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Incidence, Clinical Manifestations and Risk Factors of Acute Rheumatic Fever: A Systematic Review and Meta-Analysis of the Global Perspective

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Incidence, Clinical Manifestations and Risk Factors of Acute Rheumatic Fever: A Systematic

Review and Meta-Analysis of the Global Perspective

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Abstract

Acute Rheumatic Fever (ARF) is a system-wide disease in which chronic, wide spread inflammatory changes occur in response to a group A streptococcal (GAS) infection that most often affects children and adolescents and those from developing countries. The aim of this study is to calculate the global incidence of ARF and identify the frequencies of major and clinical manifestations and risk factors globally to provide a better indication of the burden of disease and additional information on the dispersion of manifestations and risk factors. A meta-analysis was conducted by pooling cross-sectional and cohort studies, and Morbidity and Mortality Weekly Reports (MMWRs) that were English, full-text, peer-reviewed articles published after 1990 that included ARF cases of any race or nationality that were aged 0 to 19 years at the time of evaluation. Measures of interest included incidence rates and frequencies of clinical and major manifestation of ARF. In total, 27 studies met all inclusion criteria; twelve (44.4%) were cross-sectional and another 12 (44.4%) were cohort studies. A linear mixed effects model was used to calculate a pooled risk ratio; however, heterogeneity was found to be significantly high across all articles. When exploring heterogeneity of the effect by study region and age, those from the Americas (β = -4.880, p <0.001) and Africa (β = -2.919, p = 0.021), and those that included children under the age of 5 (β = -2.103, p = 0.006) had incidence estimates that were significantly lower compared to their respective stratifications, indicating that characteristics of these populations may be introducing bias. Clinical and major manifestations were unable to be explored due to the way that these variables were presented. Although substantial heterogeneity existed between studies, the results provide evidence of where gaps exist regarding ARF research on a global scale. Properly describing the characteristics of this disease is the first step towards creating adequate criteria and guidelines that will lead to better health outcomes for those

suffering from ARF, reduce the economic burden of this disease, and improve the quality of life of these individuals.

Table of Contents

List of Tables

List of Figures

Abbreviations

AC – accessory cell

ARF – Acute Rheumatic Fever

CDC – Centers for Disease Control and Prevention

CRP – C reactive protein

EM – erythema marginatum

ESR – erythrocyte sedimentation rate

FCN – ficolin

GAS – Group A Streptococcus/Streptococcal

GlcNAc – N-acetylglucosamine

HLA – human leukocyte antigen

IL – interleukin

mAbs – monoclonal antibodies

MBL – mannose-binding lectin

MHC – major histocompatibility complex

MMWR – Morbidity and Mortality Weekly Reports

NCOS – NewCastle Ottawa Scale

RHD – Rheumatic Heart Disease

SCC – subclinical carditis

SES – socioeconomic status

SN – subcutaneous nodules

TLR – Toll-like receptor

TNF-α – Tumor necrosis factor α

VCAM – vascular cell adhesion molecule

WHO – World Health Organization

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Chapter 1 Introduction

Acute Rheumatic Fever (ARF) is a system-wide disease in which chronic, wide spread

inflammatory changes occur in response to a group A streptococcal (GAS) infection (Chang,

2012). This disease most often affects children and adolescents (aged 3-19 years old), can also

affect adults and children younger than three years of age, (Carapetis, McDonald & Wilson,

2005; Chang, 2012). ARF occurs more frequently in developing countries and is considered a

rare event in most developed countries, except for Australia and New Zealand, due to its low

incidence rates by use of antibiotics (Azevedo, Pereira & Guilherme, 2012). Many of the signs

and symptoms of this disease are non-specific, so a wide range of differential diagnoses are

considered to reduce the underestimation of this disease (The Australian Guidelines, 2015). The

involvement of the heart, joints, skin, nervous system, and immune system are common among

individuals with this disease, with cardiac damage being of major concern (Chang, 2012). Each

year, 500,000 new ARF cases are seen world-wide, with an overall global incidence estimated

between 5 and 51 per 100,000 population (Tibazarwa, Volmink & Mayosi, 2008). About

280,000 of these new cases will then develop Rheumatic Heart Disease [RHD] and 233,000

individuals die to either ARF or RHD each year (Eroğlu, 2015).

Children who acquire a GAS infection and subsequently develop ARF, they are then at

risk for developing RHD, which is a prominent cause of morbidity and mortality in developing

countries, especially Africa and Asia (Kumar & Tandon, 2013; Steer, Carapetis, Nolan & Shann,

2002). RHD develops after long-term damage has occurred within the heart valves from

repeated manifestations of ARF (Baroux et al., 2013; Chang, 2012). RHD prevalence peaks in

individuals aged 30 to 40 years and is responsible for numerous premature deaths (World Health Organization [WHO], 2005). While the number of affected individuals has decreased in developing countries, at least 15,600,000 individuals globally live with RHD (Eroğlu, 2015). Studies suggest that, based on an annual 1.5% mortality rate, global deaths caused by RHD are between 233,000 and 294,000 per year, but Asian countries, where it is more prevalent, showed an annual 3.3% mortality rate accounting for 356,000 to 524,000 deaths per year (Carapetis, Steer, Mulholland & Weber, 2005; Carapetis, 2008). This data suggests that the global mortality rate may be higher than what has been previously proposed.

Definitions

Definitions for the introduction are listed here (Merriam-Webster, n.d.):

[1]Pyogenic – marked by pus production

[2]Collectin – soluble pattern recognition receptors

[3]Laminin – a fibrous protein present in the basal lamina of the epithelia

[4]GlcNAc – a monosaccharide/derivative of glucose; part of a biopolymer in the bacterial cell wall

[5]Toll like receptors – single, membrane-spanning, non-catalytic receptors usually expressed on cells, such as macrophages and dendritic cells that recognize structurally conserved molecules derived from microbes

[6]Ficolins – a group of oligomeric lectins with subunits consisting of both collagen-like long thin stretches and fibrinogen-like globular domains with lectin activity usually specific for N-acetylglucosamine (GlcNAc)

[7]Lipoproteins – any of a group of soluble proteins that combine with, and transport fat, or other lipids, in the blood plasma

[8]Peptidoglycan – a substance that forms the cell walls of many bacteria, consisting of glycosaminoglycan chains interlinked with short peptides

[9]Lipotechioic acid – a surface-associated adhesion amphiphile from Gram-positive bacteria; released from the bacterial cells after bacteriolysis

[10]Complement – a group of proteins present in blood plasma and tissue fluid that combine with an antigen–antibody complex to bring about the lysis of foreign cells

[11]Proinflammatory – a type of signaling molecule that promotes inflammation

[12]Cytokines – any of a number of substances, such as interferon, interleukin, and growth factors, that are secreted by certain cells of the immune system and cause inflammation

[13]Immunocomplexes – complexes formed between an antigen and an antibody

[14]Myosin – a fibrous protein that forms half of the contractile filaments of muscle cells; involved in motion in other types of cells

[15]Tropomyosin – a protein involved in muscle contraction; related to myosin and occurs together with troponin in the thin filaments of muscle tissue

[16]VCAM-1 – mediates both adhesion and signal transduction

[17]Keratinocytes – an epidermal cell that produces keratin

[18]Ligand – a molecule that binds to another molecule

[19]Protein factor H – a complement control protein; regulate the Alternative Pathway of the complement system; ensures that the complement system is directed towards pathogens or other dangerous material and does not damage host tissue

[20]Fibrinogen – a soluble protein present in blood plasma, from which fibrin is produced

[21]Monoclonal antibodies – an antibody produced by a single clone of cells or cell line; consists of identical antibody molecules

[22]Vimentin – a major intermediate filament with roles in cell adhesion, migration, and signaling

[23]Human leukocyte antigen – helps the immune system distinguish the body's own proteins from proteins made by foreign invaders, such as viruses and bacteria

[24]Superantigens – a class of antigens that cause non-specific activation of T-cells resulting in polyclonal T cell activation and massive cytokine release

[25]Accessory cells – any of various cells of the immune system that interact with T cells in the initiation of the immune response

[26]Jurkat cells – an immortalized line of human T lymphocyte cells that are used to study acute T cell leukemia, T cell signaling, and the expression of various chemokine receptors susceptible to viral entry

[27]Tumor Necrosis Factor (TNF)-α – a major pro-inflammatory cytokine involved in early inflammatory events; triggers a series of various inflammatory molecules

<center>**Chapter 2 Literature Review**</center>

<center>***Streptococcus pyogenes* and ARF**</center>

Streptococcus pyogenes (GAS) is a Gram-positive extracellular bacterial pathogen that colonizes the throat or skin (Cunningham, 2000). These bacteria produce a variety of pyogenic[1] infections involving the mucous membranes, tonsils, skin and deeper tissues, which in turn cause diseases such as pharyngitis, impetigo, necrotizing fasciitis, and scarlet fever (Cunningham, 2000). GAS also plays a significant role in the development of post-streptococcal infection sequelae, such as ARF, acute glomerulonephritis, and reactive arthritis. Of these, ARF and RHD have been shown to be the most serious autoimmune sequelae caused by a GAS infection (Cunningham, 2000). ARF results from the production of autoreactive antibodies and T cells that cross-react with components of the GAS and host tissues, specifically in the heart (Cunningham, 2000).

Pathogenesis of *S. pyogenes* in ARF

The pathophysiological model of this disease begins with a pharynx infection caused by *S. pyogenes*. This bacterium bears epitopes that are similar to the structures of cardiac and skeletal muscles (molecular mimicry), which means they are cross-reactive, or recognize both human and bacterial epitopes (Azevedo et al., 2012). This cross-reactivity is initially fought by the innate immune system, which employs the mannose-binding lectin (MBL) pathway (Azevedo, et al., 2012). MBL is an innate pattern-recognition collectin[2], an acute phase protein, that binds to N-acetylglucosamine[4] (GlcNAc) (or surface sugar) in the streptococci cell wall, which is similar in structure with the laminin[3] in the heart (Reason, Schafranski, Jensenius & Steffensen, 2006; Ramasawmy et al., 2008; Schafranski et al., 2008). Toll-like receptors[5] (TLRs) and ficolins[6] (FCNs) in innate immunity also play a role in mediating inflammatory reactions

against GAS infections. TLRs have the responsibility to mediate inflammatory reactions against a wide variety of pathogens by binding to bacterial sites that are broadly shared by pathogens (Azevedo et al., 2012). It has been previously reported that TLR-2 interacts with the lipoproteins[7], peptidoglycan[8] and lipotechoic acid[9] structures found on the surface of *S. pyogenes*, which then initiates an immune response (Berdeli et al., 2005). On the other hand, FCNs are pattern-recognizing proteins that bind to bacterial cells, which then activates the innate immune response by either binding to collectin cellular receptors or initiating the complement[10] lectin pathway (Azevedo et al., 2012).

The innate immune system, which was triggered when the bacterial cells stimulated various immune system components, then activates the immune components of the adaptive immune system, causing the body to increase the production of proinflammatory[11] cytokine[12] and antibodies. Cytokines that are often involved in inflammation include interleukin-1 (IL-1), IL-6, and TNF-α (Azevedo et al., 2012). The over production of cytokines via this reaction then furthers the inflammatory process and expands the lymphocytes. For example, rheumatoid arthritis manifests in the joints due to antibodies precipitating into immunocomplexes[13] and activating complement, which causes inflammation to occur (Azevedo et al., 2012). Autoimmunity is then triggered via molecular mimicry, producing autoantibodies that target both bacterial and human cells. Autoantibodies act against cardiac structures, mainly myosin[14], laminin, and tropomyosin[15], by promoting the adhesion molecule vascular cell adhesion protein 1 (VCAM-1[16]) to recruit monocytes and macrophages that are also proinflammatory in nature. (Azevedo et al., 2012).

Colonization

For infection to take place, *S. pyogenes* must adhere and colonize the skin or the throat.

Colonization is described in the literature as a weak interaction with the mucosa at first, followed

by a second adherence event that confers specific tissue specificity and high-avidity adherence

(Hasty, Ofek, Courtney & Doyle, 1992). The initial reaction is potentially between lipoteichoic

acid (LTA) and the host cells, since it can recognize a wide range of molecules, and the second

adhesion event is dependent on which proteins are involved. Schrager et al. (1998) found that the

role of the M protein, a major virulence factor for ARF, in the second step of adhesion is

dependent on the serotype and host cell source. M protein types 6 and 24 were shown to adhere

to keratinocytes[17] in skin cells, but not type 18 M protein. The authors hypothesized that these

proteins expressed a ligand[18] that attaches to external skin keratinocytes, but not ones taken from

the oropharynx (Schrager et al., 1998). Environmental factors expressed in the respective areas

of the body may also be important cues for which adhesion molecules need to be expressed for

survival (Cunningham, 2000). This provides evidence that GAS which invade the skin are

different than those that cause pharyngitis.

Virulence Factors of *S. pyogenes*

M protein

The major virulence factor that determines how disease progresses after a GAS infection

is the M protein. Eighty M proteins have been identified, and there exists over 180 different M

serotypes defined by M protein gene (*emm*) typing (Chang, 2012; Cunningham, 2012). The M

protein is directly involved in the pathogenesis of *S. pyogenes* with different M serotypes

translating into different degrees of virulence (Chang, 2012). This protein is located on the

surface of the cell wall and cell membrane of the bacteria, and binds to complement regulatory

protein factor H[19] and fibrinogen[20] (Chang, 2012). Binding to protein factor H activates the

bacteria's antiphagocytic properties, but binding to fibrinogen activates the complement/contact

pathways, depending on how severe the infection is (Chang, 2012). Activating the immune

system produces cytokines, which are responsible for the wide-spread inflammation that is

associated with ARF.

Through investigating outbreaks of ARF, 16 M proteins have been shown to be

associated with the disease: M1, M3, M5, M6, M11, M12, M14, M17, M18, M19, M24, M27,

M29, M30, M32 and M41 (Cunningham, 2000). Of these, Type M1 and M3 are the most

commonly associated with rheumatic fever (Cunningham, 2000). In 1989, it was shown that

there were two distinct classes of streptococcal M proteins; serotypes that were often associated

with ARF shared a surface exposed antigenic domain that was localized on the C repeat block of

the M6 protein (Bessen & Fischetti, 1989). The repeat in this conserved antigenic domain is said

to be present in M proteins that cause ARF and is missing in strains with M proteins that do not

cause ARF, providing further evidence that these two groups have different virulence properties

(Bessen & Fischetti, 1989). In addition, there are certain *emm* types that are more rheumatogenic

than others (Stollerman, 1991). Analyzing strains of bacteria during outbreaks in the United

States showed that the most common emm subtypes associated with ARF were M types 1, 3, 5,

6, and 18 (Smoot et al., 2004). To further support this, studies have shown that M serotypes 2,

49, 35, 40, 60, and 61 are associated with pyoderma and glomerulonephritis while serotypes 1, 3,

5, 6, 14, 18, and 19 and 24 are associated with pharyngitis and rheumatic fever (Bisno, 1995a;

Bisno, 1995b; Stollerman, 1997;).

The M protein is a strong virulence factor because this protein has a high rate of

molecular mimicry. This protein has an alpha-helical heptad with a repeating structure that

resembles human proteins like tropomyosin, vimentin, laminin and keratin (Cunningham et al., 1992; Cunningham et al., 1993; Fenderson, Fischetti & Cunningham, 1989; Manjula & Fischetti, 1986). Though exact pathogenesis has not been determined, it appears that the cytotoxic antibodies recognize epitopes on the surface of heart cells, and once they interact they cause damage (Gulizia, Cunningham & McManus, 1991; Gulizia, Cunningham & McManus, 1993). In 2000, a study conducted by Galvin and colleagues showed that anti-GlcNAc/anti-myosin monoclonal antibody[21] (mAb) 3.B6 from rheumatic carditis patients were cytotoxic to human endothelial cell lines and reacted with human valvular endothelium and its underlying basement membrane (Galvin, Hemrick, Ward & Cunningham, 2000). The other important feature of this mAb is that it also reacts with the protein laminin, which may explain its reactivity with the valve surface. The authors determined that this data supports the hypothesis that cross-reactivity in carditis association with ARF causes injury at the endothelium and the underlying matrix of the valve (Galvin et al., 2000). The T-cell response to M proteins has also been investigated regarding its role in the immune response to *S. pyogenes* in ARF patients, with evidence suggesting that cytotoxic T-cells are stimulated by M proteins, which causes the T-cells to attack and damage the heart (Dale & Beachey, 1987; Hutto & Ayoub, 1980).

Molecular Mimicry

Molecular mimicry between GAS and host antigens is the main mechanism for the development of manifestations of ARF (Galvin, Hemric, Ward & Cunningham, 2000). This phenomenon is the sharing of epitopes between different antigens, in this case between GAS and the host (Cunningham, 2000). The main protein that has been researched regarding its cross-reactivity with cardiac muscle is the M protein. When the crystallized GAS M1 protein was evaluated, it showed how the alpha helical coiled-coil structure and epitopes of the protein are

recognized in alpha helical proteins by host cells, causing cross-reactivity between GAS and cardiac myosin (McNamara et al., 2008). The authors found that mutations in the M1 protein, which produces the alpha helix shape, stabilized the shape and diminished the virulent proinflammatory and cardiac myosin cross-reactive properties of the M1 protein, which is opposite of what is normally expected. However, it must be emphasized that what allows the function of the M protein to bind to the cross-reactive sites and the subsequent inadvertent production of antibodies is the irregularities that are found in the M protein structure.

Autoantibodies

The presence of autoantibodies against the heart have shown to be associated with ARF since 1945 (Cavelti, 1945). Then in 1964, antibody and complement complexes were reported to be deposited in the hearts of patients with RHD (Kaplan, Bolande, Rakita & Blair, 1964). These anti-heart antibodies persisted in patients with rheumatic reoccurrences but did decline after the initial episode. When it was demonstrated that anti-heart antibodies could be absorbed from human sera by GAS or their cell walls or membranes, it was the first indication that these antibodies reacted with GAS (Kaplan, 1963; Kaplan & Suchy, 1964; Kaplan & Svec, 1964; Zabriskie & Freimer, 1966). Sera from these patients reacted with heart and skeletal muscle (Zabriskie, 1967). With the use of mAbs, it was discovered that myosin was the autoantigen in the heart and streptococcal cross-reactive antigens were present in both the cell walls and the membranes of the bacterium (Barnett & Cunningham, 1990; Barnett, Ferretti & Cunningham, 1992). In addition, these same mAbs have been shown to also recognize streptococcal M protein (Dale & Beachey, 1985; Dale & Beachey, 1986; Dale & Beachey, 1987). Antibodies that react towards the GlcNAc in the cell walls of streptococci display cross-reactivity against laminin,

cardiac myosin, and vimentin[22], which results in the phenomenon of molecular mimicry (Cunningham, 2000).

Human Leukocyte Antigen mechanisms

Though the mechanism for the association of human leukocyte antigens[23] (HLAs) and ARF is unknown, there are two theories that exist as to what the relationship may be (Bryant et al., 2009). One theory postulates that similarities exist between the GAS antigens causing ARF and the HLA molecules. Support for this theory was found when investigators discovered that anti-streptococcal serum caused significantly increased toxicity to B lymphocytes with HLA-DR4 containing cells compared with DR4 negative lymphocytes (Rajapakse et al., 1990). They suggested that what led to the defective B-cell antigen presentation was the strong antigenic similarity between HLA-DR4 and the streptococcal antigen. The defect in the antigen presentation then leads to aberrant cytokine production and antibody formation against proteins on heart valves, myocardium, brain, and joint tissue (Galvin, Hemric, Ward & Cunningham, 2000). However, this pathway exists in both ARF patients and the controls, which does not accurately describe the progression of the disease in some individuals. The second theory is that structural similarities cause GAS antigens to mimic HLA molecules, which in turn initiates an over abundant immune response (Kil, Cunningham & Barnett, 1994). MHC class II antigens, like HLA, has a structure that contains both an alpha and a beta chain (Paul, Schwartz, & Datta, 1989). Kil, Cunningham and Barnett (1994) showed that the beta chain of HLA was similar to the 67-kDa streptococcal protein they used as their GAS antigen. In addition, they found that all the ARF serum tested reacted strongly with the antigen. This suggests that there is cross-reactivity between this antigen and MHC class II molecules.

More recently, another theory has been suggested. After binding to the antigenic peptide, the HLA complexes involved may initiate an inappropriate T-cell activation (Fae et al., 2005). This model posits that the HLA complex on the surface of the antigen presenting cell presents the streptococcal peptide to peripheral T-cells that have escaped immune tolerance. The peptides recognize and then activate the T-cells (Fae et al., 2005). They then cross-react with similar self-antigens that are unable to identify as self, which then initiates an immune response. The same study provided further evidence for this theory, describing an immunodominant peptide in the M5 protein that was bound to HLA-DR53 (Fae et al., 2005). This protein was recognized by an infiltrating T-cell clone, suggesting that the peptide presents itself to cells.

