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The maggot therapy supply chain – a review of the literature and practice

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Running Head

The maggot therapy supply chain

Key Words

Lucilia sericata, Lucilia cuprina, biotherapy, larval therapy, maggot debridement therapy, wound care

ABSTRACT

Maggot therapy is the clinical application of living fly larvae for the treatment of non-healing wounds and wounds that require debridement. This systematised and expanded literature review is the first study to investigate maggot therapy through the conceptual and disciplinary framework of supply chain management. The review of 491 selected academic papers was expanded to include grey literature and online information resources to construct a first-pass theory of the maggot therapy supply chain. It shows that the literature to date has focused on isolated discussions of echelon-specific issues such as diet improvement and sterilisation protocols in the production echelon, or the relative effectiveness of medicinal maggot application methods in the treatment echelon. There is little knowledge in the public domain regarding the transport and distribution of medicinal maggots, but existing supply chains for vaccines, blood and pathology specimens may provide learning and supply chain integration opportunities. Maggot therapy knowledge across the treatment echelon is generally substantive but there is still insufficient knowledge regarding patients' and healthcare providers' attitude toward the therapy, and their experience receiving and administering maggot therapy. Moreover, there is no research concerned with the humane disposal of medicinal flies during production and after treatment.

Introduction

Wounds are a significant healthcare problem the world over. On any given day, 50,000 Australian patients live with diabetic ulcers, and 12 of these patients receive an amputation (Diabetic Foot Australia, 2018). In the United States, the situation is very similar. According to Nussbaum and colleagues (2017), 14.5% of American Medicare patients had a wound or wound infection in 2014. A conservative estimate for Medicare spending in that year was $32 billion, with the top two categories being surgical wound infections (4%) and diabetic wound infections (3.4%). Modern lifestyle changes in low- and middle-income countries (LMICs) are bringing about a rapid rise in obesity, vascular disease and diabetes, which in many cases lead to chronic foot and leg ulcers (Bhurosy & Jeewon, 2014; Misra *et al.*, 2014). World-wide, 629 million people will have diabetes by 2045 (e.g. 82 million in North Africa, 41 million in Sub-Saharan Africa, and 183 million across SE Asia, China, Australia and the Pacific) (IDF, 2017), and of these up to 156 million may develop foot ulcers. Moreover, other diseases such as road traffic injury, immobility and disability, and cancer also lead to wounds and add to the massive wound burden in LMICs (Alexander, 2009; Amir *et al.*, 2013; Dhillon *et al.*, 2014). Options that are evidence-based, affordable, and have a long track record of use and success are needed to address these challenges. Maggot therapy (MT), also known as maggot debridement therapy, larval therapy or biosurgery, is one of these options.

MT is the therapeutic use of fly larvae, commonly referred to as ‘maggots’, for the treatment of wounds. As opposed to myiasis (the infestation of wounds by wild maggots), MT is the deliberate clinical application of sterilized medicinal maggots that have been reared under controlled laboratory conditions with strict quality control procedures in place. Currently, MT is mainly carried out using two closely related species of fly, the green bottle blowfly *Lucilia sericata* (Sherman, 2009), and the sheep blowfly *Lucilia cuprina* (Paul et al., 2009). In 2004, the Food and Drugs Administration in the USA granted permission to supply medicinal maggots as a prescription only device (FDA, 2007). In that year, approval was also granted in the UK to prescribe maggot therapy (Geary et al., 2009). The historical context of MT has been comprehensively summarized elsewhere (Kruglikova & Chernysh, 2013; Whitaker et al., 2006), and numerous studies have demonstrated the efficaciousness of MT (Nigam & Morgan, 2016; Sun *et al.*, 2014).

