Adherence to secondary prophylaxis for acute rheumatic fever and rheumatic heart disease: a systematic review

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Abstract

Background: Optimal delivery of regular benzathine penicillin G (BPG) injections prescribed as secondary prophylaxis for acute rheumatic fever (ARF) and rheumatic heart disease (RHD) is vital to preventing disease morbidity and cardiac sequelae in affected pediatric and young adult populations. However, poor uptake of secondary prophylaxis remains a significant challenge to ARF/RHD control programs.

Objective: In order to facilitate better understanding of this challenge and thereby identify means to improve service delivery, this systematic literature review explored rates of adherence and factors associated with adherence to secondary prophylaxis for ARF and RHD worldwide.

Methods: MEDLINE was searched for relevant primary studies published in the English language from 1994-2014, and a search of reference lists of eligible articles was performed. The methodological quality of included studies was evaluated using a modified assessment tool.

Results: Twenty studies were included in the review. There was a range of adherence to varying regimens of secondary prophylaxis reported globally, and a number of patient demographic, clinical, socio-cultural and health care service delivery factors associated with adherence to secondary prophylaxis were identified.

Conclusion: Insights into factors associated with lower and higher adherence to secondary prophylaxis may be utilized to facilitate improved delivery of secondary prophylaxis for ARF and RHD. Strategies may include ensuring an effective active recall system, providing holistic care, involving community health workers and delivering ARF/RHD health education.

Keywords

Acute rheumatic fever, rheumatic heart disease, benzathine penicillin, benzathine benzylpenicillin, penicillin G benzathine, secondary prophylaxis, adherence, compliance

Introduction

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are a cause of significant morbidity and cardiac mortality amongst pediatric and young adult populations in developing countries, migrants from these nations and minority populations in developed countries.[1] The annual worldwide incidence of ARF has been estimated at over 471 000,[2] with major and minor clinical manifestations including carditis, arthritis, chorea, erythema marginatum, subcutaneous nodules, arthralgia and fever.[3] RHD resulting from recurrent episodes of ARF has an estimated prevalence of at least 15.6 million people globally.[2] An approximate worldwide mortality of 233 000 people per annum[2] is attributed to complications of valvular disease including arrhythmias, heart failure, thromboembolism and infective endocarditis.[3]

Secondary prophylaxis with regular intramuscular injections of benzathine penicillin G (BPG) is a key component of ARF and RHD control programs. This approach aims to prevent group A beta-hemolytic streptococci (GAS) infections and subsequent recurrent episodes of ARF.[4] The World Health Organization (WHO) recommends 3-4 weekly BPG continued for a duration dependent on factors including age, time since the last episode of ARF, risk of streptococcal infections in the area and presence of RHD.[4] According to WHO guidelines, secondary prophylaxis should continue for at least 5 years after the last episode of ARF or until the age of 18 years (whichever is longer) and for a greater length of time in cases of carditis or RHD.[4, 5] However, local health authorities give slightly varying recommendations for the frequency and duration of BPG injections.[5]

Low adherence with secondary prophylaxis is one of the main challenges to effective control of ARF and RHD.[4] To the best of our knowledge, a systematic literature review to summarize what is known regarding rates of adherence and factors associated with adherence to secondary prophylaxis does not exist. This study aims to systematically summarize and evaluate published rates of adherence and factors associated with adherence to BPG injections prescribed as secondary prophylaxis for ARF and RHD, and thereby identify means to improve secondary prophylaxis interventions. In contrast to other studies of adherence in chronic disease management, of particular interest and importance in this review is the focus of adherence amongst poor and underserved population groups.

Methods

Protocol and focus

This systematic review has been conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[6] The review focuses on studies that explored rates of adherence and factors associated with adherence to BPG injections recommended as secondary prophylaxis for ARF and RHD worldwide.

Search criteria

A search of the MEDLINE database via OvidSP was conducted on 28 June 2014. All articles written in the English language between January 1, 1994 and June Week 3, 2014, using the Medical Subject Headings (MeSH) and keywords, ("acute rheumatic fever" OR "rheumatic fever" OR "rheumatic heart disease") AND ("secondary prophylaxis" OR "secondary prevention" OR "benzathine penicillin G" OR "penicillin G benzathine" OR "benzathine penicillin" OR "benzathine benzylpenicillin" OR "disease management" OR "management") AND ("patient compliance" OR "compliance" OR "non-compliance" OR "noncompliance" OR "treatment refusal" OR "guideline adherence" OR "medication adherence" OR "adherence" OR "non-adherence" OR "nonadherence" OR "alignment" OR "non-alignment" OR "nonalignment"), were retrieved. A single investigator (PK) screened the titles and abstracts of all retrieved citations and performed full text reviews of relevant studies. Reference lists of relevant studies were hand searched to identify additional relevant publications.

Eligibility criteria

Eligibility criteria were determined with expert input from two pediatricians. Primary studies published from January 1, 1994 to June Week 3, 2014, were included in the literature review if they reported rates of adherence to secondary prophylaxis for ARF/RHD or discussed factors associated with adherence to BPG injections recommended as secondary prophylaxis for ARF/RHD.

Articles that were not primary studies or were irrelevant to the focus of this review were excluded. This included articles written about the epidemiology and clinical presentation of ARF/RHD, symptomatic treatment of ARF episodes, the efficacy of differing antibiotic regimens prescribed as secondary prophylaxis for ARF/RHD and guidelines for delivery of secondary prophylaxis for ARF/RHD, without reference to rates of adherence or factors associated with adherence to secondary prophylaxis for ARF/RHD.

Data extraction and quality assessment

One investigator (PK) used a standardized sheet to extract data from included studies. Data extracted included the author, year of publication, source, location of study, study design and study population characteristics. Study findings addressing rates of adherence to secondary prophylaxis for ARF/RHD and factors associated with adherence to secondary prophylaxis for ARF/RHD were also summarized.

We created a quality assessment tool to evaluate the methodological quality of included studies incorporating validated elements of Pluye et al.'s Mixed Methods Assessment Tool (MMAT)[7] and Wells et al.'s checklists for non-randomized studies in systematic reviews[8]. Our tool assessed methodological quality in ten domains including the incorporation of clear study objectives with suitable data collection, clarity of adherence definition, sample size adequacy, recruitment method, comparability of participant groups, outcome measure rate/response rate, use of inferential statistical analysis, inclusion of multivariate analysis, consideration given to the contextual relation of findings and consideration given to researchers' influence on study findings (Table 1).

Table 1: Quality assessment tool

Assessment criteria	Yes	No
Clear research objectives with suitable data collection	Research objectives clearly outlined and data collected addresses research objectives	Research objectives not clearly outlined or data collected does not adequately address research objectives
Definition of adherence to secondary prophylaxis clear	Adherence and non-adherence or levels of adherence to secondary prophylaxis clearly defined	Adherence, non-adherence or levels of adherence to secondary prophylaxis not clearly defined
Sample size calculation reported and target sample size reached	Sample size calculation performed and target sample size reached	Sample size calculation not performed or reported, or sample size calculation performed and target sample size not reached
Recruitment of participants used probability sampling	All or a randomly selected proportion of all persons on a register included	Neither all nor a randomly selected proportion of all persons on a register included
Participant groups comparable	Key demographic information comparing participant groups is presented and there are no obvious dissimilarities that may account for differences in outcomes, or dissimilarities are taken into account in data analysis.	There are apparent dissimilarities between participant groups that may account for differences in outcomes and these dissimilarities are not taken into account in data analysis.
Outcome data complete/Response rate acceptable	Outcome data ≥80% complete/Response rate ≥60%	Outcome data <80% complete/Response rate <60%
Any inferential statistical analysis	Inferential statistical analysis performed	Inferential statistical analysis not performed
Multivariate analysis of factors associated with adherence	Multivariate analysis of factors associated with adherence performed	Multivariate analysis of factors associated with adherence not performed
Consideration given to contextual relation of findings (qualitative studies)	Explanation of how study findings relate to the study context or context characteristics given	Explanation of how study findings relate to the study context or context characteristics not given
Consideration given to researchers' influence in relation to findings (qualitative studies)	Researchers critically explained how findings relate to their perspectives, roles and interactions with participants	Researchers did not critically explain how findings relate to their perspectives, roles and interactions with participants

Results

Search results and quality assessment

Electronic searching retrieved 61 citations from MEDLINE. Based on inclusion and exclusion criteria, 15 of these publications were included in this review (Figure 1). Four additional publications identified through reference list searching and one additional publication known to be relevant through prior knowledge were also included in the review. All of the included studies were published in peer-reviewed, scientific journals.

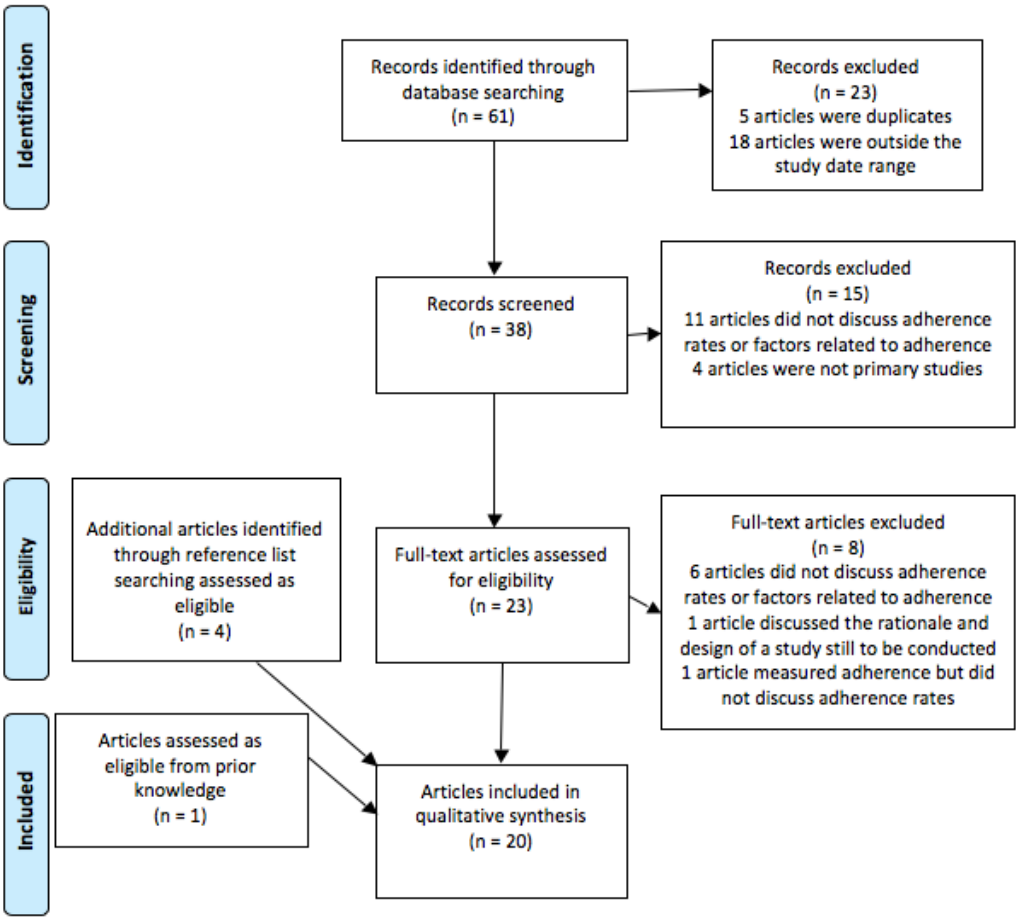

Figure 1: modified PRISMA flow diagram[a]

