vaccination, and enhanced prophylactic regimens under protocol evaluation, which is rifampicin–bedaquiline and PEP++ (rifampicin–clarithromycin). Follow-up durations were evenly distributed between 24 and 48 months. The synthesized evidence indicates that SDR reduces leprosy incidence primarily within the first two years (≈57%), although the protective effect tends to attenuate during years 2–4. In contrast, SDDR-PEP (20 mg/kg) was associated with a reduction in individual-level risk (IRR 0.55; 95% CI: 0.36–0.83), with stronger protection among household contacts (IRR 0.35; 95% CI: 0.15–0.82). Overall, rifampicin-based PEP appears to reduce leprosy occurrence among close contacts, particularly in the early post-intervention period; however, the magnitude of impact is influenced by transmission dynamics, the breadth of contact targeting, and the quality of screening and program implementation. Evidence for enhanced PEP regimens remains preliminary and requires definitive effectiveness results before broad recommendation.

Keywords: *Leprosy; rifampicin; post-exposure prophylaxis and close contacts.*

I. INTRODUCTION

Leprosy (Hansen's disease) is a chronic infectious disease caused by Mycobacterium leprae and remains a public health problem in many endemic countries. Although multidrug therapy (MDT) has been available and has successfully reduced global prevalence, the number of new cases globally has shown a slow decline and tends to stagnate in the last decade, indicating that transmission is still active. 1 Leprosy transmission occurs primarily through close and prolonged contact with untreated sufferers, so household contacts and other close contacts have a higher risk of infection and development of clinical disease. 2 Leprosy prevention strategies for close contacts have long been developed through immunoprophylaxis and chemoprophylaxis approaches. The Bacillus Calmette–Guérin (BCG) vaccine is known to have a protective effect against leprosy, although its effectiveness varies across populations. 3 In relation to chemoprophylaxis, the Contact Transmission and Chemoprophylaxis in Leprosy (COLEP) clinical trial in Bangladesh showed that administering a single-dose rifampicin (SDR) to contacts of leprosy patients reduced leprosy incidence by 57% in the first two years after intervention. The results of this study formed the basis for the World Health Organization (WHO) recommendation for the use of SDR as post-exposure prophylaxis (PEP) for leprosy contacts. 1,4 However, the effectiveness of SDR is not always consistent across regions, particularly endemic areas.

Studies conducted in areas with high case numbers have shown that PEP effectiveness can be influenced by the level of community exposure and spatial proximity to the index case. 5 A large-scale cluster-randomized trial in the PEOPLE study showed that a broader community-based approach, including multiple doses of rifampin (20 mg/kg), provided individual protection against leprosy, although the population-level effect was lower than expected. 1 In addition, strengthening the PEP regimen through a combination of antibiotics, namely the administration of rifampicin and clarithromycin in the PEP++ protocol, is being studied to increase the effectiveness of prevention, especially in high-risk groups. such as household contacts and biological relatives of multibacillary patients. The variation in results between these studies highlights the need for a comprehensive synthesis of evidence, not only from quantitative trials of clinical effectiveness, but also from qualitative studies evaluating acceptability, feasibility of implementation, and social factors such as perceptions and stigma regarding leprosy. A combination of quantitative and qualitative evidence is needed to fully understand the effectiveness of rifampin chemoprophylaxis in the context of leprosy elimination programs.6 Based on this background, this systematic review aims to comprehensively evaluate the effectiveness of rifampin chemoprophylaxis in preventing leprosy in patient contacts, integrating quantitative evidence on incidence reduction and qualitative evidence on the implementation and acceptability of the intervention. This synthesis is expected to provide a stronger scientific basis for developing leprosy prevention strategies in endemic countries.

II. METHODS

2.1. Research Design

This study is a systematic review compiled following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure that the process of identifying, selecting, and reporting studies is carried out transparently and systematically.

2.2. Data Sources and Search Strategy

A systematic literature search was conducted to identify evidence regarding the effectiveness of rifampin chemoprophylaxis in preventing leprosy in close contacts. The search was conducted through the electronic databases PubMed and Google Scholar, with restrictions on human studies. A keyword strategy was developed using a combination of terms related to leprosy or Mycobacterium leprae and rifampicin, and close contacts. The search included publications up to a predetermined time limit and was not restricted by language.

