Final Project Summary

Project title	Managing concurrent evolution of resistance to fungicides (PhD)		
Project number	21120062	**Student Report**	59
Start date	September 2018	**End date**	December 2024
AHDB funding	£63,960	**Total cost**	£70,500

What was the challenge/demand for the work?

When two or more single-site acting fungicide modes of action (MoA) are used (e.g. SDHIs and azoles), pathogens will evolve resistance to them at the same time. The challenge is to determine how best to use MoAs in mixtures and alternation to maximise mutual protection against resistance. Evidence from UK and global experiments is based on studies where selection for resistance against only one of the MOA was measured. Therefore, we rely on inference to derive strategies to manage concurrent evolution.

Restrictions on the maximum number of treatments per crop with a MoA are widely used. There is a trade-off, however, because this limits the ability to use each MoA in a mixture to protect other MoA. Limiting the maximum number of treatments constrains the availability of effective mixtures at some spray timings and moves practice towards alternation or the use of less effective mixtures.

The aim of the project was to investigate which strategies are likely to provide both good resistance management and robust disease control in cases where pathogen resistance to two or more fungicidal MOA is evolving at the same time.

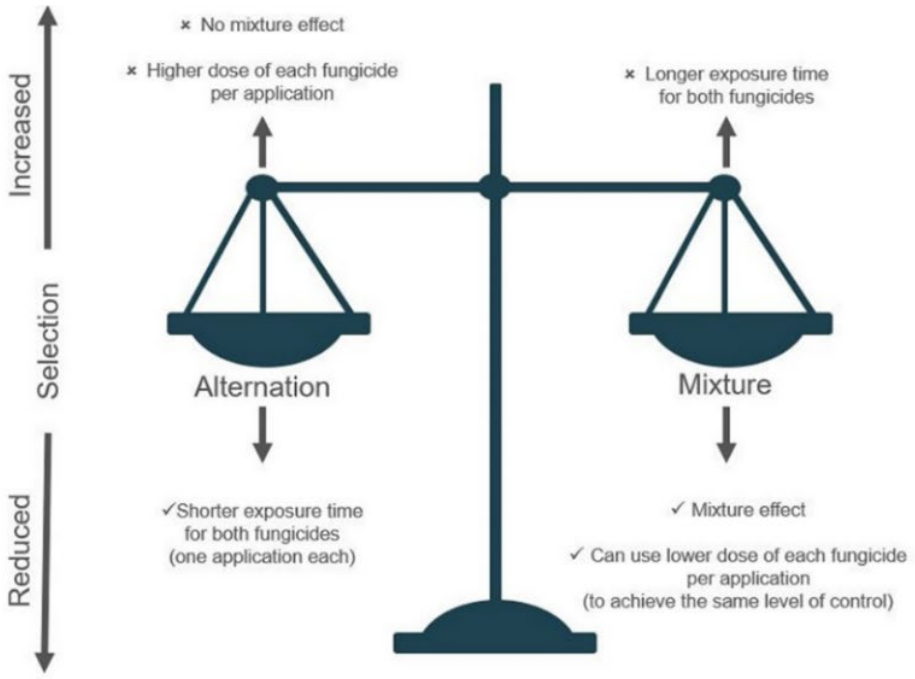

Figure 1. A balancing act: trade-offs of alternating or 'splitting & mixing' two at-risk fungicidal MoAs

Final Project Summary

How did the project address this?
This PhD project developed modelling approaches, in close collaboration with field experimentation, to inform guidance for fungicide resistance management programmes where resistance is evolving to multiple MOA. The models tracked pathogen life cycles, including infection of the crop and the effect of fungicides on resistant and sensitive pathogen strains, allowing comparison of the effects of different fungicide programmes on selection for fungicide resistance and the length of time for which a fungicide programme gives sufficient disease control ('effective life').

What are the project outputs?

The following research questions were addressed:

1. What information supports the choice of fungicide resistance management strategies, and what barriers prevent uptake of fungicide resistance management strategies?

This was addressed in a review paper, which summarised experimental and modelling evidence on the effect of fungicide dose rates, application timing, mixture and alternation strategies on selection for resistance, as well as social, economic and information barriers preventing full uptake of fungicide resistance management strategies. I found abundant evidence to support resistance management strategies against evolution of resistance to a single at-risk fungicide, but little evidence on which strategies are likely to work against concurrent evolution of resistance.