Notwithstanding this clinical evidence, there are few commercial producers of medicinal maggots around the world, and production is mostly small-scale. The uptake of MT is being hindered by social and technical barriers. On one hand the uptake of MT depends on ministries of health, healthcare administrators, practitioners, and patients accepting the therapy. On the other hand, healthcare providers and patients make decisions based on the quality, efficacy, availability, cost and practicality of therapeutic services. This causation cycle results in a lack of access to MT for patients in LMIC healthcare settings, but also in many high-income countries. It appears that breaking the cycle must involve the improvement of the MT supply chain. This is supported by the observation that the two most prominent commercial providers of medicinal maggots, Monarch Labs (http://www.monarchlabs.com/) and BioMonde (https://biomonde.com/en), are located in the United States, and the UK and Europe, respectively. The companies have modern laboratory facilities and operate in jurisdictions with good transport infrastructure and a sophisticated courier network (Harb, 2015). A supply chain can be understood as “the network of organizations that are involved, through upstream and downstream linkages, in the different processes and activities that produce value in the form of products and services in the hands of the ultimate consumer” (Christopher, 2011, p. 13). In other words, the MT supply chain involves upstream the production laboratory and its suppliers, which are linked to downstream healthcare providers and patients via transport service providers (Figure 1).

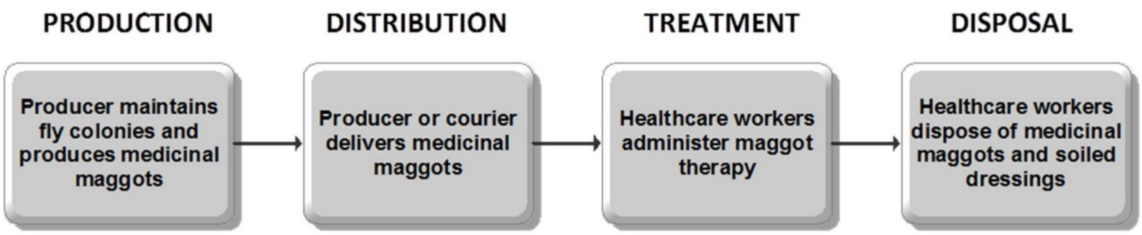

Figure 1: The simplified supply chain for maggot therapy.

Given the centrality of the supply chain to service provision, it was timely to survey what is known about MT supply chains and their management. The task was to bring together disparate, but yet connected lines of inquiry, in order to build a first-pass coherent theory of the MT supply chain with currently available information. The review takes an inter- and trans-disciplinary approach and interrogates literature pertinent to each performance cycle of the MT supply chain: i) production of medicinal maggots and required supplies; ii) the distribution of medicinal maggots; and iii) maggot debridement therapy itself, and iv) the final disposal of dressings and used maggots. There is a constant flow of information and materials between these performance cycles, and this is the domain of logistics within the supply chain. Consequently, the review draws on literature from dipteran-, forensic- and medical entomology, wound care and MT. Moreover, supply chain management for medicinal maggots and related products poses challenges similar to those experienced by other perishable product lines such as vaccines (Kumru *et al.*, 2014) and blood products (Belien & Force, 2012), and this is why some relevant literature from these domains has also been considered.

Materials and Methods

In order to comprehensively examine the literature and evidence on the MT supply chain, the English language peer-reviewed literature published in academic Journals was interrogated in a systematized fashion (Grant & Booth, 2009). Because of the interdisciplinary nature of MT supply chain issues, seven discrete searches across five academic databases were performed as outlined in Table 1. The search algorithms were determined by the need to understand a) the biology of flies currently used for MT and of potential new candidate species, b) fly rearing and medicinal maggot production and distribution practice, and c) maggot debridement therapy practice. Algorithms and search field combinations were explored by trial and error to find those that yielded the most comprehensive and relevant literature without identifying obviously irrelevant literature. Searches of the literature up to December 2018 were conducted at five time points between January 2015 and December 2018. Search results were systematically evaluated (Figure 2) and references were collated into EndNote X7™ (Clarivate Analytics), and duplicates were removed. Articles were further preselected based on titles and abstracts, and a thorough assessment of relevance by reading full texts. The full-text review resulted in papers being scored on a scale of 1 to 5 with one being least relevant and five being most relevant to MT supply chain knowledge, and only articles with scores of three and higher were considered.