Secondary prophylaxis regimens and definitions of adherence

Prescribed regimens of BPG varied between health authorities worldwide and included recommendations for 2-weekly, 3-weekly, 4-weekly and monthly BPG. Additionally, there were a number of definitions of "adherence" to secondary prophylaxis employed in the reviewed literature. In some studies, a benchmark

[a] Modified from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

percentage or fraction of recommended injections was defined as a case of "adherence",[9, 10] whilst in others, rates of adherence were reported as a percentage of those who received 100% of their prescribed BPG, or a percentage of the total number of recommended injections administered to the study population.[11] Some authors utilized the terms "regular compliance", "irregular compliance" and "non-compliance" as defined by the WHO[12], whilst others created their own definitions of terms such as "complete compliance", "partial compliance" and "dropout" to describe levels of adherence.[13]

Rates of adherence

Nineteen publications discussed rates of adherence to secondary prophylaxis; two of these articles utilized the same data set (Table 2). The majority of these were retrospective observational studies, with the exception of one randomized controlled trial measuring outcomes of patients on a 3-weekly versus a 4-weekly regimen[13], one measure of past adherence by questionnaire[14], and one assessment of adherence based on qualitative interviews.[15]

Table 2: Rates of adherence to secondary prophylaxis for ARF And RHD

Author, Year	Source	Country/ Continent	City/Region/ State/Territory	Prophylaxis regimen/Study population	Study design	Summary of findings
Gasse et al., 2013 [9]	BioMed Central Public Health	French Territory, Oceania	Lifou, New Caledonia	Patients recommended to receive 3-weekly BPG (n=70) Mean age 22.3 ± 11.6yrs (43%<16yrs); 63% females.	Retrospective cohort study over 12 months in 2011	54% good-adherent[b] 46% poor-adherent[c] Mean adherence 77 ± 22% Median adherence 82.2% (IQR 76.5- 94.1) Median number of injections: 14 (range 2-18)
Remond et al., 2013 [16]	Internal Medicine Journal	Australia, Oceania	Kimberley Region, Western Australia; Far North Queensland	Patients recommended to receive 3-4 weekly BPG (n=293)	Retrospective observational study over 12 months (patients identified Nov 2008 – Mar 2009)	17.7% received ≥80% of recommended BPG
Kearns et al., 2010 [17]	Rural and Remote Health	Australia, Oceania	Central Australia, Northern Territory	Patients recommended to receive 4-weekly BPG (n=47] Median age 28yrs (range 8-58yrs); 82% females.	Retrospective observational study – adherence measured 2 years before and after implementation of Full Moon Strategy in May 2006	June 2004 - May 2006: 47% overall uptake of recommended BPG (95% CI 44-51) May 2006 – June 2008: 57% overall uptake of recommended BPG (95% CI 56-60)
Stewart et al., 2007 [18]	Australian Journal of Rural Health	Australia, Oceania	Katherine, Northern Territory	Patients recommended to receive monthly BPG (n=59) Age <18yrs 32%; 66% females.	Retrospective observational study over 24 months from Sept 2002 to Sept 2004	Mean adherence 56% of all recommended BPG Median adherence 54% of all recommended BPG (range 0-100%)
Harrington et al., 2006 [10]	Medical Journal of Australia	Australia, Oceania	North East Arnhem Land, Northern Territory	Patients recommended to receive monthly BPG (n=27)	Retrospective observational study from Jan 2002 to Sept 2003	59% received adequate prophylaxis[d]

[b] Good-adherent defined as ≥80% of recommended BPG received
[c] Poor-adherent defined as <80% of recommended BPG received
[d] Adequate prophylaxis defined as >75% recommended BPG received

Author, Year	Source	Country/ Continent	City/Region/ State/Territory	Prophylaxis regimen/Study population	Study design	Summary of findings
Eissa et al., 2005 [19]	Australian and New Zealand Journal of Public Health	Australia, Oceania	Northern Territory	Patients recommended to receive 3-4 weekly BPG (n=52) Male n=15	Retrospective observational study over 12 months (patients identified in Aug 2004)	22 (42%) patients received at least 80% of the minimum recommended doses[e] Median number of doses received in the previous 12 months: 9
Mincham et al., 2002 [20]	Australian and New Zealand Journal of Public Health	Australia, Oceania	Kimberley, Western Australia	Patients recommended to receive monthly BPG (n=78)	Retrospective observational study of patients diagnosed with ARF or RHD from 1982 to 1996 over 2 years from Jan 1996 – Dec 1997	67% of all prescribed BPG doses administered, with individuals receiving 8-100% of doses prescribed. 19% median injection interval 3.5-4.5 weeks
Grayson et al., 2006 [11]	New Zealand Medical Journal	New Zealand, Oceania	Auckland	Patients recommended to receive 3-4 weekly BPG (n=433 in 1998, n=428 in 2000)	Retrospective observational study of data from 1998 and 2000	86-96% total compliance[f]
Seckeler et al., 2010 [21]	Pediatric Cardiology	Common-wealth of the United States of America, North America	Northern Mariana Islands	Patients recommended to receive 4-weekly BPG (n=144) Aged <21yrs	Retrospective observational study from 1984 to 2006	Mean adherence 58.3% of all recommended BPG Median adherence 69.2% of all recommended BPG (range 0-100%)
Nordet et al., 2008 [22]	Cardiovascular Journal of Africa	Cuba, North America	Pinar del Rio	School children recommended to receive monthly BPG (n=52 in 1986, n=193 in 1996) Age range 5-15yrs	Retrospective cross-sectional studies in 1986 and 1996 (first and last years of a 10 year prevention program) + comparison with a report on prevention activities in 2002	1986: 50% regular compliance[g] 36.5% irregular compliance[h] 13.5% non-compliance[i] 1996: 93.8% regular compliance 6.2% irregular compliance 2002: > 80% regular compliance

[e] Minimum recommended number of doses was 13 injections in 12 months

[f] Total compliance defined as administration of all scheduled injections within predetermined time frames

[g] Regular compliance defined as a minimum of 10-11 BPG injections received per year

[h] Irregular compliance defined as 6-9 BPG injections received per year

[i] Non-compliance defined as ≤5 BPG injections received per year

Author, Year	Source	Country/ Continent	City/Region/ State/Territory	Prophylaxis regimen/Study population	Study design	Summary of findings
Pelajo et al., 2010 [23]	Paediatric Rheumatology	Brazil, South America	Rio de Janeiro	Patients recommended to receive monthly BPG (n=536) Mean age 13 ± 3.9yrs; 53% females.	Retrospective observational study of patients with a diagnosis of ARF from 1985 to 2005	Non-adherence[j] detected in 35% (188 out of 536) patients
Robertson et al., 2005 [15]	South African Medical Journal	South Africa, Africa	Cape Town	Patients recommended to receive monthly BPG or oral penicillin (n=8; 7 receiving monthly BPG, 1 receiving oral penicillin)	Qualitative semi-structured interviews with patients/guardians; date not specified	In 7/8 cases, adherence with all recommended BPG was reported
Bassili et al., 2000 [24]	Eastern Mediterranean Health Journal	Egypt, Africa	Alexandria	Patients receiving secondary prophylaxis (n=127; 104 prescribed 2-weekly BPG, 14 prescribed 4-weekly BPG and 9 prescribed oral penicillin) Age 0-15yrs	Retrospective observational study of patients over 6-12 months (patients identified in Jan-Apr 1998)	71.2% of patients compliant[k] in 2-weekly BPG group 28.6% of patients compliant in 4-weekly BPG group
Abdel-Moula et al., 1998 [14]	Journal of the Egyptian Public Health Association	Egypt, Africa	Alexandria	Patients receiving secondary prophylaxis (n=29; 20 prescribed monthly BPG, 3 prescribed 3-weekly BPG, 5 prescribed 2-weekly BPG and 1 prescribed oral penicillin) Age range 6-16yrs	Prospective case-control study with questionnaire regarding compliance over one year (patients identified in scholastic year 1993-1994)	31% of patients not compliant[l]

[j] Patient classified as non-adherent if they missed or delayed >1 dose of BPG during a 6-month period (interval between appointments)
[k] Patient considered compliant if received at least 11 BPG injections in the last 6 months or 22 BPG injections in the last year
[l] Patient considered not compliant if received <80% of prescribed BPG injections per year

Author, Year	Source	Country/ Continent	City/Region/ State/Territory	Prophylaxis regimen/Study population	Study design	Summary of findings
Kassem et al., 1995 [25]	Egyptian Heart Journal	Egypt, Africa	Alexandria	Patients recommended to receive secondary prophylaxis, unspecified regimen (n=86) Age range 16-32yrs (mean 20.8±3.15yrs); 63% females	Retrospective observational study over 11-20 years (patients identified 1972-1980)	Approximately 35% of patients uncompliant[m]
Kumar et al., 2002 [26]	Indian Heart Journal	India, Asia	Ambala, Haryana	Patients recommended to receive monthly BPG (n=257, 23-134 patients eligible per year) Age 6-20yrs 70.8%	Retrospective observational study 1988-1999	Mean yearly compliance[n]: 92%; annual variation 82.4-100%
Kumar et al., 1997 [27]	Indian Heart Journal	India, Asia	Ambala, Haryana	Patients recommended to receive monthly BPG (n=110 in 1995, n=17-106 in 1988-1994) In 1995, age range 6-50yrs (43.7% aged 6-15yrs, 43.7% aged 16-25yrs); 48.2% male	Retrospective observational study 1988-1995	1995: 83.6% of patients compliant[o] 1988-1994: >90% of patients compliant
Lue et al., 1996 [28] Lue et al, 1994 [13]	Journal of Pediatrics	Taiwan, Asia	Taipei	Patients prescribed 3-weekly and 4-weekly BPG (n=249; 124 prescribed 3-weekly BPG, 125 prescribed 4-weekly BPG Age range 3-25yrs	Randomized controlled trial 1979-1989	3-weekly BPG group: 66.9% stay-in (complete) compliance[p], 15.3% partial compliance[q], 9.7% dropout[r] 4-weekly BPG group: 73.6% stay-in (complete) compliance, 15.2% partial compliance, 9.2% dropout