2.3. Inclusion and Exclusion Criteria

Inclusion criteria for this study included studies discussing the use of rifampin as post-exposure prophylaxis (PEP), clearly reporting sample size and outcomes, and using valid assessment methods. Exclusion criteria included studies irrelevant to rifampin prophylaxis in leprosy, animal studies, articles with only abstracts, literature reviews, or articles not available in full text, case reports, editorials, conference proceedings, duplicate publications, and studies that did not provide required outcome data.

2.4. Study Selection Process

All titles and abstracts obtained from the literature search were managed using a reference management tool to identify and remove multiple articles. Next, titles and abstracts were screened to assess their initial suitability to the research topic. Articles meeting the inclusion criteria during the screening stage were then evaluated through full-text review based on the established inclusion and exclusion criteria. If disagreements arose at any stage of the selection process, the final decision was made through discussion and resolved by a third researcher.

2.5. Study Quality Assessment

Assessment of study quality is carried out using criteria that cover several main aspects, namely clarity of the research population and selection criteria used, clarity of procedures or interventions and methods of measuring outcomes, the basis for determining results, and the adequacy of the completeness of the reported data, such as the proportion of valid or successfully completed data.

2.6. Data Extraction

Data were extracted using a standardized form by two researchers independently. Variables recorded included author, year, country, study design, population, sample size, follow-up duration, type of rifampin intervention used (SDR, SDDR-PEP, PEP++), and the main outcomes of the study. A summary of study characteristics and results is then presented in a table.

2.7. Data Synthesis

The synthesis was conducted narratively, summarizing differences in design, population, interventions, and outcomes between studies. In this study, the summary of study results was primarily presented in tabular form and comparative interpretations between interventions.