Algorithm	Pub Med[1]	CINAHL[2]	SCOPUS[3]	ProQuest[4]	Web of Science[5]
(maggot* OR larva*) AND	X		X	X	X
(maggot* OR larva*) AND (debridement OR wound)		X			
(rear* OR diet) AND Calliphoridae			X	X	X
(development* OR egg OR larva* OR pupa* OR adult) AND Calliphoridae			X	X	X
myiasis AND Calliphoridae AND	X		X	X	
myiasis AND human		X			
myiasis AND Calliphoridae					X

Table 1: Database searches. Algorithms and search field combinations for each database were explored by trial and error to find those that yielded the most comprehensive and relevant literature. Database fields searched: 1 = all, 2 = all text, 3 = titles, abstracts, and keywords, 4 = abstracts, 5 = titles.

chain.

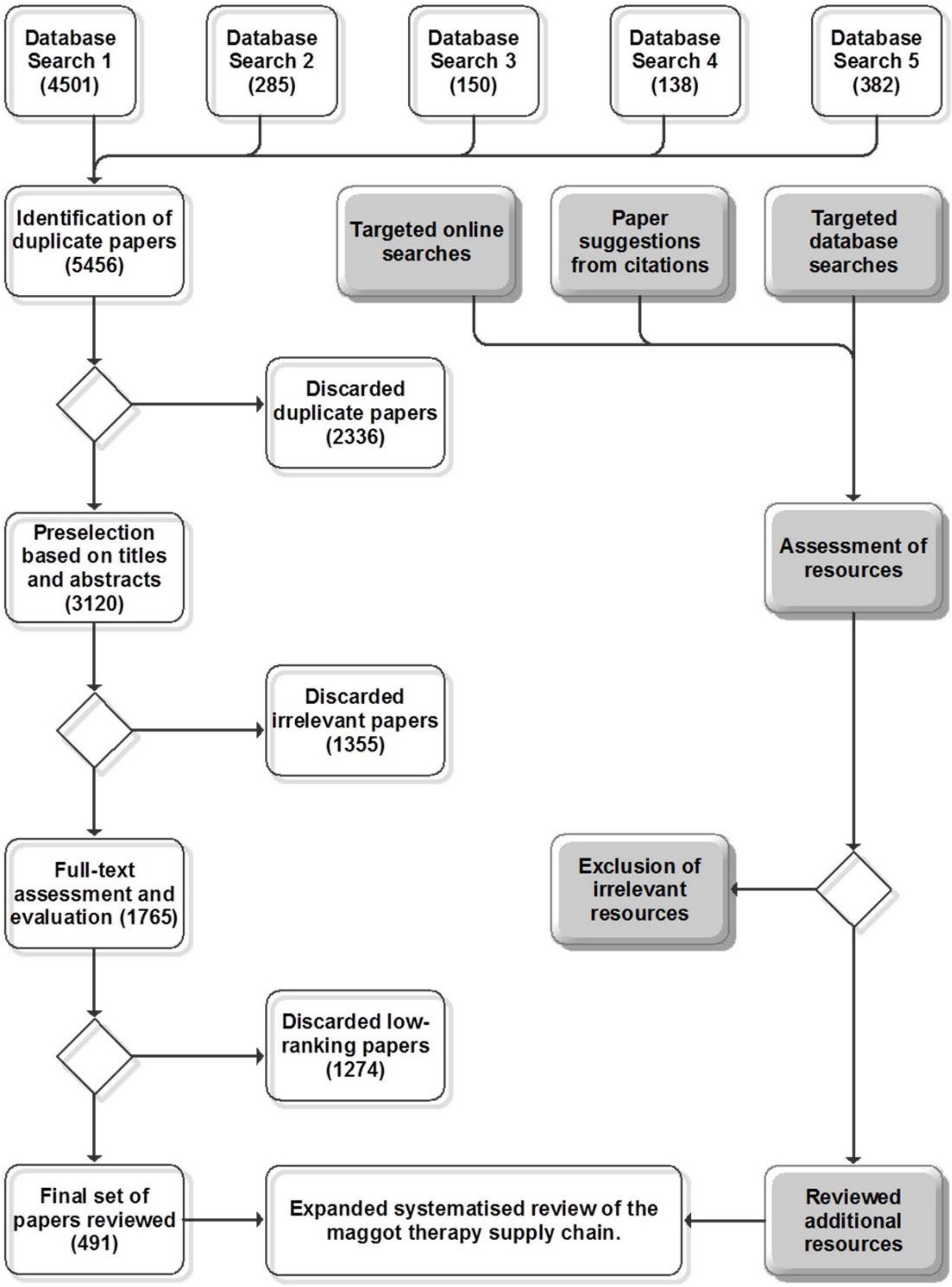

Figure 2: Flow chart outlining the search and selection process for academic and grey literature underpinning the expanded systematised review of the maggot therapy supply chain.