[m] Definition of uncompliant not provided
[n] Compliance defined as percentage of those eligible for secondary prophylaxis who received secondary prophylaxis
[o] Missed no more than 1 BPG injection per year
[p] Complete compliance defined as ≤ 1 BPG injection missed per year
[q] Partial compliance defined as 2-3 BPG injections missed per year
[r] Dropout defined as ≥ 4 BPG injections missed per year

Factors associated with adherence

Ten of the included studies discussed factors associated with adherence to secondary prophylaxis (Table 3). Qualitative, semi-structured interviews were conducted in seven of these studies, two of which additionally included questionnaires. Multivariate logistic regression was performed in one study[9] and other inferential statistical analysis was performed in two studies.[18, 19]

Table 3: Factors associated with adherence to secondary prophylaxis for ARF and RHD

Authors	Source	Location	Prophylaxis regimen/Study population	Study design	Summary of Findings
Gasse et al., 2013 [9]	BioMed Central Public Health	Lifou, New Caledonia	Patients recommended to receive 3-weekly BPG (n=70) Mean age 22.3 ± 11.6yrs (43%<16yrs); 63% females.	Retrospective cohort study over 12 months in 2011 Multivariate logistic regression model	Factors protective against poor adherence: a household with >5 people (odds ratio 0.25, 95% CI 0.08-0.75), a previous medical history of symptomatic ARF (odds ratio 0.20, 95% CI 0.04 to 0.98), adequate healthcare coverage (odds ratio 0.21, 95% CI 0.06-0.72).
Stewart et al., 2007 [18]	Australian Journal of Rural Health	Katherine, Northern Territory, Australia	Patients recommended to receive monthly BPG (n=59) Age <18yrs 32%; 66% females.	Retrospective observational study over 24 months from Sept 2002 to Sept 2004	In those who received ≥50% of prescribed BPG, non-significant trend towards improved adherence seen in patients aged <18 years (RR=1.26) and those who attended a health clinic more frequently for other reasons (RR=1.42). Patients with more severe disease less likely to receive monthly BPG (RR=0.60). Men and women equally likely to receive monthly BPG (RR=1.09).
Harrington et al., 2006 [10]	Medical Journal of Australia	North East Arnhem Land, Northern Territory, Australia	Patients recommended to receive monthly BPG, relatives and health care workers (n=51; 15 patients, 18 relatives, 18 health care workers) Patient age range 20-60yrs (range of time since diagnosis 1-30yrs); female n=45, male n=6	Qualitative semi-structured interviews conducted Apr-Aug 2003	Staff factors promoting uptake: appropriately trained, socially and culturally competent staff, an active recall system, staff willingness to treat the patient at home. Patient factors promoting uptake: an appropriate location for receiving injections, belief that the disease is chronic and serious, confidence in the health service and receipt of holistic care, family support for and belief in the efficacy of treatment. Staff factors inhibiting uptake: negative perception of the secondary prophylaxis program, conflicting priorities for staff, no effective strategy for dealing with absent patients, staff fatigue and frustration Patient factors inhibiting uptake: conscientious refusal of treatment, inconvenience to the patient, not "belonging" to the health service, lack of family support, lack of confidence in the treatment. Factors not clearly related to treatment uptake: patient biomedical understanding of the disease, taking responsibility for health and perception of painfulness of the treatment.
Eissa et al., 2005 [19]	Australian and New Zealand Journal of Public Health	Northern Territory, Australia	Patients recommended to receive 3-4 weekly BPG (n=52) Male n=15	Retrospective observational study over 12 months (patients identified in Aug 2004)	Females significantly more likely to receive treatment than males (p=0.004). Higher adherence rate (median doses 10/year) in moderate or severe disease compared with mild disease (median doses 8/year).
Mincham et al., 2003 [29]	Australian Journal of Rural Health	Kimberley, Western Australia, Australia	Patients/parents of patients recommended to receive monthly BPG (n=7)	Qualitative semi-structured interviews in 1998	Compliance with secondary prophylaxis associated with positive patient–staff interactions. Living in a remote location was a negative influence.

					Participants had variable levels of understanding of the disease and need for BPG.

Authors	Source	Location	Prophylaxis regimen/Study population	Study design	Summary of Findings
Grayson et al., 2006 [11]	New Zealand Medical Journal	Auckland, New Zealand	Nurses involved with delivery of 3-4 weekly BPG (n=9)	Qualitative semi-structured interviews; date not specified	Presence of community health workers, a rheumatic fever resource nurse and communication from other services used by rheumatic fever patients impacted positively on the delivery of secondary prophylaxis.
Robertson et al., 2005 [15]	South African Medical Journal	Cape Town, South Africa	Caregivers of patients (n=8); physicians (n=24)	Qualitative semi-structured interviews with caregivers of patients + 24 physician questionnaires; date not specified	There was very poor knowledge of the disease amongst patients/guardians, however this was not associated with non-adherence to secondary prophylaxis.
Bassili et al., 2000 [24]	Eastern Mediterranean Health Journal	Alexandria, Egypt	Caregivers of children and children receiving secondary prophylaxis (n=127; 104 prescribed 2-weekly BPG, 14 prescribed 4-weekly BPG and 9 prescribed oral penicillin)	Retrospective chart review of compliance over 6-12 months (patients identified in Jan-Apr 1998) + questionnaire based qualitative interviews in Jan-Apr 1998 Stepwise logistic regression	Non-compliance was more common among children whose parents had lower educational and occupational levels, those whose parents had only fair to poor knowledge of the disease, those living in semi-urban and rural areas, those with health insurance and those whose families were not satisfied with the health care provided.
Kumar et al., 2002 [26]	Indian Heart Journal	Ambala, Haryana, India	Patients recommended to receive monthly BPG (n=unclear; 40 non-compliant patients + an unknown number of compliant patients – total number of participants in associated quantitative study = 257)	Qualitative, semi-structured interviews in 1999	Reasons for non-compliance: fear/dislike of injections, belief that injections were no longer required given seemingly good health, lack of awareness of the importance of secondary prophylaxis and services not available locally.
Kumar et al., 1997 [27]	Indian Heart Journal	Haryana, India	Patients recommended to receive monthly BPG (n=110) Mean age 18.4 ± 8.6yrs; 48.2% male.	Qualitative semi-structured interviews conducted in 1995	Reasons for non-compliance: private doctors ceasing BPG injections, unsupportive family members, a disinterest in BPG injections and long distances of travel to health clinics. No significant association between non-adherence and low socioeconomic background. No significant association between non-adherence and level of education of parents.

Quality assessment

Use of the quality assessment tool demonstrated the methodological quality of each of the included studies (Table 4).

Table 4: Quality~~yative~~ assessment

Study, Year	Clear research objectives with suitable data collection	Definition of adherence clear	Sample size calculation reported and target sample size reached	Recruitment of participants using probability sampling	Participant groups comparable	Outcome data complete /Response rate acceptable	Any inferential statistical analysis	Multivariate analysis of factors associated with adherence	Consideration given to contextual relation of findings	Consideration given to researchers' influence in relation to findings
Abdel-Moula et al., 1998 [14]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Not relevant	Not relevant
Bassili et al., 2000 [24]	Yes	Yes	No	Yes	Not relevant	Yes	Yes	Yes	Not relevant	Not relevant
Eissa et al., 2005 [19]	Yes	Yes	No	Yes	Unknown	Yes	Yes	No	Not relevant	Not relevant
Gasse et al., 2013 [9]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not relevant	Not relevant
Grayson et al., 2006 [11]	Yes	No	Quantitative component: No Qualitative component: not relevant	Quantitative component: Yes Qualitative component: not relevant	Not relevant	Yes	No	No	Quantitative component: not relevant Qualitative component: No	Quantitative component: not relevant Qualitative component: No
Harrington et al., 2006[10]	Yes	Yes	Not relevant	Not relevant	Not relevant	No	No	No	Yes	Yes
Kassem et al., 1995 [25]	Yes	No	No	Unknown	Not relevant	No	No	No	Not relevant	Not relevant
Kearns et al., 2010 [17]	Yes	Yes	Quantitative component: No Qualitative component: not relevant	Quantitative component: Yes Qualitative component: not relevant	Not relevant	No	Yes	No	Quantitative component: not relevant Qualitative component: Yes	Quantitative component: not relevant Qualitative component: Yes

Study, Year	Clear research objectives with suitable data collection	Definition of adherence clear	Sample size calculation reported and target sample size reached	Recruitment of participants using probability sampling	Participant groups comparable	Outcome data complete /Response rate acceptable	Any inferential statistical analysis	Multivariate analysis of factors associated with adherence	Consideration given to contextual relation of findings	Consideration given to researchers' influence in relation to findings
Kumar et al., 2002 [26]	Yes	No	Quantitative component: No Qualitative component: not relevant	Quantitative component: Yes Qualitative component: not relevant	Not relevant	Yes	Yes	No	Quantitative component: not relevant Qualitative component: No	Quantitative component: not relevant Qualitative component: No
Kumar et al., 1997 [27]	Yes	Yes	Quantitative component: No Qualitative component: not relevant	Quantitative component: Yes Qualitative component: not relevant	Not relevant	Yes	Yes	No	Quantitative component: not relevant Qualitative component: No	Quantitative component: not relevant Qualitative component: No
Lue et al., 1996 [28]; Lue et al., 1994 [13]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Not relevant	Not relevant
Mincham et al., 2003 [29]	Yes	No	Not relevant	Not relevant	Not relevant	Yes	No	No	Yes	Yes
Mincham et al., 2002 [20]	Yes	Yes	No	Yes	Not relevant	Yes	No	No	Not relevant	Not relevant
Nordet et al., 2008 [22]	Yes	Yes	No	Yes	Not relevant	Yes	Yes	No	Not relevant	Not relevant
Pelajo et al., 2010 [23]	Yes	Yes	No	Yes	Yes	No	Yes	No	Not relevant	Not relevant
Remond et al., 2013 [16]	Yes	Yes	No	Unknown	Not relevant	Yes	Yes	No	Not relevant	Not relevant

Study, Year	Clear research objectives with suitable data collection	Definition of adherence clear	Sample size calculation reported and target sample size reached	Recruitment of participants using probability sampling	Participant groups comparable	Outcome data complete /Response rate acceptable	Any inferential statistical analysis	Multivariate analysis of factors associated with adherence	Consideration given to contextual relation of findings	Consideration given to researchers' influence in relation to findings
Robertson et al., 2005[15]	Yes	No	Quantitative component: No Qualitative component: not relevant	Quantitative component: Yes Qualitative component: not relevant	Not relevant	Yes	No	No	Quantitative component: not relevant Qualitative component: Yes	Quantitative component: not relevant Qualitative component: No
Seckeler et al., 2010 [21]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Not relevant	Not relevant
Stewart et al., 2007 [18]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Not relevant	Not relevant

