Adopting epidemiological approaches for herbicide resistance monitoring and management

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Abstract
The widespread use and increasing reliance on herbicides for weed control has resulted in a global epidemic of evolved herbicide resistance in weed populations. In response, there has been a great deal of research effort to document resistance cases, understand the genetic and physiological mechanisms of resistance and use models and model organisms to explore resistance management strategies. Here, we argue that the field of epidemiology, which systematically studies the extent, distribution and determinants of a harmful organism or condition, can greatly contribute to our efforts to understand the emergence, selection and spread of herbicide resistance. By systematically collecting data on weed abundance and distribution, the frequency and mechanisms of resistance, and agronomic and environmental metadata, it is possible to develop statistical models that identify the underlying relationships between these elements. In doing so, these approaches can provide novel insight into the relative importance, origin and spread of different resistance mechanisms, and the agronomic, ecological and evolutionary drivers that dictate the dynamics of resistance evolution at local to global scales. Emerging technologies in weed surveillance, genomics and resistance diagnostics, statistics and data science will greatly facilitate the collection and analysis of large-scale data sets, providing unprecedented potential for epidemiological analyses of the evolution of herbicide resistance at landscape scales.

Keywords
epidemiology, herbicide resistance, resistance evolution

1 | THE RESISTANCE EPIDEMIC

The human-driven evolution of resistance to pesticides and antimicrobials has become one of the key issues of our age, impacting human health and food security (Fisher et al., 2018; Gould et al., 2018). Whether in medical or agricultural settings, cases of resistance represent a rapid evolutionary response to extremely strong selection by chemicals; selection which ultimately results in the loss of control of the target organism by that chemistry. Across disciplines, there is a common need to understand the mechanism by which resistance is conveyed and the processes by which it is transmitted throughout populations and across the landscape. Armed with this knowledge, it is possible to design resistance management strategies that mitigate, or considerably delay, selection for resistance (Norsworthy et al., 2012; Bourguet et al., 2013; Neve et al., 2014).

In response to herbicide use, 262 weed species, distributed over 70 countries, have evolved herbicide resistance—representing an ongoing, global epidemic (Heap, 2020) (Figure 1). Many studies of herbicide resistance have explored localised cases of control failure, with a focus on determining the resistance mechanism in single or a few populations. Whilst these focussed, mechanistic studies are important, there has also been a call for more integrated research, involving weed scientists, plant ecologists,
geneticists and evolutionary biologists to better understand the ‘gene to landscape’ components of resistance evolution in weed populations (Busi et al., 2013). Very few studies have focused on the epidemiology of herbicide resistance to unravel the agronomic, ecological and evolutionary drivers for its emergence, selection and spread in agroecosystems and across landscapes and continents (but see Gressel, 2002). Given the vast amount of research to catalogue cases of resistance, we argue here for a greater effort to explore the epidemiology of resistance at regional to global scales.

2 | WHAT DO WE MEAN BY EPIDEMIOLOGY?

Most frequently associated with biomedical science, epidemiology is the systematic study of the distribution and determinants of a harmful organism, disorder or event. Rather than focusing on single cases in isolation, epidemiology involves a large-scale, systematic and data-driven approach to (a) surveillance of the target organism, (b) collection of appropriate and standardised metadata for each observed case and (c) statistical analyses to identify potentially causal relationships amongst the data. Whilst such data can be difficult and time-consuming to collect, this approach can be invaluable in identifying key factors underpinning the origin, selection and transmission of an epidemic, and has formed the basis of the study of public health risks and disease outbreaks across the world (Rothman, 2012; Samet, 2016; Deen et al., 2019). More recently, advances in computing power, genome sequencing and the availability of genetic resources have allowed researchers to track the evolution and spread of epidemics in near real-time, for example reconstructing the adaptation and spread of the Ebola virus during recent outbreaks in Central Africa (Hadfield et al., 2018, see www.nextstrain.org). Using such approaches in combination with collection of case-by-case contextual data, such as the patient’s location and environment, date of contracting the illness, and recent movements and activities, has helped researchers and practitioners to understand the source and transmission of these epidemics (e.g., Gire et al., 2014; Faria et al., 2017).

3 | HOW CAN EPIDEMIOLOGY BE USED FOR RESISTANCE RESEARCH?

In the context of resistance research, we can view epidemiology as an approach to understand the causes underpinning the emergence and rapid proliferation of a resistant organism or genotype, and the extent of its spread across the landscape. Perhaps because of its close association with biomedical science, epidemiology has played a pivotal role in the study of antimicrobial resistance.