It is important to note the gap in years since these theories have been published and the year that this information is presented in this article. The mechanisms that have been described previously are all viable theories as to the pathogenesis of ARF, however, nothing has been ruled out or studied further to the author's knowledge. However, it should be emphasized that *in vivo* research should be conducted to determine the real-time processing of the M protein molecule during active infection (Wang et al., 1993). This would help establish a consensus as to which of these theories, or if all of them, accurately describe the pathogenesis of *S. pyogenes* during an ARF attack.

Superantigen[24]

In 1990, it was still thought that since the effects of the M protein on large populations of T cells did not parallel classical T cell epitope activation like conventional antigens, that this protein could possibly be a superantigen (White et al., 1989). To test this, one study evaluated the possible superantigenic properties by using Pep M5 to stimulate highly purified human peripheral T cells with or without the presence of accessory cells[25] (ACs) (Tomai et al., 1990).

They found that although MHC class II molecules were required for the presentation of the antigen, there was no MHC restriction evident. After binding to MHC class II molecules, M5 stimulates T cells bearing $V\beta$ 8 sequences (e.g. Jurkat cells[26]), which is a location that is known to bind with other superantigens, indicating that M5 is a superantigen (Fleischer, Schrezenmeier & Conradt, 1989; Kappler et al., 1989; Tomai et al., 1990). To date, it has been determined that pep M5 is a superantigen to human T cells bearing $V\beta2$, $V\beta3$, and $V\beta8$ elements (Tomai et al., 1991). Another study conducted by Kotb and colleagues (1990) showed that if the M5 protein was immobilized or cross-linked, it had the ability to stimulate Jurkat cells, but not normally purified human T cells, to produce the cytokine IL-2.

Risk Factors

Though there is limited research on the risk factors, there are three elements that are thought to be responsible for ARF and RHD: host genetic susceptibility, virulence factors of *Streptococcus pyogenes* and environmental factors such as poverty, household overcrowding, low educational attainment, poor nutrition, and reduced access to medical care (Baroux et al., 2013; Steer et al., 2002). Studies have shown that incidence rates of ARF are not only higher in developing countries but are also higher among minority populations in higher income countries, such as Aboriginal communities in Australian's Northern Territory, the Hamilton and Maori populations in New Zealand, and Samoa populations in the South Pacific (Steer et al., 2002). However, it is unclear if the differences between ethnic groups are attributed to streptococcal exposure, clinical and major manifestations of ARF, treatment of infection, or genetic susceptibility (Carapetis & Currie, 1996; Carapetis, Currie, & Matthews, 2000).

22

Genetic Susceptibility

Just as not all GAS strains are capable of causing ARF, not everyone is susceptible to contracting ARF (The Australian Guidelines, 2015). Research suggests that approximately 3-5% of individuals in any population have an inherent susceptibility to ARF, but the cause of this is unknown (Carapetis, Currie, & Matthews, 2000). Before diagnostic criteria had even been revised, family studies suggested that ARF could be familial, but the unknown genetic factor was thought to be autosomal recessive and had limited penetrance (Wilson, Schweitzer & Lubschez, 1943). A few decades later, twin studies showed that both twins did not usually develop ARF and lower than expected concordance indicated that it is not a simple mendelian single-gene inheritance (Taranta et al., 1959). The fact that both twins did not usually develop ARF also provides evidence that an environmental factor plays a role in the susceptibility of this disease. If it had solely been genetic, then both twins would get ARF. However, a meta-analysis in 2011 looked at twin pairs to estimate the heritability of ARF and found that the pooled proband-wise concordance risk for ARF was 44% in monozygotic twins and 12% in dizygotic twins (Engel et al., 2011). These results showed that the risk of ARF in a monozygotic twin with a history of ARF, the co-twin has an increased risk of ARF by more than 6 times compared to that of dizygotic twins. With the heritability estimate at 60%, there is evidence that shows the importance of genetic factors in ARF (Engel et al., 2011).

It is unlikely that a single gene is responsible for how the host responds to the pathogenesis of GAS (Bryant et al., 2009). ARF potentially involves different bacterial antigenic triggers, differences in humoral and cellular immune responses, and differences in what areas of the body are damaged. Although strong associations exist between susceptibility and disease, genetically susceptible individuals do not invariably develop ARF after exposure to rheumatic

strains of GAS (Kuttner & Krumwiede, 1941). During their investigation of 3 outbreaks of ARF with different types of *S. pyogenes* at a sanitarium, Kuttner & Krumweide (1941) found that the incidence of recurrences varied greatly. The first outbreak had a recurrence rate of 50%, the second had no recurrences recorded, and the third had a very small amount of recurrence occur. However, no differences were found between the effective and non-effective strains when they were compared (Kuttner & Krumwiede, 1941). This could reveal that certain combinations of genes and environmental factors are needed for the progression of a pharyngeal infection to ARF.

Immune System

Genetic susceptibility to ARF is no surprise considering autoimmune and rheumatic type diseases are often associated with susceptibility related to expression of a particular MHC antigen phenotype (Cunningham, 2000). Major histocompatibility antigens and potential tissue-specific antigens are under investigation to show if there are potential risk determinants associated with ARF (Cunningham, 2000). Different HLA class II antigens have been found to be associated with ARF and no associations have been found between HLA class I antigens (Ayoub et al., 1986; Azevedo et al., 2012). No single HLA haplotype or combination exists that is consistently associated with susceptibility (Bryant et al., 2009). Also, some studies have found that only particular clinical features of ARF are associated with HLA. For example, one study found a significant association between HLA-A10 and HLC-DR11 in individuals with carditis, but not with those without carditis, who had higher frequencies of HLA-C2 (Ölmez et al., 1993). However, the association may manifest, differences exist between these antigens and ethnic groups.

The HLA-D7 is the most frequent HLA to be associated with ARF among populations (Guilherme & Kalil, 2010). As research in this field has expanded, more HLAs have been shown to be associated with ARF. There is a higher frequency of HLA-DR4 in Caucasian patients with ARF and higher frequencies of HLA-DR2 in African American populations with ARF (Ayoub, Barrett, Maclaren & Krischer, 1986). In another study, South African populations with ARF were shown to have higher rates of HLA-DR1 and HLA-DRw6 (Maharaj et al., 1987). In Brazilian populations, it was shown that individuals with ARF have an increased frequency of HLA-DR7 and HLA-DRw53 (Guilherme et al., 1995). Conflicting associations of HLA phenotypes and ARF between ethnic groups provides evidence that MHC associations in ARF are more complex than originally believed (Cunningham, 2000). This also provides evidence that different strains are responsible for the development of ARF in different countries (Azevedo et al., 2012).

A non-HLA B-cell marker used to identify ARF patients has also been studied, providing 100% accuracy in diagnosing ARF in the United States (Khanna et al., 1989; Patarroyo et al., 1979). This marker is known as D8/17 or 883 and is so accurate because Mab D8/17 reacts with 33 to 40% of B cells from patients with a history of ARF compared to only 5 to 7% in patients without a history of ARF (Khanna et al., 1989). The highest percentage of positive cells were found in probands with ARF (33.5%), with unaffected siblings having 2.96% and parents having 3.86% positive cells. These results are consistent with an autosomal recessive mode of inheritance, which is consistent with previous research. Another study that looked at this same marker in an Aboriginal Australian population showed similar results (Harrington et al., 2006). The mean proportion of D8/17-positive B cells was 39.3% in previous ARF cases, 22.5% in first degree relatives, and 83.7% in patients with current ARF.

However, this B cell marker does not seem to be this robust in all populations. Though the percentage of positive cells was higher among all ethnic groups, one study found that only 66% of North Indians with ARF were found to test positive for D8/17 cells (Kaur et al., 1998). The authors developed a new Mab called PGI/MNII to test as a potentially more accurate B-cell marker on North Indians with ARF. This Mab reacted with samples from 86% of North Indians with ARF, suggesting that there may be differences in B-cell markers between ethnic groups. To further explore this association in the North Indian population, Kumar, Kaul, Grover and Ganguly (2000) found that the antibodies PG-12A, PG-13A, and PG-20A were found in higher amounts compared to controls. There were approximately 90% rheumatic fever patients positive with these monoclonal antibodies compared to only 4% of controls. This suggests that stratifying by ethnic group is required when using markers to identify individuals who have had or currently have ARF.

Gene Polymorphisms. There have been several studies that examine the role of polymorphisms in the promoter region of Tumor Necrosis Factor-α[27] (TNF-α). It has been shown that associations exist between RHD and Mexican individuals, both in allele (TNF-α-308A and -238G) and genotype (Hernandez-Pacheco et al., 2003). Another association was found with valve damage, but the specific valve affected showed no association. Further supporting evidence was found in Brazilian ARF individuals who also had an increased number of TNF-α-308A polymorphisms (Ramasawmy et al., 2007). However, an Egyptian study found that this was only true in individuals that were homozygous for the TNF-α-308A gene (Settin, Abdel-Hady, El-Baz & Saber, 2007). The authors also found evidence of a higher number of the *TNF-α-238* gene, but it was the A allele, not the G allele. On the other hand, a Turkish study found no association between TNF-α polymorphisms and ARF (Settin et al., 2007).

Few other gene polymorphisms have been studied in association with ARF. One study found an association between immunoglobulin *Fcγ-RIIA* polymorphisms and susceptibility to ARF (Berdeli, Celik, Ozyurek & Aydin, 2004). They suggested that a possible mechanism for this association was that this polymorphism caused an inability of the immune system to remove immune complexes that ultimately cause the damage associated with this disease. Another study evaluated the association between T-cell polymorphisms and the development of RHD. The authors found no associations between polymorphisms in T-cell α- and β-chains and RHD when looking at Maori and Caucasian populations (Abbott et al., 1995). Toll-like receptor (TLR) polymorphisms have only recently been studied, but it has been shown that TLR-2 receptor has a strong association with ARF in children (Berdeli et al., 2005).

The contradictory results in both cases discussed previously indicate that it is still unclear if these polymorphisms are related to ARF susceptibility. In addition, other polymorphisms may exist that have not been studied to date. On the other hand, these results could also suggest that just the presence of a genetic polymorphism alone is not enough for an individual to develop ARF. It may be that genetic polymorphisms in TNF-α or *Fcγ-RIIA* must be paired with other genetic susceptibilities, such as HLA, or with various environmental factors that are thought to be associated with ARF.

Gender

Gender has not always been considered a risk factor for ARF because most evidence suggests that this disease occurs equally between males and females (Karaaslan, Oran, Reisli & Erkul, 2000; Olgunturk, Canter, Tunaoglu & Kula, 2006; Örün et al., 2012). However, research has shown conflicting evidence for this. Some studies have shown that males have up to a 1.4 times higher risk of contracting ARF compared to females (Breda et al., 2012; Quarshi, 2009). In

addition, another study found that a similar risk for males, and this association remained after stratifying by ethnicity (RR: 0.80, 95% CI: 0.70-0.93; Gurney, 2015). However, the authors did not hypothesize as to why this association occurred. In contrast, female preponderance for ARF has been suggested in Australian populations (Hanna & Clark, 2010).

Environmental Factors

ARF was once considered a disease of temperate climates, but is now more common in tropical areas and developing countries since it was rarely seen elsewhere (Steeg, Walsh & Glickstein, 2000). With few exceptions, most racial or ethnic differences in incidence are attributed to low socioeconomic status (SES), poor housing, and overcrowding (Quarashi, 2009). SES has been the longest assumed environmental influence on ARF (Steer, Carapetis, Nolan & Shann, 2002). In two large Northern Territory Aboriginal communities where ARF is endemic, extreme levels of overcrowding was found. The median number of individuals per house was 17 and 14 and a median number of individuals per bedroom of 6.9 and 7.5, respectively (Brown et al., 2007; McDonald et al., 2006). In a small town in the Democratic Republic of Congo, children living in households with more than 8 individuals had an increased risk of RHD (Longo-Mbenza et al., 1998). However, evidence for the association between overcrowding and ARF is not always consistent. In Serbia, overcrowding has not been found to be associated with ARF (Adanja, Vlajinac & Jarebinski, 1988). This suggests that overcrowding and its relationship to ARF are more complex in how populations contract ARF and how the disease progresses, or may act as a confounder since it can occur in both rural and urban areas.

Rurality has also been suggested to be a risk factor for ARF, but the evidence is conflicting. Urban areas have been thought to be a risk factor for ARF because of overcrowding, and often these places have poor sanitation and hygiene practices (Chagani & Aziz, 2002; Steeg,

Walsh & Glickstein, 2000). Gurney et al. (2015) found that rurality had a somewhat protective effect; those that lived in rural areas were nearly half as likely to sustain ARF compared to those living in urban areas. However, a study conducted in India has shown that there is a rural predilection in diagnosed ARF cases, which was accompanied by high amounts of overcrowding and all cases came from a low SES status (Ramu & Shankar, 2015). Indigenous Australian populations are known for having the highest incidence rate, and they often live in remote or rural areas (Noonan et al., 2013). This provides evidence that there must be set environmental conditions and host susceptibility, taken into geographical context, might be what causes ARF to manifest.

Access to medical services is a risk factors to those who live in rural areas or those who have low SES and may not have health insurance. Poverty leads to delayed access to medical care, which means children are not receiving the appropriate care and timely antibiotics (Chagani & Aziz, 2002). In addition, living in remote or rural areas also increases the likelihood that health services are not able to be used. Smith et al. (2011) stated that their evidence supported the claim that delayed presentation to a hospital by children in rural and remote areas is a significant cause of delayed treatment and an increased risk for more severe symptoms of ARF. In addition, the authors showed that it is almost guaranteed that if the individual lives in an area where there is access to medical care (i.e. urban areas) that they will have an early diagnosis.

Overall, it is unlikely that there is only one environmental factor that puts an individual at a higher risk of developing ARF, but rather an association, or an interaction, of many factors. For example, living in a remote or rural region may mean that there is limited access to health care, that the family has an issue with overcrowding and poor housing conditions, and have a low

SES. If a household contains these risk factors, or only certain ones, it can cause variations in the risk across populations.

Diagnostic Criteria

The diagnostic criteria for ARF was originally created by Dr. T. Duckett Jones in 1944 to remedy the over diagnosis of ARF in the United States and has remained the benchmark for diagnosis for the past 70 years (Hajar, 2016; Seckeler & Hoke, 2011). These criteria are based on signs and symptoms that are often associated with this disease and are known as major and minor manifestations. Major and minor manifestations were separated into different categories, which was based on the diagnostic importance of a finding (Dajani et al., 1992). If there is evidence of a preceding GAS infection via a rapid strep test, the presence of two major manifestations or one major and two minor manifestations indicate a high probability that the individual has ARF (AHA, 1992). If there is no evidence of a preceding infection, then ARF is considered to be unlikely in that individual. Major manifestations consist of carditis, arthritis, subcutaneous nodules (SN), erythema marginatum (EM), and chorea. Minor manifestations include fever, arthralgia, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, and prolonged PR interval on an electrocardiogram. The PR interval is the onset of the P wave in an echocardiogram to the start of the QRS complex, and when this is prolonged (i.e. greater than 200 ms) it is indicative of a first-degree heart block (Cheng et al., 2009). This blockage causes damage to the heart, which is a hallmark of ARF.

In 1992, an update to the Jones Criteria established the initial attack in ARF, expanded on the available tools for diagnosis and clarified the available antibody testing for detecting GAS infections (American Heart Association [AHA], 1992). However, when applying these guidelines, the diagnosis is often missed in some populations (Hajar, 2016). In addition, since

these criteria were first developed, our knowledge of the global epidemiology and its variable presentation have changed. Due to the dangers of the sequalae, modifications have been made by the American Heart Association in 2015 to take current epidemiology and evidence supporting echocardiography in the diagnosis of carditis, instead of electrocardiography (Gewitz et al., 2015). Even though there have been updates to increase the sensitivity of the criteria, diagnosis has proven to be difficult, especially in regions where incidence is high (Eroğlu, 2015).

Before 2015, the diagnosis of ARF was most commonly conducted using the 1992 modified Jones Criteria that consists of major and minor manifestations that occur when this disease is acquired (Eroğlu, 2015). When this update was released, there was still no single symptom, sign, or laboratory test that could be used to diagnose ARF, and this is still true today (AHA, 1992; Kumar & Tandon, 2013). In addition, this update was only designed to establish the diagnosis in those who have an initial attack and was not designed to include individuals who had previously had the disease and have a recurrent attack (AHA, 1992).

Even though more individuals were better able to be diagnosed when these guidelines were introduced, there are three circumstances in which ARF diagnosis does not entirely fit (AHA, 1992). Chorea, and in some cases insolent carditis, may be the only manifestation that occurs in an individual who has ARF. In both these cases, individuals often seek medical attention months after initial onset of disease, thus presenting with insufficient evidence to fulfill the criteria (AHA, 1992). The third circumstance is when an individual has a recurrent attack (e.g. a new episode in an individual with a previous history), because these cases can be less apparent. A key example is that evidence of carditis is difficult to establish in these individuals unless a different valve is affected in the recurrent compared to the initial attack, or pericarditis is present (AHA, 1992). Thus, diagnosis must be made with caution when using these criteria.

In 2006, the National Heart Foundation of Australia (NHFA) and the Cardiac Society of Australia and New Zealand (CSANZ) drafted guidelines for the diagnosis and management of ARF and RHD (Carapetis, Brown, Wilson & Edwards, 2007). Revisions included the development of high and low risk groups and the addition of subclinical carditis (SCC), polyarthralgia, and aseptic mono-arthritis as major manifestations. The new diagnostic criteria created for high and low risk groups was based on evidence suggesting that ARF is observed more commonly among Australia and New Zealand's native and indigenous populations (Carapetis et al., 2007). Thus, high risk groups include individuals living in communities with an incidence of ARF of more than 30 per 100,000 per year in those aged 5 to 14 years, and low risk groups include all other groups in the population. Differentiation between initial and recurrent episodes of ARF was also established in this update. For both high and low risk groups, the diagnosis of ARF includes 2 major OR 1 major and 2 minor manifestations, PLUS evidence of a preceding GAS infection (Carapetis et al., 2007). The diagnosis of recurrent attacks of ARF was also the same for both high and risk groups, with an individual needing 2 major OR 1 major and 2 minor manifestations OR 3 minor manifestations, PLUS evidence of a preceding streptococcal infection.

Even though the diagnosis of ARF is the same between these groups, the major and minor manifestations used to diagnose individuals varies between high and low risk groups. Evidence of polyarthralgia or aseptic mono-arthritis is included as a minor manifestation for individuals in low-risk groups, but it is considered a major manifestation for individuals in high risk groups (Carapetis et al., 2007). The diagnosis of carditis in ARF patients in high risk groups must include subclinical evidence of rheumatic valvular disease on an echocardiogram, or subclinical carditis, but is not needed when diagnosing carditis in low risk groups. Even with

these changes, under diagnosis of ARF, especially in Australia, was still a primary concern (Carapetis et al., 2007).

The next major update was developed by the NFHA in 2015. Among the most important changes made to the document was a new definition for Probable ARF, a definition change to recurrent episodes of ARF, and expansions on the sections for echocardiography and subclinical carditis (The Australian Guidelines, 2015). In addition, there were several major changes made to the diagnosis of ARF in definite cases, including: (1) the ability to diagnose recurrent cases of ARF that occur in high-risk groups with only one major PLUS one minor manifestation, (2) the inclusion of mono-arthralgia as a minor manifestation in high-risk individuals, (3) classifying fever as a minor manifestation based on the availability of reliable history of the use anti-inflammatory medication in the individual (The Australian Guidelines, 2015). Adding echocardiography to the criteria did not mean that it was mandated, since endemic countries often cannot afford this technology. Ideally, these countries need access to echocardiography, but it costs 40 times as much as an electrocardiogram. This may be easier for countries like Australia, where they have a national healthcare program that covers 75% of general practitioners, 85% of specialists and 100% of public in-hospital costs, but not for countries where healthcare is not universal (Australian Institute of Health and Welfare (AIHW), 2012). These changes make the Jones Criteria less restrictive in its diagnosis towards certain high-risk groups that may have atypical or delayed presentations, such as the Indigenous population in Australia and New Zealand.

The importance of these changes can be seen when exploring the literature focused on indigenous populations. One study looking at Australia's Northern Territory found that 31% of individuals with suspected ARF had a range of presentations that did not fit the Jones Criteria

33

(Ralph et al., 2006). The authors suggested the creation of probable and possible cases of ARF to capture this group and to provide them with the correct dose of antibiotics for treatment, which was taken into consideration in this revision. A probable ARF can be either highly-suspect or uncertain, can happen in an initial or a recurrent attack, and is defined as an individual whose clinical presentations fall short by either one major or one minor manifestation or does not have a positive serology result, but ARF is the most likely diagnosis (The Australian Guidelines, 2015). Delayed presentation and incomplete investigation of clinical testing can also cause cases to fall within this group of individuals.