Discussion

Over the last 20 years, studies addressing adherence to secondary prophylaxis for ARF/RHD have been conducted in India, Egypt, South Africa, Brazil, Cuba, the Northern Mariana Islands, Australia, New Zealand, New Caledonia and Taiwan. On review of this literature, there was a range of adherence to different regimens of BPG prescribed as secondary prophylaxis worldwide. Whilst a small number of studies conducted in Cuba, India and New Zealand reported good overall adherence, adherence measured in the majority of studies was sub-optimal. An individual range of 0-100% of prescribed injections also indicated that despite overall adherence rates, some patients received inadequate BPG injections whilst others received appropriate prophylaxis. Adherence to BPG was not evidently better or worse amongst minority groups and migrants in developed countries compared with adherence in developing countries. Very few studies assessed adherence over time in comparable populations with the same definitions, so global trends regarding this could not be established. In the Cuban study, adherence improved over time from 50% regular compliance in 1986 to >80% regular compliance in 2002,[22] whilst Indian studies demonstrated an adherence decline from 100% compliance in 1988 to 82.4% compliance in 1999.[26, 27]

Factors associated with lower adherence

In underprivileged settings where ARF and RHD remain prevalent, there are a number of interrelated factors associated with low adherence to secondary prophylaxis. Rurality with limited access to health care was one important theme in four studies, one involving logistic regression analysis (Bassili et al.) and three others including qualitative semi-structured interviews. Bassili et al. reported non-adherence to be more common amongst children in semi-urban and rural areas,[24] Mincham et al. found that living in a remote location was a negative influence on adherence[29] and two Indian studies identified lack of local services and long distances of travel as reasons for non-adherence.[26, 27] It follows that for patients living in rural and remote areas with lesser access to health care, adhering to secondary prophylaxis regimens may be more difficult.

Negative patient, staff and health service interactions were also reported as contributors to non-adherence in three studies. Bassili et al.'s logistic regression analysis found non-adherence to be more

common among children whose families were not satisfied with the health care provided,[24] and qualitative semi-structured interviews performed by Mincham et al. and Harrington et al. in Australia highlighted that negative patient-staff interactions, limited confidence in the treatment and a lack of sense of "belonging" to the health service could reduce adherence.[10, 29] Mincham et al. and Harrington et al.'s studies also discussed staff factors inhibiting uptake, including the transient nature of staff in remote settings, a negative perception of the secondary prophylaxis program, conflicting health priorities, and no effective strategy for dealing with absent patients leading to staff frustration and fatigue.[10, 29] These findings may be most relevant to Australian Indigenous populations and other minority groups in developed countries, where a difference in cultural values, attitudes and beliefs between the patient/caregiver and health care provider may exist. In Mincham et al.'s study, lack of an effective reminder system for due injections additionally led to non-adherence to secondary prophylaxis.[29]

Other factors associated with non-adherence included lack of family support (observed in two qualitative studies)[10, 27] a disinterest in or conscientious refusal of treatment (discussed in two qualitative studies)[10, 27] and inconvenience of the treatment or treatment interference with personal priorities (identified in two qualitative studies).[10, 29]

On the field, lack of BPG supply is another known factor leading to lower rates of BPG administration, however this was not raised in the studies reviewed. In prospective studies, this is likely because BPG supply was ensured for the study population. In retrospective observational studies, it may be that supply was assumed to have been adequate by the researchers, and in qualitative interviews and questionnaires perhaps the focus was on individual and health service factors, without consideration of pharmaceutical supply.

Factors associated with higher adherence

Factors associated with higher adherence were also identified in the literature reviewed. Positive patient, staff and health system interactions promoted adherence in three small qualitative studies in Australia and New Zealand. Mincham et al. found that adherence was closely linked with positive patient-staff interactions[29] whilst Harrington et al. identified that patient confidence in the health

service and receipt of holistic care, as well as family support for and belief in the treatment, were important to adherence.[10] The presence of appropriately trained, socially and culturally competent staff was discussed by Harrington et al. as a factor associated with higher adherence[10] and supported by Grayson et al.'s report that the presence of community health workers and a rheumatic fever resource nurse impacted positively on adherence.[11] Harrington et al. additionally found that an appropriate location for injections and staff willingness to treat patients at home promoted uptake.[10] These study findings may have greater applicability in countries similar to Australia and New Zealand, where ARF/RHD is most prevalent amongst migrant and minority groups. In Harrington et al.'s study, recall systems for patients with due BPG injections were also associated with higher adherence.[10]

Opportunistic communications may improve adherence to secondary prophylaxis. A qualitative study by Grayson et al. found that communication from other services used by rheumatic fever patients impacted positively on adherence,[11] and Stewart et al.'s retrospective study involving inferential analysis described a non-significant trend towards improved adherence in patients who attended a health clinic more frequently for reasons other than secondary prophylaxis.[18]

Patient demographic factors including younger age and greater number of people per household could also positively influence adherence to secondary prophylaxis. Stewart et al. found a non-significant trend towards improved adherence in patients aged <18 years compared with patients aged ≥18 years amongst those who received ≥50% of prescribed BPG.[18] Perhaps this is because parents/caregivers are overseeing adherence in younger patients; young adults newly responsible for their own health care may have a tendency towards non-adherence. Meanwhile, Gasse et al.'s retrospective study involving multivariate logistic regression analysis identified that a household with ≥6 people was protective against poor adherence. It is postulated that this may be because older siblings in the household are able to assist with health care seeking.[9]

Factors with unclear association to adherence

A number of factors had an unclear association with adherence to secondary prophylaxis. Biomedical knowledge of ARF and RHD was poor amongst patients and their families, yet whilst Bassili et al. described non-adherence to be more common in patients who's parents had only a fair to poor

knowledge of the disease,[24] Robertson et al. reported no association between knowledge of the disease and adherence.[10, 15, 29] Harrington et al. found that an understanding of the chronic and serious nature of the disease was more relevant than biomedical knowledge.[10] The fact that indicated BPG injections were ceased by patients due to seemingly good health in Kumar et al.'s study also suggests that a level of understanding of the disease course is needed.[26] Certainly, delivering education was thought to be a worthwhile intervention by many and remains an intuitively key aspect of health care.[9, 26, 29] Conflicting results regarding the relationship between patients' parents' level of education and adherence to secondary prophylaxis were also reported, with Bassili et al. describing non-adherence to be more common amongst children whose parents had lower levels of education and occupation[24] and Kumar et al. finding no association between parents' level of education and patients' adherence to secondary prophylaxis.[27]

Certain patient demographic and clinical factors also have an unclear association with secondary prophylaxis adherence. Eissa et al. found that service delivery was better for females than males,[19] however Stewart et al. found that males and females were equally likely to receive monthly BPG.[18] Gasse et al. reported adequate healthcare coverage was protective against poor adherence, [9] yet Bassili et al. described non-adherence as more common in children with health insurance compared to those without.[24] Eissa et al. also found that adherence was higher among patients with moderate or severe disease compared to patients with mild disease.[19] In similar vein, Gasse et al. found that a previous medical history of symptomatic ARF was protective against poor adherence.[9] However, in Stewart et al.'s study patients with more severe disease were less likely to receive monthly BPG.[18]

Pain and dislike of injections as well as the issue of responsibility for injection delivery are other important considerations in adherence. According to one qualitative study, pain associated with injections was not necessarily a deterrent to secondary prophylaxis uptake,[10] however in two qualitative studies, fear/dislike of injections was given as a reason for non-adherence.[26, 27] Harrington et al. and Mincham et al. both commented on the balance of health seeking and health delivery responsibility between patients, caregivers and health staff, [10, 29] A common understanding of roles and responsibilities in a given community appears important to ensuring BPG administration occurs.[10, 29] This balance may differ in urban compared to rural settings, especially in Australia

where historically a more paternalistic approach to rural Indigenous health care delivery has been taken.[10] Adherence to secondary prophylaxis for ARF and RHD is evidently a complex and multi-factorial issue.

Strengths and weaknesses

To the best of our knowledge, this is the first systematic review exploring rates of adherence and factors associated with adherence to secondary prophylaxis for ARF and RHD. Our review was conducted using PRISMA guidelines to ensure a transparent and complete reporting system. However, formal data synthesis with meta-analysis was unable to be performed as authors used different study designs and definitions of adherence, and there were differing regimens for secondary prophylaxis recommended worldwide. Despite this limitation, our use of a modified validated tool for methodological quality assessment allows for the appraisal of included studies.

When examining factors associated with adherence to secondary prophylaxis, it should be taken into consideration that the number of studies from different geographical regions is not proportional to the prevalence of ARF and RHD in those regions. There were six studies from Oceania (four conducted in Australia), two from India, one from Egypt and one from South Africa, whereas India has the highest prevalence of ARF/RHD among these locations. Care must be taken when interpreting and applying review findings within a local context. However, an overlap in factors pertinent to adherence in the different study regions, such as the effect of rurality and access to health services, suggests that some findings may be universally relevant.

What is the current knowledge gap?

Knowledge of rates of adherence to secondary prophylaxis for ARF and RHD promotes an accurate appreciation of the problem of poor uptake. Further studies reporting rates of adherence worldwide are hence warranted, as these data are not available in many countries and may be outdated in others.

Future research may also further explore factors associated with adherence to BPG injections given the limited number of studies addressing this worldwide and global variation in population sociocultural demographics. An understanding of factors associated with adherence can be used by doctors, nurses,

community health workers and policy makers to improve service delivery. Patient self-awareness of these factors may also assist in overcoming barriers to receiving secondary prophylaxis.

Can the situation be improved?

Interventions to improve adherence to secondary prophylaxis that could be adopted by established ARF/RHD control programs include ensuring an effective active recall system,[9, 23] involving community health workers[30] and delivering education about the disease and its management.[9] It is commonly said, "What gets measured gets managed." Thus, it may be worthwhile to record reasons for failure of patients to attend for BPG injections. This could be made part of a specific protocol for when secondary prophylaxis is missed, with individual follow-up and troubleshooting by a community health worker who has knowledge of local sociocultural and geographic influences. Facilitating a holistic approach in service delivery so that patients and their families feel supported and confident in the care received is vital.[10, 24, 27] It should be noted that these interventions can only be achieved with adequate and sustained financial support and staff resources.[19]

Conclusion

Current literature provides some insight into levels of adherence and factors associated with adherence to secondary prophylaxis for ARF and RHD. However, further studies are warranted to develop a better understanding of current adherence rates and factors associated with adherence worldwide. Improved delivery of secondary prophylaxis is necessary to ensure best health outcomes for affected pediatric and young adult populations. Interventions to achieve this should target patient demographic, clinical, sociocultural and health service delivery factors with known association to adherence, and may include implementation of an active recall system, provision of holistic care, involvement of community health workers and delivery of ARF/RHD health education.