The screening and reporting of antibiotic resistance is widespread and often compulsory, and therefore large, global data sets on the incidence and mechanisms of resistance have become available (Shaikh et al., 2015). Correlation of these data with the demographic and clinical information routinely collected for each patient forms the basis of epidemiological study of antimicrobial resistance (Johnson, 2015) and has facilitated resistance research in pathogenic, commensal and environmental bacteria at the level of whole microbial communities (Crofts et al., 2017). For example, epidemiological analyses have been used to highlight the importance of environmental and human-mediated transmission of antimicrobial resistant Escherichia coli (Lazarus et al., 2015; Abernethy et al., 2017; Day et al., 2019) and to identify the clinical factors associated with increased risk of hospital-acquired Clostridium difficile infection (Forster et al., 2017).

Epidemiology has also played a crucial part in studying the evolution of insecticide resistance, particularly in mosquito species.
which act as malarial vectors. Access to simple assays for screening of insecticide resistance provided by the World Health Organisation has led to extensive data sets on phenotypic resistance in mosquitoes across large geographical regions (Moyes et al., 2019). These databases of resistance in mosquito disease vectors include important contextual data such as geo-location, timing and methodology of insect capture, the frequency of resistant individuals within the trapped sample, and where possible, the mutational basis of resistance (Dialynas et al., 2009). These data sets have been incorporated into the online tools ‘VectorBase’ (https://www.vectorbase.org/) and ‘MAP-IR’ (http://www.irmapper.com/), allowing the high-resolution visualisation and analysis of spatiotemporal trends of insecticide resistance in these invertebrate vectors of human pathogens (Giraldo-Calderón et al., 2015; Coleman et al., 2017) and facilitating large-scale, multi-continent epidemiological analysis of insecticide resistance (Cook et al., 2018).

Whilst these examples represent very different target organisms, they demonstrate the important considerations required for an epidemiological analysis of herbicide resistance (Figure 2). First and foremost, sampling must be systematic and standardised to facilitate comparison between samples. Importantly, where a population is being investigated, sufficient individuals must be assessed to allow...
the results to be representative of that population. Additionally, a set of contextual data must also be collected for each case to facilitate analysis. At the very least, this should include location (geo-reference) and time (date, year) information to allow spatiotemporal analysis of resistance evolution. However, environmental, climatic and management/treatment data are also crucially important to fully unravel the ecological and evolutionary drivers of resistance.

4 | OPPORTUNITIES FOR EPIDEMIOLOGY IN HERBICIDE RESISTANCE RESEARCH

Weed species are generally easy to locate and identify, and methodologies have been developed to allow rapid and systematic spatial monitoring of weed presence and abundance at biologically and agronomically relevant scales (e.g., Queenborough et al., 2011). Collection of seeds, leaf material or even whole plants enables phenotypic or genetic screening of resistance, using standardised assays (e.g., Délye and Boucansaud, 2008; Kaundun et al., 2011; Beffa et al., 2012; Marshall et al., 2013). In contrast to highly mobile insect pests or fungal pathogens, weeds generally have more limited dispersal (with exceptions, see: Shields et al., 2006; Farmer et al., 2017), with seeds maintained in soil seed banks. This ensures that weed populations often remain relatively static. For epidemiological studies, this means that field management histories reflect the selection history for that weed population, allowing investigation of the association between current weed presence and genotype, with past and present weed management. Therefore, where field histories are available alongside data on weed abundance and resistance status, there is the potential for epidemiological analyses of the origin, selection and spread of herbicide resistance within- and between-weed populations.

Where systematic, epidemiological studies of herbicide resistance have been performed, they have provided detailed insight into the extent of resistance and the agronomic practices driving resistance evolution (Evans et al., 2016; Mascanzoni et al., 2018). A detailed, epidemiological study of over 130 geo-referenced Alopecurus myosuroides populations in the UK combined weed abundance monitoring, resistance screening for multiple herbicide active ingredients and collation of up to 11 years of management history per field to identify the key evolutionary drivers of resistance to post-emergence selective herbicides (Hicks et al., 2018) (Figure 3). Through subsequent screening for glyphosate sensitivity alongside experimental evolution and quantitative genetics approaches, a further epidemiological analysis was able to pro-actively reveal directional selection for glyphosate resistance in these populations (Comont et al., 2019). By combining these systematic studies of A. myosuroides abundance and herbicide
resistance with high-resolution yield data, the full economic cost of this pernicious herbicide-resistant weed was quantified at a national scale (Varah et al., 2020). Finally, it has been noted that many cultural and other management strategies that may be employed to combat resistant weed populations demonstrate large site-to-site and year-to-year variability (e.g., Lutman et al., 2013). In this case, epidemiological approaches may be able to unravel some of the environmental interactions contributing to this variability (e.g., Freckleton et al., 2018), allowing these management practices to be targeted to where they will have the greatest impact.

