Rifampin-Ofloxacin-Minocycline (ROM) for the Treatment of Paucibacillary Leprosy: A Systematic Review

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Introduction

- Standard WHO multi-drug treatment (MDT) for leprosy consists of medications that are potentially harmful and cause a range of adverse systemic effects
- Paucibacillary leprosy, characterized by limited skin lesions and a low bacillary load, may be most amenable to a fluoroquinolone-based treatment protocol
- Monthly- or single dosing of ROM has emerged as a potential treatment option for leprosy, however, a synthesis of the evidence supporting ROM does not exist

Methods

- Databases were searched using combinations of the search terms “Rif*,” “Oflox*,” “Mino*,” “ROM” and “Leprosy” from inception to March 2019 to include reporting of the efficacy & safety of monthly ROM treatment in paucibacillary leprosy in human patients (Figure 1)
- Inclusion Criteria: Systematic reviews, randomized controlled trials, clinical trials, cohort studies, observational studies, case-control studies, case series (N>5), non-English publications
- Exclusion Criteria: Case reports, case series (N<4)

Results

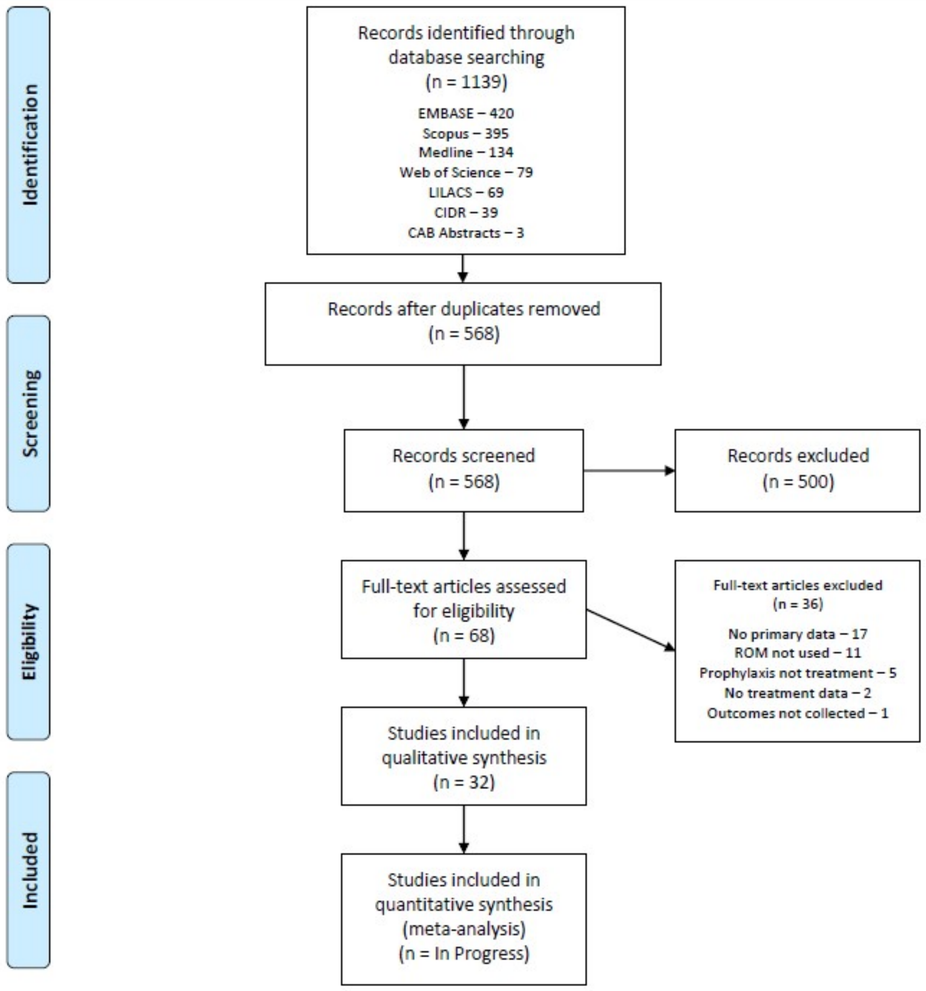

Figure 1. PRISMA Flowchart

Study	Study Design	Sample Size, No.	Mean Age (SD), y	Male, %	Follow-Up, (SD), mo	Diagnosis of Leprosy	# Lesions	Treatment	Comparator
Alam et al., 2007, Bangladesh[1]	Retrospective	270	-	-	96	Not reported	Single	ROM, single dose	No Comparator
Ebenezer et al., 1999, India[2]	Case series	13	26 (11.4)	62	12	Clinical	1-3	ROM, single dose	No Comparator
Ganapati et al., 1999, India[3]	Case series	634	-	-	-	Clinical	2-5	ROM, single dose	No Comparator
Girdhar et al., 2011, India[4]	Randomized control trial	300	30.9 (16.2)	41	36.76 (14.8)	Clinical	Single	ROM, single dose	ROM + clarithromycin
