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Herbicide resistance management strategies: how do they compare with those for insecticides, fungicides and antibiotics?

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Abstract

Herbicides are the largest category of pesticides used in global agriculture, which is reflected in the rate of increase in the number of unique cases of herbicide-resistant weed biotypes since the late 1950s. Recommended herbicide resistance management strategies and tactics have evolved over the past 50 years through cumulative research and experience and have been regularly reviewed. Nevertheless, new perspectives may be gained by viewing current recommended strategies through the lens of insecticide, fungicide, and antibiotic resistance management. What commonalities exist and what is the basis for disparate strategies? Although pesticide and antibiotic mixtures (or combinations) are generally more effective than rotations (or alternations) in mitigating or managing resistance, the latter strategy is often employed because of greater ease of implementation and other reasons. We conclude that there are more common than different strategies for mitigating or managing pesticide and antibiotic resistance. Overall, a reduction in selection pressure for resistance evolution through diverse multi-tactic management programmes, and disruption or mitigation of the dispersal or transmission of problematic genotypes are needed to sustain the longevity of current and future mode-of-action products for crop and human health protection.
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Keywords: antibiotic resistance; fungicide resistance; herbicide resistance; insecticide resistance; integrated pest management; resistance management

1 INTRODUCTION

Since the first reported case of a herbicide-resistant weed biotype in 1957, there are now over 500 unique cases involving over 260 weed species resistant to one or more of 167 herbicides belonging to 23 modes of action in 93 crops in 70 countries.[1] Resistance to acetolactate synthase inhibitors, photosystem-II inhibitors, enolpyruvylshikimatephosphate synthase inhibitors (glyphosate), and acetyl-CoA carboxylase inhibitors constitute the majority of cases. Since the first case of insecticide resistance in 1914, there are now about 600 insect (and mite) species resistant to one or more of over 325 insecticides and five genetically-engineered insecticidal traits.[2] Cases of resistance in plant pathogens to fungicides in key crops have increased in number, significance, and geographical spread since the 1960s; a total of 273 resistance cases involving more than 100 active ingredients have been reported globally.[3,4] Incidence of antibiotic resistance, which was first reported in the 1940s, has increased exponentially over time, similar to that of pesticide resistance.[5]

The biology and ecology of weeds, insects, and plant or human pathogens differ greatly, which impacts resistance evolutionary dynamics. Moreover, prevalence of target site *versus* non-target site resistance mechanisms in populations has practical implications for resistance risk assessment and management. In a review by Hawkins *et al.*,[6] it was concluded that fungicide resistance evolves in most cases by *de novo* point mutations in the target site-encoding genes, herbicide resistance often evolves through selection of polygenic metabolic resistance from standing variation, and insecticide resistance evolves through a combination of standing variation and *de novo* mutations in the target site or major metabolic resistance genes. Similar to resistance to pesticides, both target site and non-target site resistance mechanisms confer antibiotic resistance.[5]

Despite the varying relative frequencies of target site and non-target site resistance mechanisms among weed, insect and pathogen populations, many commonalities in selection and evolution of resistance exist. The common denominator is recurrent usage of the same pesticide or antibiotic mode of action, which selects for naturally-occurring resistant individuals that eventually dominate the population over time. Today, many weed, insect

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and pathogen populations exhibit resistance to multiple mode-of-action xenobiotics.

During the past 30 years, few forums have been held globally where weed scientists, entomologists and pathologists have the opportunity to discuss resistance issues. Perhaps the most prominent and enduring forum has been a successive series of conferences that commenced at the University of Southampton, United Kingdom (UK) in 1986 and continued at Rothamsted Research, UK from 1991 to 2019 (on six occasions). These conferences highlighted the latest pesticide resistance research from fundamental to applied, such as recent monitoring efforts and characterization of novel resistant biotypes; mechanisms, inheritance, and evolutionary dynamics of resistance; and integrated pest management strategies. Despite these interdisciplinary forums, collaborations among weed scientists, entomologists and pathologists in pesticide resistance research are still relatively rare. Even more infrequent is interaction of these scientists with medical researchers or practitioners. One such notable event, hosted by the American Society of Microbiology, was held in Philadelphia in 2012.[7]

In this *In Focus Perspective* article, we revisit current recommended herbicide resistance management strategies and compare them with strategies recommended to mitigate or manage insecticide, fungicide and antibiotic resistance. What commonalities exist and what is the basis for disparate strategies? Just as pesticide resistance is an ever-increasing threat to global food security, antibiotic resistance is an increasing threat to human health. Can strategies to manage antibiotic resistance inform strategies for resistance management in agriculture?