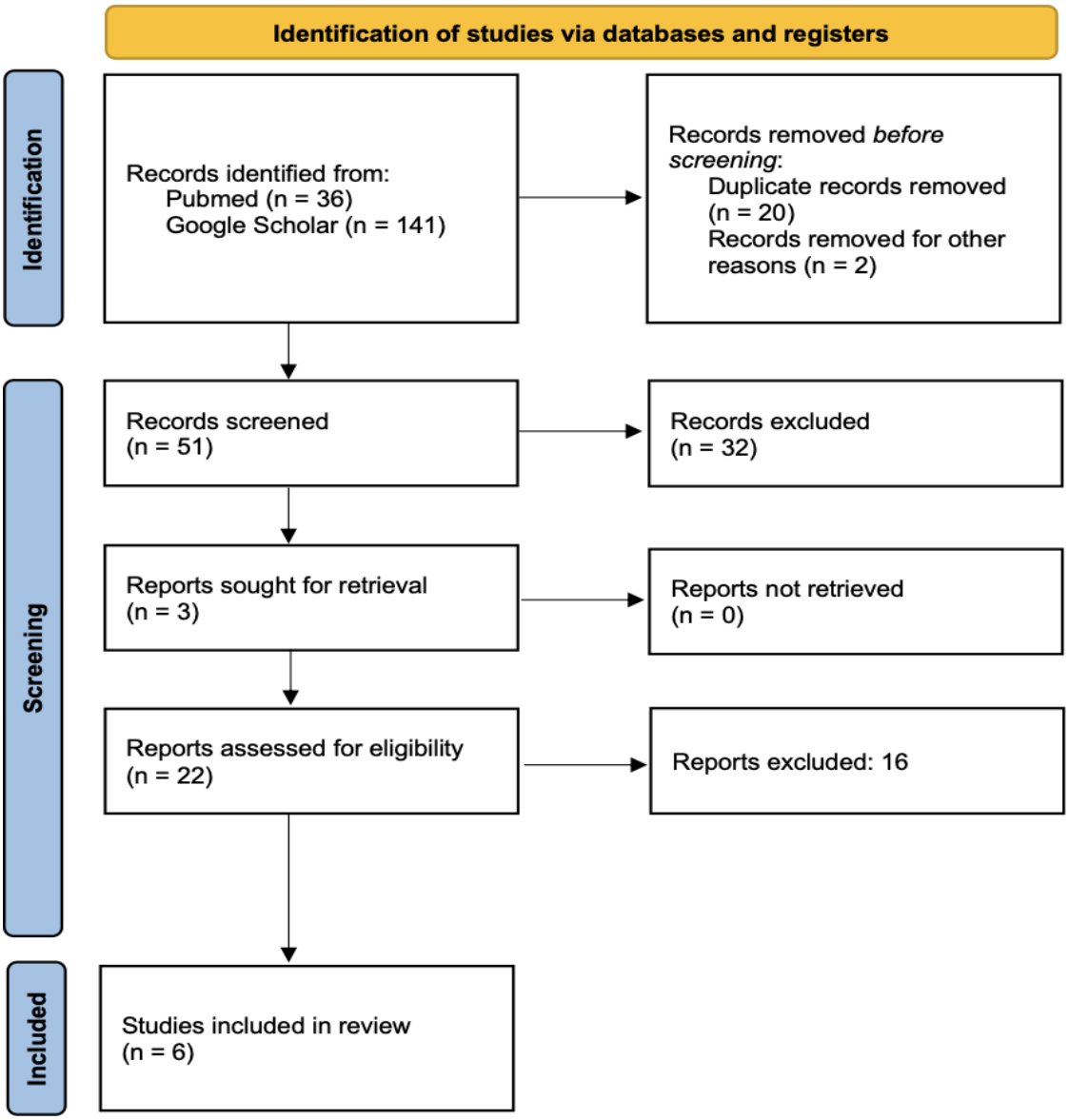

Fig 1. PRISM

III. RESULT AND DISCUSSION

3.1 CharacteristicsStudies

A total of six studies were included in this review. Based on publication year, these studies were published between 2008 and 2024. The highest proportion of publications occurred in 2019 and 2024, with two studies (33.33%) each. Meanwhile, one study (16.67%) each was published in 2008 and 2023. This distribution indicates that research related to post-exposure prophylaxis of leprosy has continued to develop in recent years.In terms of research design, the majority of studies used a two-arm randomized trial design,

amounting to three studies (50.00%). Two other studies (33.33%) used a four-arm randomized controlled trial design, while one study (16.67%) used a randomized controlled trial without specifying a specific phase. Overall, all studies included in this review adopted an experimental approach with random allocation, indicating a relatively strong level of methodological evidence.Based on research location, the studies were conducted in various endemic regions. Most were conducted in Africa (n = 3; 50.00%). Bangladesh and Brazil were each represented in two studies (33.33%), while India and Nepal were each represented in one study (16.67%).

This geographic distribution reflects the research focus on countries with a significant leprosy burden.In terms of intervention type, there was a wide variety of prophylaxis regimens evaluated. The most frequently studied intervention was single-dose rifampicin at a double dose of 20 mg/kg (double-dose SDR-PEP), which was used in two studies (33.33%). Meanwhile, one study each (16.67%) evaluated standard single-dose rifampicin (SDR), a combination of rifampicin and bedaquiline, a combination of rifampicin and clarithromycin, and a combination of SDR and Bacillus Calmette–Guérin (BCG). This variation suggests efforts to increase prophylaxis effectiveness through regimen enhancement or drug combinations.Based on intervention duration, there was an even distribution between 24-month and 48-month studies, with three studies each (50.00%). This indicates that some studies focused on evaluating medium-term effects (two years), while others assessed the impact of the intervention over a longer period (four years).

Table 3.1. Characteristics of Inclusion Studies

Publication Year	
Characteristics	**N(%)**
2008	1 (16.67%)
2019	2 (33.33%)
2023	1 (16.67%)
2024	2 (33.33%)
Study Design	
Randomized trial, 2 arms	3 (50.00%)
Randomized controlled trial 4 arms	2 (33.33%)
Randomized controlled trial (non-phase specific)	1 (16.67%)
Research Location	
Bangladesh	2 (33.33%)
Africa	3 (50.00%)
India	1 (16.67%)
Brazil	2 (33.33%)
Nepal	1 (16.67%)
Intervention Sector	
SDR	1 (16.67%)
Rifampicin + Bedaquiline	1 (33.33%)
Rifampicin + Clarithromycin	1 (16.67%)
SDR-PEP double dose 20 mg/kg	2 (33.33%)
SDR + BCG	1 (16.67%)
Duration of Intervention	
24 months	3 (50.00%)
48 months	3 (50.00%)

Based on the literature search results, six articles met the inclusion and exclusion criteria for this systematic review. A complete summary of the study results is presented in Table 3.2.