Majumder et al., 2000, India[5]	Clinical control trial	90	-	-	12	Clinical + histological	Single	ROM, single dose	ROM, single dose + Convit vaccine*
Mane et al., 1997, Senegal[6]	Case series	220	-	60	12	Clinical + histological	2-5	ROM, monthly	No Comparator
Manickam et al., 2012, India[7]	Randomized control trial	1526	27	47.5	36	Clinical	2-5	ROM, single dose	WHO-MDT
Martelli et al., 2000, Brazil[8]	No outcomes reported	259	32.4 (16.0)	38.22	-	Clinical + histological	Single	ROM, single dose	No Comparator
Pai et al., 1999; Revankar et al., 1999, India[9]	Case series	634	-	-	-	Clinical	1-5	ROM, single dose	No Comparator
Revankar., 2002, India[10]	Case series	335	-	-	-	Clinical	1-5	ROM, single dose	No Comparator
Shetty et al, 2011, India[11]	Retrospective cohort	62	-	-	-	Clinical + histological	1-5	ROM, single dose	i) WHO-MDT, ii) dapsone, iii) RO
Shinde et al., 2000, India[12]	Case series	26	-	-	-	Clinical	Single	ROM, single dose	No Comparator
Sousa et al., 2007, Brazil[13]	Case series	135	30.5 (15.4)	44.4	31.4	Clinical	Single	ROM, single dose	No Comparator
Stefani et al., 2003, Brazil[14]	Case series	39	33.4 (15.3)	51.28	32.4 (16.0)	Histological	Single	ROM, single dose	No Comparator
Vivekkumar et al., 2010, India[15]	Randomized control trial	72	-	61	6	Clinical	1-5	ROM, single dose	RLM, single dose

Table 1. Preliminary Baseline Characteristics of Included Studies
Abbreviations: Rifampin + Ofloxacin (RO), Standard World Health Organization Multi-drug therapy (WHO-MDT), Rifampin + Levofloxacin + Minocycline (RLM), Rifampin + Ofloxacin + Minocycline (ROM)
*Low-dose Convit vaccine contained 1.6x10^7 heat-killed M. *leprae* in 0.1ml saline and 1.5x10^{7}BCG in 0.1ml saline