After the Australian Guidelines had been published, the American Heart Association created another update to the Jones Criteria. The addition of high and low risk population groups to the Australian Guideline directly influenced the creation of the low-risk and moderate- to high-risk populations in this update (Gewitz et al., 2015). Any populations with an ARF incidence of $\leq 2/100,000$ in school age children and RHD prevalence of $\leq 1/1,000$ at all ages were defined as low-risk populations and all others were defined as high-risk populations (Eroğlu, 2015). This update also included initial and recurrent attacks and possible cases of ARF, with the same definitions and manifestations as those used in the Australian Guidelines (Gewitz et al., 2015).

Purpose of Current Study

The aim of this meta-analysis is to first calculate the global incidence of ARF and identify the frequencies of major and clinical manifestations and risk factors globally. The second aim of this study is to further explore incidence, major and clinical manifestations and risk factors by looking at differences between populations. Robustness of the study will also be explored by comparing data between diagnostic methods. This can provide a better indication of

the burden of disease and provide additional information on the dispersion of manifestations and risk factors to offer insight towards possible revisions to the Jones Criteria that can result in increased sensitivity in classifying ARF cases compared to other updates.

Chapter 3 Methods

The review protocol has been registered in the systematic review registry on PROSPERO in January 2018 (registry CRD42018080673).

Criteria for considering this meta-analysis

Studies

For articles to be included, they had to have contained calculations of incidence of ARF. Articles could also have information pertaining to the frequencies of risk factors and clinical and major manifestations of ARF. Studies had to be written in English, be published after 1990, and the populations evaluated had to have been done so after 1990.

Participants

To be included in the review, participants in the studies had to have been assessed or evaluated for the study using the Jones Criteria 1992 update, the associated ICD 9/10 code, the 2015 Jones Criteria update (Dajani et al., 1992; Eroğlu, 2016) or any variation of the Australian Guidelines for the diagnosis of ARF (Carapetis et al., 2007; Eroğlu, 2016). The ICD 9 & 10 are the hospital billing codes associated with ARF that directly correspond to the 1992 Jones Criteria Revision (Eroğlu, 2016). These codes included: 390-398 from the ICD-9 and ICD I0.0-I09.9 from the ICD-10 (Aato-Carr et al., 2008; Beaudoin et al., 2015; Milne et al., 2012; Smith et al., 2011). The age range of all the participants were between 0 and 19 years of age, and were from any ethnicity or nationality.

Types of Outcome Data

Results of the included studies contained estimates for the following quantitative data: incidence, risk factors, clinical manifestations, major manifestations or any combination of these variables.

Primary Outcomes

The primary outcomes for this meta-analysis included estimates for incidence of ARF and frequencies of clinical and major manifestations within varying populations. Incidence was calculated using incidence rates. Clinical manifestations, or minor criteria, included are polyarthralgia, joint pain, fever, ESR and prolonged PR on an ECG. Major manifestations, or major criteria, included are carditis, arthritis, chorea, erythema marginatum, and subcutaneous nodules. Carditis measurements include mitral and aortic regurgitation, mitral and aortic stenosis, tricuspid regurgitation, and any combination of these measurements.

Secondary Outcomes

The secondary outcomes for this meta-analysis include risk factors for ARF. Risk factors included in the analyses are: socioeconomic status, ethnicity, gender deprivation status, and house crowding, and rurality.

Search methods for identification of studies

Manual and electronic searches were performed to collect all relevant studies, which was completed in December 2017. Only full-text peer-reviewed articles were included in the meta-analysis. All articles included in the searches and meta-analysis were published between 1990 and 2017, and are in English.

Electronic searches

Over 300 electronic databases, including PubMed, PNAS, and JSTOR were searched using the Grand Valley State University (GVSU) Library website, which is backed by Summon. The University Libraries at GVSU purposefully collect, teach, display, discover, disseminate and preserve information, in all its forms, connecting scholars and learners to resources (Grand Valley State University Library [GVSU], 2017). We additionally searched the Centers for

Disease Control and Prevention (CDC) archive for Morbidity and Mortality Weekly [MMWR] reports that included information on Acute Rheumatic Fever. Full text of articles or MMWR that could not be obtained using the GVSU library or CDC archives were obtained via Google Scholar search.

Filters used while searching for journal articles included: date rage of 1990 to 2017, journal articles, and full-text only while on the GVSU Library website. The search words that were used in Keyword searches on the GVSU Library website include: Rheumatic fever + Causes, Incidence of Rheumatic Fever, Prevalence of Rheumatic Fever, and Acute Rheumatic Fever MMWR. No keywords were used while searching for articles on Google Scholar, only the title of the article or the citation was used to search for specific papers that were unavailable through the GVSU library.

Manual Searches

The references list from all selected eligible studies from the electronic searches was used to find additional sources. The articles searched manually were then analyzed using the inclusion criteria listed above to determine if the articles could be included in the study.

Selection of studies

Studies included in the meta-analysis include cross-sectional, cohort studies and MMWRs. Cohort studies could be either retrospective or prospective observational studies.

Data extraction and management

Data extracted from the studies include estimates for incidence of ARF and frequencies and percentages from risk factors, major manifestations and minor manifestations. Data management was done in Microsoft Excel. Data analysis was performed in R version 3.4.3.

Assessment of risk of bias in included studies

Each paper included in the meta-analyses was assessed for risk of bias by a single reviewer using the NewCastle-Ottawa Quality Assessment Scale (NCOS; Wellis et al., 2014). Quality assessment was determined the tool's criteria that include the following elements: selection, comparability, and exposure. Each element has a list of criteria within them that should be present for the study to be considered minimally biased (Wellis et al., 2014). To do this, a "star" system is employed that marks whether the criteria is present within the study in question. Within the selection and exposure elements, one star can be awarded to each of the following items: case definition, representativeness of cases, selection of controls, definition of controls, ascertainment of exposure, same method of ascertainment for cases and controls, and non-response rate. Within the comparability element, two stars can be awarded to the following criteria: comparability of cases and controls and ascertainment of exposure based on the design or analysis. Each article can obtain a maximum of 9 stars through this system. The higher the star ratings in each category, the less likely bias will influence the study. A minimum score of 5 was required for the study to be considered for inclusion in the analyses, resulting in the exclusion of two articles.

Measures of incidence

Incidence was calculated using incidence rates provided from the studies when population denominator data was reported, or abstracted and calculated based on number of cases reported by the authors and populations at risk from government census websites. A linear mixed-effects model was used to calculate the pooled risk ratio for the incidence of ARF and 95% confidence intervals for all eligible studies. Linear mixed-effect models incorporate both fixed and random-effects terms in a linear predictor expression from which the conditional mean

of the response can be evaluated (Bates et al., 2014). Since this meta-analysis attempts to explore many covariates and the data points are not truly independent since they represent a group of individuals and not individuals separately, the linear mixed effects model seemed to be appropriate to use. This is because this model allows for analysis to be completed even when highly structured data has a low sample size and there are many covariates to explore (Hajduk, 2017). This method is also beneficial in cases where data points are not truly independent from one another, since the model does take this into account when pooling data.

Measures of risk factors, clinical and major manifestations

Clinical and major manifestations were abstracted and summarized using frequencies and presented in tables.

Data synthesis, assessment and investigation of heterogeneity

Heterogeneity refers to any kind of variation across studies, whether it is between patients, interventions, outcomes definitions or study design, which is important to consider when pooling data (Blend, n.d.; Ryan, 2016). Clinical and methodological heterogeneity, which refer to differences among participants and in data collection methods, respectively, was taken into consideration when synthesizing data (Ryan, 2016). Heterogeneity across studies was evaluated using the Cochrane Q χ^2 test set at a significance threshold of 10%, and the τ^2 and I^2 statistics were calculated to quantify the proportion of variance due to heterogeneity (Ryan, 2016). The same test was used when evaluating moderators, and is denoted QM. If the χ^2 value is greater than the degrees of freedom, has a low p-value and a high I^2 statistic, this indicates heterogeneity across the studies. The 'meta' package in R was used to determine heterogeneity using the 'metarate' function and the 'metafor' package in R was used to test for heterogeneity using the meta-regression function.

Sensitivity analyses

A series of sensitivity analyses were conducted to explore the robustness of the results. Meta-regression was used to examine the impact of moderator variables on the effect size of the studies and assessed the appropriateness of comparing studies based on heterogeneity. When significant heterogeneity exists, the information was not pooled. Additionally, due to a number of papers without exact population denominator values, these papers were excluded and the main analyses were replicated to account for papers in which exact population denominators could not be determined.

Chapter 4 Results

After searching through three of the search word combinations, our literature search identified 50 journal articles and MMWRs through electronic searches. Once manual references were found, 241 studies were searched and evaluated for inclusion (Figure 1).
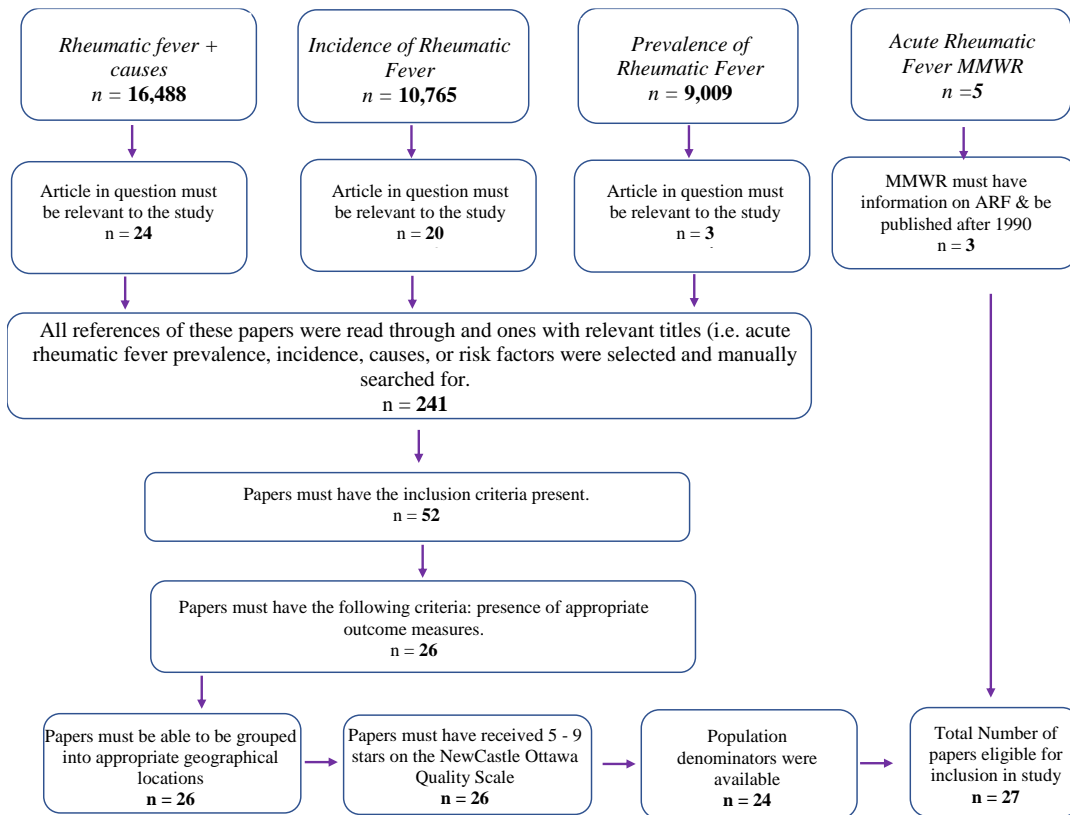
Figure 1. Article Search Flow Chart. This figure illustrates the steps taken to retrieve all relevant articles to include in the meta-analysis.

Of these, 52 articles contained the elements of the inclusion criteria. Those that included the outcome measures of interest (26) were then evaluated using the NCOS quality assessment score. All articles scored a 5 or higher, which meant they were all appropriate to include. Population denominators were unable to be calculated for two of the 26 articles due to lack of census data availability. In total, 27 studies met all inclusion criteria. Twelve (44.4%) were cross-sectional and another 12 (44.4%) were cohort studies. The median NCOS score was 6 (range 5 to 9).

NCOS scores were not required for the MMWRs since they did not contain any other information other than incidence rates, and are not considered cross-sectional nor cohort studies.

The World Health Organization's (WHO) Study regions were used to describe the geographical distribution of studies selected for inclusion: 3 from the Americas, 7 from the Western Pacific and European regions, 6 from South-East Asia, 2 from Africa and the Eastern Mediterranean Regions (WHO, n.d.). Nineteen (70.4%) of the studies included children under the age of 5. Study populations were evaluated in the 1990s (22.2%), 2000s (44.4%), or spanned both decades (33.3%). The most common diagnostic criteria used for the diagnosis of ARF was the 1992 Jones Criteria (77.8%), followed by the ICD 9 & 10 (18.5%), and the 2012 Australian Guidelines (3.7%). Characteristics of the studies can be found in Table 1.

Table 1

Characteristics of Included Studies

Article	Study Years	WHOSR	Study Design	Cases	NewCastle Ottawa Scale
Noonan et al.	2007-2010	Western Pacific	Cross-sectional	151	7
Smith et al.	2000-2008	Western Pacific	Cohort	26	5
Beaudoin et al.	2011-2012	Western Pacific	MMWR	65	5
Corsenac et al.	2012-2013	Western Pacific	Cross-sectional	38	5
Steer et al.	2005-2007	Western Pacific	Cross-sectional	24	7
Milne et al.	1993-2009	Western Pacific	Cross-sectional	1007	6
Atato-Carr et al.	1998-2004	Western Pacific	Cohort	68	5
Bavdekar	1995	Southeast Asia	Cohort	86	7
Ramu et al. (a)	2004-2006	Southeast Asia	Cross-sectional	36	6
Ramu et al. (b)	2004-2006	Southeast Asia	Cross-sectional	36	6
Routray	1991-2000	Southeast Asia	Cohort	1330	5
Zaman et al.	2005	Southeast Asia	Cross-sectional	36	5
Ahmed et al.	1991	Southeast Asia	Cross-sectional	7	5
Vinker et al.	2000-2005	European	Cross-sectional	40	6
Grassi et al.	1992-2006	European	Cohort	135	7
Breda et al.	2000-2009	European	Cohort	88	5
Kocevar et al.	2008-2014	European	Cohort	19	5
Qurashi	1994-2004	Eastern Mediterranean	Cohort	83	5
Cilliers	1993-2010	African	Cohort	207	6
Gapu et al.	2012-2013	African	Cross-sectional	16	6
Roodpeyma et al.	1992-2002	Eastern Mediterranean	Cohort	102	6

Karademir et al.	1990-1992	European	Cross-sectional	228	6
Karaaslan et al.	1993-1998	European	Cohort	274	7
Narin et al.	1998-2011	European	Cohort	624	6
Tunks et al.	1998-2008	Americas	Cross-sectional	59	5
Koo et al. (a)	1993	Americas	MMWR	69	-
Koo et al. (b)	1994	Americas	MMWR	54	-

Overall incidence rates from all 27 studies were pooled to determine the amount of heterogeneity found between studies (Figure 2).

Study	Events	Time	Events per 100000 population	Events	95%-CI	Weight (fixed)	Weight (random)
Ahmed	7	19509.00		35.88	[17.11; 75.26]	0.1%	3.6%
Atato-Carr	68	364986.00		18.63	[14.69; 23.63]	1.4%	3.7%
Bavdekar	86	2524476.00		3.41	[2.76; 4.21]	1.8%	3.7%
Beaudoin	65	23419.40		277.55	[217.65; 353.93]	1.3%	3.7%
Breda	88	2158929.00		4.08	[3.31; 5.02]	1.8%	3.7%
Cilliers	207	12890113.60		1.61	[1.40; 1.84]	4.2%	3.7%
Corsenac	38	8843.00		429.72	[312.68; 590.56]	0.8%	3.7%
Gapu	16	532403.67		3.01	[1.84; 4.91]	0.3%	3.7%
Grassi	135	471402.00		28.64	[24.19; 33.90]	2.8%	3.7%
Karaaslan	274	17112638.40		1.60	[1.42; 1.80]	5.6%	3.7%
Karademir	228	975707.00		23.37	[20.52; 26.61]	4.6%	3.7%
Kocevar	19	241192.80		7.88	[5.02; 12.35]	0.4%	3.7%
Koo(a)	69	71321886.00		0.10	[0.08; 0.12]	1.4%	3.7%
Koo(b)	54	71321886.00		0.08	[0.06; 0.10]	1.1%	3.7%
Milne	1007	552474.00		182.27	[171.35; 193.88]	20.5%	3.7%
Narin	624	6011210.00		10.38	[9.60; 11.23]	12.7%	3.7%
Noonan	151	4215683.00		3.58	[3.05; 4.20]	3.1%	3.7%
Qurashi	83	1567482.00		5.30	[4.27; 6.57]	1.7%	3.7%
Ramu(a)	36	1117571.00		3.22	[2.32; 4.47]	0.7%	3.7%
Ramu(b)	36	1117571.00		3.22	[2.32; 4.47]	0.7%	3.7%
Roodpeyma	102	444030.00		22.97	[18.92; 27.89]	2.1%	3.7%
Routray	1330	4869267.00		27.31	[25.88; 28.82]	27.1%	3.7%
Smith	26	805032.00		3.23	[2.20; 4.74]	0.5%	3.7%
Steer	24	63495.00		37.80	[25.34; 56.39]	0.5%	3.7%
Tunks	59	1476216.61		4.00	[3.10; 5.16]	1.2%	3.7%
Vinker	40	228432.00		17.51	[12.84; 23.87]	0.8%	3.7%
Zaman	36	56827.00		63.35	[45.70; 87.82]	0.7%	3.7%
Fixed effect model				19.20	[18.67; 19.75]	100.0%	--
Random effects model				8.88	[4.40; 17.93]	--	100.0%

Heterogeneity: $I^2 = 100\%$, $\tau^2 = 3.4513$, $p = 0$

Figure 2. Overall Incidence Rates of ARF among included studies.

Due to high heterogeneity in the overall model, the cause of the heterogeneity was explored in separate models by stratifying by: WHO study region, inclusion of children under the age of 5 in the study, decade the study was conducted in, and diagnostic criteria used (Appendix 1). Heterogeneity was found to be high among all stratifications (Table 2).

Table 2

Heterogeneity in the Overall Incidence Rates of Acute Rheumatic Fever

Stratification	I^2 (%)	τ^2	*p*-value
Overall	100	3.451	<0.001
WHO Study Region			
Americas	100	4.842	<0.001
Western Pacific	100	4.364	<0.001
South-East Asia	99	1.802	<0.001
European	100	1.256	<0.001
African	83	0.163	0.02
Eastern Mediterranean	99	1.066	<0.001
Age 5			
< Age 5	100	2.585	<0.001
≥ Age 5	100	3.186	<0.001
Decade			
1990	100	5.069	<0.001
2000s	99	3.566	<0.001
Spans both	100	2.310	<0.001
Diagnostic Criteria			
1992 Jones Criteria	100	2.455	<0.001
ICD 9/10	100	2.564	<0.001
2012 Australian Guidelines	N/A	N/A	N/A

Note. I^2 values of 100% were rounded.

For example, in the instance of WHO study region, the I^2 statistic was broken down for each region, ranging from 83 to 100%. This percentage represents the amount of heterogeneity between the articles in each region, and indicates how much heterogeneity is being introduced into the analysis.

Significant heterogeneity was observed via meta-regression within all strata (Table 3). The mixed effects model for WHO study region and children under the age of 5 years for overall incidence were both statistically significant, indicating that part of the heterogeneity in the true effects are related to some of these two predictors (QM = 22.148, *df* = 5, *p* = 0.0005; QM = 7.631, *df* = 1, *p* = 0.006, respectively).

Table 3

Meta-regression in the Overall Incidence Rates of Acute Rheumatic Fever

Stratification	QM	β	I^2 (%)	*p*-value
WHO Study Region	22.148		99.62	0.0005
Americas		-4.880		<0.001
Western Pacific		REF		REF
South-East Asia		-1.277		0.144
European		-1.467		0.080
African		-2.917		0.021
Eastern Mediterranean		-1.301		0.300
Age 5	7.631		99.79	0.006
< Age 5		-2.103		0.006
≥ Age 5		REF		REF
Decade	5.598		99.82	0.061
1990		REF		REF
2000s		2.073		0.029
Spans both		2.075		0.037
Diagnostic Criteria	2.998		99.81	0.223
1992 Jones Criteria		REF		REF
ICD 9/10		1.795		0.096
2012 Australian Guidelines		-0.666		0.742

Note. I^2 values of 100% were rounded.

When exploring heterogeneity of the effect by study region and age, those from the Americas and Africa, and those that included children under the age of 5 had incidence estimates that were significantly different from their respective stratifications, indicating that characteristics of these populations may be introducing bias into the present study (Figure 3; Figure 4). The estimated average risk ratio is significantly lower for the Americans and Africa compared to the West Pacific (β = -4.880, *p* <0.001; β = -2.919, *p* = 0.021, respectively). The estimated average risk ratio was also significantly lower for studies that included children under the age of 5 compared to those that did not (β = -2.103, *p* = 0.006).