The benefits of this type of epidemiological approach are many. Previously, modelling (e.g., Diggle et al., 2003; Renton et al., 2014) and experimental evolutionary (e.g., Beckie and Rebound, 2009; Lagator et al., 2013) studies have sought to assess the relative effectiveness of resistance management strategies. These studies are sometimes criticised as being difficult to validate and/or too abstract. The types of epidemiological analyses that we advocate here provide a means to test the effectiveness of these strategies at scale, in field populations of agricultural weeds. Any resultant identification of factors affecting selection and transmission of resistant genotypes could help with the implementation of effective resistance management strategies.

5 | FUTURE PROSPECTS FOR HERBICIDE RESISTANCE EPIDEMIOLOGY

The reduced cost of next-generation sequencing is facilitating population genomic studies which have helped to identify the origin and spread of herbicide resistance (e.g., Kreiner et al., 2019), and current efforts to sequence a range of weed genomes will further aid these approaches (Ravet et al., 2018). The availability of remote sensing data and UAV imagery has increased considerably in recent years, providing a potential means for rapid, large-scale mapping of weed abundance (Louargant et al., 2017; Lambert et al., 2019). More reliable and higher-throughput diagnostics for resistance are also being developed, allowing for more rapid identification of resistance mechanisms in a greater range of populations (Délye et al., 2019). As a result, large-scale studies of herbicide resistance are becoming increasingly affordable, and many regional and national surveys of herbicide resistance are now being undertaken (Délye et al., 2010; Schultz et al., 2015; Han et al., 2016). Nevertheless, single studies which include collection of all the phenotypic, genotypic and contextual data that enable epidemiological analyses are still rare.

In many cases, the burden of data collection required for a successful epidemiological approach will be too great for any one group or study. In particular, contextual data representing the environmental and agronomic selection history can take considerable effort to collect. In order to facilitate future epidemiological analyses, we need to ensure that the monitoring, metadata and phenotypic or genotypic resistance data collected within individual studies follow similar, standardised methodologies to allow future collation and analyses. Furthermore, there is a need for a more coordinated database to which this information can be submitted and collectively evaluated. The online ‘International Survey of Herbicide Resistant Weeds’ (www.weedscience.org) provides a resource for collation of herbicide resistance information; however, the motivation behind this database is to report instances of the occurrence of resistance by species and country. Whilst useful, this lacks the necessary breadth of surveyed populations, or accurate geographical and contextual data needed to provide the basis of an epidemiological analysis (see Dialynas et al., 2009). The introduction of tools for data interoperability and collation in other resistance disciplines have been pivotal for subsequent evolutionary and epidemiological insight (Dialynas et al., 2009; Giraldo-Calderón et al., 2015; Coleman et al., 2017), and establishment of these tools should be a priority within herbicide resistance research.

6 | CONCLUSIONS

Over the last few decades, the study of herbicide resistance has considerably advanced our understanding of how rapidly, and by which mechanisms weed species can evolve resistance (Powles and Yu, 2010; Busi et al., 2013). Nevertheless, there are still many outstanding questions on the fundamental processes governing the origin, evolution and spread of herbicide resistant genotypes. Epidemiological analysis of resistance in other disciplines has highlighted the utility of this approach in answering these questions (e.g., Cook et al., 2018; Day et al., 2019), and the few epidemiological herbicide resistance studies to date have demonstrated important insight on the extent, economic costs and evolutionary drivers of herbicide resistance (Hicks et al., 2018; Comont et al., 2019; Varah et al., 2020). In healthcare, there has been an effort to emphasise the importance of prevention over treatment in the effective management of human disease (Marvasti and Stafford, 2012; Kaeberlein et al., 2015). The effective management of herbicide resistance could benefit from a similar change in motivation, from reactively diagnosing mechanisms after control failure, to more pro-actively surveying for early signatures of the evolution and spread of resistance genotypes. The confluence of emerging technologies for (a) remote sensing of weed populations, (b) diagnostics for rapid detection of resistance, (c) genomics and population genomics to understand the origin and spread of resistance, (d) better access to farmer generated data and environmental metadata (‘big data’ in general) and finally, (e) the computing power to integrate and interrogate these multi-layered data sets, provides new and exciting opportunities to expand the scope and ambition of future herbicide resistance studies, to better understand the origin, selection and spread of resistance at landscape scales.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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