Conflict of Interest/Acknowledgements

The authors declare that there are no conflicts of interest. All funding was provided by James Cook University.

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Abstract

Background: Optimal delivery of regular benzathine penicillin G (BPG) injections prescribed as secondary prophylaxis for acute rheumatic fever (ARF) and rheumatic heart disease (RHD) is vital to preventing disease morbidity and cardiac sequelae in affected pediatric and young adult populations. However, poor uptake of secondary prophylaxis remains a significant challenge to ARF/RHD control programs.

Objective: In order to facilitate better understanding of this challenge and thereby identify means to improve service delivery, this systematic literature review explored rates of adherence and factors associated with adherence to secondary prophylaxis for ARF and RHD worldwide.

Methods: MEDLINE was searched for relevant primary studies published in the English language from 1994-2014, and a search of reference lists of eligible articles was performed. The methodological quality of included studies was evaluated using a modified assessment tool.

Results: Twenty studies were included in the review. There was a range of adherence to varying regimens of secondary prophylaxis reported globally, and a number of patient demographic, clinical, socio-cultural and health care service delivery factors associated with adherence to secondary prophylaxis were identified.

Conclusion: Insights into factors associated with lower and higher adherence to secondary prophylaxis may be utilized to facilitate improved delivery of secondary prophylaxis for ARF and RHD. Strategies may include ensuring an effective active recall system, providing holistic care, involving community health workers and delivering ARF/RHD health education.

Keywords

Acute rheumatic fever, rheumatic heart disease, benzathine penicillin, benzathine benzylpenicillin, penicillin G benzathine, secondary prophylaxis, adherence, compliance

Introduction

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are a cause of significant morbidity and cardiac mortality amongst pediatric and young adult populations in developing countries, migrants from these nations and minority populations in developed countries.[1] The annual worldwide incidence of ARF has been estimated at over 471 000,[2] with major and minor clinical manifestations including carditis, arthritis, chorea, erythema marginatum, subcutaneous nodules, arthralgia and fever.[3] RHD resulting from recurrent episodes of ARF has an estimated prevalence of at least 15.6 million people globally.[2] An approximate worldwide mortality of 233 000 people per annum[2] is attributed to complications of valvular disease including arrhythmias, heart failure, thromboembolism and infective endocarditis.[3]

Secondary prophylaxis with regular intramuscular injections of benzathine penicillin G (BPG) is a key component of ARF and RHD control programs. This approach aims to prevent group A beta-hemolytic streptococci (GAS) infections and subsequent recurrent episodes of ARF.[4] The World Health Organization (WHO) recommends 3-4 weekly BPG continued for a duration dependent on factors including age, time since the last episode of ARF, risk of streptococcal infections in the area and presence of RHD.[4] According to WHO guidelines, secondary prophylaxis should continue for at least 5 years after the last episode of ARF or until the age of 18 years (whichever is longer) and for a greater length of time in cases of carditis or RHD.[4, 5] However, local health authorities give slightly varying recommendations for the frequency and duration of BPG injections.[5]

Low adherence with secondary prophylaxis is one of the main challenges to effective control of ARF and RHD.[4] To the best of our knowledge, a systematic literature review to summarize what is known regarding rates of adherence and factors associated with adherence to secondary prophylaxis does not exist. This study aims to systematically summarize and evaluate published rates of adherence and factors associated with adherence to BPG injections prescribed as secondary prophylaxis for ARF and RHD, and thereby identify means to improve secondary prophylaxis interventions. In contrast to other studies of adherence in chronic disease management, of particular interest and importance in this review is the focus of adherence amongst poor and underserved population groups.

Methods

Protocol and focus

This systematic review has been conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[6] The review focuses on studies that explored rates of adherence and factors associated with adherence to BPG injections recommended as secondary prophylaxis for ARF and RHD worldwide.

Search criteria

A search of the MEDLINE database via OvidSP was conducted on 28 June 2014. All articles written in the English language between January 1, 1994 and June Week 3, 2014, using the Medical Subject Headings (MeSH) and keywords, ("acute rheumatic fever" OR "rheumatic fever" OR "rheumatic heart disease") AND ("secondary prophylaxis" OR "secondary prevention" OR "benzathine penicillin G" OR "penicillin G benzathine" OR "benzathine penicillin" OR "benzathine benzylpenicillin" OR "disease management" OR "management") AND ("patient compliance" OR "compliance" OR "non-compliance" OR "noncompliance" OR "treatment refusal" OR "guideline adherence" OR "medication adherence" OR "adherence" OR "non-adherence" OR "nonadherence" OR "alignment" OR "non-alignment" OR "nonalignment"), were retrieved. A single investigator (PK) screened the titles and abstracts of all retrieved citations and performed full text reviews of relevant studies. Reference lists of relevant studies were hand searched to identify additional relevant publications.

Eligibility criteria

Eligibility criteria were determined with expert input from two pediatricians. Primary studies published from January 1, 1994 to June Week 3, 2014, were included in the literature review if they reported rates of adherence to secondary prophylaxis for ARF/RHD or discussed factors associated with adherence to BPG injections recommended as secondary prophylaxis for ARF/RHD.

Articles that were not primary studies or were irrelevant to the focus of this review were excluded. This included articles written about the epidemiology and clinical presentation of ARF/RHD, symptomatic treatment of ARF episodes, the efficacy of differing antibiotic regimens prescribed as secondary prophylaxis for ARF/RHD and guidelines for delivery of secondary prophylaxis for ARF/RHD, without reference to rates of adherence or factors associated with adherence to secondary prophylaxis for ARF/RHD.

Data extraction and quality assessment

One investigator (PK) used a standardized sheet to extract data from included studies. Data extracted included the author, year of publication, source, location of study, study design and study population characteristics. Study findings addressing rates of adherence to secondary prophylaxis for ARF/RHD and factors associated with adherence to secondary prophylaxis for ARF/RHD were also summarized.

We created a quality assessment tool to evaluate the methodological quality of included studies incorporating validated elements of Pluye et al.'s Mixed Methods Assessment Tool (MMAT)[7] and Wells et al.'s checklists for non-randomized studies in systematic reviews[8]. Our tool assessed methodological quality in ten domains including the incorporation of clear study objectives with suitable data collection, clarity of adherence definition, sample size adequacy, recruitment method, comparability of participant groups, outcome measure rate/response rate, use of inferential statistical analysis, inclusion of multivariate analysis, consideration given to the contextual relation of findings and consideration given to researchers' influence on study findings (Table 1).

Table 1: Quality assessment tool

Assessment criteria	Yes	No
Clear research objectives with suitable data collection	Research objectives clearly outlined and data collected addresses research objectives	Research objectives not clearly outlined or data collected does not adequately address research objectives
Definition of adherence to secondary prophylaxis clear	Adherence and non-adherence or levels of adherence to secondary prophylaxis clearly defined	Adherence, non-adherence or levels of adherence to secondary prophylaxis not clearly defined
Sample size calculation reported and target sample size reached	Sample size calculation performed and target sample size reached	Sample size calculation not performed or reported, or sample size calculation performed and target sample size not reached
Recruitment of participants used probability sampling	All or a randomly selected proportion of all persons on a register included	Neither all nor a randomly selected proportion of all persons on a register included
Participant groups comparable	Key demographic information comparing participant groups is presented and there are no obvious dissimilarities that may account for differences in outcomes, or dissimilarities are taken into account in data analysis.	There are apparent dissimilarities between participant groups that may account for differences in outcomes and these dissimilarities are not taken into account in data analysis.
Outcome data complete/Response rate acceptable	Outcome data ≥80% complete/Response rate ≥60%	Outcome data <80% complete/Response rate <60%
Any inferential statistical analysis	Inferential statistical analysis performed	Inferential statistical analysis not performed
Multivariate analysis of factors associated with adherence	Multivariate analysis of factors associated with adherence performed	Multivariate analysis of factors associated with adherence not performed
Consideration given to contextual relation of findings (qualitative studies)	Explanation of how study findings relate to the study context or context characteristics given	Explanation of how study findings relate to the study context or context characteristics not given
Consideration given to researchers' influence in relation to findings (qualitative studies)	Researchers critically explained how findings relate to their perspectives, roles and interactions with participants	Researchers did not critically explain how findings relate to their perspectives, roles and interactions with participants

Results

Search results and quality assessment

Electronic searching retrieved 61 citations from MEDLINE. Based on inclusion and exclusion criteria, 15 of these publications were included in this review (Figure 1). Four additional publications identified through reference list searching and one additional publication known to be relevant through prior knowledge were also included in the review. All of the included studies were published in peer-reviewed, scientific journals.

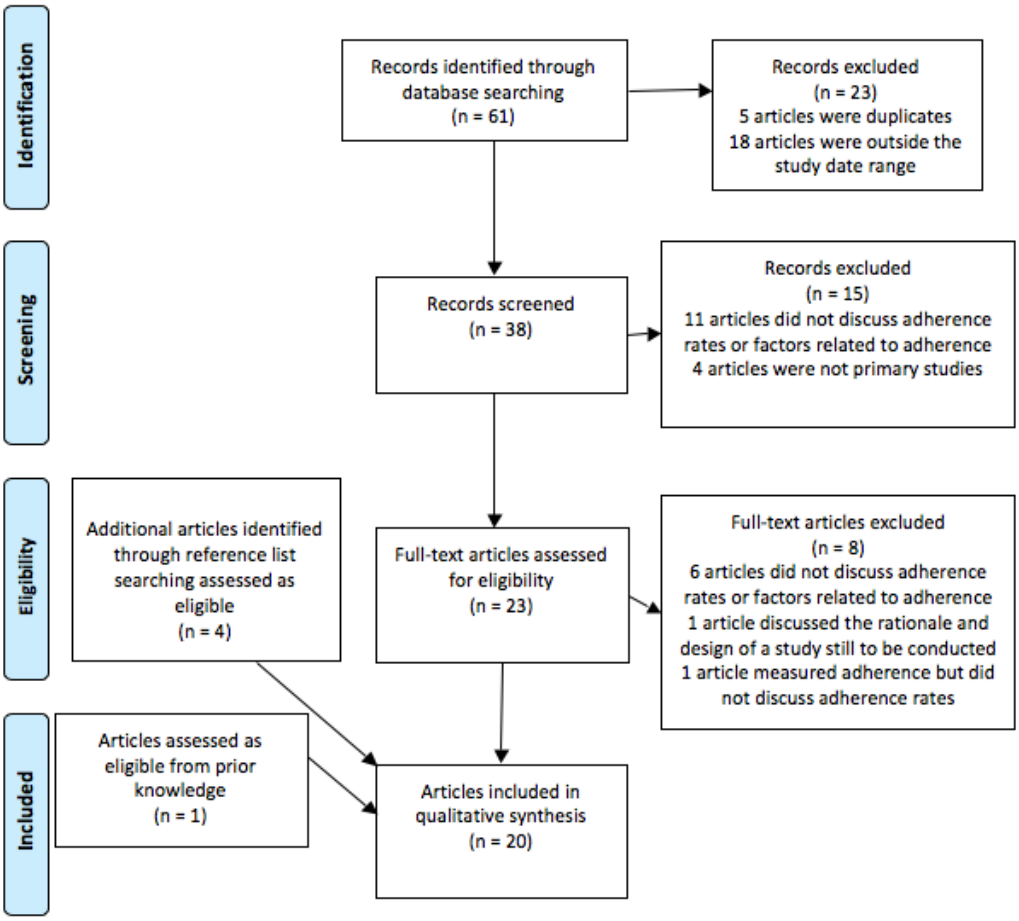

Figure 1: modified PRISMA flow diagram[a]