Table 3.2. Summary of Study Results

No.	Writer Amount	Country	Population	Sample	Study Design	Duration	Intervention	Results
1	Moet et al., 2008	Bangladesh	New leprosy patient	21,711 monthpatient	RCT	48	▪ Single-dose rifampicin (versus placebo), given in the 2nd month of therapy in the index patient; 4-year follow-up ▪ Control placebo	▪ Case: placebo 91/9452 vs rifampicin 59/9417 ▪ 57% reduction in incidence in the first 2 years; no difference in years 2–4; NNT 297 ▪ Single-dose rifampicin was effective in preventing clinical leprosy at 2 years and the effect persisted but after 2 years there was no difference between groups.
2	Assoumani Younoussa et al., 2023	Africa Cluster	Village in Comoros	Age contact ≥5 years within a 100 m radius of case index (special2–4 years of age (rifampicin only)	RCT 2 *arms*	48 months	▪ Intervention: bedaquiline (400-800 mg) + rifampicin (at a dose appropriate to age/weight (150-600 mg); in this arm, household contacts stairs can get the 2nd dose 4 weeks later) ▪ Control rifampicin alone (SDR- PEP)	▪ Conclusion not yet (protocol): combination effectiveness test bedaquiline+rifampicin vs rifampicin alone as PEP in leprosy contacts
3	Duane C. Hinders et al., 2024	India, Brazil, Bangladesh, Nepal	Close contact patients	Contactnear leprosy cases (India, Brazil, Bangladesh, Nepal); follow-up 2 years after the last dose	RCT 2 months *arms*	24	▪ PEP++: 3 doses of rifampicin + clarithromycin every 4 weeks ▪ Control SDR-PEP (single dose rifampicin)	▪ Conclusions yet (protocol): testing whether PEP++ (multi-dose combination antibiotics) is more effective than SDR-PEP

4	Nimer Ortuno-Gutierrez et al., 2019	Africa	Participants will be recruited from 48 villages in Comoros (32 in Anjouan and 16 in Mohéli) and an unspecified number of villages in the Miandrivazo district, Madagascar.	Permanent residents are screened annually; eligible contacts receive SDR-PEP according to arm	RCT 4 months *arms*	48	▪ (1) Arm 2: PEP for household; Arm 3: household + neighbors ≤100m; Arm 4: household + ≤100m who are anti-PGL-I positive (SDR- PEP double dose 20 mg/kg) ▪ Control Arm 1: no PEP (comparator)	▪ Conclusion yet (protocol): comparing 3 PEP implementation strategies vs. no PEP to see which is most effective
5	Renate Richardus et al., 2019	Bangladesh	New leprosy patient	14,988 patient	RCT 2 months *arms*	24	▪ Intervention: BCG (0.1 ml) then SDR 8–12 weeks later (SDR+) (150 mg) ▪ Control BCG only (SDR -)	▪ The incidence rate per 10,000 person-years at risk was 44 in the SDR group and 31 in the SDR+ group at year 1. ▪ The incidence rate was 34 in the SDR group and 41 in the SDR+ group at year 2. ▪ There was a reduction that was not statistically significant (p = 0.148; 42%) for paucibacillary (PB) leprosy in the SDR+ group in the 1st year. ▪ Of all new cases, 33.6% occurred within 8–12 weeks of BCG vaccination. ▪ No significant reduction in incidence was found in the intervention arm compared with the control arm: arm 2 (IRR 0.95), arm 3 (IRR 0.80), and arm 4 (IRR 0.58).
6	Epco Hasker et al., 2019	Africa	All residentspermanent residents of leprosy-endemic villages in Comoros and Madagascar who participated	95,762 patient	RCT4 months *arms*	24	▪ SDDR-PEP (rifampicin 20 mg/kg): arm 2 household; arm 3 ≤100m; arm 4 household + ≤100 m who are anti-PGL-I positive ▪ Control without PEP	▪ Arm 3 (blanket approach up to a radius of 100 meters) showed a significant reduction in incidence (IRR 0.56; p=0.0030).

	in leprosy screening during the period 2019–2023		▪ At the individual level analysis, SDDR-PEP administration was associated with a 45% reduction in leprosy risk (IRR 0.55; 95% CI 0.36–0.83). ▪ A stronger protective effect was found in household contacts (IRR 0.35; 95% CI 0.15–0.82).

Information:BCG, Bacillus Calmette–Guérin; IRR, incidence rate ratio; NNT, number needed to treat; PB, paucibacillary; PEP, post-exposure prophylaxis; PEP++, enhanced post-exposure prophylaxis (three doses of rifampicin plus clarithromycin); RCT, randomized controlled trial; SDR, single-dose rifampicin; SDR-PEP, single-dose rifampicin post-exposure prophylaxis; SDDR-PEP, single double-dose rifampicin post-exposure prophylaxis (rifampicin 20 mg/kg); SDR+, BCG followed by single-dose rifampicin; SDR−, BCG alone; anti-PGL-I, anti–phenolic glycolipid-I antibody; BB, body weight.