The systematic searches of this specific academic literature were complemented by a more organic process of targeted database searches for information that relates to other supply chain relevant issues such as vaccine or blood supply logistics, or general supply chain management theory and practice. Due to the nature of MT supply chains, much information is held in grey literature and organization websites, and this information was accessed via targeted Google™ searches. This literature review was designed to surface research findings and other information that describes MT supply chain characteristics. Inevitably, the process identified a multitude of characteristics which emerged from disparate sources of information, from various disciplines, and from various supply chain echelons. This information was integrated following the conceptual organization of a generic MT supply chain, in order to construct a general theory of the MT supply chain from upstream production to downstream point-of-care and treatment.

Results

This literature review constitutes the first, and a near-exhaustive, review of the relevant literature. The resulting MT supply chain knowledge and emerging supply chain theory is far too extensive for this publication but can be accessed elsewhere (Stadler, 2018). Instead, the purpose of this article is to provide a summary and critical analysis of the review findings, while only citing key publications as necessary.

Fly colony maintenance

There are few publications fully dedicated to the rearing of maggots for medicinal purposes. The earliest papers on the subject of rearing medicinal maggots and their application in wound care are by Baer and McKeever, which were republished in recent years (Baer, 2011; McKeever, 2008). Subsequent publications on medicinal maggot production lean heavily on these seminal works and offer methodological improvements rather than radical changes. Research has focused on the refinement of rearing techniques. For example, noteworthy effort has been made in recent years in the testing of new fly species for MT in addition to the widely used *L. sericata* and *L. cuprina* (Dallavecchia *et al.*, 2014; Díaz-Roa *et al.,* 2016; Masiero *et al.*, 2015); the development of artificial diets for both adult and larval flies (Tachibana & Numata, 2001; Zhang *et al.*, 2009); the development of efficacy assays for medicinal maggots (Blake *et al.*, 2007; Čičková *et al.*, 2015; Pickles & Pritchard, 2017; Wilson *et al.*, 2016); the potential for sterile rearing of flies from egg to adult (Gasz & Harvey, 2017); and the development of transgenic *L. sericata* to enhance MT wound healing properties (Linger *et al.*, 2016). However, whilst there is much information on the rearing of *L. sericata* and other calliphorid flies that comes from the forensic and other entomological literature, there is considerable variation in rearing setups and conditions depending on the nature of study, species of fly and field of research. This relative dearth of literature on mass production of medicinal maggots is in all likelihood due to small-scale production in hospital laboratories. For local MT demand even antiquated and inefficient rearing methods may suffice, provided the sterility of maggots is ensured. More importantly, large-scale commercial producers are expected to guard their current production methods and any production innovations in order to maintain competitive advantage and make market entry for competitors difficult.

Of critical importance to the reliable and responsive production of sufficient quantities of sterile maggots for MT is a thorough knowledge of the reproductive and developmental performance of medicinal fly species and strains. Under ideal conditions and at a temperature of 25^{O}C, female *L. sericata are* able to lay eggs as soon as 4-5 days after emergence and then every 2-3 days thereafter (Hayes *et al.*, 1999). Females in the laboratory can produce in excess of 10 egg batches with around 200 eggs per batch (Mackerras, 1933; Wall, 1993), which amounts to a fecundity of around 2000 eggs per female and a useful lifespan of 22-32 days, after which unproductive old flies need to be replaced with new fly stock reared for colony replenishment. Harvested eggs can be used for medicinal maggot production or diverted into rearing of flies for colony propagation. Development of embryos, larvae and pupae depends on species, strain, nutrition and temperature among other things, but the most important factor is temperature - the higher it is, the faster the development.