Secondary prophylaxis regimens and definitions of adherence

Prescribed regimens of BPG varied between health authorities worldwide and included recommendations for 2-weekly, 3-weekly, 4-weekly and monthly BPG. Additionally, there were a number of definitions of "adherence" to secondary prophylaxis employed in the reviewed literature. In some studies, a benchmark

[a] Modified from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

percentage or fraction of recommended injections was defined as a case of "adherence",[9, 10] whilst in others, rates of adherence were reported as a percentage of those who received 100% of their prescribed BPG, or a percentage of the total number of recommended injections administered to the study population.[11] Some authors utilized the terms "regular compliance", "irregular compliance" and "non-compliance" as defined by the WHO[12], whilst others created their own definitions of terms such as "complete compliance", "partial compliance" and "dropout" to describe levels of adherence.[13]

Rates of adherence

Nineteen publications discussed rates of adherence to secondary prophylaxis; two of these articles utilized the same data set (Table 2). The majority of these were retrospective observational studies, with the exception of one randomized controlled trial measuring outcomes of patients on a 3-weekly versus a 4-weekly regimen[13], one measure of past adherence by questionnaire[14], and one assessment of adherence based on qualitative interviews.[15]

Table 2: Rates of adherence to secondary prophylaxis for ARF And RHD

Author, Year	Source	Country/ Continent	City/Region/ State/Territory	Prophylaxis regimen/Study population	Study design	Summary of findings
Gasse et al., 2013 [9]	BioMed Central Public Health	French Territory, Oceania	Lifou, New Caledonia	Patients recommended to receive 3-weekly BPG (n=70) Mean age 22.3 ± 11.6yrs (43%<16yrs); 63% females.	Retrospective cohort study over 12 months in 2011	54% good-adherent[b] 46% poor-adherent[c] Mean adherence 77 ± 22% Median adherence 82.2% (IQR 76.5- 94.1) Median number of injections: 14 (range 2-18)
Remond et al., 2013 [16]	Internal Medicine Journal	Australia, Oceania	Kimberley Region, Western Australia; Far North Queensland	Patients recommended to receive 3-4 weekly BPG (n=293)	Retrospective observational study over 12 months (patients identified Nov 2008 – Mar 2009)	17.7% received ≥80% of recommended BPG
Kearns et al., 2010 [17]	Rural and Remote Health	Australia, Oceania	Central Australia, Northern Territory	Patients recommended to receive 4-weekly BPG (n=47] Median age 28yrs (range 8-58yrs); 82% females.	Retrospective observational study – adherence measured 2 years before and after implementation of Full Moon Strategy in May 2006	June 2004 - May 2006: 47% overall uptake of recommended BPG (95% CI 44-51) May 2006 – June 2008: 57% overall uptake of recommended BPG (95% CI 56-60)
Stewart et al., 2007 [18]	Australian Journal of Rural Health	Australia, Oceania	Katherine, Northern Territory	Patients recommended to receive monthly BPG (n=59) Age <18yrs 32%; 66% females.	Retrospective observational study over 24 months from Sept 2002 to Sept 2004	Mean adherence 56% of all recommended BPG Median adherence 54% of all recommended BPG (range 0-100%)
Harrington et al., 2006 [10]	Medical Journal of Australia	Australia, Oceania	North East Arnhem Land, Northern Territory	Patients recommended to receive monthly BPG (n=27)	Retrospective observational study from Jan 2002 to Sept 2003	59% received adequate prophylaxis[d]

[b] Good-adherent defined as ≥80% of recommended BPG received
[c] Poor-adherent defined as <80% of recommended BPG received
[d] Adequate prophylaxis defined as >75% recommended BPG received

Author, Year	Source	Country/ Continent	City/Region/ State/Territory	Prophylaxis regimen/Study population	Study design	Summary of findings
Eissa et al., 2005 [19]	Australian and New Zealand Journal of Public Health	Australia, Oceania	Northern Territory	Patients recommended to receive 3-4 weekly BPG (n=52) Male n=15	Retrospective observational study over 12 months (patients identified in Aug 2004)	22 (42%) patients received at least 80% of the minimum recommended doses[e] Median number of doses received in the previous 12 months: 9
Mincham et al., 2002 [20]	Australian and New Zealand Journal of Public Health	Australia, Oceania	Kimberley, Western Australia	Patients recommended to receive monthly BPG (n=78)	Retrospective observational study of patients diagnosed with ARF or RHD from 1982 to 1996 over 2 years from Jan 1996 – Dec 1997	67% of all prescribed BPG doses administered, with individuals receiving 8-100% of doses prescribed. 19% median injection interval 3.5-4.5 weeks
Grayson et al., 2006 [11]	New Zealand Medical Journal	New Zealand, Oceania	Auckland	Patients recommended to receive 3-4 weekly BPG (n=433 in 1998, n=428 in 2000)	Retrospective observational study of data from 1998 and 2000	86-96% total compliance[f]
Seckeler et al., 2010 [21]	Pediatric Cardiology	Common-wealth of the United States of America, North America	Northern Mariana Islands	Patients recommended to receive 4-weekly BPG (n=144) Aged <21yrs	Retrospective observational study from 1984 to 2006	Mean adherence 58.3% of all recommended BPG Median adherence 69.2% of all recommended BPG (range 0-100%)
Nordet et al., 2008 [22]	Cardiovascular Journal of Africa	Cuba, North America	Pinar del Rio	School children recommended to receive monthly BPG (n=52 in 1986, n=193 in 1996) Age range 5-15yrs	Retrospective cross-sectional studies in 1986 and 1996 (first and last years of a 10 year prevention program) + comparison with a report on prevention activities in 2002	1986: 50% regular compliance[g] 36.5% irregular compliance[h] 13.5% non-compliance[i] 1996: 93.8% regular compliance 6.2% irregular compliance 2002: > 80% regular compliance

[e] Minimum recommended number of doses was 13 injections in 12 months

[f] Total compliance defined as administration of all scheduled injections within predetermined time frames

[g] Regular compliance defined as a minimum of 10-11 BPG injections received per year

[h] Irregular compliance defined as 6-9 BPG injections received per year

[i] Non-compliance defined as ≤5 BPG injections received per year

Author, Year	Source	Country/ Continent	City/Region/ State/Territory	Prophylaxis regimen/Study population	Study design	Summary of findings
Pelajo et al., 2010 [23]	Paediatric Rheumatology	Brazil, South America	Rio de Janeiro	Patients recommended to receive monthly BPG (n=536) Mean age 13 ± 3.9yrs; 53% females.	Retrospective observational study of patients with a diagnosis of ARF from 1985 to 2005	Non-adherence[j] detected in 35% (188 out of 536) patients
Robertson et al., 2005 [15]	South African Medical Journal	South Africa, Africa	Cape Town	Patients recommended to receive monthly BPG or oral penicillin (n=8; 7 receiving monthly BPG, 1 receiving oral penicillin)	Qualitative semi-structured interviews with patients/guardians; date not specified	In 7/8 cases, adherence with all recommended BPG was reported
Bassili et al., 2000 [24]	Eastern Mediterranean Health Journal	Egypt, Africa	Alexandria	Patients receiving secondary prophylaxis (n=127; 104 prescribed 2-weekly BPG, 14 prescribed 4-weekly BPG and 9 prescribed oral penicillin) Age 0-15yrs	Retrospective observational study of patients over 6-12 months (patients identified in Jan-Apr 1998)	71.2% of patients compliant[k] in 2-weekly BPG group 28.6% of patients compliant in 4-weekly BPG group
Abdel-Moula et al., 1998 [14]	Journal of the Egyptian Public Health Association	Egypt, Africa	Alexandria	Patients receiving secondary prophylaxis (n=29; 20 prescribed monthly BPG, 3 prescribed 3-weekly BPG, 5 prescribed 2-weekly BPG and 1 prescribed oral penicillin) Age range 6-16yrs	Prospective case-control study with questionnaire regarding compliance over one year (patients identified in scholastic year 1993-1994)	31% of patients not compliant[l]

[j] Patient classified as non-adherent if they missed or delayed >1 dose of BPG during a 6-month period (interval between appointments)
[k] Patient considered compliant if received at least 11 BPG injections in the last 6 months or 22 BPG injections in the last year
[l] Patient considered not compliant if received <80% of prescribed BPG injections per year

Author, Year	Source	Country/ Continent	City/Region/ State/Territory	Prophylaxis regimen/Study population	Study design	Summary of findings
Kassem et al., 1995 [25]	Egyptian Heart Journal	Egypt, Africa	Alexandria	Patients recommended to receive secondary prophylaxis, unspecified regimen (n=86) Age range 16-32yrs (mean 20.8±3.15yrs); 63% females	Retrospective observational study over 11-20 years (patients identified 1972-1980)	Approximately 35% of patients uncompliant[m]
Kumar et al., 2002 [26]	Indian Heart Journal	India, Asia	Ambala, Haryana	Patients recommended to receive monthly BPG (n=257, 23-134 patients eligible per year) Age 6-20yrs 70.8%	Retrospective observational study 1988-1999	Mean yearly compliance[n]: 92%; annual variation 82.4-100%
Kumar et al., 1997 [27]	Indian Heart Journal	India, Asia	Ambala, Haryana	Patients recommended to receive monthly BPG (n=110 in 1995, n=17-106 in 1988-1994) In 1995, age range 6-50yrs (43.7% aged 6-15yrs, 43.7% aged 16-25yrs); 48.2% male	Retrospective observational study 1988-1995	1995: 83.6% of patients compliant[o] 1988-1994: >90% of patients compliant
Lue et al., 1996 [28] Lue et al, 1994 [13]	Journal of Pediatrics	Taiwan, Asia	Taipei	Patients prescribed 3-weekly and 4-weekly BPG (n=249; 124 prescribed 3-weekly BPG, 125 prescribed 4-weekly BPG Age range 3-25yrs	Randomized controlled trial 1979-1989	3-weekly BPG group: 66.9% stay-in (complete) compliance[p], 15.3% partial compliance[q], 9.7% dropout[r] 4-weekly BPG group: 73.6% stay-in (complete) compliance, 15.2% partial compliance, 9.2% dropout