Discussion

Despite the widespread implementation of multidrug therapy (MDT), the number of new leprosy cases remains high each year. This indicates that at this stage, control efforts should not only focus on patient treatment but also need to strengthen transmission prevention strategies, especially in high-risk groups such as close contacts, such as household contacts or contacts with intense exposure to leprosy sufferers. 7 In general, leprosy cases can be cured if patients adhere to regular MDT, but the continued emergence of new cases confirms that transmission is still ongoing in the community. Therefore, post-exposure prophylaxis (PEP) with rifampin is an important strategy to reduce the risk of developing leprosy in exposed individuals, especially those who have close contact with cases. This study was conducted to assess the effectiveness of rifampin as PEP in preventing leprosy incidence in close contacts and to describe the characteristics of the interventions used, namely single-dose or modified regimens, the duration of follow-up, and the results reported in various studies.This study summarizes six studies that assessed chemoprophylaxis using rifampicin as post-exposure prophylaxis (PEP) in people in contact with leprosy patients, with a publication year range of 2008–2024 with a fairly wide variety of designs and interventions, namely with the administration of SDR (single-dose rifampicin), SDDR-PEP 20 mg/kg, a combination of SDR and BCG, to enhanced regimen protocols such as the administration of PEP++ and a combination of rifampicin and bedaquiline.

In this study, six studies evaluated rifampicin as PEP in close contacts of leprosy patients, where in general it was found that SDR reduced the incidence of leprosy in the first 2 years (±57%) but the effect weakened in years 2 to 4, while SDDR-PEP (20 mg/kg) also showed a risk reduction at the individual level (IRR 0.55; 95% CI: 0.36– 0.83) especially in household contacts (IRR 0.35; 95% CI: 0.15–0.82).7,8

Overall, all the research results show that PEP rifampicin has significant potential to reduce the incidence of leprosy in the early period after case identification, but the long-term impact and impact of rifampicin have not been fully understood. Population is strongly influenced by differences in transmission, contact coverage, and the intensity of screening and case detection that accompany PEP implementation. The COLEP cluster randomized trial study in Bangladesh showed that single-dose rifampicin (SDR) was able to reduce the incidence of leprosy in contacts significantly in the first two years, but the effect was no longer clear and significant in the period of years 2 to 4. The results of other studies also show a similar pattern, stating a decrease in incidence of around 57% in the first 2 years but no significant difference in the reduction in years 2–4. 9 The long incubation period of leprosy leads to the phenomenon of strong early and weak late results in rifampicin administration, based on epidemiological science. Single-dose rifampicin (SDR) is likely most effective in preventing some cases already in the advanced subclinical phase. However, in leprosy-endemic areas, repeated community exposure can increase the risk of infection or progression in subsequent years, thus narrowing the differences between groups.

In other words, the COLEP results implicitly state that SDR is not simply a one-time intervention, but rather part of a transmission interruption strategy whose effects depend heavily on whether the primary source of exposure is household-based or community-based. 9 These differences in transmission context are key explanations when comparing results across studies in this review. The PEOPLE study demonstrated that PEP effectiveness is determined not only by the drug or dose, but also by the contact targeting strategy and population-level implementation, for example, through a household-only approach versus radius-based or community-based expansion. The PEOPLE study showed that at the individual level, SDDR-PEP administration was associated with a reduced risk (IRR 0.55; 95% CI 0.36–0.83), and a stronger protective effect among household contacts (IRR 0.35; 95% CI 0.15–0.82). These results emphasize that in areas with transmission that extends beyond the household, strategies that extend PEP coverage to the neighborhood of the index case may be more relevant for population impact. This also explains why studies in highly endemic areas can show Different effect estimates are available compared to areas or conditions where transmission is more concentrated in households. At the same time, the difference in follow-up time between 24 months and 48 months in the studies examined requires careful interpretation, as the difference in follow-up time will determine whether the evaluation captures an early protective effect or has already entered a phase where new infections from community exposure begin to dominate.10