2. What is the value of phytosanitary cultural control for fungicide resistance management?

Integrated pest management (IPM) measures have value for disease control and are typically at lower risk than fungicides from evolution of resistance or pathogen adaptation. In addition, IPM measures that directly suppress pathogen growth rates will minimise the difference between the growth rates of sensitive and resistant strains, directly reducing the fitness advantage of resistant strains and therefore contributing to fungicide resistance management. The fungicide resistance management value of phytosanitary cultural control methods that do not suppress pathogen growth rates after the onset of infection is less clear.

I modelled the fungicide resistance management impact of a key phytosanitary IPM strategy in Brazil used to control Asian soybean rust (*Phakopsora pachyrhizi*): the delay of *P. pachyrhizi* inoculum influx through soybean-free periods, mandated through restrictions on sowing dates to reduce transmission of disease between growing seasons. A comparable IPM measure in the UK is the control of potato late blight (*Phytophthora infestans*) inoculum between seasons through covering of potato discard piles.

My results show that phytosanitary cultural control can contribute to fungicide resistance management. Delaying infection timing relative to crop emergence both reduced selection for fungicide-resistant strains and increased fungicide effective life, for two reasons:

a. A reduction in the length of exposure time of the pathogen to fungicide
b. A reduction in total disease pressure over time enables effective control to be maintained with lower fungicide inputs, which reduces the difference between the growth rates of resistant and sensitive strains. Also, with reduced disease pressure, a wider range of fungicide programmes provided effective control, even after increases in frequency of partially resistant strains.

These results have been published as a paper in Plant Pathology.

Final Project Summary

3. How does the impact of dose splitting vary with fungicide properties and the type and magnitude of resistance?

Dose splitting is a key trade-off for management of concurrent evolution of resistance, as if multiple applications are needed to control disease, use of mixture would require splitting the total dose of a fungicide across two or more applications. However, the drivers of variation in the effects of dose splitting were not well understood. I used a compartmental epidemiological model of septoria tritici blotch (*Zymoseptoria tritici*) to investigate how the effect of dose splitting on selection for resistance to a single fungicide varies with fungicide properties and the type and magnitude of resistance.

The modelling approach describes the fungicide dose response curve as a combination of the foliar fungicide decay rate, which is used to track the 'effective dose' remaining at any point in time $D(t)$, and the effect of that dose on pathogen life cycle parameters such as transmission rate and latent period, measured as a fractional reduction, $f(t)$. The impact of the fungicide on the pathogen life cycle is greatest at large effective doses, where the maximum effect is defined by an 'asymptote parameter', and the rate at which the effect decreases with reducing fungicide doses is defined by a 'curvature parameter'. The type and magnitude of fungicide resistance is defined by its effect on the dose response of pathogen strains to the fungicide, reducing the asymptote or curvature parameters (Figure 2). I refer to these cases as 'asymptote shifts' and 'curvature shifts' respectively.

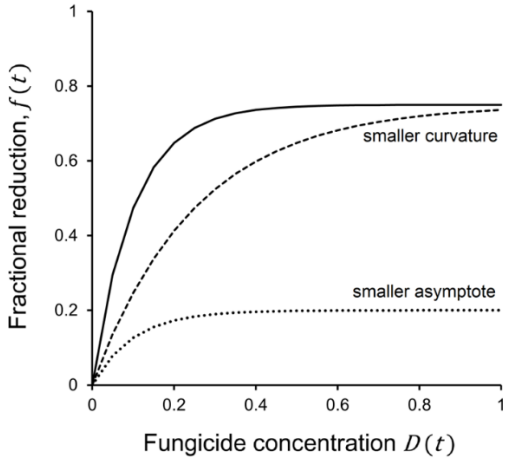

Figure 2. Fungicide dose response: effect of asymptote, curvature, and fungicide concentration, $D(t)$, on the fractional reduction $f(t)$ of pathogen life cycle parameters. $D(t)$ is expressed as a proportion of the maximum permitted individual dose (as defined on the product label)

I found that the effects of dose splitting were variable but, in general, it increased selection for both target-site and non-target-site resistance. Within the range of dose response parameters expected for commercial fungicides, dose splitting increased selection most for partial resistance mechanisms that result in a reduction in fungicide efficacy at low fungicide concentrations but not at high concentrations ('curvature shifts'). Dose splitting of a succinate dehydrogenase inhibitor (SDHI) fungicide (solo) is predicted to increase selection for target-site and non-target-site resistance by between 20-35%.

These results have been published as a paper in Plant Pathology.