Study	Events	Time	Events per 100000 population	Events	95%-CI	Weight (fixed)	Weight (random)
WHOSR2 = African							
Cilliers	207	12890113.60		1.61	[1.40; 1.84]	4.2%	3.7%
Gapu	16	532403.67		3.01	[1.84; 4.91]	0.3%	3.7%
Fixed effect model				1.68	[1.47; 1.92]	4.5%	—
Random effects model				2.10	[1.14; 3.85]	—	7.4%
Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.1627$, $p = 0.02$							
WHOSR2 = Americas							
Koo(a)	69	71321886.00		0.10	[0.08; 0.12]	1.4%	3.7%
Koo(b)	54	71321886.00		0.08	[0.06; 0.10]	1.1%	3.7%
Tunks	59	1476216.61		4.00	[3.10; 5.16]	1.2%	3.7%
Fixed effect model				0.30	[0.26; 0.35]	3.7%	—
Random effects model				0.31	[0.03; 3.73]	—	11.1%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 4.8416$, $p < 0.01$							
WHOSR2 = Eastern Mediterranean							
Qurashi	83	1567482.00		5.30	[4.27; 6.57]	1.7%	3.7%
Roodpeyma	102	444030.00		22.97	[18.92; 27.89]	2.1%	3.7%
Fixed effect model				11.89	[10.30; 13.74]	3.8%	—
Random effects model						—	7.4%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.0858$, $p < 0.01$							
WHOSR2 = European							
Breda	88	2158929.00		4.08	[3.31; 5.02]	1.8%	3.7%
Grassi	135	471402.00		28.64	[24.19; 33.90]	2.8%	3.7%
Karaaslan	274	17112638.40		1.60	[1.42; 1.80]	5.6%	3.7%
Karademir	228	975707.00		23.37	[20.52; 26.61]	4.6%	3.7%
Kocevar	19	241192.80		7.88	[5.02; 12.35]	0.4%	3.7%
Narin	624	6011210.00		10.38	[9.60; 11.23]	12.7%	3.7%
Vinker	40	228432.00		17.51	[12.84; 23.87]	0.8%	3.7%
Fixed effect model				8.65	[8.21; 9.11]	28.7%	—
Random effects model				9.35	[4.06; 21.55]	—	26.0%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 1.2561$, $p < 0.01$							
WHOSR2 = Southeast Asia							
Ahmed	7	19509.00		35.88	[17.11; 75.26]	0.1%	3.6%
Bavdekar	86	2524476.00		3.41	[2.76; 4.21]	1.8%	3.7%
Ramu(a)	36	1117571.00		3.22	[2.32; 4.47]	0.7%	3.7%
Ramu(b)	36	1117571.00		3.22	[2.32; 4.47]	0.7%	3.7%
Routray	1330	4869267.00		27.31	[25.88; 28.82]	27.1%	3.7%
Zaman	36	56827.00		63.35	[45.70; 87.82]	0.7%	3.7%
Fixed effect model				22.44	[21.35; 23.60]	31.2%	—
Random effects model						—	22.1%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.8022$, $p < 0.01$							
WHOSR2 = Western Pacific							
Atato-Carr	68	364986.00		18.63	[14.69; 23.63]	1.4%	3.7%
Beaudoin	65	23419.40		277.55	[217.65; 353.93]	1.3%	3.7%
Corsenac	38	8843.00		429.72	[312.68; 590.56]	0.8%	3.7%
Milne	1007	552474.00		182.27	[171.35; 193.88]	20.5%	3.7%
Noonan	151	4215683.00		3.58	[3.05; 4.20]	3.1%	3.7%
Smith	26	805032.00		3.23	[2.20; 4.74]	0.5%	3.7%
Steer	24	63495.00		37.80	[25.34; 56.39]	0.5%	3.7%
Fixed effect model				99.76	[94.63; 105.17]	28.1%	—
Random effects model							
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 4.3641$, $p = 0$							
Fixed effect model				19.20	[18.67; 19.75]	100.0%	—
Random effects model				8.88	[4.40; 17.93]	—	100.0%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 3.4513$, $p = 0$							

0   5   10   15   20

Figure 3. Overall Incidence Rates of Acute Rheumatic Fever in included studies stratified by

WHO Study Region.

Study	Events	Time	Events per 100000 population	Events	95%–CI	Weight (fixed)	Weight (random)
Age5_2 = Over 5							
Ahmed	7	19509.00		35.88	[17.11; 75.26]	0.1%	3.6%
Atato–Carr	68	364986.00		18.63	[14.69; 23.63]	1.4%	3.7%
Corsenac	38	8843.00		429.72	[312.68; 590.56]	0.8%	3.7%
Karaaslan	274	17112638.40		1.60	[1.42; 1.80]	5.6%	3.7%
Milne	1007	552474.00		182.27	[171.35; 193.88]	20.5%	3.7%
Routray	1330	4869267.00		27.31	[25.88; 28.82]	27.1%	3.7%
Steer	24	63495.00		37.80	[25.34; 56.39]	0.5%	3.7%
Zaman	36	56827.00		63.35	[45.70; 87.82]	0.7%	3.7%
Fixed effect model				42.84	[41.28; 44.46]	56.7%	—
Random effects model							
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 3.1855$, $p = 0$							
Age5_2 = Under 5							
Bavdekar	86	2524476.00		3.41	[2.76; 4.21]	1.8%	3.7%
Beaudoin	65	23419.40		277.55	[217.65; 353.93]	1.3%	3.7%
Breda	88	2158929.00		4.08	[3.31; 5.02]	1.8%	3.7%
Cilliers	207	12890113.60		1.61	[1.40; 1.84]	4.2%	3.7%
Gapu	16	532403.67		3.01	[1.84; 4.91]	0.3%	3.7%
Grassi	135	471402.00		28.64	[24.19; 33.90]	2.8%	3.7%
Karademir	228	975707.00		23.37	[20.52; 26.61]	4.6%	3.7%
Kocevar	19	241192.80		7.88	[5.02; 12.35]	0.4%	3.7%
Koo(a)	69	71321886.00		0.10	[0.08; 0.12]	1.4%	3.7%
Koo(b)	54	71321886.00		0.08	[0.06; 0.10]	1.1%	3.7%
Narin	624	6011210.00		10.38	[9.60; 11.23]	12.7%	3.7%
Noonan	151	4215683.00		3.58	[3.05; 4.20]	3.1%	3.7%
Qurashi	83	1567482.00		5.30	[4.27; 6.57]	1.7%	3.7%
Ramu(a)	36	1117571.00		3.22	[2.32; 4.47]	0.7%	3.7%
Ramu(b)	36	1117571.00		3.22	[2.32; 4.47]	0.7%	3.7%
Roodpeyma	102	444030.00		22.97	[18.92; 27.89]	2.1%	3.7%
Smith	26	805032.00		3.23	[2.20; 4.74]	0.5%	3.7%
Tunks	59	1476216.61		4.00	[3.10; 5.16]	1.2%	3.7%
Vinker	40	228432.00		17.51	[12.84; 23.87]	0.8%	3.7%
Fixed effect model				6.71	[6.43; 7.00]	43.3%	—
Random effects model				4.77	[2.31; 9.85]	—	70.4%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 2.5848$, $p = 0$							
Fixed effect model				19.20	[18.67; 19.75]	100.0%	—
Random effects model				8.88	[4.40; 17.93]	—	100.0%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 3.4513$, $p = 0$							

0   5   10   15   20

Figure 4. Overall Incidence Rates of Acute Rheumatic Fever stratified by inclusion of children under or over the age of 5 for included studies.

The mixed effect model for overall incidence by decade (1990s vs. 2000s) revealed a suggestive trend towards heterogeneity being related to the decade in which the study was conducted but did not meet the threshold for statistical significance (QM = 5.598, *df* = 2, *p* = 0.061). The estimated average risk ratio was higher for studies that evaluated incidence rates of ARF spanning both the 1990s and 2000s compared to studies exclusively evaluating ARF incidence rates in the 1990s (β = 2.075, *p* = 0.037). The estimated average risk ratio was also

statistically higher for studies that only evaluated incidence rates of ARF in the 2000s, compared

to those that were exclusively studied in the 1990s ($\beta = 2.073$, $p = 0.029$).

Incidence rates for males and females from 19 articles were pooled to determine

heterogeneity (Figure 5; Figure 6).

Study	Events	Time	Events per 100000 population	Events	95%-CI	Weight (fixed)	Weight (random)
Ahmed	.	.				0.0%	0.0%
Atato–Carr	36	185457.00		19.41	[14.00; 26.91]	2.4%	5.3%
Bavdekar	.	.				0.0%	0.0%
Beaudoin	26	11782.85		220.66	[150.24; 324.08]	1.8%	5.3%
Breda	37	1048118.97		3.53	[2.56; 4.87]	2.5%	5.3%
Cilliers	113	6462055.60		1.75	[1.45; 2.10]	7.7%	5.4%
Corsenac	.	.				0.0%	0.0%
Gapu	10	275252.70		3.63	[1.95; 6.75]	0.7%	5.0%
Grassi	65	228280.00		28.47	[22.33; 36.31]	4.4%	5.4%
Karaaslan	147	8312016.27		1.77	[1.50; 2.08]	10.0%	5.4%
Karademir	106	474424.00		22.34	[18.47; 27.03]	7.2%	5.4%
Kocevar	6	124445.00		4.82	[2.17; 10.73]	0.4%	4.8%
Koo(a)	.	.				0.0%	0.0%
Koo(b)	.	.				0.0%	0.0%
Milne	.	.				0.0%	0.0%
Narin	362	3486501.80		10.38	[9.37; 11.51]	24.6%	5.4%
Noonan	67	2051352.00		3.27	[2.57; 4.15]	4.5%	5.4%
Qurashi	34	2014986.00		1.69	[1.21; 2.36]	2.3%	5.3%
Ramu(a)	.	.				0.0%	0.0%
Ramu(b)	18	550102.00		3.27	[2.06; 5.19]	1.2%	5.2%
Roodpeyma	48	337111.75		14.24	[10.73; 18.89]	3.3%	5.3%
Routray	324	2398601.74		13.51	[12.11; 15.06]	22.0%	5.4%
Smith	11	390485.00		2.82	[1.56; 5.09]	0.7%	5.1%
Steer	12	33820.00		35.48	[20.15; 62.48]	0.8%	5.1%
Tunks	33	3081175.11		1.07	[0.76; 1.51]	2.2%	5.3%
Vinker	.	.				0.0%	0.0%
Zaman	18	27828.00		64.68	[40.75; 102.66]	1.2%	5.2%
Fixed effect model				8.08	[7.68; 8.51]	100.0%	--
Random effects model				7.96	[4.72; 13.45]	--	100.0%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.3168$, $p = 0$			0 5 10 15 20				

Figure 5. Female Incidence Rates of Acute Rheumatic Fever among included studies.

Study	Events	Time	Events per 100000 population	Events	95%-CI	Weight (fixed)	Weight (random)
Ahmed	.	.				0.0%	0.0%
Atato-Carr	32	179529.00		17.82	[12.60; 25.21]	1.5%	5.3%
Bavdekar	.	.				0.0%	0.0%
Beaudoin	39	12653.05	>	308.23	[225.20; 421.86]	1.9%	5.3%
Breda	51	1110905.21		4.59	[3.49; 6.04]	2.4%	5.3%
Cilliers	94	6428188.00		1.46	[1.19; 1.79]	4.5%	5.3%
Corsenac	.	.				0.0%	0.0%
Gapu	6	257150.97		2.33	[1.05; 5.19]	0.3%	5.0%
Grassi	69	243122.00	>	28.38	[22.42; 35.93]	3.3%	5.3%
Karaaslan	127	8800622.13		1.44	[1.21; 1.72]	6.1%	5.3%
Karademir	122	501283.00	>	24.34	[20.38; 29.06]	5.8%	5.3%
Kocevar	13	117048.80		11.11	[6.45; 19.13]	0.6%	5.2%
Koo(a)	.	.				0.0%	0.0%
Koo(b)	.	.				0.0%	0.0%
Milne	.	.				0.0%	0.0%
Narin	262	2524708.20		10.38	[9.19; 11.71]	12.5%	5.3%
Noonan	84	2164331.00		3.88	[3.13; 4.81]	4.0%	5.3%
Qurashi	49	2552742.00		1.92	[1.45; 2.54]	2.3%	5.3%
Ramu(a)	.	.				0.0%	0.0%
Ramu(b)	18	567469.00		3.17	[2.00; 5.03]	0.9%	5.2%
Roodpeyma	54	227852.06	>	23.70	[18.15; 30.94]	2.6%	5.3%
Routray	1006	2470665.65	>	40.72	[38.28; 43.31]	48.0%	5.3%
Smith	15	414547.00		3.62	[2.18; 6.00]	0.7%	5.2%
Steer	12	33108.00	>	36.25	[20.58; 63.82]	0.6%	5.2%
Tunks	26	2924179.17		0.89	[0.61; 1.31]	1.2%	5.3%
Vinker	.	.				0.0%	0.0%
Zaman	18	28999.00	>	62.07	[39.11; 98.52]	0.9%	5.2%
Fixed effect model				**17.03**	**[16.32; 17.78]**	**100.0%**	--
Random effects model				**9.12**	**[4.66; 17.84]**	--	**100.0%**

Heterogeneity: $I^2 = 99\%$, $\tau^2 = 2.1912$, $p = 0$

0   5   10   15   20

Figure 6. Male Incidence Rates of Acute Rhematic Fever among included studies.

Using the same stratifications as before, heterogeneity was assessed, with high I^2 values being present for all variables (Appendix 2; Table 4; Table 5).

Table 4

Heterogeneity in the Female Incidence Rates of Acute Rheumatic Fever

Stratification	I^2 (%)	τ^2	*p*-value
Overall	99	1.317	<0.001
WHO Study Region			
Americas	N/A	N/A	N/A
Western Pacific	99	3.484	<0.001
South-East Asia	98	1.176	<0.001
European	99	1.220	<0.001
African	80	0.313	0.03
Eastern Mediterranean	99	2.249	<0.001
Age 5			
< Age 5	99	1.486	<0.001
≥ Age 5	99	1.849	<0.001
Decade			
1990	100	3.208	<0.001
2000s	98	2.948	<0.001
Spans both	99	0.947	<0.001
Diagnostic Criteria			
1992 Jones Criteria	99	1.163	<0.001
ICD 9/10	99	3.801	<0.001
2012 Australian Guidelines	N/A	N/A	N/A

Note. I^2 values of 100% were rounded.

Table 5

Heterogeneity in the male incidence rates of ARF

Stratification	I^2 (%)	τ^2	*p*-value
Overall	99	2.1912	<0.001
WHO Study Region			
Americas	N/A	N/A	N/A
Western Pacific	99	4.296	<0.001
South-East Asia	98	1.669	<0.001
European	99	1.382	<0.001
African	19	0.021	0.27
Eastern Mediterranean	99	3.139	<0.001
Age 5			
< Age 5	99	1.852	<0.001
≥ Age 5	100	3.817	<0.001
Decade			
1990	100	3.983	<0.001
2000s	99	3.310	<0.001
Spans both	100	1.975	<0.001
Diagnostic Criteria			
1992 Jones Criteria	100	2.134	<0.001
ICD 9/10	99	4.917	<0.001
2012 Australian Guidelines	N/A	N/A	N/A

Note. I^2 values of 100% were rounded.

When fixed effect models for male and female incidence were explored using meta-regression, we observed that heterogeneity was not explained by any of the moderators (Table 6; Table 7).

Table 6

Meta-regression in the Female Incidence Rates of Acute Rheumatic Fever

Stratification	QM	B	I^2 (%)	*p*-value
WHO Study Region	5.517		99.09	0.356
Americas		-2.764		0.074
Western Pacific		REF		REF
South-East Asia		-0.180		0.862
European		-0.793		0.355
African		-1.916		0.107
Eastern Mediterranean		-1.241		0.294
Age 5	1.609		99.18	0.205
< Age 5		-0.934		0.205
≥ Age 5		REF		REF
Decade	0.380		99.32	0.827
1990		REF		REF
2000s		0.464		0.692
Spans both		0.047		0.968
Diagnostic Criteria	2.275		99.31	0.321
1992 Jones Criteria		REF		REF
ICD 9/10		1.229		0.173
2012 Australian Guidelines		-0.737		0.614

Note. I^2 values of 100% were rounded.

Table 7

Meta-regression in the Male Incidence Rates of Acute Rheumatic Fever

Stratification	QM	β	I^2 (%)	*p*-value
WHO Study Region	7.085		99.18	0.214
Americas		-3.087		0.056
Western Pacific		REF		REF
South-East Asia		0.033		0.976
European		-0.775		0.385
African		-2.364		0.057
Eastern Mediterranean		-1.061		0.389
Age 5	1.472		99.35	0.225
< Age 5		-0.972		0.225
≥ Age 5		REF		REF
Decade	0.4223		99.51	0.810
1990		REF		REF
2000s		0.6750		0.595
Spans both		0.268		0.835
Diagnostic Criteria	1.963		99.52	0.375
1992 Jones Criteria		REF		REF
ICD 9/10		1.263		0.200
2012 Australian Guidelines		-0.691		0.666

Note. I^2 values of 100% were rounded.

Sensitivity analyses were also performed in which articles without exact population denominators were excluded from analyses. Analyses revealed that heterogeneity did not differ significantly between models, but did decrease slightly after the articles had been excluded. In addition, there were no articles left in the African and Eastern Mediterranean countries after exclusion. Meta-regression of the overall incidence rates showed negligible change in significance levels for the moderators discussed previously. When stratified by gender, articles that included children under the age of 5 were found to now introduce a significant amount of heterogeneity in the models for both males and females (β = -1.515, *p* = 0.003; β = -1.368, *p* = 0.017, respectively). However, only 11 articles were used for this model, and all of them

included children under the age of 5, indicating that no substantive change was made in the

significance levels of the moderators when accounting for how the population denominators

were calculated.

The proportion of studies that investigated the clinical and minor manifestations of ARF

can be found listed in Tables 7 & 8.

Table 7

Major Manifestations of Acute Rheumatic Fever

Article	Carditis n (%)	Arthritis n (%)	Chorea n (%)	SN n (%)	EM n (%)
Noonan et al.	90 (60)	87 (58)	29 (19)	3 (2)	8 (5)
Smith et al.	21 (81)	10 (38)	4 (15)	-	-
Beaudoin et al.	-	-	-	-	-
Corsenac et al.	-	-	-	-	-
Steer et al.	-	-	-	-	-
Milne et al.	-	-	-	-	-
Atato-Carr et al.	-	-	-	-	-
Bavdekar	47 (55)	17 (20)	10 (12)	4 (5)	0 (0)
Ramu et al. (a)	36 (100)	12 (33)	3 (8)	3 (8)	0 (0)
Ramu et al. (b)	36 (100)	12 (33)	3 (8)	3 (8)	0 (0)
Routray	1021 (77)	589 (44)	699 (53)	148 (11)	0 (0)
Zaman et al.	-	-	-	-	-
Ahmed et al.	-	-	-	-	-
Vinker et al.	-	-	-	-	-
Grassi et al.	102 (76)	71 (53)	29 (21)	1 (1)	8 (6)
Breda et al.	43 (49)	52 (59)	5 (6)	4 (5)	10 (11)
Kocevar et al.	19 (100)	-	6 (32)	0 (0)	1 (5)
Qurashi	44 (53)	64 (77)	17 (20)	0 (0)	0 (0)
Cilliers	-	-	-	-	-
Gapu et al.	10 (63)	5 (31)	5 (31)	0 (0)	0 (0)
Roodpeyma et al.	68 (67)	67 (66)	4 (4)	0 (0)	1 (1)
Karademir et al.	59 (26)	100 (44)	40 (18)	0 (0)	0 (0)
Karaaslan et al.	137 (50)	223 (81)	49 (18)	2 (1)	1 (0.4)
Narin et al.	339 (54)	218 (35)	158 (25)	3 (0.5)	1 (0.2)
Tunks et al.	35 (59)	27 (46)	23 (39)	0 (0)	3 (5)
Koo et al. (a)	-	-	-	-	-
Koo et al. (b)	-	-	-	-	-

Table 8

Minor Manifestations of Acute Rheumatic Fever

Article	Fever n (%)	Arthralgia n (%)	Elevated ESR n (%)	Elevated CRP n (%)	Prolonged PR Interval n (%)
Noonan et al.	96 (64)	36 (24)	-	-	8 (5)
Smith et al.	19 (73)	7 (27)	19 (73)	11 (42)	-
Beaudoin et al.	-	-	-	-	-
Corsenac et al.	-	-	-	-	-
Steer et al.	-	-	-	-	-
Milne et al.	-	-	-	-	-
Atato-Carr et al.	-	-	-	-	-
Bavdekar	-	-	80 (93)	58 (67)	7 (8)
Ramu et al. (a)	24 (67)	5 (14)	17 (47)	31 (86)	2 (6)
Ramu et al. (b)	24 (67)	5 (14)	17 (47)	31 (86)	2 (6)
Routray	1170 (88)	-	-	-	-
Zaman et al.	-	-	-	-	-
Ahmed et al.	-	-	-	-	-
Vinker et al.	-	-	-	-	-
Grassi et al.	68 (50)	22 (16)	-	-	2 (1)
Breda et al.	70 (80)	42 (48)	-	-	5 (6)
Kocevar et al.	15 (79)	12 (63)	14 (74)	11 (58)	5 (26)
Qurashi	69 (83)	9 (11)	74 (89)	-	19 (23)
Cilliers	-	-	-	-	-
Gapu et al.	11 (69)	6 (38)	8 (50)	7 (44)	2 (13)
Roodpeyma et al.	-	-	102 (100)	-	-
Karademir et al.	113 (50)	164 (72)	223 (98)	182 (80)	44 (19)
Karaaslan et al.	-	-	225 (82)	-	66 (24)
Narin et al.	109 (17)	211 (34)	376 (60)	280 (45)	108 (17)
Tunks et al.	-	-	-	-	-
Koo et al. (a)	-	-	-	-	-
Koo et al. (b)	-	-	-	-	-

However, because this information was extremely limited in how these were measured, it was not appropriate to explore these further. Information on risk factors associated with ARF was also not consistent between studies, so this data was unable to be pooled (data not shown).