Results

Outcome	Study	ROM		Comparator		Difference (%)
		% of patients	Proportion	% of patients	Proportion	
Lesion Clearance	*Alam et al., 2007*[1]	75.93	205/270	-	-	-
	Ebenezer, G. J., & Job, C. K., 1999[2]	84.62	11/13	-	-	-
	Girdhar et al. , 2011[4]	-	-	-	-	-
	6mo	72.85	110/151	78.52	117/149	-
	12mo	89.40	135/151	89.26	133/149	-
	18mo	94.59	140/148	91.72	133/145	-
	Mean of first 3 f/u	86.61	-	86.50	-	0.11
	Majumder et al., 2000[5]	46.67	14/30	33.30	20/60	13.37
	Mane et al. , 1997[6]	25.00	14/56	-	-	-
	Manickam et al., 2012[7]	72.11	486/674	72.12	494/685	-0.01
	Revankar et al., 2002[10]	98.74	626/634	-	-	-
	Stefani et al., 2003[14]	44.00	11/25	-	-	-
	Vivekkumar et al., 2010[15]	36.11	13/36	75.00	27/36	-38.89
	Mean	**63.20**	-	**66.74**	-	-3.54
	Median	**72.11**	-	**73.56**	-	-1.45
	Range	**25.00-98.74**	-	**33.33-86.50**	-	**Negative in favour for ROM**
Treatment Failure	*Majumder et al., 2000*[5]	23.33	7/30	18.33	11/60	5.00
	Mane et al. , 1997[6]	0.98	1/102	-	-	-
	Manickam et al., 2012[7]	0.30	2/674	0.58	4/685	-0.28
	Revankar et al., 2002[10]	3.79	24/634	-	-	-
	Sousa et al., 2007[13]	1.48	2/135	-	-	-
	Stefani et al., 2003[14]	2.70	1/37	-	-	-
	Mean	**5.43**	-	**9.46**	-	-4.03
	Median	**2.09**	-	**9.46**	-	-7.37
	Range	**0.30-23.33**	-	**0.58-18.33**	-	**Positive in favour for ROM**
Relapse	*Alam et al., 2007*[1]	3.70	10/270	-	-	-
	Girdhar et al. ,2011[4]	2.22	3/135	1.43	2/140	
	Revankar et al., 2002[10]	1.49	5/335	-	-	-
	Manickam et al., 2012[7] *	-	29/100py	-	9/100py	20/100py
	Mean	**2.47**	-	**1.43**	-	**1.04**
	Median	**2.22**	-	**1.43**	-	**0.79**
	Range	**1.49-3.70**	-	**1.43**	-	**Negative in favour for ROM**
Adverse Side Effects	*Majumder et al., 2000*[5]	0.00	0/30	0.00	0/60	0
	Mane et al. , 1997[6]	0.00	0/220	-	-	-
	Martelli et al., 2000[8]	5.79	15/259	-	-	-
	Vivekkumar et al., 2010[15]	0.00	0/36	0.00	0/36	0
	Mean	**1.45**	-	**0.00**	-	**1.45**
	Median	**2.90**	-	**0.00**	-	**2.90**
	Range	**0.00-5.79**	-	**0.00-0.00**	-	**Negative in favour for ROM**
Reversal Reactions (Type 1&2	*Mane et al. , 1997*[6]	3.33	1/30	-	-	-
	Sousa et al., 2007[13]	14.81	20/135	-	-	-
	Stefani et al., 2003[14]	33.33	13/39	-	-	-
	Mean	**17.16**	-	-	-	-
	Median	**14.81**	-	-	-	-
	Range	**3.33-33.33**	-	-	-	**Cannot Ascertain**

Table 2. Preliminary Summary of Primary Outcomes
*Not included in mean/median/range

Discussion

- Interim analysis suggests that ROM maybe less efficacious than its comparator, however only half of the data has been extracted thus far and a more robust analysis is necessary
- Qualitatively, several determinants of health were identified throughout this analysis including:
  - Social environments – 50% of non-compliant patients denied having leprosy due to potential loss of jobs and/or marriage prospects[16]
  - Patient education – 86% of respondents did not understand the concept of their disease[17]
  - Gender – Women only completed treatment at a rate of 65.6% and men at 79.2% (p<0.05)[18]
- Synthesizing the current evidence discussing the efficacy of monthly ROM, will strengthen the current body of knowledge surrounding the treatment of paucibacillary leprosy, and may allow for the development of standardized fluoroquinolone-based treatment protocols.