Conservative application of these development rates at 25^{O}C suggests that a full cycle from egg to egg takes around 20 days. This time span is important if, for example, due to the impact of a disaster, demand forecasts or sudden demand fluctuations need to be met with increased production. It demonstrates that, in the absence of long-term egg storage technology, the response time for a single facility to increase production is probably in excess of 20 days, unless the facility maintains production capacity buffer in form of surplus fly stock of all development stages. This incurs additional costs in feed and maintenance which under a lean production strategy would have to be avoided. It is then a matter for the producer to reconcile the benefits of responsiveness and agility with the additional costs incurred by the maintenance of surplus inventory in form of fly stock. This agrees with Melnyk and colleagues' (2010) suggestion that in real life supply chain outcomes need to be adjusted and blended rather than optimized across the board.

Medicinal maggot production

Eggs and larvae destined for medicinal maggot production may be surface sterilized and there are a number of disinfection methods and reagents used for this purpose (e.g. Dallavecchia *et al.*, 2014; Wang *et al.*, 2010). Sterility testing is performed on both the newly sterilized egg and the hatched larvae, and takes 24-48 hours (e.g. Graninger *et al.*, 2002; Nuesch *et al.*, 2002). Because embryo and larval development is rapid, the slow testing of sterility presents a bottle neck in production. However, it is typically managed by temporary cool storage of hatched larvae until quality is assured, after which they can be packaged and shipped.

Commercial producers of medicinal maggots can fulfil orders for next-day delivery provided the order is received in time for processing and shipment. Once packed for shipment, the maggots are highly perishable and, given current production and distribution practices, must be distributed and applied to the wound within 48 hours (Čičková *et al.*, 2013). This means that medicinal maggot producers must be highly responsive to demand fluctuations and be able to produce required quantities of sterile medicinal maggots at short notice. In future, it would be desirable to store eggs, pupae or adult flies over extended periods of time which would equate to the holding of buffer inventory of completed product or product components in conventional production (Christopher, 2011). This would support supply and demand management of medicinal maggots, particularly with regard to demand fluctuations and rapid demand spikes in the aftermath of, for example, a mass casualty event which would bring about many injuries amenable to MT (Stadler *et al.*, 2016). Unfortunately, longer-term cold storage or cryopreservation is not yet an operationally feasible option in medicinal maggot production.

Distribution and packaging

There is very little information and discussion in the literature regarding packaging requirements and solutions for medicinal maggot distribution, but examination of the wider medical cool chain highlights the existence of a range of packaging systems that are available for the distribution of perishable medical goods. These include disposable expanded foam packaging or packaging systems designed for multiple re-use in closed-loop reverse logistics operations (Forcinio, 2014). For a producer and distributor, reverse logistics can result in significant financial savings and a greatly reduced environmental and greenhouse gas footprint. This is because far fewer packaging containers are needed to do the job and end-of-life recycling is greatly facilitated, resulting in reduced greenhouse gas emissions and other environmental impacts such as acidification, eutrophication, ozone emissions, toxic emissions and post-consumer waste (Mohan, 2013). The primary specification for the safe distribution of medicinal maggots is the internal temperature range of 6-25^{O}C irrespective of environmental temperature conditions (Biomonde, n.d.; Čičková *et al.*, 2015). In this regard it will be appreciated that the performance demands on cool chain packaging increase under the harsh and hot environmental conditions that are often found in developing countries. In this respect, there are similarities between the MT and vaccine supply chain. Although there is no literature on the shipment of maggots under harsh climatic conditions, the lessons learned from vaccine logistics suggest that many existing cool and cold chain solutions may also be applicable in MT logistics, provided accidental freezing can be avoided (PATH, 2018).