2 HERBICIDE RESISTANCE MANAGEMENT

Recommended herbicide-resistant weed management strategies and tactics have been reviewed previously (e.g. Beckie[8]; Norsworthy *et al.*[9]; Beckie and Harker[10]). Recent developments and trends in herbicide resistance management were outlined by Beckie *et al.*[11] They include renewed efforts by the crop protection industry in herbicide discovery and commercialization of new modes of action (see other papers in this *In Focus* section), cultivation of crops such as maize (*Zea mays* L.), soybean (*Glycine max* L. Merr.), and cotton (*Gossypium hirsutum* L.) with combined (stacked) herbicide-resistance traits, increasing reliance on pre-emergence, soil-residual herbicides *versus* post-emergence herbicides, breeding for weed-competitive cereal crop cultivars, expansion of harvest weed seed control practices, and advances in site-specific or precision weed management in real time or via prescription maps. Additionally, crop protection companies are focusing on pesticide (herbicide, insecticide and fungicide) formulations and spray application technologies to optimize delivery and efficacy on target pests.

The unifying strategy underlying these developments is mitigating the entry of viable weed seeds into the soil seed bank and maintaining low weed seed banks to minimize population proliferation, the evolution of resistance to additional herbicide modes of action, and the spread of resistance alleles. Consequently, use of economic thresholds, while commonly used in entomology and pathology, is no longer recommended by weed scientists or practitioners. However, increasing attention is now focused on areawide weed management of resistance-prone species with high propagule mobility, such as *Amaranthus palmeri* S. Watson (Palmer amaranth), *Conyza* spp. (fleabane) and *Kochia scoparia* L. Schrad. (kochia).[12,13]

Management of herbicide resistance, similar to insecticide, fungicide and antibiotic resistance, relies upon different chemical modes of action to provide the primary efficacy against the target organism(s). Integration of chemical use with non-chemical practices is strongly advocated by the scientific community, although their adoption and utility by end-users is largely a secondary consideration until few effective chemical options remain. Financial incentives from both the public and private sectors have been advocated as a means of increasing adoption of diverse chemical and non-chemical practices such as herbicide mixtures, crop rotation diversity, cover crops and weed sanitation to help sustain the longevity of herbicides (reviewed in Beckie *et al.*[14]).

Resistance in a target weed population to multiple herbicide modes of action,[1] particularly conferred by non-target site-based mechanisms, threatens the utility of both registered products and potential compounds still in the discovery phase. Simulation models and experimental evidence indicate that mixtures of chemicals each applied at label rates (or sequential application to the same weed population cohort) are more effective than rotations in mitigating or managing resistance (e.g. Beckie and Reboud[15]; Busi *et al.*[16]; Busi and Beckie[17]; Fig. 1). Individuals with mutations conferring resistance to multiple herbicides occur at a rate equivalent to the product of the mutation rate of each herbicide (e.g. mutation rate to herbicide A at 1×10^{-6}; mutation rate to herbicide B at 1×10^{-8} = mutation rate to herbicides A + B at 1×10^{-14}). However, herbicide rotation is easier to implement and is practiced more often because mixtures must meet strict criteria to be effective for resistance management, such as redundant control of the target weed by the mixing partners having different modes of action and similar soil residual activity.[18] It is important to know the cross-resistance status of field weed populations to inform herbicide-use strategies, e.g. prevalence of group 15 (long-chain fatty acid inhibitors) cross-resistance in *Lolium rigidum* Gaud. (annual ryegrass) or absence of cross-resistance between group 3 (microtubule inhibitors) and group 15 (Fig. 1).[19] Even though a herbicide-resistant weed may be resistant to each component in a mixture, recent research has found that it may be controlled by a mixture of both components applied at label rates for reasons that are still unclear.[17]