Final Project Summary

4. Which is the better strategy against concurrent evolution of resistance: alternation or splitting and mixing?

I used *Z. tritici* as a case study to investigate the rate of selection for double-resistant strains when two at-risk MoA are either mixed (with dose-splitting) or alternated (without dose-splitting). The model of *Z. tritici* developed to answer research question 3 was extended to include the effects of sexual reproduction on the frequencies of sensitive, single-resistant and double-resistant strains. Since the results on dose-splitting of a solo fungicide showed that the effects on selection vary with fungicide properties and the type and magnitude of resistance, I modelled concurrent evolution across a large range of combinations of fungicide dose response parameters and resistance scenarios.

I found that the tactic that minimised selection for the double-resistant strain varied with fungicide properties and the magnitude of the sensitivity shift: neither splitting and mixing nor alternation was consistently better. In addition, across much of the parameter space explored, the difference in selection between splitting and mixing and alternation was small. Overall, for all resistance type scenarios, splitting and mixing was more likely to outperform alternation for resistance management when both fungicides had strong, long-lasting efficacy, and the magnitude of resistance differed between MoAs. Alternation was more likely to minimise selection for double-resistant strains when both fungicides were weakly or moderately effective.

These results were presented at the Resistance 2024 conference and the BCPC Diseases Review 2024. A scientific paper is in preparation.

5. Can incomplete cross-resistance within a fungicidal mode of action be useful for resistance management?

The success of mixture of different MoA as a resistance management strategy relies on the general absence of cross-resistance between MoAs: that pathogen strains that are resistant to one MoA are not also resistant to the second MoA. Strong positive cross-resistance implies that pathogen strains that are sensitive to one fungicide are also sensitive to the second fungicide, and pathogen strains that are highly resistant to one fungicide are also highly resistant to the second fungicide. Most existing modelling studies of the evolution of resistance assume that there is complete cross-resistance between fungicides with the same MoA, and a complete lack of cross-resistance between fungicides with different MoA, in the case of single-resistant strains, with these cases modelled using an additive dose model (ADM) or a multiplicative survival model (MSM) respectively.

However, there are important examples of incomplete cross-resistance within a MoA, including azole fungicides in the demethylation inhibitor (DMI) group: a large number of combinations of target-site mutations in the target CYP51 enzyme have led to pathogen strains with variable resistance profiles against different azoles. It has been proposed that this incomplete cross-resistance could be utilised for fungicide resistance management. However, neither the ADM or MSM modelling approaches are adequate for this case. To model the resistance management benefits of 'azole diversity', it was therefore necessary to develop a novel mathematical model representing the joint target-site action of fungicides with the same MoA but incomplete cross-resistance.

The modelling results showed that there are resistance management benefits of using mixtures, alternation or mosaics of azole active substances with incomplete cross-resistance. The best method of deployment (mixture, alternation or mosaic) varied between years and depended on exact product combinations and pathogen strain frequencies. On average, across all scenarios simulated,

programmes with more azole active substances resulted in a lower rate of selection for resistance, although there were diminishing returns as additional azoles were added to the programme, and some two-way azole combinations had the same or lower rates of selection as three- or four-way combinations. Mixtures of azoles with low or negative cross-resistance maximised resistance management benefits, but any degree of incomplete cross-resistance was useful.

These results were presented at the 20th International Reinhardsbrunn Symposium and published in the conference proceedings. An additional scientific paper is in preparation.

Table 1: Outputs relating to the project.