Clinical decision making and practice

Apart from the forensic and biological aspects of fly development and nutrition, the clinical literature is most instructive. There is a growing body of reviews (e.g. Abela, 2017; Arabloo *et al.*, 2016; Sun *et al.*, 2014; Wood & Hughes, 2013), literature reporting on MT case studies (e.g. Din *et al.*, 2018; Nasoori & Hoomand, 2017; Nishijima *et al.*, 2017), and studies examining the efficacy of MT based on larger patient cohorts (e.g. Dumville *et al.*, 2009; Igari *et al.*, 2013; Mirabzadeh *et al.*, 2017). Likewise, the principle mode of action of maggot excretions and secretions is also under close scrutiny (e.g. Dauros Singorenko *et al.*, 2017; Laverde-Paz *et al.*, 2018; Ratcliffe *et al.*, 2015). What emerges is a significant potential market size represented by a wide spectrum of chronic and acute wounds qualifying for MT, with non-healing ulcers being the prime indication. The broad spectrum of indications and the triple benefit of debridement, infection control and tissue regeneration conveyed by MT also highlights its usefulness for wound care in compromised healthcare settings. Contraindications for, and side effects of, MT are well understood and can be managed effectively (Chadwick *et al.*, 2015). A number of nursing guidelines have been written on MT. In addition, commercial producers offer training programs, information material and clinical helplines to support practitioners. There is also good but limited evidence that patients are responsive to information and welcome MT despite minor downsides such as increased pain, increased odour and occasional maggot escapes from free-range dressings (e.g. McCaughan *et al.*, 2015; Spilsbury *et al.*, 2008; Steenvoorde *et al.*, 2005a). There has been very little effort to date to understand awareness deficits, and negative attitudes and perceptions held by many healthcare professionals toward MT.

Maggots can be applied in two ways, free range or bagged. In free-range application, maggots are applied directly to the wound with a containment dressing that keeps the maggots in place, allows for exudate drainage, and for oxygen supply to maggots. Alternatively, maggots are sealed within a mesh bag that can be fabricated from a variety of materials. The porous bag allows maggots to feed on necrotic tissue while preventing escapes and making application and change of dressings more convenient. This point of difference conveys a competitive advantage over free-range application but, from a clinical standpoint, there is evidence that debridement is more effective with maggots that are not bagged and have free access to necrotic tissue (Steenvoorde *et al.*, 2005b).

There is also solid research and experiential evidence from practitioners and the industry suggesting that the ideal dosage of maggots is in the order of 4-8 per cm^2 of wound applied for 48 to 72 hours depending on progress and application technology (Wilson *et al.*, 2016; Wilson *et al.*, 2018), with each maggot removing approximately 25 mg of dead tissue per day (Mumcuoglu et al., 2001). Maggot therapy can be repeated multiple times if necessary. Flexibility regarding the application duration allows for the bridging of supply interruptions if, for example, suppliers do not deliver on weekends. Alternatively, if seamless re-application is not possible then MT may be paused for a day or two.

Given that maggot therapy dressings at the end of their application are soiled with body fluids and maggot excretions, it is widely accepted practice to dispose of them in the clinical waste stream. The prime consideration here is clinical safety and infection control. However, there is no consideration for the humane treatment of medicinal flies throughout production and distribution, and little attention is paid to humane euthanasia at the end of treatment. This is to a large part because invertebrate animals have not been included in research ethics guidelines, and there has been little research regarding pain perception, analgesia, anaesthesia and euthanasia.

Discussion

MT is a therapy that has been used for thousands of years in tribal medicine and there is sound clinical and biomedical evidence that MT is efficacious (Nigam & Morgan, 2016; Sherman, 2014; Sun et al., 2014). Yet, there are still surprising knowledge gaps in the academic literature with regard to the design and management of the MT supply chain. The present study sought to systematically take stock of current MT supply chain knowledge and provide a gap analysis.

The type of literature consulted for this systematized review was broader than in conventional academic literature reviews as it included not only peer reviewed literature of all types (Grant & Booth, 2009), but also grey literature and online resources such as company websites. It was necessary to cast the net wide because, for some aspects of the MT and related SCs, there was little information available in the scientific literature alone. For example, much of the vaccine SC literature consists of reports published by the Global Alliance for Vaccines and Immunization, the Program for Appropriate Technology in Health (PATH) and other NGOs. Moreover, a review of company websites of medicinal maggot producers provides industry information on current production-, product-, service-, and distribution practices in functioning healthcare settings.