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The Treatment of Multibacillary Leprosy utilizing Rifampin-Ofloxacin-Minocycline (ROM): A Systematic Review

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Introduction

- From a diagnostic and management perspective, leprosy is a complex tropical infection.
- Patients who are affected by leprosy are at risk of several complications associated with the disease itself and its treatment
- Standard WHO multi-drug treatment (MDT) for leprosy consists of medications that are potentially harmful and cause a range of adverse systemic effects
- Alternative options for potential treatment have emerged such as monthly dosing of Rifampin-Ofloxacin-Minocycline (ROM) combination therapy, however, there is limited synthesized evidence of efficacy
- Multibacillary leprosy, characterized by many skin lesions and a high bacillary load, may be amenable to a fluoroquinolone-based treatment protocol
- Monthly dosing of ROM has emerged as a potential treatment option for leprosy, however, a synthesis of the evidence supporting ROM does not exist

Methods

- Databases were searched using combinations of the search terms “Rif*,” “Oflox*,” “Mino*,” “ROM” and “Leprosy” from inception to March 2019 to include reporting of the efficacy & safety of monthly ROM treatment in paucibacillary leprosy in human patients (Figure 1)
- Non-English publications were included and translated using Google Translate
- During all phases of screening a tertiary arbitrator will mitigate any inclusion/exclusion discrepancies

Included
Systematic reviews
Randomized controlled trials
Clinical trials
Cohort studies
Observational studies
Case-control studies
Case series (N>5)
Excluded
Case reports
Case series (N<4)

Table 1. Inclusion and exclusion criteria implemented during title and abstract screening

Primary Outcome Measures	Secondary Outcome Measures
Lesion clearance	Social environments
Treatment failure	Patient education
Relapse	Health Services
Adverse effects	Income
Reversal reactions	Sex/Gender