Press articles
The computer model that predicts fungicide resistance | AHDB
Events & conference presentations, papers or posters
• BCPC Diseases Review 2024 (15 October 2024, NIAB, Cambridge). Poster presentation: 'Managing concurrent evolution of resistance to fungicides: insights from modelling. • Resistance 2024 (23–25 September 2024, Rothamsted Research, Harpenden). Oral presentation: 'Which resistance management strategies work against concurrent evolution of resistance to fungicides?' • Calleva international workshop on Evolutionary and genomic design principles for durable genetic control of crop pathogens (15–16 April 2024, Magdalen College, Oxford). Invited talk: 'Fungicide resistance management and epidemiology'. • Frontier Agriculture Eastern Region Agronomists' conference, Dec 2023: Invited talk: 'Modelling concurrent evolution of resistance to fungicides'. • 20th International Reinhardsbrunn Symposium, Modern Fungicides and Antifungal Compounds (23–27 April 2023, Friedrichroda, Germany). Oral presentation and proceedings paper: 'Modelling resistance management benefits of diversity within a fungicidal mode of action with incomplete cross-resistance: the azoles example'. • Resistance '19 (16–18 September 2019, Rothamsted Research, Harpenden). Poster presentation: 'A method to translate field trial efficacy data into model parameters representing the effect of fungicides on pathogen life cycles.
Scientific papers
• **Corkley I.**, Fraaije B. & Hawkins N. (2022). Fungicide resistance management: Maximizing the effective life of plant protection products. *Plant Pathology* 71:150-169. **https://doi.org/10.1111/ppa.13467** • **Corkley I.**, Mikaberidze A., Paveley N.D., van den Bosch F., Shaw M.W., Milne A.E. (2025). Dose splitting increases selection for both target-site and non-target-site fungicide resistance – a modelling analysis. *Plant Pathology*. **https://doi.org/10.1111/ppa.14080** • **Corkley I.**, Helps J., van den Bosch F., Paveley N.D., Milne A.E., Mikaberidze A. et al. (2025). Delaying infection through phytosanitary soybean-free periods contributes to fungicide resistance management in *Phakopsora pachyrhizi*: A modelling analysis. *Plant Pathology*. **https://doi.org/10.1111/ppa.14074** • **Corkley I.**, van den Bosch F., Fraaije B.A., Shaw M.W., Helps, J. Mikaberidze A. et al. (2023). Modelling resistance management benefits of diversity within a fungicidal mode of action with incomplete cross-resistance: the azoles example. In: Deising HB; Fraaije B; Mehl A; Oerke EC; Sierotzki H; Stammler G (Eds), "Modern Fungicides and Antifungal Compounds", Vol. X, pp. 291-296. © 2023. Deutsche Phytomedizinische Gesellschaft, Braunschweig, ISBN: 978-3-941261-17-4 • Paveley N., Young C., Fraaije B., van den Bosch F., Kildea S., Burnett F., Havis N., Lees A., Lynott J., Bain R., **Corkley I.**, Ritchie F. (2023). Choice of resistance management tactics: how flexible should we be? In: Deising HB; Fraaije B; Mehl A; Oerke EC; Sierotzki H; Stammler G (Eds), "Modern Fungicides and

Final Project Summary

Antifungal Compounds", Vol. X, pp. 205-211. © 2023. Deutsche Phytomedizinische Gesellschaft, Braunschweig, ISBN: 978-3-941261-17-4

- **Corkley I.**, Mikaberidze A., van den Bosch F., Paveley N.D., Milne A.E. Which resistance management strategies work against concurrent evolution of resistance to fungicides? *Manuscript in preparation.*
- **Corkley I.**, Paveley N.D., Fraaije B.A., Helps J., Shaw M.W., Milne A.E. et al. Azole mixtures: Modelling resistance management benefits of incomplete cross-resistance within a fungicidal mode of action. *Manuscript in preparation.*

Other

- Co-author on ADAS project report No. 637 to AHDB for linked project 21120058, 'Managing resistance evolving concurrently against two or more modes of action to extend the effective life of new fungicides'.
- Oral and poster presentations at internal AHDB, Rothamsted Research and University of Reading PhD conferences and department seminars.
- Teaching on University of Reading 'Principles of Integrated Pest Management course, 2023 & 2024. Developed ideas, prepared teaching materials & presented seminar 'Case study: Decision-making in the control of *Zymoseptoria tritici*'.
- Reviewing papers for scientific journals.

Who will benefit from this project and why?

The insights into fungicide resistance management can guide future resistance management strategies, especially as concurrent evolution of resistance is an increasing concern. The findings will be of relevance to growers, industry and government. The PhD findings have been shared with the scientific community through published papers, and with the wider community through industry events.

How have you benefited from this studentship?

Studying for a PhD has enabled me to improve my modelling and statistics skills. It has been an excellent opportunity to focus on a topic of interest in depth, as well as developing a greater breadth and depth of knowledge of the agriculture sector.

I have greatly benefitted from opportunities to present posters and talks at events and conferences with varied audiences including researchers, industry representatives and agronomists. This has improved my public speaking and scientific communication skills and confidence, with valuable guidance received from my supervisors on presentational style. The PhD has also given me an excellent introduction to the art of scientific paper writing.

I am grateful to have had the opportunity to pursue my PhD part-time alongside my role as a Senior Research Scientist at RSK ADAS Ltd. I will continue in this role following completion of my PhD, with opportunities to continue to research fungicide resistance evolution and management strategies, and also to provide statistical input to agricultural research projects.

Lead partner	Isabel Corkley (PhD student) – Rothamsted Research, University of Reading Dr Alice Milne (supervisor) – Rothamsted Research Dr Alexey Mikaberidze (supervisor) – University of Reading
Industry partners	RSK ADAS Ltd, BASF, Syngenta
Government sponsor	Rothamsted Research receives strategic funding from the Biotechnology and Biological Sciences Research Council of the United Kingdom.