3 INSECTICIDE RESISTANCE MANAGEMENT

There are several biological factors unique to insects (and mites) that dictate management. For example, many insects are highly mobile, with pest populations in agricultural fields fluctuating annually. Although geographic spread of resistance alleles can be rapid, this mobility can help to dilute intense local selection pressure for resistance evolution. Areawide management is therefore one of the most efficient ways to mitigate the incidence and economic impact of insect pest outbreaks and resistance. Throughout history, there have been many documented case studies of successful, cost-effective areawide management of insect pests in agriculture, such as the pink bollworm (*Pectinophora gossypiella* Saunders) and corn rootworm (*Diabrotica* spp.) in the United States.[20]

Farmers and land managers commonly utilize economic injury thresholds to rationalize spray decisions when managing insect pests. Given their mobility and frequent occurrence of sub-threshold population infestations resulting in little crop yield loss, there is often little incentive to continually reduce insect pest populations. Additionally, beneficial arthropods play a key role

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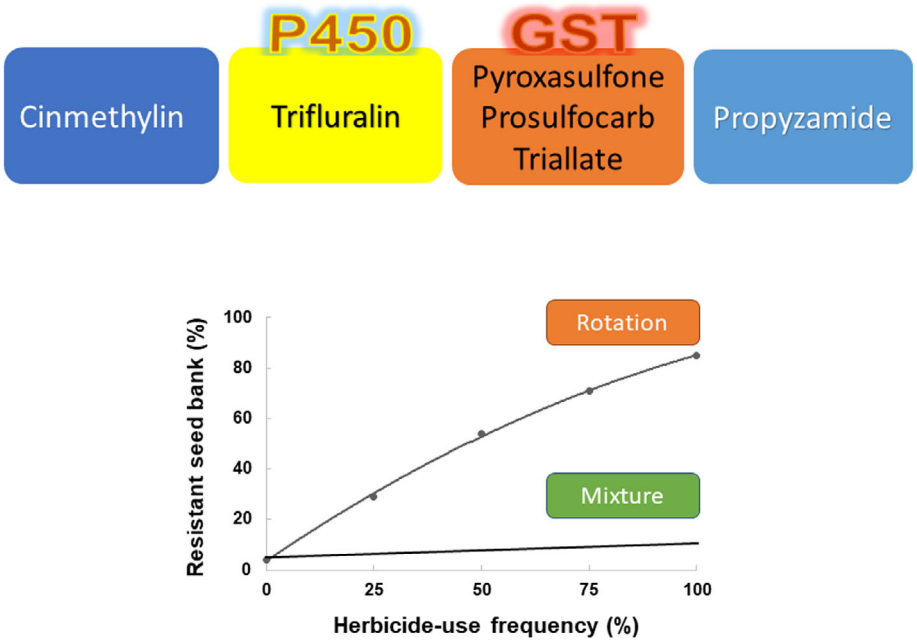

Figure 1. Herbicide rotation recommendations for *Lolium rigidum* (annual ryegrass) in Australia (top): based on site of action (WSSA group 3: trifluralin, propyzamide = pronamide; group 8: triallate, prosulfocarb; group 15: pyroxasulfone; group 30: cinmethylin) and mode of metabolism (P450, GST enzyme families); (bottom) effect of herbicide mixtures (bromoxynil/MCPA and ethalmetsulfuron) *versus* rotations (ethametsulfuron used one, two, or three times over 4 years) on the herbicide-resistant seed bank of *Thlaspi arvense* L. (field pennycress) in western Canada (adapted from Beckie and Reboud[15]).

in insect pest management. The utilization of biological control, which is not commonly applied to weed and disease management in agriculture, reduces the need for chemical interventions and therefore reduces the selection pressure for resistance evolution. Beneficials can also play a key role in insect resistance management, whereby they 'mop up' individuals in the pest population that are resistant and survive an insecticide application.[21] The success of the Australian Cotton Insecticide Resistance Management Strategy has, in large part, been realized through increased usage by farmers of biological controls.[22]

