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Understanding the Role of the Scabies Mite Microbiota in the Development of Novel Control Strategies

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Introduction

With a global prevalence of approximately 300 million people, scabies is one of the most common dermatological infectious diseases worldwide, and was recognised as a neglected tropical disease in 2017 by the World Health Organisation [1]. Scabies is especially prevalent in economically disadvantaged communities and disproportionately affects children in poor and over-crowded living conditions [2]. The causative agent of human scabies is the parasitic mite *Sarcoptes scabiei var hominis*. These microscopic acarid arthropods burrow into the superficial layers of the skin where they lay eggs, from which larvae hatch and develop into nymphs and adults. It is thought that mite material, in particular allergens in the faeces and saliva trigger an immune response in the host that leads to intense itching [3,4]. Both, the host scratching in response to the itch and the burrowing of the mite result in mechanical damage of the skin, and the disruption of this key physiological barrier can lead to opportunistic bacterial infections that have severe downstream consequences. *Staphylococcus aureus* and *Streptococcus pyogenes* are the most well recognised opportunistic pathogens associated with scabies infestations [5-14] and have been clearly linked to pyoderma, and cellulitis which can lead to life-threatening *S. aureus* associated bacteraemia, or severe post-streptococcal sequelae such as glomerulonephritis and rheumatic fever/heart disease [15]. Indeed, particularly in tropical climates, scabies infections have proven links to serious *S. pyogenes* and *S. aureus* associated disease [6,8,14,15] which can be life-threatening [16]. In addition, scabies causes decreased quality of life due to the stigmatisation associated with the disease, with a perceived impact on schooling and social engagement especially in communities where recurrent infection is common [17]. Scabies and associated secondary infections amount to a substantial, yet widely overlooked morbidity and mortality burden worldwide, particularly in endemic resource poor communities where prevalence is estimated to be anywhere between 40-80% [18,19]. Increased research is urgently required to tackle this disease complex.

There is increasing evidence of bacterial involvement in parasitic arthropod infections [20], raising questions for future research into the microbial communities associated with scabies mites, both, regarding their pathogenicity, and whether mite-associated bacteria essential for mite survival could be a novel scabicide target [21]. Many parasitic arthropods, such as the tick *Ixodes sp.,* are known to act as vectors for pathogenic bacteria, for example, in this case *Borrelia burgdorferi* is the causative agent of Lyme's disease [22]. The emerging role of parasitic arthropods as vectors for severe bacterial infections has prompted increased interest into the bacterial species associated with these arthropods and whether direct transmission is possible. A comparable arthropod to the scabies mite is the head and body louse *Pediculus humanus,* as both species have an obligate parasitic life cycle. The head louse is a known vector for *Rickettsia prowazekkii (*typhus), *Borrelia recurrentis (*relapsing fever), and *Bartonella Quintana (*trench fever) [23]. More recent research has found that body lice harbour the mutli-drug resistance (MDR) Gram-negative *Acinetobacter baumannii* bacteria [23,24]. A study by Houhamdi and Raoult, found that body lice feeding on *A. baumannii* infected rabbits acquired

the pathogen, however, failed to transmit the bacteria to other rabbits by bite, and no evidence of transmission to the louse progeny was observed [24]. They did however, find that live bacteria was excreted in their faeces, and that *A. baumannii* was pathogenic to body lice, with increased mortality seen between the second and third days post infection [24].

Any pathogen that comes in contact with vertebrate body fluid must defend itself against the onslaught of the host innate immune system. Many parasites have anti-complement proteins, which help them to evade the primary immune defences [25,26]. In scabies mites the SMIPP-Ss have been proven to inhibit the binding of the lectin pathway [4], and further research indicates that several classes of proteins could target different mechanisms in the host complement pathway, making it a sophisticated immune diversion tactic for the mites [3,4]. Understanding the role of mite proteins in immunomodulation is key to understanding how serious secondary bacterial infections result from scabies infestation, and how these mites interact with their own microbiome and their host's microbiome. However, little is understood about the internal mite microbiota and the potential pathogenic or symbiotic organisms it carries. Symbiotic bacteria that have proven to be beneficial to their host species often provide essential nutrients that the host is unable to synthesise, or they produce compounds that protect the host species [21,27]. As such these endosymbiont species have become interesting target candidates for therapeutic control of parasitic diseases [28,29].