Overall, a bimodal distribution of knowledge along the MT supply chain has emerged, with the production and treatment echelons of the supply chain receiving most attention. While there are only few papers discussing the rearing of flies and maggots for medicinal purposes, the wider literature on calliphorid flies and their developmental biology is more substantive. However, rearing methods vary, and the emphasis is mostly on forensically relevant development parameters such as minimum development times, whereas in relation to medicinal maggot production, the aim is to achieve uniformity of development across the laboratory colonies. Apart from one recent study exploring whether genetic modification can enhance the therapeutic benefits of medicinal maggots (Linger *et al.*, 2016), there appears to be no literature regarding conventional breeding and genetic improvement of *L. sericata* or *L.*

cuprina fly strains and lab populations in order to maximise their medicinal performance. A sizable body of knowledge is, however, available regarding the nutritional requirements of medicinal and allied fly species and the development and performance of artificial diets. There also appears to be a steady interest in advancing quality control and sterilization methodologies, as well as the therapeutic performance of medicinal flies. In summary, there is considerable relevant knowledge that applies to medicinal maggot production, albeit dispersed across disciplines including forensic science, agricultural science and ecology.

In contrast, there is very little published literature regarding the distribution and transport logistics for medicinal maggots. Most information on this MT echelon comes from producers themselves via product information material, and the general cool chain management literature such as for vaccine distribution. Noteworthy exceptions are the paper by (Peck *et al.*, 2015) who tested the airworthiness of medicinal maggots, Tatham *et al.* (2017) who explored the use of drones for distribution of medicinal maggots, and (Čičková *et al.*, 2015) who examined the performance and survival of bagged and free-range maggots in relation to their storage duration at a treatment facility after delivery.

Although the treatment echelon has received much attention, there are still knowledge deficits in the literature regarding the patient and practitioner experience of receiving and administering maggot therapy. A closer investigation of the user experience in MT may well highlight important improvement requirements that would strengthen the supply chain performance. Whilst patient acceptance and willingness to try MT has been shown in a limited number of studies, the attitude of healthcare providers and its impact on MT uptake is very little understood even though healthcare providers determine to a large extent the treatment options available to a patient. Consequently, lack of awareness or negative attitudes held by healthcare providers toward MT may represent major barriers to MT uptake and effective supply chain management. In addition, it would be beneficial to clinical practice if more controlled trials were to be conducted, and more case reports on successful and unsuccessful MT were to be shared in the literature.

Regarding disposal practices, guidelines are precise about the need to safely dispose of dressings and used maggots in the clinical waste stream, but this review could not identify research investigating the ethical aspects of maggot anaesthesia or euthanasia prior to disposal.

Conclusion

The MT literature has not yet discussed the provision of MT services in the conceptual and disciplinary framework of supply chain management, neither in high-resource healthcare practice, nor in compromised healthcare settings. Apart from the present study, there appears to be no MT supply chain research that explicitly and holistically connects all echelons of the MT supply chain. Instead, the literature to date has focused on isolated discussions of specific issues such as diet improvement and sterilization protocols in the production process (e.g. Blystone & Hansen, 2014; Limsopatham *et al.*, 2017; Thyssen *et al.*, 2013; Zhang *et al.*, 2009), or the relative effectiveness of medicinal maggot application methods in the treatment echelon (e.g. Čičková *et al.*, 2013; Steenvoorde *et al.*, 2005b). It is difficult to ascertain from this expanded literature review how sophisticated commercial producers are, and the extent to which they have improved the basic production methods reported in the literature. Moreover, there is little knowledge in the public domain regarding transport and distribution of medicinal maggots, but existing supply chains for vaccines, blood, and pathology specimens may provide learning and supply chain integration opportunities. MT knowledge across the treatment echelon is generally substantive, but there is insufficient knowledge as to how patients and healthcare providers experience MT, and the impact of awareness deficits and negative attitudes toward MT, especially by healthcare providers. Finally, it can be concluded that all parts of the MT supply chain would benefit from research that specifically identifies barriers to the implementation of MT – especially in compromised healthcare settings - and from research that develops solutions to overcome these barriers.

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