There are a number of chemical strategies to manage insecticide resistance, including: (i) the rotational use across pest generations of different modes of action; (ii) simultaneous mixtures of different modes of action with no cross-resistance and with similar residual activity; and (iii) spatial mosaic (geographical separation of different modes of action) or refuge (untreated) areas.[23] Several studies have been conducted to ascertain which strategy best mitigates the evolution of resistance (e.g. Parker *et al.*[24]; Stratonovitch *et al.*[25]). A review from the REX Consortium[26] that examined experimental and theoretical studies in herbicide, insecticide, fungicide and antibiotic resistance research concluded that mixtures, where each chemical was used at its full label dose, was the optimal resistance management strategy. For insecticides, 14 of 16 examined studies showed that mixing chemicals was the most effective strategy. When recessive resistance alleles are initially present at a low frequency in a population, they are almost always in a heterozygous state and therefore not phenotypically resistant. In these cases, only very rare homozygous individuals will be resistant; if these can be eliminated by a chemical in a mixture with a different mode of action, resistance evolution can be slowed, particularly if there is a continuous influx of individuals that are susceptible to either of the two chemicals.[27–29]

However, mixtures of insecticides with each component applied at their label dose are often not used because they increase the amount of active ingredient applied with greater cost and environmental impact, and can be inefficient or wasteful if each mixing partner targets different insect species that are damaging at different times in the crop's life cycle.[30,31] A further risk is that mixtures may increase the selection for resistance, as some pests that are exposed will not be at economic injury thresholds and thus are unnecessarily exposed. Moreover, mixtures can more rapidly select for mechanisms of resistance that are common to both chemicals, such as particular detoxification mechanisms.[32] Thus, mixture partners should not only have different modes of action, but also different metabolic pathways in the target species.[7,19] Mixtures can also have synergistic toxic effects on beneficial arthropods, which exceed the effects of the active ingredients used singly.[33,34] Therefore, mixtures can lead to greater insecticide use due to the suppression of natural biological control.

For these reasons and more, the Insecticide Resistance Action Committee (IRAC) advises that rotating different modes of action is often the most practical strategy for insecticide resistance management.[35] A rotation approach typically uses a 'window' or block strategy that is frequently defined by the length of a pest generation or crop growth stage. This strategy involves rotating compounds with different modes of action according to a series of defined windows during the crop growing season to minimize selection for cross-resistance.[2,36]

For genetically-engineered crops such as maize and cotton, the deployment of cultivars possessing *Bacillus thuringiensis* (*Bt*) resistance (or other resistance traits) provides continuous selection pressure across consecutive pest generations. This approach provides little opportunity for chemical rotation; thus a spatial mosaic strategy (e.g. mandated non-resistant host plant refuges) is often deployed, which has been shown to be effective in delaying resistance evolution.[37–39]

Because insects are typically highly mobile and can actively seek out suitable crop hosts, refuge strategies can also prove successful in the absence of genetically-engineered crops. In this context, a

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refuge is a portion of the field (or part of the landscape) that is left unsprayed, allowing susceptible individuals to build up and interbreed with resistant individuals. These type of strategies have proven successful, but their value is contingent upon several biological factors such as the genetics underlying the resistance (e.g. recessive inheritance) and the fitness cost of resistance.[40] Important resistance management strategies to minimize the selection for insecticide resistance are summarized in Fig. 2.

4 FUNGICIDE RESISTANCE MANAGEMENT

Three general strategies to mitigate fungicide resistance are to: (i) reduce the amount of fungal inoculum (minimize population size); (ii) minimize fungicide selection pressure by using the minimum dose able to provide effective disease control (i.e. the minimum effective dose); and (iii) use diverse, low-risk resistance modes of action (with no cross-resistance) in mixtures or alternations (rotations).[41] Fungicide rates at the lower end of the label may be appropriate when there is low disease pressure and the crop variety has some level of genetic disease resistance. Modelling and experimental evidence from many studies show that mixtures of different modes of action are generally more effective than alternations in slowing the evolution of fungicide resistance.[42–44] However, both mixtures and alternations are recommended strategies. Ideally, multi-site inhibitors such as mancozeb or clorothalonil are favoured mixing partners because of reduced risk of resistance evolution.[45]

Although experimental evidence is sparse, the full recommended (high) dose strategy is advocated to mitigate polygenic resistance.[45] Generally, the labelled dose or dose range should be used to manage the target pathogen.[42] Fungicide resistance evolves in two stages: the emergence period (beginning with the initial use of a fungicide until resistant mutants are able to persist in the population) and the selection phase (commensurate with selection pressure). Although the use of higher doses generally leads to faster evolution of resistance in the selection phase, the impact on the emergence period is less certain.[46,47]