Chapter 5 Discussion

This meta-analysis provides evidence that heterogeneity exists as an issue when

exploring the global incidence rates of ARF. Significant heterogeneity was found between and

even within the WHO Study Regions and in articles that included children under the age of 5

years. The estimated average risk ratio was found to be significantly higher for the Americas and

the African countries compared to the Western Pacific. This confirms previous findings that the

incidence rates in the Western Pacific are typically the highest seen globally (Kumar & Tandon,

2013). In the case of WHO study region, heterogeneity could have been introduced in the study

methods or the populations within this region compared to other regions. On the other hand, the

estimated average risk ratio was significantly lower for studies that included children under the

age of 5 compared to those that did not. This suggests that heterogeneity could have been caused

by the way the studies were conducted or differences in case definitions used in each study. The

trend seen for the year of inclusion was also interesting since incidence rates to not appear to be

increasing. The increase in sensitivity of the diagnostic criteria for ARF from 1992 to 2015, this

may be showing an increased incidence due to decreased misdiagnosis of ARF. The substantial

amount of heterogeneity emphasizes the need for a more standardized approach when evaluating

and studying ARF. Without a cohesive method for assessing ARF cases, a true global estimate

cannot be determined.

The results also indicated that other variables need to be evaluated to determine the cause

of heterogeneity among male and female cases of ARF, since the variables in the present study

did not explain the source of the heterogeneity. However, a few trends were present among

males. Even though overall the WHO study region was not significant, the Western Pacific

Region and the Southeast Asia Region both had borderline significant *p*-values (0.057 and 0.077,

respectively). This suggests that heterogeneity may be introduced by these specific regions, but the same was not apparent for females. More than likely, there are some other characteristics of these populations or differences between study methods that are introducing heterogeneity into the current study. Future studies should explore possible explanations, such as percent disadvantaged population studied, case definition for ARF and inclusion/exclusion criteria.

This study was unable to further explore the manifestations associated with ARF due to limited availability of information provided by the authors. However, when comparing proportions of major manifestations with recent reviews on the manifestations of ARF, some interesting observations were made (Bono-Neri, 2017; Gewitz et al., 2015; Webb et al., 2015). After pooling data from articles describing ARF, Webb et al. (2015) found that 50-65% of ARF patients presented with carditis, globally. However, the articles included in the current meta-analysis revealed a range of 26-100% of patients presenting with carditis. In addition, Gewitz et al. (2015) suggested that arthritis manifests in 50-70% of ARF patients, but the current analysis showed a range of 31-81%. Lastly, previous research indicates that Sydenham's Chorea manifests in 10-30% of patients, differing slightly from the range of 4-39% found in the current study. Subcutaneous nodules and erythema marginatum were the only two manifestations that did not appear to diverge from what has been found in the literature (Bono-Neri, 2017; Gewitz et al., 2015). These observations suggest that we do not fully understand the extent of how these manifestations are distributed globally, especially the manifestations that are considered severe. The limited availability further indicates the needs for a more systematic approach when studying ARF.

Future research should explore the clinical manifestations, and explore the possibility that differences may exist depending on geographical region, or possibly the strain of *S. pyogenes*. It

is obvious with the results of the current meta-analysis that there is a large degree of uncertainty in the description of the range of manifestations that are attributable to ARF. The results also indicate that there may be a large underestimation in symptoms, such as carditis and arthritis. The underestimation found in carditis could possibly reflect the issue of diagnosing subclinical carditis in patients (Eroğlu, 2015; Gewitz et al., 2015). It is possible that studies using echocardiogram technology instead of electrocardiography, they had the ability to diagnose more cases of carditis (Eroğlu, 2015). The difference between the ranges found for arthritis could possibly be due to similarities between the signs and symptoms of arthritis and arthralgia (Braun et al., 1990). Patients may have not have understood the difference between these manifestations, thus causing them to be misclassified. Unfortunately, no ranges were available on minor criteria, such as arthralgia, so the answer to the discrepancy remains uncertain. Since these reviews did not report ranges for any of the minor manifestations, it may be beneficial to explore the possibility of differences also existing between groups for some of these symptoms.

The ability to accurately describe ARF reflects our ability to accurately diagnose ARF. This is vital in ensuring that all individuals with this disease are properly evaluated and treated. Underdiagnoses of ARF may lead to recurrent attacks, which increases the chance of cardiac damage and premature death (The Australian Guidelines, 2015). Although the sensitivity of the Jones Criteria has increased with each revision, there are still cases that are missed. One study that investigated the impact of the addition of subclinical carditis, mono-arthritis, and low-grade fever to the 1992 Jones Criteria found that, before the modification, only 71.4% of cases met the criteria (Carapetis & Currie, 2001). With the modification, 91.8% of the cases satisfied the criteria. Of those who did not meet the traditional criteria, 42% developed RHD, which means that they had cases of ARF that went untreated (Carapetis & Currie, 2001). With further

understanding of ARF in each population, interventions can be created and implemented that better target each respective group.

Issues with the Jones Criteria

In areas where ARF is endemic, the definition of the "high-risk populations" category is still not sensitive enough to capture all cases (Eroğlu, 2015). Research suggests that host genetic susceptibility, virulence factors of *Streptococcus pyogenes* and environmental factors are all individual and community level risk factors that may contribute to the development of ARF, but they are not included in the definition for high-risk populations in the Jones Criteria (Baroux et al., 2013; Steer et al., 2002). With the Jones Criteria only accounting for the incidence of the population as the sole determinant of risk, this fails to consider any individual level predictors of ARF that may put an individual at a higher risk of developing the disease. Including these predictors could redefine levels of risk within the Jones Criteria to better diagnose ARF cases that fall outside the current definition of high-risk populations.

Though SCC is now considered a major manifestation, individuals who have SCC are still being missed during diagnosis. Carditis is the manifestation most often used in determining disease status, which means atypical presentation of this manifestation can result in a misdiagnosis (Eroğlu, 2015). SCC is a condition that can occur in ARF cases in which they develop carditis due to the disease, but it is not able to be detected by an ECG during diagnosis. This condition is better detected by echocardiography, which is included in the current diagnostic criteria, but endemic regions often do not have access to this type of technology (Eroğlu, 2015; Kumar & Tandon, 2013). Approximately 65% of individuals with ARF develop carditis as a symptom, which means the other 35% could potentially have undetected SCC (Carapetis, Steer, Mulholland & Weber, 2005; Kumar & Tandon, 2013).

A systematic review that pooled data from studies looking at SCC in ARF cases suggested that the weighted pooled prevalence of SCC among exposed individuals was 16.8% (Tubridy-Clark & Carapetis, 2007). Another study found that clinically identifiable carditis was present in 64% of cases, whereas SCC was diagnosed in 27% of cases resulting in an overall prevalence of 91% (Veasy, 1999). When patients were followed up in a longitudinal study, initial evaluation went from 56% having clinical carditis and 35% having SCC to 65% having clinical carditis by the end of the follow-up time (Araújo, Goulart, & Meira, 2012). This not only suggests that a large amount of cases of ARF go undiagnosed, but also that SCC can get worse and turn into clinical carditis if not detected (Kumar & Tandon, 2013). Thus, the estimated burden of this disease is an underestimate of the actual burden of the disease.

Due to geographical differences between cases of ARF, it is important that future revisions of the Jones Criteria consider individual and genetic differences in addition to the current groupings in the Guidelines when defining the level of risk associated with each group. Individual characteristics that should be considered include SES, overcrowding status, and rurality that may put certain individuals at an even higher risk of ARF. The more specific the criteria are, less cases are missed in areas where the disease is endemic. In addition, once biomarkers continue to be identified for ARF, adding these tests to the diagnostic criteria may more accurately identify abnormal cases of ARF that may have been missed previously due to incompatible symptoms. This would ensure that cases that do not have the typical symptoms, such as in recurrent cases, are not missed.

Gaps in the Research

Information on the major and clinical manifestations and the risk factors associated with ARF were not well documented in the literature. Most articles are concerned with the major

criteria, with even less reporting statistics on the minor, non-specific criteria. Even so, it is evident that manifestations are not consistent across studies. The literature shows that carditis and arthritis compete for the most frequent major manifestation, and chorea rates tend to have a large range (6 to 36%). In one case, involuntary body movements was the most common manifestation (Narin et al., 2013). The only consistency seems to appear in the instance of SN and EM due to their infrequency across geographical location. However, one author hypothesized that EM may be less apparent on darker skin, which means this symptom could be underdiagnosed in regions of the world where the disease is epidemic (Steer et al., 2009). Further exploring minor manifestations in addition to risk factors may help in identifying differences that may exist between groups that have not been previously identified due to lack of available data.

Now that the Jones Criteria differentiates between initial and recurrent attacks, it would be beneficial to understand what differences arise between these groups. Two recent papers have explored the differences in manifestations between initial and recurrent attacks. Sheikh, Sadiq and Rehman (2016) showed that arthritis, fever, and history of sore throat occurred more often in initial episodes, while carditis, subcutaneous nodules, and arthralgia occurred more often in recurrent episodes. Chorea and EM were found in neither recurrent nor initial attacks in this sample. The results from Chagani and Aziz (2003) found similar results, with arthritis and history of sore throat being more common in initial attacks, and carditis and arthralgia was more common among recurrent attacks. However, they found that subcutaneous nodules were more common among initial attacks and fever occurred more often during recurrent attacks. In addition, their sample showed that both chorea and erythema marginatum was more common in initial attacks. This research shows that not only do symptoms differ between initial and recurrent attacks, but these manifestations also differ in frequency between populations. This

provides evidence that definitions for initial and recurrent attacks that is currently used in the Jones Criteria is not generalizable to all populations. However, there is not enough research currently available that can accurately define these groups, which prompts the needs for researchers to explore these differences. Another piece of evidence that may provide insight is knowing the frequency of ARF attacks among patients, and not just if it is recurrent or initial. Though with underreporting being so high with this disease, this may not be information that is easily acquired. If this information can be obtained, a dose-response relationship may be able to be identified. However, research has shown that damage accumulates over time with repeated ARF attacks (Chang, 2012; Cunningham, 2000). With repeated infections means recurring cardiac damage that can either target the same place or travel to other parts of the heart, often ending in pancarditis (Eroğlu, 2015). This emphasizes the need to track and understand the progression of this disease.

Only one study investigated the differences found between high and low risk group classifications for ARF. Noonan et al. (2013) found that there were some differences between manifestations that were apparent in each group. Aseptic monoarthritis was common among children in the high-risk group (19%), but was only seen in one child in the low-risk group. The authors also found that the proportion of raised inflammatory markers, chorea and cutaneous manifestations were more common among the low risk group. Future research should explore the differences between these groups among different populations to better describe what this disease looks like for these groups. If differences are significant, major and minor classifications may be revised to reflect which manifestations are more frequent for each group.

There are also limited current studies that explore the inheritance of ARF among family members. Research indicates that heritability is still a factor in determining the development of

ARF. Noonan et al. (2013) discovered that 9% of children with ARF had at least one sibling that

had a history of ARF. Similarly, Narin et al. (2015) found that 7.4% of Turkish patients had a

family history of ARF. A study in Italy showed 8% of their patients had a family history of ARF

(Breda et al., 2012). Globally, it appears that heritability remains consistent across populations.

Comprehensive studies on siblings and families would be beneficial to determine the

concordance of symptoms among family members that may help identify specific genes that may

be associated with the development of ARF.

Reducing the gaps in the research is the first step towards developing a more concrete

description of what this disease looks like today, on a global scale. Not only can a more sensitive

criterion be created once the holes in the data are filled, but individuals will have a better chance

of being identified and receive the treatment that they need.

Public Health Implications

The public health implications of this disease span across multiple aspects of prevention.

The proper diagnosis of sore throats is important in preventing the progression from pharyngitis

to ARF, in addition to providing antibiotics at this stage if clinical diagnosis is confirmed.

Surveillance of this disease needs to be established in endemic countries to help provide a better

system for following up with cases in addition to allowing for a more systematic way of

collecting data for analysis. Primary prevention with a suitable vaccine would be the most ideal

solution to prevent initial infection with *S. pyogenes*, since it would then reduce the number of

those who have both ARF and RHD. Since a vaccine is not yet feasible due to the variability of

this disease, public health interventions should focus on providing individuals clinically

diagnosed with pharyngitis with the antibiotic treatment they need. Awareness and education of

health care staff and patients is also needed to increase the amount of confirmed ARF cases

receiving treatment. For those who do have ARF, proper management of this disease needs to be

emphasized so as to reduce potential damage that may occur if protocol is not followed and that

recurrence of ARF does not occur. These strategies should be employed in places where this

disease is endemic to increase the quality of life for these individuals and to reduce the burden of

ARF and RHD.

Diagnosing Sore Throats

In most developed and developing countries, the diagnosis of GAS pharyngitis is made

via a laboratory culture of a throat swab of the suspected patient (Kerdemelidis et al., 2010 et al.,

2010). These swabs are either plated on agar for growth in a lab or a rapid strep test is used. The

sensitivity of this test seems to vary across populations and studies, but do take into account that

some individuals have this bacterium as normal flora (Kaplan, Top, Dudding & Wannamaker,

1971). If a rapid strep test comes back negative, it is recommended that a throat swab be done to

confirm those results (Bisno et al., 2002). In places like New Zealand where ARF is endemic,

however, the sensitivity of this test has not been validated (Kerdemelidis et al., 2010). Why this

is so important, is because the individuals in New Zealand have a high likelihood of testing

positive for GAS pharyngitis, which could result in the overuse of antibiotics. To combat this,

Kerdemelidis et al. (2010) proposed an algorithm that accounts for other risk factors (high pretest

probability of GAS infection) to properly prescribe the right patient with antibiotics. However,

the sensitivity needs to be assessed in different populations to determine the correct method to

prescribe medications.

Surveillance of ARF

In places where ARF is endemic, such as in New Zealand and Australia, there are

surveillance systems in place to track the disease. Other developed countries where ARF is still

prevalent do not have these types of systems in place. In addition, developed countries no longer

closely track ARF cases except for hospital records. This is evident in the fact that in 1995, ARF

was taken off the notifiable disease list in the United States since the incidence rate had dropped

so low (CDC, 1995). Other places where this disease is endemic may also not have any

surveillance system at all. To better coordinate care, reduce recurrent ARF, and increase the

number of individuals who follow up for proper health care, registries must exist in countries

where ARF incidence is high.

Prevention Strategies

Primary and secondary prevention have both been employed as strategies to prevent or

treat ARF. It is critical that individuals with ARF receive adequate treatment and preventative

care to reduce the morbidity associated with this disease. Vaccines to protect against infection

with GAS has also been evaluated as the next step towards primary prevention of ARF

(Cunningham, 2000). Failure to provide secondary prophylaxis can be due to a missed diagnosis,

lack of continuity of professional care, lack of trust between patients and physicians, high staff

turnover, lack of appropriate health education on ARF, and lack of a political or bureaucratic

commitment to see that this problem is fixed (Brown, McDonald & Calma, 2007). In order for

these methods to be efficient, the underlying social determinants associated with ARF must first

be determined and alleviated.

Awareness and Education

It has been shown that not only do families not understand the risk of ARF, but hospital

staff in endemic areas often do not have adequate education on ARF prevention and treatment

(Zühlke et al., 2017). Hospital staff should be adequately trained in identifying the signs and

symptoms of this disease in places where it is endemic. Another method of increasing education

is for hospitals to provide staff with materials that educate them on the signs and symptoms associated with GAS and the importance of getting treated. Then, the staff can pass this information on to the parent which, in-turn, will hopefully increase the chance of continuity of care. Public Service Announcements (PSAs) in the form of infographics have been used recently to try and bring awareness to this disease in places like New Zealand. However, it cannot be determined if those living in remote regions have access to this information. Increasing the use of PSAs in developing countries should increase the likelihood that someone seeks treatment for sore throats, thus decreasing the incidence of ARF. If these individuals go in for treatment, they should further be educated by hospital staff, and can take home information on ARF.

Primary Prevention

Currently, primary prevention of ARF is the treatment of a GAS infection with antibiotics (Kumar & Tandon, 2013). This prevents the progression of strep throat to ARF from occurring in the first place, and is the second-best form of primary prevention besides the creation of a vaccine for *S. pyogenes*. However, limited access to adequate medical care makes it less likely that individuals who are affected by ARF are receiving treatment at this stage. So, in the instance of pharyngitis cases that turn into ARF, antibiotics are also used to treat the patient with ARF if they still test positive for an infection with *S. pyogenes* to prevent recurrent infections from occurring (Commerford, 2006).

GAS have remained sensitive to penicillin, but little has been done to reduce the number of those who are affected by ARF in socially disadvantaged populations (Kumar & Tandon, 2013). In the United States, generic antibiotic prescriptions are available for either very reduced prices or free of charge to those that have a valid prescription for it provided by a doctor (National Conference of State Legislature [NCSL], 2012). Employing a similar program in

developing countries could potentially help reduce the rates of ARF by ensuring access to antibiotics when children are clinically shown to have developed pharyngitis due to *S. pyogenes*. This may not completely alleviate the problem, especially in populations that live in remote areas and may not have transportation to pick up antibiotics. In this case, it may be beneficial to employ mobile units to these areas to distribute antibiotics to those who need them. However, some research suggests that antibiotics may not completely prevent outbreaks from occurring, but since *S. pyogenes* can still be treated with penicillin, resistance is not thought to be the main culprit.

In developed countries where treatment with antibiotics is expected after a GAS infection, unexplained resurgences of these infections have been observed since the mid-1980s (Kaplan, 1991). Between the mid-1980s to the 1990s, there were eight ARF outbreaks documented in the United States, all of them of increased severity compared to previous decades (Ayoub, 1992; Bisno, 1993; Kaplan, 1991; Veasy, Wiedmeir & Orsmon, 1987). These strains also deviated from past outbreaks in that middle-class families were at a higher risk of contracting ARF compared to lower income families that were more commonly affected by ARF previously (Bisno, 1993). If these patterns persist, the definition of high and low risk populations will need to be shifted to appropriately diagnose future patients that may fall outside previous definitions or expectations of this disease.

Previous vaccine strategies have been targeted towards specific M proteins, specifically the type specific N-terminal region or the conserved C-terminal region (Bessen & Fischetti, 1997). Vaccines that target the N-terminal region, or the start of a polypeptide that has a free anime group, induced protective bactericidal and opsonic antibody against the serotype (Beachey et al., 1981; Beachey et al., 1986). This ultimately leads to phagocytosis of the organism (Chang,

2012). Unfortunately, these antibodies are generally type specific, and since there are 80 M

subtypes, multiple coverage type vaccines seem unlikely (McNeil et al., 2005). An alternative

strategy is a vaccine that targets the C-terminal region, or the region of a polypeptide that has a

free carboxyl group, which were able to protect against multiple serotypes and prevented

colonization at mucosal surfaces (Dale, 1999; Dale, Chiang & Chiang, 1993). This broadened

the coverage of M proteins, but this highly conserved region possesses molecules that cross-react

with tropomyosin and myosin (Chang, 2012). Another vaccine is in development in Australia

that targets the B cell epitope on the conserved region of the M protein called J8 (Padney,

Batzloff & Good, 2009). They created a conjugate vaccine with the diphtheria toxoid (DT) and

an adjuvant that did produce immunity in mice, but the protection was not long lasting.