What We Know about the Scabies Mite Microbiota

The advancements in high-throughput metagenomics technologies have provided a critical resource for understanding the structure, activities, functions and population dynamics of microbial communities in a variety of environments [30]. The potential role of these technologies in understanding the dynamics of infection could provide crucial information for understanding the complex microbial communities associated with parasitic arthropod species, as well as the affects this has on the human host's microbiota. In a first study of this kind, Swe et al. investigated the *Sarcoptes scabiei* internal microbiota through high-throughput metagenome sequencing, and used Fluorescent *in situ* hybridisation (FISH) to demonstrate the presence of intestinal symbionts. As most scabies patients harbour only a few mites at any time on the body, it is extremely difficult to collect sufficient mite numbers for experimental studies, as such a porcine scabies model, developed by Mounsey et al. in 2010 [31] has provided the opportunity for crucial developments in scabies research. Pigs and humans share a remarkably similar skin physiology meaning clinical manifestation of *S. scabiei* infestation are remarkably similar between the two species [32, 33]. Human and pig biovars of the mites are very closely related [34], making this *in vivo* model an optimal tool for basic molecular biology research [32-34] and will prove useful in future scabicide discovery and development.

Using this porcine scabies model, Swe et al. isolated female mites and eggs from crusted skin lesions, washed them to remove external microorganisms, and extracted DNA. Illumina sequencing highlighted marked differences between the bacterial species present in the adult mites versus the eggs [35]. 89% of the adult female microbiome was comprised of the phylum Proteobacteria, with *Klebsiella* being the most abundant in this phylum at 78%. *Klebsiella sp.* has been noted in other arthropod species, for example *Ceratitis capitate* (Mediterranean fruit fly) where it has been found in the gut and has been shown to increase fecundity [36]. Actinobacteria accounted for 9% of the adult scabies mite microbiome, with *Corynbacterium* being the most abundant from this phylum. *Corynebacteria* have been found in the alimentary tracts of a number of parasitic arthropod species that are of human and veterinary importance, such as the tick *Ixodes ricinus* [37]. In comparison to the adult mite microbiome, the scabies egg metagenome contained much fewer microbial reads, of which less than 40% were assigned to a bacterial taxon. The study provided no clear evidence of egg internal microbiota.

Streptomyces is a common symbiotic bacteria of plants, animals and fungi belonging to the phylum Actinobacteria. It is ubiquitous in soil where it plays an important ecological role in organic material turnover [38], and it can be pathogenic to humans [38]. The study by Swe et al., predicted through Kraken analysis, and confirmed by PCR, that *Streptomyces sp.* was associated with both, scabies eggs and mites [35]. *In situ* hybridization (FISH) clearly localised *Streptomyces* and *Klebsiella* to the mite guts and faeces, however, neither were detected within or on the surface of eggs [35]. This may tell us that *Streptomyces* and *Klebsiella* species dominate and are adapted to the mite intestinal environment. It was suggested by Swe at el., that *Streptomyces,* as a known producer of enzymes that degrade complex carbohydrates, may assist in the digestion of skin and serum, which is the proposed nutrient source of *Sarcoptes* mites [39]. It is also possible that the presence of *Streptomyces* may inhibit unfavourable bacteria through the production of anti-microbial compounds, thus making it an important component of the mite gut microflora, and a potential therapeutic target [35].

Interactions with the Host Microbiome During Scabies Infestation

In addition to understanding the mite's internal microbiota, *in vivo* work has been done using the porcine scabies model to understand whether scabies mites alter the skin microbiome and promote growth of opportunistic pathogens. In 2014 Swe et al. conducted the first *in vivo* testing to support the hypothesis that scabies infections allow for the establishment of pathogenic bacteria [40]. They conducted a 21 week trial using *Sarcoptes scabiei var suis* infected pigs and non-infected pigs. They collected skin samples before, during and after treatment with an acaricide. This research found that there was an increase in *Staphylococcus* species on infected pigs, with a shift from the commensal *S. hominis* to the more virulent *S. chromogenes,* which is recognised as the causative agent of exudative epidermitis in pigs [40]. Comparatively, *Staphylococcus* levels stayed low in the non-infected control group, indicating that scabies infestations favour the colonisation of *Staphylococcus* on the skin [40]. This correlates with clinical scabies infections in humans, where a definitive link with *S. aureus* secondary infections is recognised, which is the likely result of a decrease in the benign commensal *S. epidermidis* [41,42]. As *S. pyogenes* is not known to infect pigs, there is to date no *in vivo* data available for coinfection of scabies mites and this important pathogen. Interestingly, in this study other *Streptococcus* species were not significantly affected by scabies infection. The findings that scabies infections dramatically increase the population of *Staphylococcus* species correlates with early work done in Ghana and the USA [43,44], that used less sensitive culture methods to determine the predominant bacterial species associated with secondarily infected scabies lesions. Both of these investigations determined that the predominant organisms in hand lesions were *S. aureus* and beta-haemolytic Streptococci [43,44].