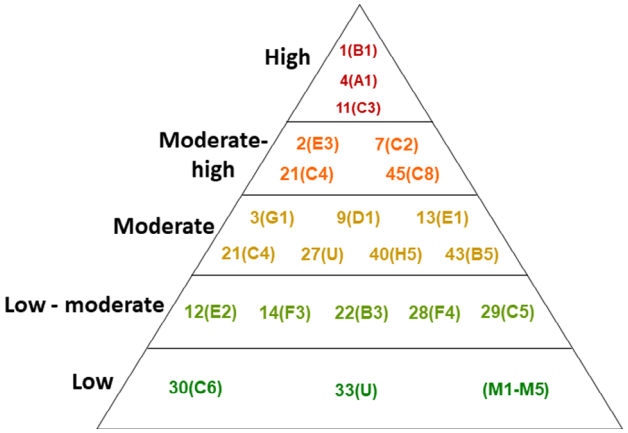

Figure 3. Resistance risk of some fungicide groups commonly used to manage agricultural fungal pathogens: Fungicide Resistance Action Committee (FRAC) group (sub-group) mode of action[4] (adapted from Hollomon[45] and Damicone[49]).

The minimum effective dose, which may or may not equate with the full-recommended dose, is considered to slow the selection of resistance to 'at-risk' fungicides, used solely or in mixtures, based on experimental evidence and modelling simulations.[43,47,48] High-risk fungicide groups include the single-site phenylamides or Pas[4] (group 4(A1)), e.g. metalaxyl; strobilurins or QoIs (group 11(C3)), e.g. azoxystrobin; and methyl benzimidazole carbamates or MBCs (group 1(B1)),

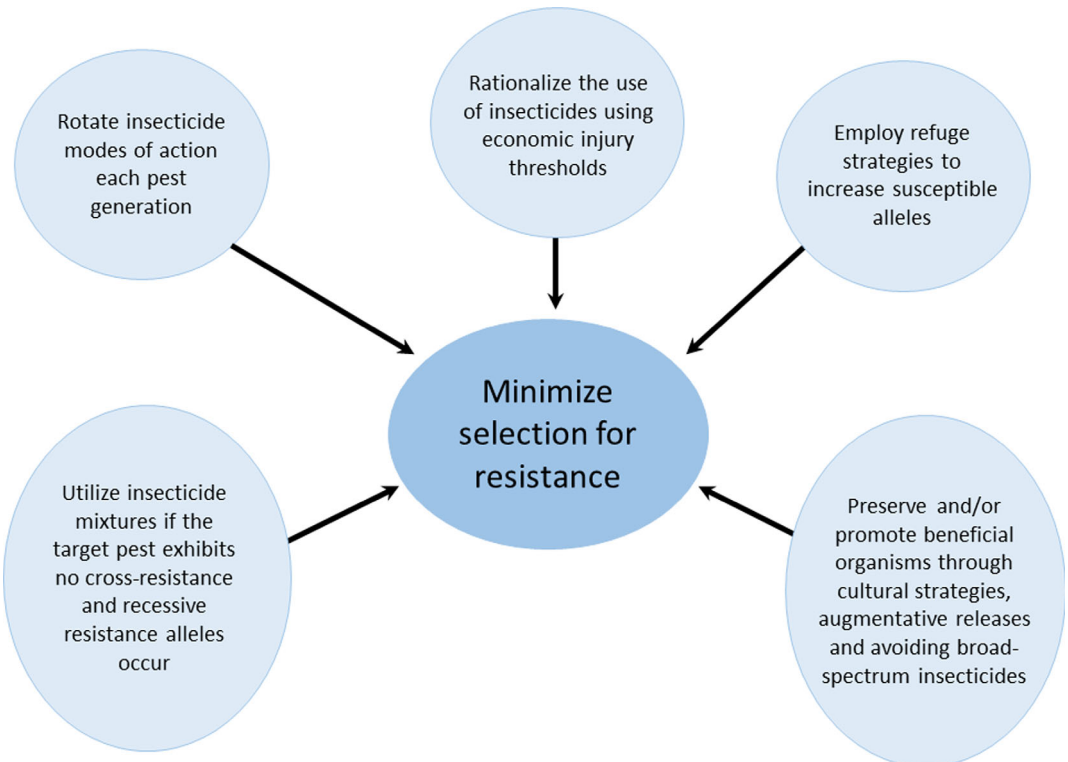

Figure 2. Key management strategies employed to minimize the evolution and spread of insecticide resistance in agricultural insect and mite pests.