Results

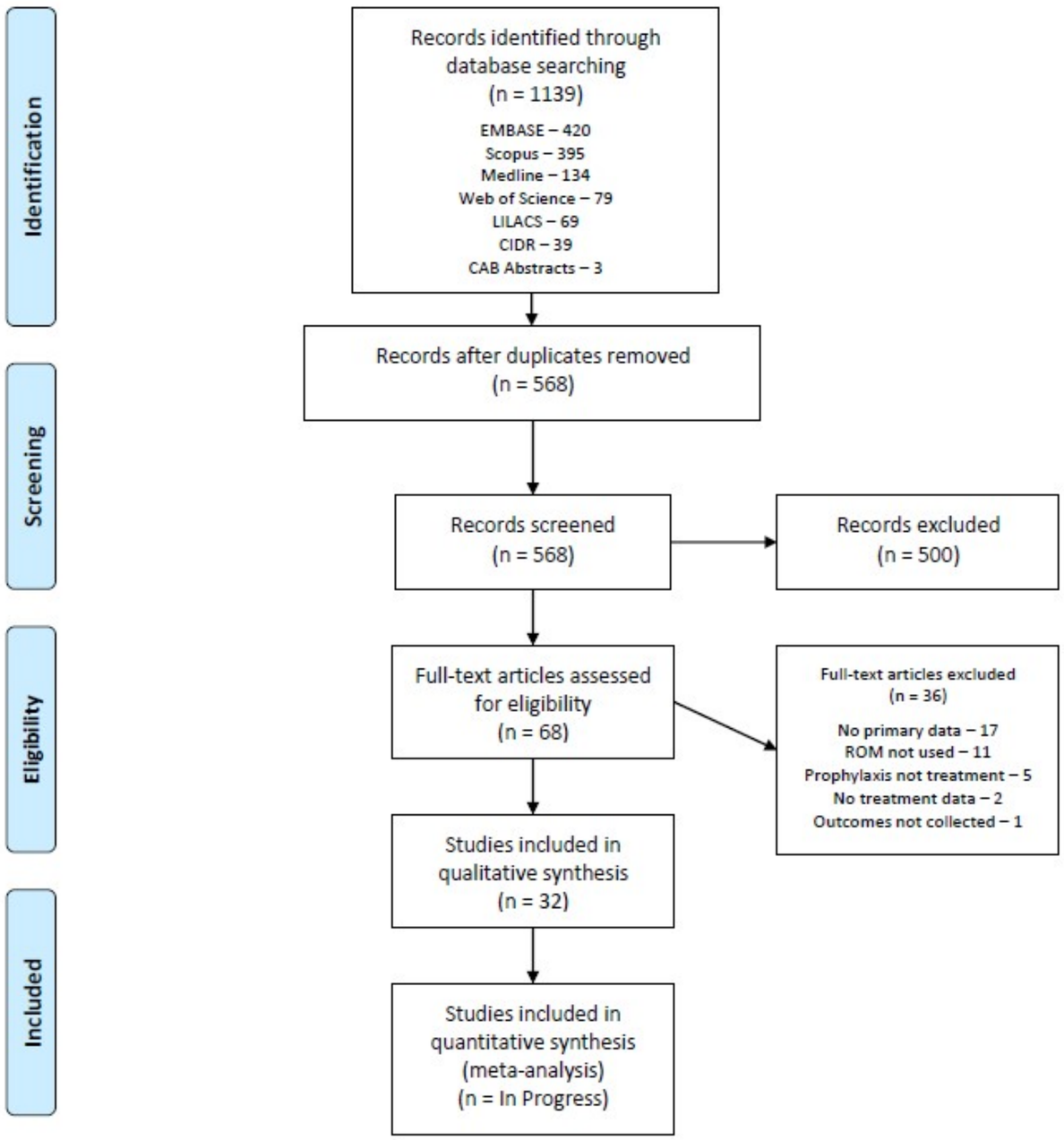

Figure 1. PRISMA Flowchart

Study	Study Design	Sample Size, No.	Mean Age (SD), y	Male, %	Follow-Up, (SD), mo	Diagnosis of Leprosy	Treatment	Comparator
Ji et al., 1998, Mali[1]	Clinical control trial	20	34 (14)	80	0.25	Clinical + histological	ROM, single dose	Ofloxacin + minocycline
Kumar et al., 2014, India[2]	Case Series	19	40.2 (4.0)	68.42	-	Clinical	ROM, monthly	No Comparator
Mane et al., 1997, Senegal[3]	Case series	220	-	60	12	Clinical + histological	ROM, monthly	No Comparator
Shetty et al, 2011, India[4]	Retrospective cohort	62	-	-	-	Clinical + histological	ROM, single dose	i) WHO-MDT, ii) dapsone, iii) RO
Villahermosa et al., 2004, Philippines[5]	Randomized control trial	21	29.4	81.5	24	Clinical + histological	ROM, monthly	WHO-MDT

Table 3. Preliminary Baseline Characteristics of Included Studies
Abbreviations: Rifampin + Ofloxacin (RO), Standard World Health Organization Multi-drug therapy (WHO-MDT, Rifampin + Ofloxacin + Minocycline (ROM)

Discussion

- Several determinants of health were identified qualitatively throughout this analysis including:
  - Social environments – 50% of non-compliant patients denied having leprosy due to potential loss of jobs and/or marriage prospects[6]
  - Patient education – 86% of respondents did not understand the concept of their disease[7]
  - Gender – Women only completed treatment at a rate of 65.6% and men at 79.2% ($p<0.05$)[8]
- Synthesizing the current evidence discussing the efficacy of monthly ROM, will strengthen the current body of knowledge surrounding the treatment of paucibacillary leprosy, and may allow for the development of standardized fluoroquinolone-based treatment protocols.

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