Even though these vaccines seem promising, there are still problems that must be

overcome. The bacterial antigens that cause cross-reactivity within host tissue is not

recommended to be used for making vaccines since host tissue could cause an adverse reaction

(Cunningham, 2000). To make a vaccine with effective protection, a combination of M protein

serotypes from rheumatogenic strains would have to be required, and now that 16 have been

identified to be associated with ARF, it makes it seem unlikely that one vaccine will suffice

(Cunningham, 2000). However, common GAS antigens that are not M proteins are currently

under investigation for their effectiveness of protecting against colonization of the bacteria

(Cunningham, 2000).

Management of ARF

Controlling inflammation to manage carditis, providing symptomatic relief and

eradicating pharyngeal streptococcal infection are techniques used to manage the symptoms of

ARF (Commerford, 2006; Zühlke et al., 2017). Suppressing the inflammatory response directly

minimizes cardiac damage, providing symptom relief (Commerford, 2006). Aspirin has been the primary anti-inflammatory used when there is no longer any evidence of an infection via a rapid strep test, but research has shown that Naproxen may have equivalent efficacy with fewer side effects (Hashkes et al., 2003). Anti-inflammatory agents are normally used in high dose for the first two weeks of infection, and then decreased by 20% each week, depending on clinical response and acute phase reactant levels (Commerford, 2006). Individuals with severe carditis are treated with heart failure therapy along with bedrest (Zühlke et al., 2017). This is usually a long-standing recommendation (Commerford, 2006). The duration is individually dependent, with ambulation starting once the fever has dissipated and the acute phase reactants return to normal. A 10-day course of penicillin is also recommended to prevent reinfection with GAS only if the individual tests positive on a rapid strep test (Commerford, 2006). This is important so that antibiotic resistance does not occur due to indiscriminate use of antibiotics. In some cases, heart transplants are necessary when cardiac damage is too severe (Chang, 2012).

The economic burden of this disease is substantial, and encompass both direct and indirect costs to the families of those affected. It is estimated that the individual cost of having a GAS infection in the United States is between $250 and $400 million, indicating that the global cost is much greater (Chang, 2012). Ongoing treatment with antibiotics, which can occur multiple times if repeated infections occur, cardiac surgery, and hospitalization contribute to the financial burden of this disease. If neurological symptoms, such as the involuntary body movements of the hands, feet and face caused by Sydenham's chorea, manifest in the child, the financial burden is greatly increased (Chang, 2012). Some indirect costs are travel to the hospital or primary care physician's office, which is a great cost for those living in rural or remote areas, loss of education of the child who is on bedrest, and caregivers lose income due to staying at

home to care for the child. If children are treated for their initial sore throat, then the cost of this disease can be greatly reduced. Penicillin, aspirin, and naproxen are all generic and relatively inexpensive drugs. The creation of an effective vaccine would ultimately reduce the price in addition to helping to eradicate the disease.

Strengths

To the author's knowledge, there has been no other meta-analysis conducted on the global incidence of ARF. Though the results were unable to be pooled due to heterogeneity, the utilization of a meta-analysis did increase the power of analyses via larger sample sizes. As this was a global perspective, greater generalizability was achieved. Finding the heterogeneity among these studies also helped to identify the current gaps in the research and provides guidelines in determining what future research should explore regarding ARF.

Limitations

Due to the nature of this study, there are a few limitations. First, the inclusion criteria for the age range excluded possible cases that may occur at ages older than 19 (Chockalingam, A., Gnanavelu, Elangovan & Chockalingam, V., 2003; Miyake et al., 2007). Research shows that the majority of ARF cases have an age of onset between 5 and 14 years of age, with papers reporting 87 to 95% of their populations falling within that age range (Narin et al., 2015; Noonan et al., 2013; Vinker et al., 2010). When looking at ages older than 19, one study showed that only 4 (9.1%) cases were between 20 and 29 (Vinker et al., 2010). Another study found that 7 (6.6%) ARF cases were in individuals over the age of 19 (Pennock et al., 2014). With the incidence rates being higher among these groups, it was important that the scope of the analyses conducted for this paper be focused on childhood ARF cases. This is evident in that the 2015 Australian Guidelines lists the high-risk group as those aged between 5 and 14 with an incidence greater

than 30 per 100,000 (Eroğlu, 2016). Understanding this disease during earlier age groups has better public health implications with the possibility of earlier implementation of interventions.

Another limitation that arose was that multiple papers did not provide information pertaining to population denominators used to calculate incidence rates. To combat this issue, population denominators were pulled from government censuses, and when incidence rates were calculated via this method, results were similar to what was reported in the corresponding papers. In some cases, the exact population groups could not be matched to the age range that was used in the study. For example, if the study looked at 0 to 15, but the government website only had number for 0 to 14 and 15 to 24. In these cases, it was assumed that there was an equal number of individuals at each age in the age group. To continue with the example above, the population denominator from the government website was divided by the number of age groups (15), and then that number was added to the total population to account for the missing value for 15-year old individuals. However, sensitivity analyses were conducted in which articles without exact population denominators were excluded from analyses, and these results indicated that significance levels of the moderators did not change when these articles were excluded.

Since risk of bias for all included studies was only reviewed by a single reviewer, there is a potential for reviewer bias to be introduced. Any issues with scoring that occurred during review were adjudicated with the co-authors. However, since the studies were comprised mainly of cross-sectional and cohort studies that strictly gave clinical profiles of ARF and did not run comparisons, it was deemed unnecessary to have more than one reviewer assess the risk of bias. In addition, research evaluating the assessment of the NOS scale between authors of studies and reviewers of studies showed that the overall NOS score was significantly higher in the reviewer's assessment compared to those by the authors of their respective articles (median = 6 vs. 5, IQR

6-6 vs. 4-6, *p* <0.001) (Lo, Mertz & Loeb, 2014). The authors argued that the one-point

difference found between these groups would likely not have any practical implications.

Another limitation for this paper was including the multiple types of diagnostic criteria

used to define a case of ARF. This could introduce misclassification bias due to differences in

sensitivity between the criteria. However, diagnostic criteria did not introduce a significant

amount of heterogeneity into the overall incidence rates. In addition, not all diagnostic criteria

mentioned in the inclusion criteria were evident in this study. Specifically, no articles used the

2015 Australian Guidelines for their case definitions of ARF. This may be because of how recent

the criteria were created, which means there is a lack of recent publications utilizing this case

definition. Future research utilizing the new diagnostic criteria may alleviate some of the issues

the current study discovered in the literature.

Chapter 6 Conclusion

Although substantial heterogeneity existed between the pooled data for this study, the results provide evidence of where gaps exist in the research regarding ARF on a global scale. Properly describing the characteristics of this disease is the first step towards creating adequate criteria and guidelines that will hopefully lead to better health outcomes for those suffering from ARF, reduce the economic burden that this disease imposes on susceptible families, and ultimately improve the quality of life of these individuals. ARF is a disease that is preventable with the use of antibiotics, calling into question why this disease is still running rampant globally. As advocates of health equity for all, it is important to remember that this not only means equity on a national level, but also on a global level.

Study	Events	Time	Events per 100000 population	Events	95%-CI	Weight (fixed)	Weight (random)
Age5_2 = Over 5							
Ahmed	7	19509.00		35.88	[17.11; 75.26]	0.1%	3.6%
Atato-Carr	68	364986.00		18.63	[14.69; 23.63]	1.4%	3.7%
Corsenac	38	8843.00		429.72	[312.68; 590.56]	0.8%	3.7%
Karaaslan	274	17112638.40		1.60	[1.42; 1.80]	5.6%	3.7%
Milne	1007	552474.00		182.27	[171.35; 193.88]	20.5%	3.7%
Routray	1330	4869267.00		27.31	[25.88; 28.82]	27.1%	3.7%
Steer	24	63495.00		37.80	[25.34; 56.39]	0.5%	3.7%
Zaman	36	56827.00		63.35	[45.70; 87.82]	0.7%	3.7%
Fixed effect model				42.84	[41.28; 44.46]	56.7%	—
Random effects model							
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 3.1855$, $p = 0$							
Age5_2 = Under 5							
Bavdekar	86	2524476.00		3.41	[2.76; 4.21]	1.8%	3.7%
Beaudoin	65	23419.40		277.55	[217.65; 353.93]	1.3%	3.7%
Breda	88	2158929.00		4.08	[3.31; 5.02]	1.8%	3.7%
Cilliers	207	12890113.60		1.61	[1.40; 1.84]	4.2%	3.7%
Gapu	16	532403.67		3.01	[1.84; 4.91]	0.3%	3.7%
Grassi	135	471402.00		28.64	[24.19; 33.90]	2.8%	3.7%
Karademir	228	975707.00		23.37	[20.52; 26.61]	4.6%	3.7%
Kocevar	19	241192.80		7.88	[5.02; 12.35]	0.4%	3.7%
Koo(a)	69	71321886.00		0.10	[0.08; 0.12]	1.4%	3.7%
Koo(b)	54	71321886.00		0.08	[0.06; 0.10]	1.1%	3.7%
Narin	624	6011210.00		10.38	[9.60; 11.23]	12.7%	3.7%
Noonan	151	4215683.00		3.58	[3.05; 4.20]	3.1%	3.7%
Qurashi	83	1567482.00		5.30	[4.27; 6.57]	1.7%	3.7%
Ramu(a)	36	1117571.00		3.22	[2.32; 4.47]	0.7%	3.7%
Ramu(b)	36	1117571.00		3.22	[2.32; 4.47]	0.7%	3.7%
Roodpeyma	102	444030.00		22.97	[18.92; 27.89]	2.1%	3.7%
Smith	26	805032.00		3.23	[2.20; 4.74]	0.5%	3.7%
Tunks	59	1476216.61		4.00	[3.10; 5.16]	1.2%	3.7%
Vinker	40	228432.00		17.51	[12.84; 23.87]	0.8%	3.7%
Fixed effect model				6.71	[6.43; 7.00]	43.3%	—
Random effects model				4.77	[2.31; 9.85]	—	70.4%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 2.5848$, $p = 0$							
Fixed effect model				19.20	[18.67; 19.75]	100.0%	—
Random effects model				8.88	[4.40; 17.93]	—	100.0%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 3.4513$, $p = 0$							

0   5   10   15   20

Figure A1. Overall Incidence Rates of Acute Rheumatic Fever in included studies stratified by inclusion of those under or over the age of 5.

Study	Events	Time	Events per 100000 population	Events	95%–CI	Weight (fixed)	Weight (random)
DC2 = 1992 Jones Criteria							
Ahmed	7	19509.00		35.88	[17.11; 75.26]	0.1%	3.6%
Bavdekar	86	2524476.00		3.41	[2.76; 4.21]	1.8%	3.7%
Breda	88	2158929.00		4.08	[3.31; 5.02]	1.8%	3.7%
Cilliers	207	12890113.60		1.61	[1.40; 1.84]	4.2%	3.7%
Corsenac	38	8843.00		429.72	[312.68; 590.56]	0.8%	3.7%
Gapu	16	532403.67		3.01	[1.84; 4.91]	0.3%	3.7%
Grassi	135	471402.00		28.64	[24.19; 33.90]	2.8%	3.7%
Karaaslan	274	17112638.40		1.60	[1.42; 1.80]	5.6%	3.7%
Karademir	228	975707.00		23.37	[20.52; 26.61]	4.6%	3.7%
Kocevar	19	241192.80		7.88	[5.02; 12.35]	0.4%	3.7%
Koo(a)	69	71321886.00		0.10	[0.08; 0.12]	1.4%	3.7%
Koo(b)	54	71321886.00		0.08	[0.06; 0.10]	1.1%	3.7%
Narin	624	6011210.00		10.38	[9.60; 11.23]	12.7%	3.7%
Qurashi	83	1567482.00		5.30	[4.27; 6.57]	1.7%	3.7%
Ramu(a)	36	1117571.00		3.22	[2.32; 4.47]	0.7%	3.7%
Ramu(b)	36	1117571.00		3.22	[2.32; 4.47]	0.7%	3.7%
Roodpeyma	102	444030.00		22.97	[18.92; 27.89]	2.1%	3.7%
Routray	1330	4869267.00		27.31	[25.88; 28.82]	27.1%	3.7%
Steer	24	63495.00		37.80	[25.34; 56.39]	0.5%	3.7%
Tunks	59	1476216.61		4.00	[3.10; 5.16]	1.2%	3.7%
Vinker	40	228432.00		17.51	[12.84; 23.87]	0.8%	3.7%
Zaman	36	56827.00		63.35	[45.70; 87.82]	0.7%	3.7%
Fixed effect model				10.59	[10.25; 10.94]	73.2%	---
Random effects model				6.96	[3.61; 13.44]	---	81.4%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 2.4550$, $p = 0$							
DC2 = 2012 Australian Guidelines							
Noonan	151	4215683.00		3.58	[3.05; 4.20]	3.1%	3.7%
Fixed effect model				3.58	[3.05; 4.20]	3.1%	---
Random effects model				3.58	[3.05; 4.20]	---	3.7%
Heterogeneity: not applicable							
DC2 = ICD9–10							
Atato–Carr	68	364986.00		18.63	[14.69; 23.63]	1.4%	3.7%
Beaudoin	65	23419.40		277.55	[217.65; 353.93]	1.3%	3.7%
Milne	1007	552474.00		182.27	[171.35; 193.88]	20.5%	3.7%
Smith	26	805032.00		3.23	[2.20; 4.74]	0.5%	3.7%
Fixed effect model				149.31	[140.98; 158.13]	23.8%	---
Random effects model							
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 2.5636$, $p < 0.01$							
Fixed effect model				19.20	[18.67; 19.75]	100.0%	---
Random effects model				8.88	[4.40; 17.93]	---	100.0%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 3.4513$, $p = 0$							

0   5   10   15   20

Figure A2. Overall Incidence Rates of Acute Rheumatic Fever in included studies stratified by the diagnostic criteria used.

Study	Events	Time	Events per 100000 population	Events	95%-CI	Weight (fixed)	Weight (random)
Decade2 = 1990s							
Ahmed	7	19509.00		35.88	[17.11; 75.26]	0.1%	3.6%
Bavdekar	86	2524476.00		3.41	[2.76; 4.21]	1.8%	3.7%
Karaaslan	274	17112638.40		1.60	[1.42; 1.80]	5.6%	3.7%
Karademir	228	975707.00		23.37	[20.52; 26.61]	4.6%	3.7%
Koo(a)	69	71321886.00		0.10	[0.08; 0.12]	1.4%	3.7%
Koo(b)	54	71321886.00		0.08	[0.06; 0.10]	1.1%	3.7%
Fixed effect model				2.57	[2.39; 2.76]	14.6%	---
Random effects model				1.78	[0.29; 10.82]	---	22.2%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 5.0692$, $p = 0$							
Decade2 = 1990s–2000s							
Atato–Carr	68	364986.00		18.63	[14.69; 23.63]	1.4%	3.7%
Cilliers	207	12890113.60		1.61	[1.40; 1.84]	4.2%	3.7%
Grassi	135	471402.00		28.64	[24.19; 33.90]	2.8%	3.7%
Milne	1007	552474.00		182.27	[171.35; 193.88]	20.5%	3.7%
Narin	624	6011210.00		10.38	[9.60; 11.23]	12.7%	3.7%
Qurashi	83	1567482.00		5.30	[4.27; 6.57]	1.7%	3.7%
Roodpeyma	102	444030.00		22.97	[18.92; 27.89]	2.1%	3.7%
Routray	1330	4869267.00		27.31	[25.88; 28.82]	27.1%	3.7%
Tunks	59	1476216.61		4.00	[3.10; 5.16]	1.2%	3.7%
Fixed effect model				30.80	[29.81; 31.82]	73.7%	---
Random effects model						---	33.5%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 2.3102$, $p = 0$							
Decade2 = 2000s							
Beaudoin	65	23419.40		277.55	[217.65; 353.93]	1.3%	3.7%
Breda	88	2158929.00		4.08	[3.31; 5.02]	1.8%	3.7%
Corsenac	38	8843.00		429.72	[312.68; 590.56]	0.8%	3.7%
Gapu	16	532403.67		3.01	[1.84; 4.91]	0.3%	3.7%
Kocevar	19	241192.80		7.88	[5.02; 12.35]	0.4%	3.7%
Noonan	151	4215683.00		3.58	[3.05; 4.20]	3.1%	3.7%
Ramu(a)	36	1117571.00		3.22	[2.32; 4.47]	0.7%	3.7%
Ramu(b)	36	1117571.00		3.22	[2.32; 4.47]	0.7%	3.7%
Smith	26	805032.00		3.23	[2.20; 4.74]	0.5%	3.7%
Steer	24	63495.00		37.80	[25.34; 56.39]	0.5%	3.7%
Vinker	40	228432.00		17.51	[12.84; 23.87]	0.8%	3.7%
Zaman	36	56827.00		63.35	[45.70; 87.82]	0.7%	3.7%
Fixed effect model				12.13	[11.18; 13.16]	11.7%	---
Random effects model						---	44.4%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 3.5664$, $p = 0$							
Fixed effect model				19.20	[18.67; 19.75]	100.0%	--
Random effects model				8.88	[4.40; 17.93]	--	100.0%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 3.4513$, $p = 0$			0 5 10 15 20				

Figure A3. Overall Incidence Rates of Acute Rheumatic Fever in included studies stratified by the decade they were evaluated.

Study	Events	Time	Events per 100000 population	Events	95%-CI	Weight (fixed)	Weight (random)
WHOSR2 = African							
Cilliers	113	6462055.60		1.75	[1.45; 2.10]	7.7%	5.4%
Gapu	10	275252.70		3.63	[1.95; 6.75]	0.7%	5.0%
Fixed effect model				1.86	[1.56; 2.21]	8.4%	—
Random effects model				2.37	[1.17; 4.80]	—	10.4%
Heterogeneity: $I^2 = 80\%$, $\tau^2 = 0.2129$, $p = 0.03$							
WHOSR2 = Americas							
Koo(a)						0.0%	0.0%
Koo(b)						0.0%	0.0%
Tunks	33	3081175.11		1.07	[0.76; 1.51]	2.2%	5.3%
Fixed effect model				1.07	[0.76; 1.51]	2.2%	—
Random effects model				1.07	[0.76; 1.51]	—	5.3%
Heterogeneity: not applicable							
WHOSR2 = Eastern Mediterranean							
Qurashi	34	2014986.00		1.69	[1.21; 2.36]	2.3%	5.3%
Roodpeyma	48	337111.75		14.24	[10.73; 18.89]	3.3%	5.3%
Fixed effect model				5.88	[4.74; 7.30]	5.6%	—
Random effects model						—	10.6%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 2.2493$, $p < 0.01$							
WHOSR2 = European							
Breda	37	1048118.97		3.53	[2.56; 4.87]	2.5%	5.3%
Grassi	65	228280.00		28.47	[22.33; 36.31]	4.4%	5.4%
Karaaslan	147	8312016.27		1.77	[1.50; 2.08]	10.0%	5.4%
Karademir	106	474424.00		22.34	[18.47; 27.03]	7.2%	5.4%
Kocevar	6	124445.00		4.82	[2.17; 10.73]	0.4%	4.8%
Narin	362	3486501.80		10.38	[9.37; 11.51]	24.6%	5.4%
Vinker						0.0%	0.0%
Fixed effect model				8.35	[7.76; 8.98]	49.1%	—
Random effects model				7.71	[3.15; 18.90]	—	31.7%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.2201$, $p < 0.01$							
WHOSR2 = Southeast Asia							
Ahmed						0.0%	0.0%
Bavdekar						0.0%	0.0%
Ramu(a)						0.0%	0.0%
Ramu(b)	18	550102.00		3.27	[2.06; 5.19]	1.2%	5.2%
Routray	324	2398601.74		13.51	[12.11; 15.06]	22.0%	5.4%
Zaman	18	27828.00		64.68	[40.75; 102.66]	1.2%	5.2%
Fixed effect model				13.61	[12.27; 15.09]	24.4%	—
Random effects model						—	15.8%
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.1760$, $p < 0.01$							
WHOSR2 = Western Pacific							
Atato-Carr	36	185457.00		19.41	[14.00; 26.91]	2.4%	5.3%
Beaudoin	26	11782.85		220.66	[150.24; 324.08]	1.8%	5.3%
Corsenac						0.0%	0.0%
Milne						0.0%	0.0%
Noonan	67	2051352.00		3.27	[2.57; 4.15]	4.5%	5.4%
Smith	11	390485.00		2.82	[1.56; 5.09]	0.7%	5.1%
Steer	12	33820.00		35.48	[20.15; 62.48]	0.8%	5.1%
Fixed effect model				12.23	[10.43; 14.34]	10.3%	—
Random effects model							
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 3.4837$, $p < 0.01$							
Fixed effect model				8.08	[7.68; 8.51]	100.0%	—
Random effects model				7.96	[4.72; 13.45]	—	100.0%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.3168$, $p = 0$							

0   5   10   15   20

Figure A4. Female Incidence Rates of Acute Rheumatic Fever in included studies stratified by WHO study region.