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e.g. thiabendazole[45,49] (Fig. 3). One strategy to extend the life of an 'at-risk' fungicide is to use a mixture whereby the dose rate of the 'at-risk' partner is decreased or the rate of the 'less-risky' partner is increased.[43] However, the lack of a diverse range of multi-site fungicides and other low-risk fungicides with high activity and broad spectrum limits the development of effective mixtures with suitable higher risk, single-site partners.

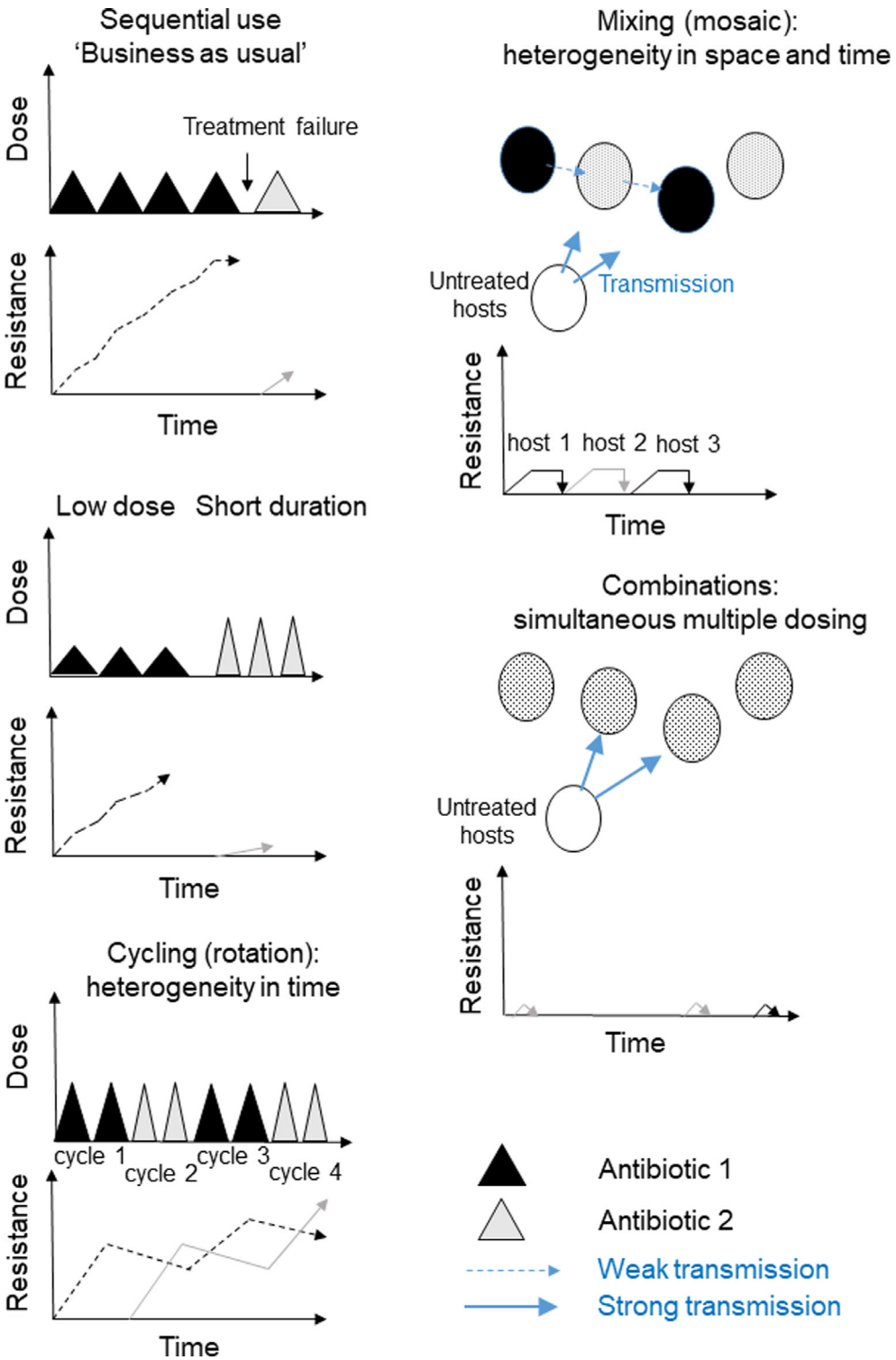

Figure 4. Major strategies employed in antibiotic resistance management with predicted potential effect on the frequency of resistance (adapted from Raymond[51]). High dose, cycling (rotation), mixing (spatial mosaic) and combinations are all recommended strategies, with choice depending on situation parameters. Mixing and combination approaches are more effective if microbes are cleared from treated patients and if transmission occurs mainly from untreated individuals.