These results appear inconsistent with other studies that used a combination of immunoprophylaxis and chemoprophylaxis. The MALTALEP trial, which compared BCG with single-dose rifampicin (SDR), which used only BCG, showed that the effect was not always clear and that cases emerged in the first week after vaccination.9 The emergence of leprosy cases soon after an intervention is implemented is often interpreted as potential unmasking, that is, cases that were already developing but were detected earlier due to increased contact with health services, more active screening, or an immune response. Increased screening often increases the number of cases diagnosed at the start of follow-up, which can reduce the evidence of intervention effectiveness if viewed only crudely without considering changes in detection.7 The trend of recent studies in this review also suggests a push to enhance the protective effect through stronger PEP regimens, particularly for high-risk groups such as household contacts and contacts of multibacillary patients. The two most recent studies examined are still in protocol or design stages, and therefore cannot yet produce final effectiveness estimates. However, they do have clear scientific results or outcomes: PEP++ and BE-PEOPLE, which assess whether regimen strengthening can improve the prevention of progression from subclinical infection to clinical leprosy. 8,10 Improved regimens have the potential to provide higher bactericidal power and longer protection, but from a public health perspective, these additional benefits must be weighed against the consequences of implementation, namely through multi-drug or multi-dose regimens while still paying attention to patient compliance, a more structured drug distribution system and Targeted interventions, safety monitoring, and higher costs.

Thus, even if trial results show a greater effect, policy decisions still depend on whether the strategy is feasible and cost-effective for leprosy programs on the ground, especially in resource-limited areas.Overall, the results of this study support that SDR-PEP is the most feasible intervention and has a strong evidence base for short-term prevention. However, its long-term impact requires a more comprehensive strategy, particularly in highly endemic areas. WHO guidelines on contact tracing and SDR-PEP emphasize the importance of contact screening, education, recording, and PEP administration as part of leprosy control, while field-scale implementation evaluations also indicate that PEP integration into leprosy programs is feasible if contact tracing is effective. Although the WHO sources are guidelines rather than trial studies, they are still relevant for interpreting the variability in effects between studies, as they often arise from differences in implementation quality, not solely due to the drug administered. Therefore, it can be concluded that rifampin-based PEP, particularly SDR, is effective in suppressing leprosy incidence in the early period and in certain risk groups. However, to achieve a broader population impact, programs need to consider targeting strategies that are appropriate to local transmission patterns and await evidence from trials of enhanced regimens for high-risk groups, while still assessing the feasibility and sustainability of services. 7,8,11This study also has several limitations that need to be considered when interpreting the results.

First, the results of the studies analyzed in this review only included six studies that met the inclusion criteria, so the data coverage is still limited and it is possible that there are still relevant studies that have not been identified or published in the databases used. Second, the sample sizes vary greatly between studies, ranging from tens of thousands to large cluster populations, so the reported effect sizes may be influenced by imbalances in statistical power and differences in baseline risk in the respective study populations. Third, there are High heterogeneity due to design differences, namely between cluster RCTs, multi-leg RCTs, and protocol studies, differences in contact targets between household contacts compared to those within a 100-meter radius or the community, differences in regimens, namely SDR, SDDR-PEP 20 mg/kg, a combination of SDR and BCG, to enhanced regimens such as PEP++ and a combination of rifampicin and bedaquiline, as well as variations in follow-up duration, namely 24 compared to 48 months.7–9 Although comparative interpretations between interventions have been undertaken, differences in screening or data collection methods and the length of surveillance periods between studies are likely to contribute to variations in results, so conclusions regarding the effectiveness of rifampin as PEP in close contacts should be read as a context-based synthesis, not as a single effect size applicable to all conditions.

IV. CONCLUSION

In this study, it was found that the administration of rifampicin as post-exposure prophylaxis (PEP) to close contacts of leprosy patients provides significant potential to reduce leprosy incidence, especially in the early period after intervention, where the COLEP study reported a reduction in incidence of up to 57% in the first two years but the effect tended to weaken in the 2nd to 4th year, while the results of the PEOPLE study showed that community-based strategies, for example coverage up to a radius of 100 meters, and the use of SDDR-PEP 20 mg/kg can provide a clearer individual protective effect (IRR 0.55; 95% CI: 0.36–0.83), especially in household contacts (IRR 0.35; 95% CI: 0.15–0.82). Thus, rifampicin as PEP can be considered as an effective prevention strategy in leprosy control programs, but the magnitude of the impact is greatly influenced by differences in endemic areas, the scope of contact targeting, as well as the quality of screening and implementation in the field, and evidence regarding improved PEP regimens, for example PEP++ or the combination of rifampicin–bedaquiline, still requires final effectiveness test results before being widely recommended.

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