As previously mentioned, *Corynebacterium* was found to be associated with the mite internal microbiota [35]. Interestingly the *in vivo* study reflected this finding. Once crust formation started in the mite-infected pig cohort a drastic decrease in the population diversity of bacterial strains was observed in the microbiome of crusted sites with over 70% of the reads being assigned to *Corynebacyerium* [40]. Likely representing the thousands of mites present in a typical crusted scabies sample. This finding links back to the role this species may play as a gut commensal in scabies mites. This was a first *in vivo* indication that there is indeed a complex link between scabies infestation and changes in the vertebrate host skin microflora, and that a dysbiosis of the normal skin microbiota continues after treatment [40]. As there are undoubtedly differences between the pig and human skin microbiomes, human specific studies are necessary. Recent studies have demonstrated the importance of the human skin microbiota in preventing immune-mediated disease [41], and evidence that links inflammatory skin diseases with dysregulation of the microbiome is increasing [41]. For example, psoriasis lesions show a significant proliferation of bacterial and fungal species in comparison to healthy skin [45]. To better understand the changes in the human skin microflora associated with increasing severity of scabies infections and how this is influenced over the course of treatment, systematic longitudinal observation of the microbiota of defined body sites, from a range of patient cohorts is required.

Future Directions for Research

It is estimated that scabies accounts for a total of 3.8 million disability-adjusted-life-years (DALYs) and that the potential incidence per year could be anywhere up to 455 million cases [46,47]. In Aboriginal children living in regional/remote Northern Australia it is estimated that prevalence is up to 50%, and Aboriginal children are 12 times more likely to develop impetigo when infected with scabies mites, a factor that contributes to the high incidence of rheumatic fever and heart disease in these communities, which is currently estimated to be around 2%, the highest reported global incidence [48,49]. The destruction of the skin barrier through scratching and the arsenal of anti-complement proteins that mites possess allow for the burden of secondary infections associated with scabies. As a result of the significant burden scabies infections pose globally, novel strategies are required to highlight and combat this serious disease. It is now understood that a healthy microbiome is important for preventing infection, and post-immune conditions [41]. Therefore, it seems apt that future scabies research focus on the host microbiome and how this is affected over the course of the disease, as well as the mite microbiome to identify additional pathogens that may be associated with this disease, and potentially to identify novel therapeutic controls through the control of symbiotic bacteria.

The studies evaluated here are the first to provide a detailed understanding of the complex changes that occur during scabies infections, and to explore the potential symbiotic bacteria associated with scabies mites. To further expand on this work Bernigaud et al., (in review) completed a two patient study in Northern Australia to identify the bacterial communities associated with crusted scabies infections. This research found that despite some differences between the two patients, the most abundant bacteria present were opportunistic pathogens, such as *S. aureus, A. baumannii,* and *Streptococcus species (*Bernigaud et al., 2021 article in review). Further to this, Bernigaud et al., are undertaking a global study that is seeking to determine the microbiome associated with ordinary scabies infections across three different countries (India, Australia and France). These studies will further

advance our understanding of the complex nature of scabies infections, how population dynamics and climate may affect scabies associated bacterial infections, as well as the most prevalent opportunistic pathogens associated with scabies. In addition to these important patient level studies, further areas of interest could be to investigate the potential of disease control through targeting symbiotic bacteria associated with scabies mites, as has been done with some success in triatomine bugs that transmit Chagas disease [50]. In order to do this, *in vitro* level studies would be needed to understand how the identified scabies mite symbionts, such as *Streptomyces sp.,* aid their host and how this affects mite mortality. Novel controls for arthropod borne diseases are of increasing importance, as the WHO has suggested that 125 different arthropod species are resistant to at least one insecticide [50,51]. Recent evidence has suggested there is increased incidence of resistance in scabies mites to the two most commonly used drugs, Ivermectin and Permethrin, making the development of novel therapeutic interventions necessary for the control and eradication of scabies [50-53]. It is evident that research into the scabies microbiome is critical for disease control, and the significant advancements that have been made in this field thanks to the use of metagenomics technologies will result in novel areas for applied research and ultimately better patient outcomes.

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