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With limited novel fungicide modes of action available to farmers, integrated disease management, particularly the deployment of disease-tolerant crop cultivars, crop rotations, and the use of crop residue and green bridge [plants such as crop volunteers or weeds being a host for diseases such as cereal rust (*Puccinia* spp.)] control techniques, becomes increasingly important to preserve existing chemistries.[3] A relatively novel resistance management strategy is the incorporation into disease control programmes of fungicides with negative cross-resistance, which allow for reductions in resistance frequencies due to their higher activity on the resistant populations.[41] However, the number of fungicides with this characteristic is very small and their activity is often reduced to controlling only some resistant genotypes and not others. Central to managing resistance in fungal pathogen populations is knowledge of any significant fitness cost, which may be influenced by environmental factors and may inform the choice of resistance management strategy.[45]

5 ANTIBIOTIC RESISTANCE MANAGEMENT

Antibiotic resistance represents one of the most important and pressing human health problems globally.[50] However, this problem also impacts the veterinary and agriculture industries. In the United States alone, at least 2.8 million people are infected with antibiotic-resistant microbes each year and more than 35 000 people die as a result.[5]

Raymond[51] reviewed the major strategies employed in antibiotic resistance management (Fig. 4) and lists five rules or axioms. These rules are quoted as the following: (i) prevention is better than the cure; (ii) fitness costs are unreliable servants; (iii) limit supply of mutations and genetic novelty; (iv) low doses do not work; short courses might; and (v) information is power. Many more options such as antibiotic cycling (rotation of classes; heterogeneity in time) and mixing (mosaic; heterogeneity in space and time) are available and effective when frequencies of resistance are still low (rule 1).[52]

Cycling or rotation rely on substantial fitness costs (ideally including negative cross-resistance) periodically driving down the frequency of resistance when use of an antibiotic is withdrawn or suspended. However, when multiple resistance genes are co-located on plasmids, withdrawal of one antibiotic may not lead to a decline in resistance (rule 2), as selection from one drug can maintain resistance to many others.[53] In that scenario, resistance persists at a level that enables a rapid response to selection when drug exposure resumes. Moreover, fitness costs associated with mutations or resistance plasmids are not necessarily stable; ongoing selection commonly produces compensatory mutations that reduce these costs.[54,55]

Limiting the supply of mutations (product of mutation rate and microbial population size) and genetic novelty (rule 3, i.e. the availability of new resistance genes) is likely best achieved through combination therapy (i.e. simultaneous use of multiple drugs with independent modes of action).[7,56] However, horizontal gene flow complicates combination therapy for bacterial infections, as several drug resistance mechanisms may be transferred at once into the target population from other species. Thus, combination therapy works best when frequencies of resistance are low or zero.[7]

There is a much greater pool of mutations, especially off-target site mutations occurring widely throughout the genome, that can confer resistance at low doses (rule 4).[57,58] Low doses can also select for polygenic resistance mechanisms that produce a small shift in dose responses.[59] Shorter treatment duration can reduce side-effects and minimize selection pressure for resistance

Table 1. Comparison of weed, insect, fungi and bacteria attributes and herbicide, insecticide, fungicide and antibiotic resistance management strategies