Study	Events	Time	Events per 100000 population	Events	95%-CI	Weight (fixed)	Weight (random)
Age5_2 = Over 5							
Ahmed	.	.				0.0%	0.0%
Atato-Carr	36	185457.00		19.41	[14.00; 26.91]	2.4%	5.3%
Corsenac						0.0%	0.0%
Karaaslan	147	8312016.27		1.77	[1.50; 2.08]	10.0%	5.4%
Milne	.	.				0.0%	0.0%
Routray	324	2398601.74		13.51	[12.11; 15.06]	22.0%	5.4%
Steer	12	33820.00		35.48	[20.15; 62.48]	0.8%	5.1%
Zaman	18	27828.00		64.68	[40.75; 102.66]	1.2%	5.2%
Fixed effect model				8.54	[7.85; 9.30]	36.5%	--
Random effects model						--	26.4%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.8490$, $p < 0.01$							
Age5_2 = Under 5							
Bavdekar	.	.				0.0%	0.0%
Beaudoin	26	11782.85		220.66	[150.24; 324.08]	1.8%	5.3%
Breda	37	1048118.97		3.53	[2.56; 4.87]	2.5%	5.3%
Cilliers	113	6462055.60		1.75	[1.45; 2.10]	7.7%	5.4%
Gapu	10	275252.70		3.63	[1.95; 6.75]	0.7%	5.0%
Grassi	65	228280.00		28.47	[22.33; 36.31]	4.4%	5.4%
Karademir	106	474424.00		22.34	[18.47; 27.03]	7.2%	5.4%
Kocevar	6	124445.00		4.82	[2.17; 10.73]	0.4%	4.8%
Koo(a)	.	.				0.0%	0.0%
Koo(b)	.	.				0.0%	0.0%
Narin	362	3486501.80		10.38	[9.37; 11.51]	24.6%	5.4%
Noonan	67	2051352.00		3.27	[2.57; 4.15]	4.5%	5.4%
Qurashi	34	2014986.00		1.69	[1.21; 2.36]	2.3%	5.3%
Ramu(a)	.	.				0.0%	0.0%
Ramu(b)	18	550102.00		3.27	[2.06; 5.19]	1.2%	5.2%
Roodpeyma	48	337111.75		14.24	[10.73; 18.89]	3.3%	5.3%
Smith	11	390485.00		2.82	[1.56; 5.09]	0.7%	5.1%
Tunks	33	3081175.11		1.07	[0.76; 1.51]	2.2%	5.3%
Vinker	.	.				0.0%	0.0%
Fixed effect model				7.83	[7.34; 8.35]	63.5%	--
Random effects model				6.23	[3.26; 11.91]	--	73.6%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.4860$, $p < 0.01$							
Fixed effect model				8.08	[7.68; 8.51]	100.0%	--
Random effects model				7.96	[4.72; 13.45]	--	100.0%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.3168$, $p = 0$							

Figure A5. Female Incidence Rates of Acute Rheumatic Fever in included studies stratified by inclusion of children over or under the age of 5.

Study	Events	Time	Events per 100000 population	Events	95%-CI	Weight (fixed)	Weight (random)
Decade2 = 1990s							
Ahmed	.	.				0.0%	0.0%
Bavdekar	.	.				0.0%	0.0%
Karaaslan	147	8312016.27		1.77	[1.50; 2.08]	10.0%	5.4%
Karademir	106	474424.00		22.34	[18.47; 27.03]	7.2%	5.4%
Koo(a)	.	.				0.0%	0.0%
Koo(b)	.	.				0.0%	0.0%
Fixed effect model				5.12	[4.52; 5.79]	17.2%	--
Random effects model							
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 3.2084$, $p < 0.01$							
Decade2 = 1990s–2000s							
Atato–Carr	36	185457.00		19.41	[14.00; 26.91]	2.4%	5.3%
Cilliers	113	6462055.60		1.75	[1.45; 2.10]	7.7%	5.4%
Grassi	65	228280.00		28.47	[22.33; 36.31]	4.4%	5.4%
Milne	.	.				0.0%	0.0%
Narin	362	3486501.80		10.38	[9.37; 11.51]	24.6%	5.4%
Qurashi	34	2014986.00		1.69	[1.21; 2.36]	2.3%	5.3%
Roodpeyma	48	337111.75		14.24	[10.73; 18.89]	3.3%	5.3%
Routray	324	2398601.74		13.51	[12.11; 15.06]	22.0%	5.4%
Tunks	33	3081175.11		1.07	[0.76; 1.51]	2.2%	5.3%
Fixed effect model				8.96	[8.43; 9.53]	68.9%	--
Random effects model				6.60	[3.34; 13.04]	--	42.8%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 0.9468$, $p < 0.01$							
Decade2 = 2000s							
Beaudoin	26	11782.85		220.66	[150.24; 324.08]	1.8%	5.3%
Breda	37	1048118.97		3.53	[2.56; 4.87]	2.5%	5.3%
Corsenac	.	.				0.0%	0.0%
Gapu	10	275252.70		3.63	[1.95; 6.75]	0.7%	5.0%
Kocevar	6	124445.00		4.82	[2.17; 10.73]	0.4%	4.8%
Noonan	67	2051352.00		3.27	[2.57; 4.15]	4.5%	5.4%
Ramu(a)	.	.				0.0%	0.0%
Ramu(b)	18	550102.00		3.27	[2.06; 5.19]	1.2%	5.2%
Smith	11	390485.00		2.82	[1.56; 5.09]	0.7%	5.1%
Steer	12	33820.00		35.48	[20.15; 62.48]	0.8%	5.1%
Vinker	.	.				0.0%	0.0%
Zaman	18	27828.00		64.68	[40.75; 102.66]	1.2%	5.2%
Fixed effect model				8.52	[7.43; 9.77]	13.9%	--
Random effects model				8.87	[-0.24; 31.03]	--	46.4%
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 2.9475$, $p < 0.01$							
Fixed effect model				8.08	[7.68; 8.51]	100.0%	--
Random effects model				7.96	[4.72; 13.45]	--	100.0%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.3168$, $p = 0$							

Figure A6. Female Incidence Rates of Acute Rheumatic Fever in included studies stratified by

the decade they were evaluated.

Study	Events	Time	Events per 100000 population	Events	95%-CI	Weight (fixed)	Weight (random)
DC2 = 1992 Jones Criteria							
Ahmed	.	.				0.0%	0.0%
Bavdekar	.	.				0.0%	0.0%
Breda	37	1048118.97		3.53	[2.56; 4.87]	2.5%	5.3%
Cilliers	113	6462055.60		1.75	[1.45; 2.10]	7.7%	5.4%
Corsenac	.	.				0.0%	0.0%
Gapu	10	275252.70		3.63	[1.95; 6.75]	0.7%	5.0%
Grassi	65	228280.00		28.47	[22.33; 36.31]	4.4%	5.4%
Karaaslan	147	8312016.27		1.77	[1.50; 2.08]	10.0%	5.4%
Karademir	106	474424.00		22.34	[18.47; 27.03]	7.2%	5.4%
Kocevar	6	124445.00		4.82	[2.17; 10.73]	0.4%	4.8%
Koo(a)	.	.				0.0%	0.0%
Koo(b)	.	.				0.0%	0.0%
Narin	362	3486501.80		10.38	[9.37; 11.51]	24.6%	5.4%
Qurashi	34	2014986.00		1.69	[1.21; 2.36]	2.3%	5.3%
Ramu(a)	.	.				0.0%	0.0%
Ramu(b)	18	550102.00		3.27	[2.06; 5.19]	1.2%	5.2%
Roodpeyma	48	337111.75		14.24	[10.73; 18.89]	3.3%	5.3%
Routray	324	2398601.74		13.51	[12.11; 15.06]	22.0%	5.4%
Steer	12	33820.00		35.48	[20.15; 62.48]	0.8%	5.1%
Tunks	33	3081175.11		1.07	[0.76; 1.51]	2.2%	5.3%
Vinker	.	.				0.0%	0.0%
Zaman	18	27828.00		64.68	[40.75; 102.66]	1.2%	5.2%
Fixed effect model				7.81	[7.40; 8.24]	90.5%	--
Random effects model				6.83	[3.92; 11.89]	--	79.0%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.1634$, $p < 0.01$							
DC2 = 2012 Australian Guidelines							
Noonan	67	2051352.00		3.27	[2.57; 4.15]	4.5%	5.4%
Fixed effect model				3.27	[2.57; 4.15]	4.5%	--
Random effects model				3.27	[2.57; 4.15]	--	5.4%
Heterogeneity: not applicable							
DC2 = ICD9-10							
Atato-Carr	36	185457.00		19.41	[14.00; 26.91]	2.4%	5.3%
Beaudoin	26	11782.85		220.66	[150.24; 324.08]	1.8%	5.3%
Milne	.	.				0.0%	0.0%
Smith	11	390485.00		2.82	[1.56; 5.09]	0.7%	5.1%
Fixed effect model				34.49	[27.42; 43.39]	5.0%	--
Random effects model							
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 3.8006$, $p < 0.01$							
Fixed effect model				8.08	[7.68; 8.51]	100.0%	--
Random effects model				7.96	[4.72; 13.45]	--	100.0%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.3168$, $p = 0$							

Scale: 0 5 10 15 20

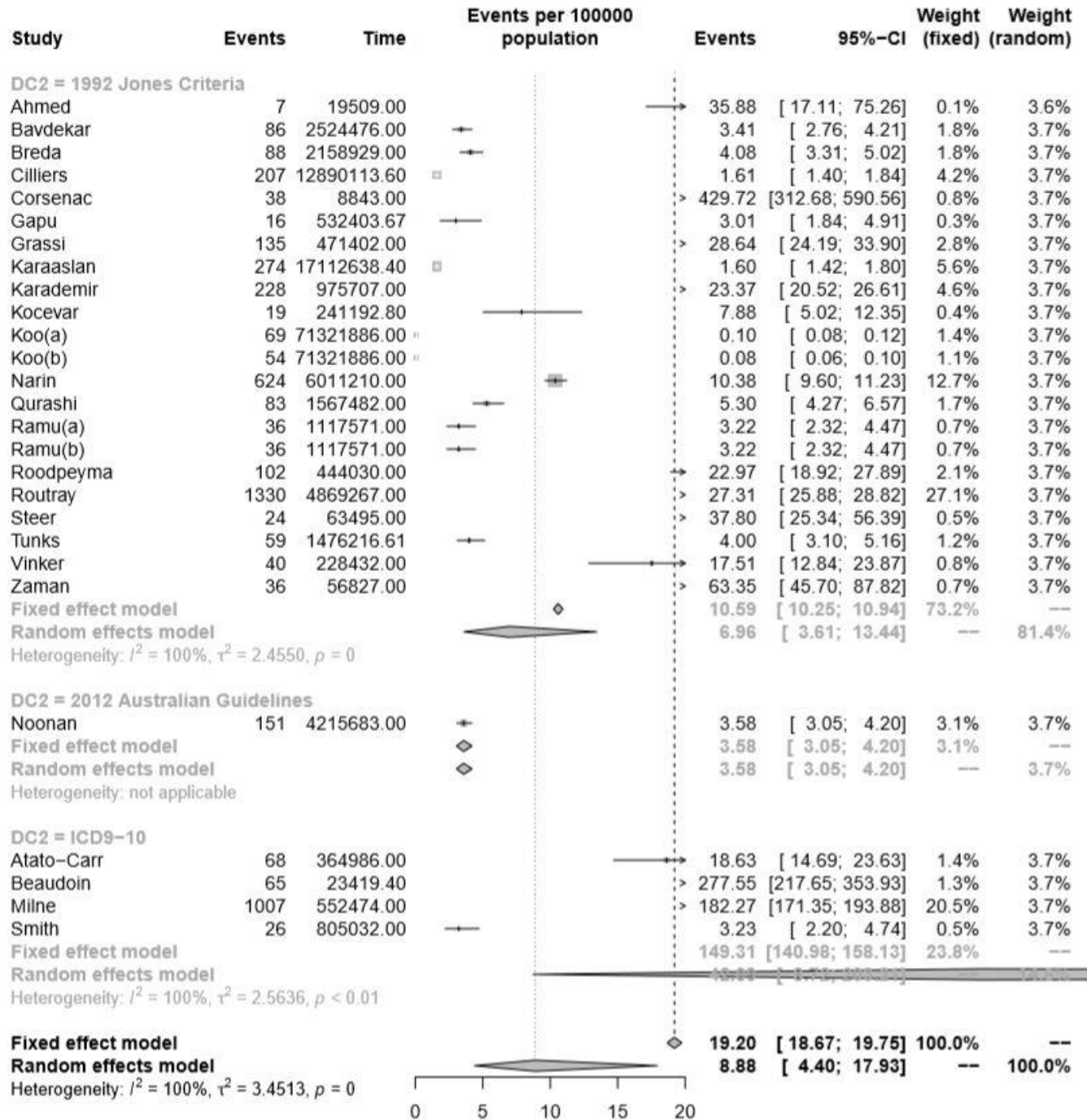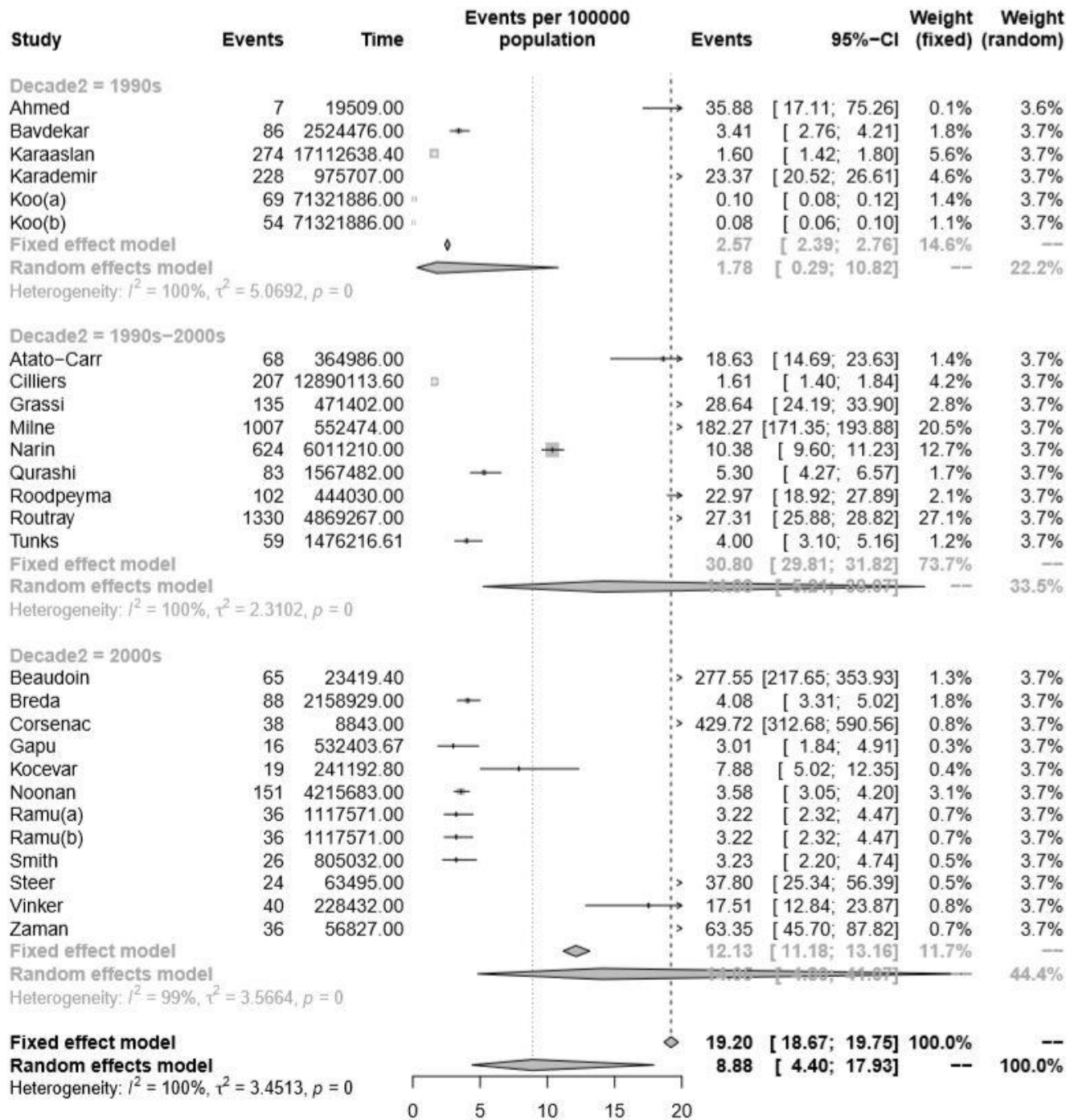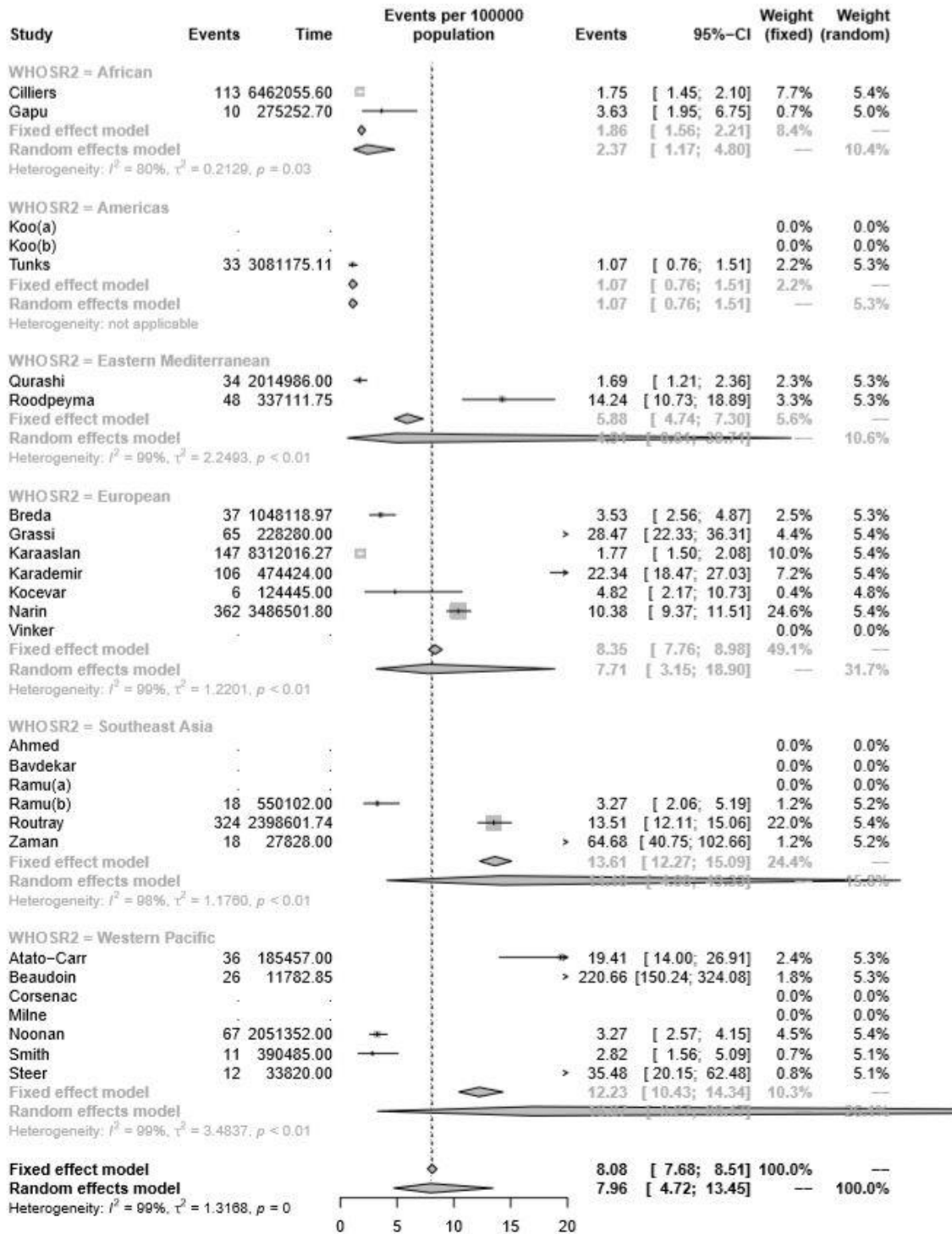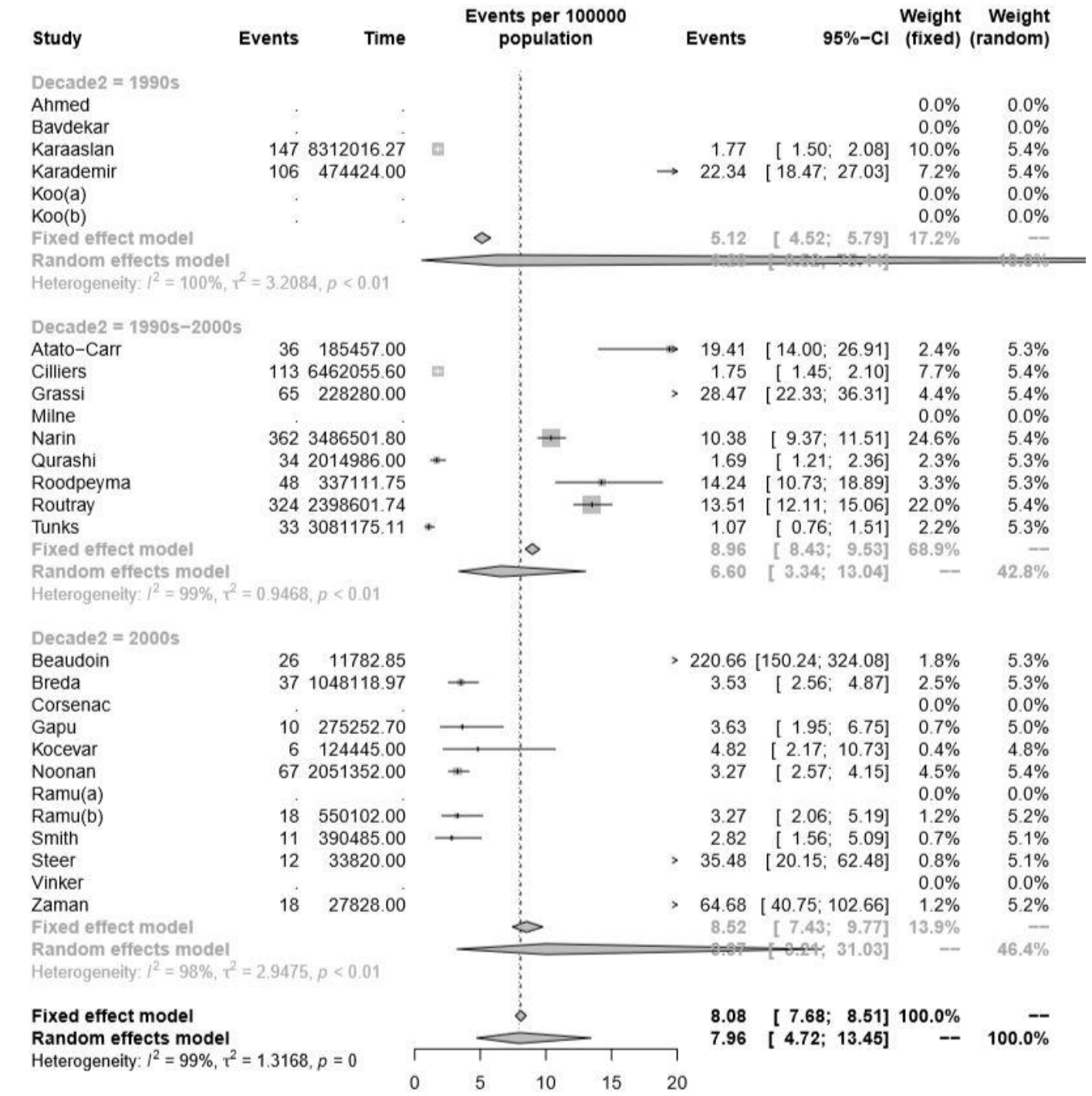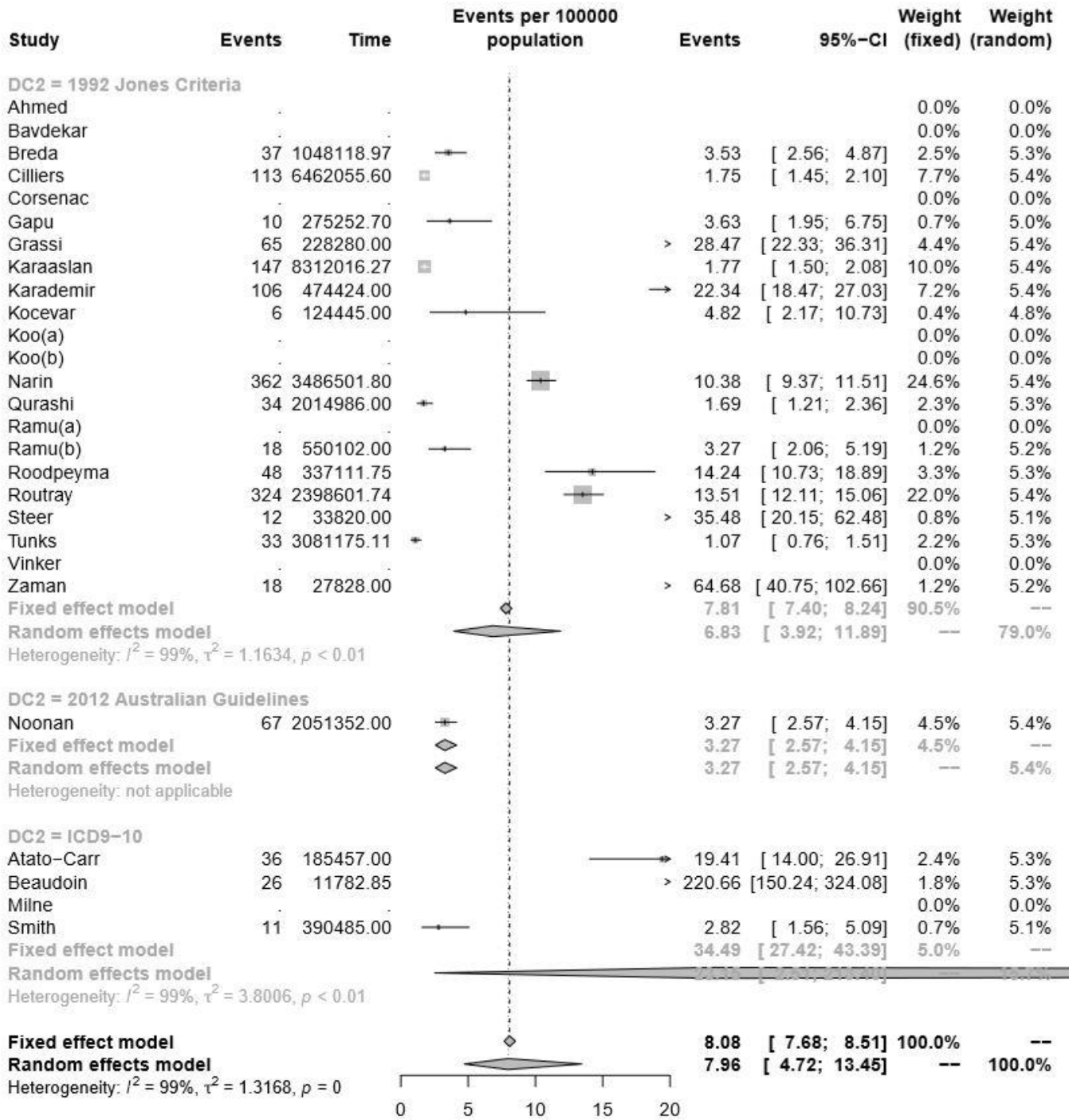*Figure A7.* Female Incidence Rates of Acute Rheumatic Fever in included studies stratified by the diagnostic criteria used.