[m] Definition of uncompliant not provided
[n] Compliance defined as percentage of those eligible for secondary prophylaxis who received secondary prophylaxis
[o] Missed no more than 1 BPG injection per year
[p] Complete compliance defined as ≤ 1 BPG injection missed per year
[q] Partial compliance defined as 2-3 BPG injections missed per year
[r] Dropout defined as ≥ 4 BPG injections missed per year

Factors associated with adherence

Ten of the included studies discussed factors associated with adherence to secondary prophylaxis (Table 3). Qualitative, semi-structured interviews were conducted in seven of these studies, two of which additionally included questionnaires. Multivariate logistic regression was performed in one study[9] and other inferential statistical analysis was performed in two studies.[18, 19]

Table 3: Factors associated with adherence to secondary prophylaxis for ARF and RHD

Authors	Source	Location	Prophylaxis regimen/Study population	Study design	Summary of Findings
Gasse et al., 2013 [9]	BioMed Central Public Health	Lifou, New Caledonia	Patients recommended to receive 3-weekly BPG (n=70) Mean age 22.3 ± 11.6yrs (43%<16yrs); 63% females.	Retrospective cohort study over 12 months in 2011 Multivariate logistic regression model	Factors protective against poor adherence: a household with >5 people (odds ratio 0.25, 95% CI 0.08-0.75), a previous medical history of symptomatic ARF (odds ratio 0.20, 95% CI 0.04 to 0.98), adequate healthcare coverage (odds ratio 0.21, 95% CI 0.06-0.72).
Stewart et al., 2007 [18]	Australian Journal of Rural Health	Katherine, Northern Territory, Australia	Patients recommended to receive monthly BPG (n=59) Age <18yrs 32%; 66% females.	Retrospective observational study over 24 months from Sept 2002 to Sept 2004	In those who received ≥50% of prescribed BPG, non-significant trend towards improved adherence seen in patients aged <18 years (RR=1.26) and those who attended a health clinic more frequently for other reasons (RR=1.42). Patients with more severe disease less likely to receive monthly BPG (RR=0.60). Men and women equally likely to receive monthly BPG (RR=1.09).
Harrington et al., 2006 [10]	Medical Journal of Australia	North East Arnhem Land, Northern Territory, Australia	Patients recommended to receive monthly BPG, relatives and health care workers (n=51; 15 patients, 18 relatives, 18 health care workers) Patient age range 20-60yrs (range of time since diagnosis 1-30yrs); female n=45, male n=6	Qualitative semi-structured interviews conducted Apr-Aug 2003	Staff factors promoting uptake: appropriately trained, socially and culturally competent staff, an active recall system, staff willingness to treat the patient at home. Patient factors promoting uptake: an appropriate location for receiving injections, belief that the disease is chronic and serious, confidence in the health service and receipt of holistic care, family support for and belief in the efficacy of treatment. Staff factors inhibiting uptake: negative perception of the secondary prophylaxis program, conflicting priorities for staff, no effective strategy for dealing with absent patients, staff fatigue and frustration Patient factors inhibiting uptake: conscientious refusal of treatment, inconvenience to the patient, not "belonging" to the health service, lack of family support, lack of confidence in the treatment. Factors not clearly related to treatment uptake: patient biomedical understanding of the disease, taking responsibility for health and perception of painfulness of the treatment.
Eissa et al., 2005 [19]	Australian and New Zealand Journal of Public Health	Northern Territory, Australia	Patients recommended to receive 3-4 weekly BPG (n=52) Male n=15	Retrospective observational study over 12 months (patients identified in Aug 2004)	Females significantly more likely to receive treatment than males (p=0.004). Higher adherence rate (median doses 10/year) in moderate or severe disease compared with mild disease (median doses 8/year).
Mincham et al., 2003 [29]	Australian Journal of Rural Health	Kimberley, Western Australia, Australia	Patients/parents of patients recommended to receive monthly BPG (n=7)	Qualitative semi-structured interviews in 1998	Compliance with secondary prophylaxis associated with positive patient–staff interactions. Living in a remote location was a negative influence.

					Participants had variable levels of understanding of the disease and need for BPG.

Authors	Source	Location	Prophylaxis regimen/Study population	Study design	Summary of Findings
Grayson et al., 2006 [11]	New Zealand Medical Journal	Auckland, New Zealand	Nurses involved with delivery of 3-4 weekly BPG (n=9)	Qualitative semi-structured interviews; date not specified	Presence of community health workers, a rheumatic fever resource nurse and communication from other services used by rheumatic fever patients impacted positively on the delivery of secondary prophylaxis.
Robertson et al., 2005 [15]	South African Medical Journal	Cape Town, South Africa	Caregivers of patients (n=8); physicians (n=24)	Qualitative semi-structured interviews with caregivers of patients + 24 physician questionnaires; date not specified	There was very poor knowledge of the disease amongst patients/guardians, however this was not associated with non-adherence to secondary prophylaxis.
Bassili et al., 2000 [24]	Eastern Mediterranean Health Journal	Alexandria, Egypt	Caregivers of children and children receiving secondary prophylaxis (n=127; 104 prescribed 2-weekly BPG, 14 prescribed 4-weekly BPG and 9 prescribed oral penicillin)	Retrospective chart review of compliance over 6-12 months (patients identified in Jan-Apr 1998) + questionnaire based qualitative interviews in Jan-Apr 1998 Stepwise logistic regression	Non-compliance was more common among children whose parents had lower educational and occupational levels, those whose parents had only fair to poor knowledge of the disease, those living in semi-urban and rural areas, those with health insurance and those whose families were not satisfied with the health care provided.
Kumar et al., 2002 [26]	Indian Heart Journal	Ambala, Haryana, India	Patients recommended to receive monthly BPG (n=unclear; 40 non-compliant patients + an unknown number of compliant patients – total number of participants in associated quantitative study = 257)	Qualitative, semi-structured interviews in 1999	Reasons for non-compliance: fear/dislike of injections, belief that injections were no longer required given seemingly good health, lack of awareness of the importance of secondary prophylaxis and services not available locally.
Kumar et al., 1997 [27]	Indian Heart Journal	Haryana, India	Patients recommended to receive monthly BPG (n=110) Mean age 18.4 ± 8.6yrs; 48.2% male.	Qualitative semi-structured interviews conducted in 1995	Reasons for non-compliance: private doctors ceasing BPG injections, unsupportive family members, a disinterest in BPG injections and long distances of travel to health clinics. No significant association between non-adherence and low socioeconomic background. No significant association between non-adherence and level of education of parents.

Quality assessment

Use of the quality assessment tool demonstrated the methodological quality of each of the included studies (Table 4).

Table 4: Quality~~yative~~ assessment

Study, Year	Clear research objectives with suitable data collection	Definition of adherence clear	Sample size calculation reported and target sample size reached	Recruitment of participants using probability sampling	Participant groups comparable	Outcome data complete /Response rate acceptable	Any inferential statistical analysis	Multivariate analysis of factors associated with adherence	Consideration given to contextual relation of findings	Consideration given to researchers' influence in relation to findings
Abdel-Moula et al., 1998 [14]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Not relevant	Not relevant
Bassili et al., 2000 [24]	Yes	Yes	No	Yes	Not relevant	Yes	Yes	Yes	Not relevant	Not relevant
Eissa et al., 2005 [19]	Yes	Yes	No	Yes	Unknown	Yes	Yes	No	Not relevant	Not relevant
Gasse et al., 2013 [9]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not relevant	Not relevant
Grayson et al., 2006 [11]	Yes	No	Quantitative component: No Qualitative component: not relevant	Quantitative component: Yes Qualitative component: not relevant	Not relevant	Yes	No	No	Quantitative component: not relevant Qualitative component: No	Quantitative component: not relevant Qualitative component: No
Harrington et al., 2006[10]	Yes	Yes	Not relevant	Not relevant	Not relevant	No	No	No	Yes	Yes
Kassem et al., 1995 [25]	Yes	No	No	Unknown	Not relevant	No	No	No	Not relevant	Not relevant
Kearns et al., 2010 [17]	Yes	Yes	Quantitative component: No Qualitative component: not relevant	Quantitative component: Yes Qualitative component: not relevant	Not relevant	No	Yes	No	Quantitative component: not relevant Qualitative component: Yes	Quantitative component: not relevant Qualitative component: Yes

Study, Year	Clear research objectives with suitable data collection	Definition of adherence clear	Sample size calculation reported and target sample size reached	Recruitment of participants using probability sampling	Participant groups comparable	Outcome data complete /Response rate acceptable	Any inferential statistical analysis	Multivariate analysis of factors associated with adherence	Consideration given to contextual relation of findings	Consideration given to researchers' influence in relation to findings
Kumar et al., 2002 [26]	Yes	No	Quantitative component: No Qualitative component: not relevant	Quantitative component: Yes Qualitative component: not relevant	Not relevant	Yes	Yes	No	Quantitative component: not relevant Qualitative component: No	Quantitative component: not relevant Qualitative component: No
Kumar et al., 1997 [27]	Yes	Yes	Quantitative component: No Qualitative component: not relevant	Quantitative component: Yes Qualitative component: not relevant	Not relevant	Yes	Yes	No	Quantitative component: not relevant Qualitative component: No	Quantitative component: not relevant Qualitative component: No
Lue et al., 1996 [28]; Lue et al., 1994 [13]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Not relevant	Not relevant
Mincham et al., 2003 [29]	Yes	No	Not relevant	Not relevant	Not relevant	Yes	No	No	Yes	Yes
Mincham et al., 2002 [20]	Yes	Yes	No	Yes	Not relevant	Yes	No	No	Not relevant	Not relevant
Nordet et al., 2008 [22]	Yes	Yes	No	Yes	Not relevant	Yes	Yes	No	Not relevant	Not relevant
Pelajo et al., 2010 [23]	Yes	Yes	No	Yes	Yes	No	Yes	No	Not relevant	Not relevant
Remond et al., 2013 [16]	Yes	Yes	No	Unknown	Not relevant	Yes	Yes	No	Not relevant	Not relevant

Study, Year	Clear research objectives with suitable data collection	Definition of adherence clear	Sample size calculation reported and target sample size reached	Recruitment of participants using probability sampling	Participant groups comparable	Outcome data complete /Response rate acceptable	Any inferential statistical analysis	Multivariate analysis of factors associated with adherence	Consideration given to contextual relation of findings	Consideration given to researchers' influence in relation to findings
Robertson et al., 2005[15]	Yes	No	Quantitative component: No Qualitative component: not relevant	Quantitative component: Yes Qualitative component: not relevant	Not relevant	Yes	No	No	Quantitative component: not relevant Qualitative component: Yes	Quantitative component: not relevant Qualitative component: No
Seckeler et al., 2010 [21]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Not relevant	Not relevant
Stewart et al., 2007 [18]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Not relevant	Not relevant