	Herbicide	Insecticide	Fungicide	Antibiotic	References
Target pest (weed, insect, fungi, bacteria) attributes					
Resistance evolves primarily via *de novo* mutations in the target site	X	✓	✓	X	2,3,6–8,23,60
Resistance evolves via both target and non-target site mechanisms	✓	X	X	✓	6–8,23,60
Rapid generation time	X	✓	✓	✓	7,23
Highly mobile	X	✓	✓	X	2,7,20,23
Occurrence of substantive fitness cost due to resistance mechanism	X	✓	✓	X	7,8,40,45,51,53–55,61
Chemical and non-chemical strategies					
Consistent use of high (full label) dose	✓	✓	X	✓	2–4,9,21,26,42,43,45,47,48,51,57–59
Rotation/alternation/cycling	✓	✓	✓	✓	2,7-10,21,23,26,28,31,35,36,41–44,51
Mixture/combination	✓	✓	✓	✓	8–10,15-18,23,26-29,41–45,51,56
Spatial mosaic/refuge areas	X	✓	X	✓	7,8,21,23,37–40,51
Minimize resistance allele spread/transmission	✓	✓	✓	✓	4,7–10,21,51
Common use of economic injury thresholds	X	✓	✓	n/a	4,11,21,23,41
Areawide/coordinated action	x	✓	x	✓	7,11–13,20,23,51
Crop resistance/tolerance	✓	✓	✓	n/a	3,4,9,11,21,37–39
Integration with biological control	x	✓	x	n/a	21,22
Integration with cultural control	✓	✓	✓	n/a	3,4,8–11,21,23

Note: n/a, not applicable; '✓' denotes recommended or supported by scientific evidence; 'X' denotes not recommended or supported by scientific evidence; 'x' denotes not commonly implemented.

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evolution without the negative consequences on mutation supply.[57] Exploring resistance management strategies with well-parameterized models and collecting key microbiological data on resistance during clinical trials can result in the most successful resistance mitigation outcomes (rule 5).[51]

6 THERE ARE MORE COMMON THAN DIFFERENT STRATEGIES

When comparing weed, insect, fungi and bacteria attributes and herbicide, insecticide, fungicide and antibiotic resistance management strategies, there are more similarities than differences (Table 1). Although the occurrence of *de novo* point mutations in the target site-encoding genes is likely to be less frequent for herbicide than insecticide or fungicide resistance,[6] herbicide resistance commonly evolves via both target and not-target site mechanisms similar to antibiotic resistance.[7,60] Additionally, some of the most problematic herbicide-resistant weed species globally have efficient gene (seed, pollen) dispersal capability, albeit not on the same magnitude as many insect pests. In many cases, a coordinated community response may be efficient and effective in minimizing spread or transmission of resistance alleles among agricultural pests and human pathogens. Although resistance should theoretically be associated with a fitness cost,[61] the frequency and unpredictability in the level of expression means this biological phenomenon is only rarely factored into resistance management strategies.

Both rotations (alternations, cycling) and mixtures (combinations) are universally recommended strategies to mitigate or manage herbicide, insecticide, fungicide and antibiotic resistance. The scientific literature indicates that mixtures are generally superior to rotations, but the latter is often employed because of ease of implementation and other reasons such as cost or off-target organism toxicity.[7] For all xenobiotics, the labelled rate is always recommended to mitigate and manage resistance. Where a range in label rates is indicated, the selected rate should be commensurate with pest population size, injury severity, or availability of supplemental effective non-chemical tools. Minimizing both evolution and spread or transmission of resistance alleles by minimizing population sizes through deployment of diverse integrated chemical and non-chemical tactics (spatially and temporally) are equally important, be it in a hospital or agricultural field. Most importantly, prophylactic usage of any xenobiotic should continue to be discouraged.

While we have outlined general strategies for mitigating or managing resistance, we are now at a point where increasing complex cross-resistance or multiple resistance in target populations demands more prescriptive or customized solutions tailored to the resistance profile of the population.[17,62] Accordingly, regular resistance surveillance and testing will become increasingly important to inform the most efficient and effective management strategies.[7] This goal will be greatly facilitated by emerging rapid and accurate diagnostic biochemical, molecular, genomic, and/or phenotypic assays.

Management strategies and tactics need to be supported by regulators to facilitate registration of diverse treatment regimes (e.g. mixtures or mosaics) and by public- and private-sector policies or financial incentives to encourage implementation of best management practices by end-users.[14,62,63] A paucity of public policies and financial incentives related to xenobiotic resistance management suggests that the longevity of newly registered modes of action will likely experience the same fate as many of their predecessors. Just as important as these regulatory or policy considerations, dissemination of consistent messaging around best management practices for greater uptake by end-users through continuing education and training opportunities across multiple extension platforms remains vitally important.

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