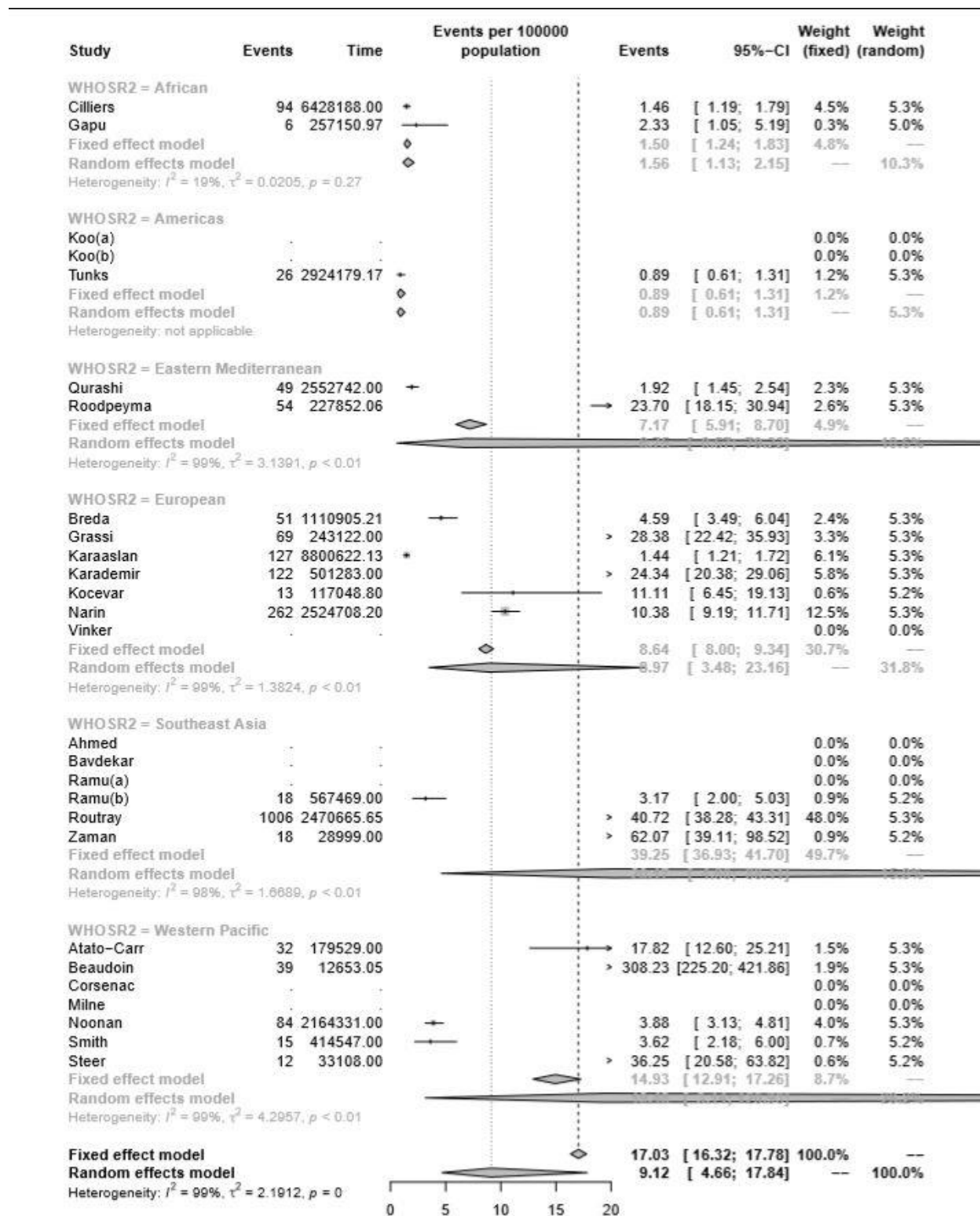| Study	Events	Time	Events per 100000 population	Events	95%-CI	Weight (fixed)	Weight (random)
WHOSR2 = African							
Cilliers	94	6428188.00		1.46	[1.19; 1.79]	4.5%	5.3%
Gapu	6	257150.97		2.33	[1.05; 5.19]	0.3%	5.0%
Fixed effect model				1.50	[1.24; 1.83]	4.8%	—
Random effects model				1.56	[1.13; 2.15]	—	10.3%
Heterogeneity: $I^2 = 19\%$, $\tau^2 = 0.0205$, $p = 0.27$							
WHOSR2 = Americas							
Koo(a)						0.0%	0.0%
Koo(b)						0.0%	0.0%
Tunks	26	2924179.17		0.89	[0.61; 1.31]	1.2%	5.3%
Fixed effect model				0.89	[0.61; 1.31]	1.2%	—
Random effects model				0.89	[0.61; 1.31]	—	5.3%
Heterogeneity: not applicable							
WHOSR2 = Eastern Mediterranean							
Qurashi	49	2552742.00		1.92	[1.45; 2.54]	2.3%	5.3%
Roodpeyma	54	227852.06		23.70	[18.15; 30.94]	2.6%	5.3%
Fixed effect model				7.17	[5.91; 8.70]	4.9%	—
Random effects model							
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 3.1391$, $p < 0.01$							
WHOSR2 = European							
Breda	51	1110905.21		4.59	[3.49; 6.04]	2.4%	5.3%
Grassi	69	243122.00		28.38	[22.42; 35.93]	3.3%	5.3%
Karaaslan	127	8800622.13		1.44	[1.21; 1.72]	6.1%	5.3%
Karademir	122	501283.00		24.34	[20.38; 29.06]	5.8%	5.3%
Kocevar	13	117048.80		11.11	[6.45; 19.13]	0.6%	5.2%
Narin	262	2524708.20		10.38	[9.19; 11.71]	12.5%	5.3%
Vinker						0.0%	0.0%
Fixed effect model				8.64	[8.00; 9.34]	30.7%	—
Random effects model				8.97	[3.48; 23.16]	—	31.8%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.3824$, $p < 0.01$							
WHOSR2 = Southeast Asia							
Ahmed						0.0%	0.0%
Bavdekar						0.0%	0.0%
Ramu(a)						0.0%	0.0%
Ramu(b)	18	567469.00		3.17	[2.00; 5.03]	0.9%	5.2%
Routray	1006	2470665.65		40.72	[38.28; 43.31]	48.0%	5.3%
Zaman	18	28999.00		62.07	[39.11; 98.52]	0.9%	5.2%
Fixed effect model				39.25	[36.93; 41.70]	49.7%	—
Random effects model							
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.6689$, $p < 0.01$							
WHOSR2 = Western Pacific							
Atato-Carr	32	179529.00		17.82	[12.60; 25.21]	1.5%	5.3%
Beaudoin	39	12653.05		308.23	[225.20; 421.86]	1.9%	5.3%
Corsenac						0.0%	0.0%
Milne						0.0%	0.0%
Noonan	84	2164331.00		3.88	[3.13; 4.81]	4.0%	5.3%
Smith	15	414547.00		3.62	[2.18; 6.00]	0.7%	5.2%
Steer	12	33108.00		36.25	[20.58; 63.82]	0.6%	5.2%
Fixed effect model				14.93	[12.91; 17.26]	8.7%	—
Random effects model							
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 4.2957$, $p < 0.01$							
Fixed effect model				17.03	[16.32; 17.78]	100.0%	—
Random effects model				9.12	[4.66; 17.84]	—	100.0%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 2.1912$, $p = 0$							

0   5   10   15   20

Figure A8. Male Incidence Rates of Acute Rheumatic Fever in included studies stratified by

WHO Study Region.

Study	Events	Time	Events per 100000 population		Events	95%-CI	Weight (fixed)	Weight (random)
Age5_2 = Over 5								
Ahmed	.	.					0.0%	0.0%
Atato–Carr	32	179529.00		>	17.82	[12.60; 25.21]	1.5%	5.3%
Corsenac	.	.					0.0%	0.0%
Karaaslan	127	8800622.13	*		1.44	[1.21; 1.72]	6.1%	5.3%
Milne	.	.					0.0%	0.0%
Routray	1006	2470665.65		>	40.72	[38.28; 43.31]	48.0%	5.3%
Steer	12	33108.00		>	36.25	[20.58; 63.82]	0.6%	5.2%
Zaman	18	28999.00		>	62.07	[39.11; 98.52]	0.9%	5.2%
Fixed effect model					28.07	[26.52; 29.71]	57.0%	--
Random effects model							--	
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 3.8174$, $p < 0.01$								
Age5_2 = Under 5								
Bavdekar	.	.					0.0%	0.0%
Beaudoin	39	12653.05		>	308.23	[225.20; 421.86]	1.9%	5.3%
Breda	51	1110905.21	—		4.59	[3.49; 6.04]	2.4%	5.3%
Cilliers	94	6428188.00	*		1.46	[1.19; 1.79]	4.5%	5.3%
Gapu	6	257150.97	—		2.33	[1.05; 5.19]	0.3%	5.0%
Grassi	69	243122.00		>	28.38	[22.42; 35.93]	3.3%	5.3%
Karademir	122	501283.00		>	24.34	[20.38; 29.06]	5.8%	5.3%
Kocevar	13	117048.80			11.11	[6.45; 19.13]	0.6%	5.2%
Koo(a)	.	.					0.0%	0.0%
Koo(b)	.	.					0.0%	0.0%
Narin	262	2524708.20	—		10.38	[9.19; 11.71]	12.5%	5.3%
Noonan	84	2164331.00	—		3.88	[3.13; 4.81]	4.0%	5.3%
Qurashi	49	2552742.00	+		1.92	[1.45; 2.54]	2.3%	5.3%
Ramu(a)	.	.					0.0%	0.0%
Ramu(b)	18	567469.00	—		3.17	[2.00; 5.03]	0.9%	5.2%
Roodpeyma	54	227852.06		→	23.70	[18.15; 30.94]	2.6%	5.3%
Smith	15	414547.00	—		3.62	[2.18; 6.00]	0.7%	5.2%
Tunks	26	2924179.17	+		0.89	[0.61; 1.31]	1.2%	5.3%
Vinker	.	.					0.0%	0.0%
Fixed effect model					8.79	[8.23; 9.38]	43.0%	--
Random effects model					7.07	[3.44; 14.52]	--	73.7%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.8515$, $p < 0.01$								
Fixed effect model					17.03	[16.32; 17.78]	100.0%	--
Random effects model					9.12	[4.66; 17.84]	--	100.0%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 2.1912$, $p = 0$			0 5 10 15 20					

Figure A9. Male Incidence Rates of Acute Rheumatic Fever in included studies stratified by

inclusion of children under or over the age of 5.

82

Study	Events	Time	Events per 100000 population	Events	95%-CI	Weight (fixed)	Weight (random)
Decade2 = 1990s							
Ahmed	.	.				0.0%	0.0%
Bavdekar	.	.				0.0%	0.0%
Karaaslan	127	8800622.13		1.44	[1.21; 1.72]	6.1%	5.3%
Karademir	122	501283.00		24.34	[20.38; 29.06]	5.8%	5.3%
Koo(a)	.	.				0.0%	0.0%
Koo(b)	.	.				0.0%	0.0%
Fixed effect model				5.76	[5.09; 6.52]	11.9%	--
Random effects model							
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 3.9830$, $p < 0.01$							
Decade2 = 1990s–2000s							
Atato–Carr	32	179529.00		17.82	[12.60; 25.21]	1.5%	5.3%
Cilliers	94	6428188.00		1.46	[1.19; 1.79]	4.5%	5.3%
Grassi	69	243122.00		28.38	[22.42; 35.93]	3.3%	5.3%
Milne	.	.				0.0%	0.0%
Narin	262	2524708.20		10.38	[9.19; 11.71]	12.5%	5.3%
Qurashi	49	2552742.00		1.92	[1.45; 2.54]	2.3%	5.3%
Roodpeyma	54	227852.06		23.70	[18.15; 30.94]	2.6%	5.3%
Routray	1006	2470665.65		40.72	[38.28; 43.31]	48.0%	5.3%
Tunks	26	2924179.17		0.89	[0.61; 1.31]	1.2%	5.3%
Fixed effect model				21.72	[20.68; 22.81]	75.9%	--
Random effects model				7.75	[2.91; 20.61]	--	42.5%
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 1.9752$, $p = 0$							
Decade2 = 2000s							
Beaudoin	39	12653.05		308.23	[225.20; 421.86]	1.9%	5.3%
Breda	51	1110905.21		4.59	[3.49; 6.04]	2.4%	5.3%
Corsenac	.	.				0.0%	0.0%
Gapu	6	257150.97		2.33	[1.05; 5.19]	0.3%	5.0%
Kocevar	13	117048.80		11.11	[6.45; 19.13]	0.6%	5.2%
Noonan	84	2164331.00		3.88	[3.13; 4.81]	4.0%	5.3%
Ramu(a)	.	.				0.0%	0.0%
Ramu(b)	18	567469.00		3.17	[2.00; 5.03]	0.9%	5.2%
Smith	15	414547.00		3.62	[2.18; 6.00]	0.7%	5.2%
Steer	12	33108.00		36.25	[20.58; 63.82]	0.6%	5.2%
Vinker	.	.				0.0%	0.0%
Zaman	18	28999.00		62.07	[39.11; 98.52]	0.9%	5.2%
Fixed effect model				10.79	[9.55; 12.20]	12.2%	--
Random effects model						--	46.9%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 3.3099$, $p < 0.01$							
Fixed effect model				17.03	[16.32; 17.78]	100.0%	--
Random effects model				9.12	[4.66; 17.84]	--	100.0%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 2.1912$, $p = 0$							

Figure A10. Male Incidence Rates of Acute Rheumatic Fever in included studies stratified by diagnostic criteria used.

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