Discussion

Over the last 20 years, studies addressing adherence to secondary prophylaxis for ARF/RHD have been conducted in India, Egypt, South Africa, Brazil, Cuba, the Northern Mariana Islands, Australia, New Zealand, New Caledonia and Taiwan. On review of this literature, there was a range of adherence to different regimens of BPG prescribed as secondary prophylaxis worldwide. Whilst a small number of studies conducted in Cuba, India and New Zealand reported good overall adherence, adherence measured in the majority of studies was sub-optimal. An individual range of 0-100% of prescribed injections also indicated that despite overall adherence rates, some patients received inadequate BPG injections whilst others received appropriate prophylaxis. Adherence to BPG was not evidently better or worse amongst minority groups and migrants in developed countries compared with adherence in developing countries. Very few studies assessed adherence over time in comparable populations with the same definitions, so global trends regarding this could not be established. In the Cuban study, adherence improved over time from 50% regular compliance in 1986 to >80% regular compliance in 2002,[22] whilst Indian studies demonstrated an adherence decline from 100% compliance in 1988 to 82.4% compliance in 1999.[26, 27]

Factors associated with lower adherence

In underprivileged settings where ARF and RHD remain prevalent, there are a number of interrelated factors associated with low adherence to secondary prophylaxis. Rurality with limited access to health care was one important theme in four studies, one involving logistic regression analysis (Bassili et al.) and three others including qualitative semi-structured interviews. Bassili et al. reported non-adherence to be more common amongst children in semi-urban and rural areas,[24] Mincham et al. found that living in a remote location was a negative influence on adherence[29] and two Indian studies identified lack of local services and long distances of travel as reasons for non-adherence.[26, 27] It follows that for patients living in rural and remote areas with lesser access to health care, adhering to secondary prophylaxis regimens may be more difficult.

Negative patient, staff and health service interactions were also reported as contributors to non-adherence in three studies. Bassili et al.'s logistic regression analysis found non-adherence to be more

common among children whose families were not satisfied with the health care provided,[24] and qualitative semi-structured interviews performed by Mincham et al. and Harrington et al. in Australia highlighted that negative patient-staff interactions, limited confidence in the treatment and a lack of sense of "belonging" to the health service could reduce adherence.[10, 29] Mincham et al. and Harrington et al.'s studies also discussed staff factors inhibiting uptake, including the transient nature of staff in remote settings, a negative perception of the secondary prophylaxis program, conflicting health priorities, and no effective strategy for dealing with absent patients leading to staff frustration and fatigue.[10, 29] These findings may be most relevant to Australian Indigenous populations and other minority groups in developed countries, where a difference in cultural values, attitudes and beliefs between the patient/caregiver and health care provider may exist. In Mincham et al.'s study, lack of an effective reminder system for due injections additionally led to non-adherence to secondary prophylaxis.[29]

Other factors associated with non-adherence included lack of family support (observed in two qualitative studies)[10, 27] a disinterest in or conscientious refusal of treatment (discussed in two qualitative studies)[10, 27] and inconvenience of the treatment or treatment interference with personal priorities (identified in two qualitative studies).[10, 29]

On the field, lack of BPG supply is another known factor leading to lower rates of BPG administration, however this was not raised in the studies reviewed. In prospective studies, this is likely because BPG supply was ensured for the study population. In retrospective observational studies, it may be that supply was assumed to have been adequate by the researchers, and in qualitative interviews and questionnaires perhaps the focus was on individual and health service factors, without consideration of pharmaceutical supply.

Factors associated with higher adherence

Factors associated with higher adherence were also identified in the literature reviewed. Positive patient, staff and health system interactions promoted adherence in three small qualitative studies in Australia and New Zealand. Mincham et al. found that adherence was closely linked with positive patient-staff interactions[29] whilst Harrington et al. identified that patient confidence in the health

service and receipt of holistic care, as well as family support for and belief in the treatment, were important to adherence.[10] The presence of appropriately trained, socially and culturally competent staff was discussed by Harrington et al. as a factor associated with higher adherence[10] and supported by Grayson et al.'s report that the presence of community health workers and a rheumatic fever resource nurse impacted positively on adherence.[11] Harrington et al. additionally found that an appropriate location for injections and staff willingness to treat patients at home promoted uptake.[10] These study findings may have greater applicability in countries similar to Australia and New Zealand, where ARF/RHD is most prevalent amongst migrant and minority groups. In Harrington et al.'s study, recall systems for patients with due BPG injections were also associated with higher adherence.[10]

Opportunistic communications may improve adherence to secondary prophylaxis. A qualitative study by Grayson et al. found that communication from other services used by rheumatic fever patients impacted positively on adherence,[11] and Stewart et al.'s retrospective study involving inferential analysis described a non-significant trend towards improved adherence in patients who attended a health clinic more frequently for reasons other than secondary prophylaxis.[18]

Patient demographic factors including younger age and greater number of people per household could also positively influence adherence to secondary prophylaxis. Stewart et al. found a non-significant trend towards improved adherence in patients aged <18 years compared with patients aged ≥18 years amongst those who received ≥50% of prescribed BPG.[18] Perhaps this is because parents/caregivers are overseeing adherence in younger patients; young adults newly responsible for their own health care may have a tendency towards non-adherence. Meanwhile, Gasse et al.'s retrospective study involving multivariate logistic regression analysis identified that a household with ≥6 people was protective against poor adherence. It is postulated that this may be because older siblings in the household are able to assist with health care seeking.[9]

Factors with unclear association to adherence

A number of factors had an unclear association with adherence to secondary prophylaxis. Biomedical knowledge of ARF and RHD was poor amongst patients and their families, yet whilst Bassili et al. described non-adherence to be more common in patients who's parents had only a fair to poor

knowledge of the disease,[24] Robertson et al. reported no association between knowledge of the disease and adherence.[10, 15, 29] Harrington et al. found that an understanding of the chronic and serious nature of the disease was more relevant than biomedical knowledge.[10] The fact that indicated BPG injections were ceased by patients due to seemingly good health in Kumar et al.'s study also suggests that a level of understanding of the disease course is needed.[26] Certainly, delivering education was thought to be a worthwhile intervention by many and remains an intuitively key aspect of health care.[9, 26, 29] Conflicting results regarding the relationship between patients' parents' level of education and adherence to secondary prophylaxis were also reported, with Bassili et al. describing non-adherence to be more common amongst children whose parents had lower levels of education and occupation[24] and Kumar et al. finding no association between parents' level of education and patients' adherence to secondary prophylaxis.[27]

Certain patient demographic and clinical factors also have an unclear association with secondary prophylaxis adherence. Eissa et al. found that service delivery was better for females than males,[19] however Stewart et al. found that males and females were equally likely to receive monthly BPG.[18] Gasse et al. reported adequate healthcare coverage was protective against poor adherence, [9] yet Bassili et al. described non-adherence as more common in children with health insurance compared to those without.[24] Eissa et al. also found that adherence was higher among patients with moderate or severe disease compared to patients with mild disease.[19] In similar vein, Gasse et al. found that a previous medical history of symptomatic ARF was protective against poor adherence.[9] However, in Stewart et al.'s study patients with more severe disease were less likely to receive monthly BPG.[18]

Pain and dislike of injections as well as the issue of responsibility for injection delivery are other important considerations in adherence. According to one qualitative study, pain associated with injections was not necessarily a deterrent to secondary prophylaxis uptake,[10] however in two qualitative studies, fear/dislike of injections was given as a reason for non-adherence.[26, 27] Harrington et al. and Mincham et al. both commented on the balance of health seeking and health delivery responsibility between patients, caregivers and health staff, [10, 29] A common understanding of roles and responsibilities in a given community appears important to ensuring BPG administration occurs.[10, 29] This balance may differ in urban compared to rural settings, especially in Australia

where historically a more paternalistic approach to rural Indigenous health care delivery has been taken.[10] Adherence to secondary prophylaxis for ARF and RHD is evidently a complex and multi-factorial issue.

Strengths and weaknesses

To the best of our knowledge, this is the first systematic review exploring rates of adherence and factors associated with adherence to secondary prophylaxis for ARF and RHD. Our review was conducted using PRISMA guidelines to ensure a transparent and complete reporting system. However, formal data synthesis with meta-analysis was unable to be performed as authors used different study designs and definitions of adherence, and there were differing regimens for secondary prophylaxis recommended worldwide. Despite this limitation, our use of a modified validated tool for methodological quality assessment allows for the appraisal of included studies.

When examining factors associated with adherence to secondary prophylaxis, it should be taken into consideration that the number of studies from different geographical regions is not proportional to the prevalence of ARF and RHD in those regions. There were six studies from Oceania (four conducted in Australia), two from India, one from Egypt and one from South Africa, whereas India has the highest prevalence of ARF/RHD among these locations. Care must be taken when interpreting and applying review findings within a local context. However, an overlap in factors pertinent to adherence in the different study regions, such as the effect of rurality and access to health services, suggests that some findings may be universally relevant.

What is the current knowledge gap?

Knowledge of rates of adherence to secondary prophylaxis for ARF and RHD promotes an accurate appreciation of the problem of poor uptake. Further studies reporting rates of adherence worldwide are hence warranted, as these data are not available in many countries and may be outdated in others.

Future research may also further explore factors associated with adherence to BPG injections given the limited number of studies addressing this worldwide and global variation in population sociocultural demographics. An understanding of factors associated with adherence can be used by doctors, nurses,

community health workers and policy makers to improve service delivery. Patient self-awareness of these factors may also assist in overcoming barriers to receiving secondary prophylaxis.

Can the situation be improved?

Interventions to improve adherence to secondary prophylaxis that could be adopted by established ARF/RHD control programs include ensuring an effective active recall system,[9, 23] involving community health workers[30] and delivering education about the disease and its management.[9] It is commonly said, "What gets measured gets managed." Thus, it may be worthwhile to record reasons for failure of patients to attend for BPG injections. This could be made part of a specific protocol for when secondary prophylaxis is missed, with individual follow-up and troubleshooting by a community health worker who has knowledge of local sociocultural and geographic influences. Facilitating a holistic approach in service delivery so that patients and their families feel supported and confident in the care received is vital.[10, 24, 27] It should be noted that these interventions can only be achieved with adequate and sustained financial support and staff resources.[19]

Conclusion

Current literature provides some insight into levels of adherence and factors associated with adherence to secondary prophylaxis for ARF and RHD. However, further studies are warranted to develop a better understanding of current adherence rates and factors associated with adherence worldwide. Improved delivery of secondary prophylaxis is necessary to ensure best health outcomes for affected pediatric and young adult populations. Interventions to achieve this should target patient demographic, clinical, sociocultural and health service delivery factors with known association to adherence, and may include implementation of an active recall system, provision of holistic care, involvement of community health workers and delivery of ARF/RHD health education.

Conflict of Interest/Acknowledgements

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