**Identifying when it is financially beneficial to increase or decrease fungicide dose as resistance develops: an evaluation from long-term field experiments**

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*Running head*: Adjusting fungicide dose when resistance develops

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**Abstract**

As the frequency of fungicide resistant strains increases in a pathogen population, there is a change in the shape of the response curve of disease severity on fungicide dose. We showed previously, in a theoretical analysis, that such changes can result in an increase or a decrease in the economically optimal dose of fungicide; depending on how the response curve changes (which is determined jointly by the degree of insensitivity and frequency of a new strain) and the shape of the disease-yield loss relationship (which is a characteristic of the pathogen and crop). Here we use field dose-response data to estimate economic optimum doses for the control of *Zymoseptoria tritici* on wheat over a 21 year period. Resistance developed to varying degrees against three modes of action (MoA). Changes of optimal dose across years differed by MoA, but there was an underlying pattern of initial increase in optimal dose, followed by a decrease (ultimately to zero dose at high levels of resistance). Fungicides are often applied in mixture. The analysis shows that, provided the mixture partner is effective, the economic optimal dose increases less as resistance develops than when the fungicide is used as solo product, but the subsequent decrease in optimal dose remains.

**Introduction**

The use of fungicides is often a cost-effective means of disease control and yield protection in agricultural crops (Hardwick *et al*., 2001; Pemsl & Waibel, 2007; Wiik & Rosenqvist, 2009; Lopez *et al*., 2015). But disease control applies a selection pressure on pathogen populations to develop resistance (Brent & Hollomon 2007).

The evolution of resistance to fungicides progresses in three phases (van den Bosch *et al*., 2008, 2014). When a new mode of action is introduced for commercial use, resistance may be present already in the genetic background of the pathogen population, or it has to emerge by genetic changes in the pathogen genome (mutations or other changes) and then go through a stochastic phase, during which it may go extinct, until it develops a large enough population to be protected against chance extinction (emergence phase). After the resistance has emerged it is selected for by fungicide applications and its frequency in the pathogen population increases (the selection phase). At some point in the selection phase the frequency of resistance reaches a level that starts to compromise effective disease control. This requires changes to the fungicide treatment programme (the adjustment phase). The use of the fungicide mode of action (MoA) against the pathogen species can be terminated, other fungicide MoA can be added to the treatment programme (as a mixture partner or by alternating MoA), or the total dose (number of applications and/or dose per application) of the fungicide may be adjusted.

These three options for adjustment of the treatment programme are interrelated (see next paragraph) and an underlying question is whether the total dose of the fungicide in the treatment programme should be increased or decreased when resistance is developing. In many European crops, doses less than the maximum permitted individual dose (the dose per application) and maximum permitted total dose (the dose per season) are used routinely (Jorgensen *et al*., 2017). It is therefore possible for growers to increase or decrease the total dose applied, whilst remaining within the legal limits of the authorisation of the fungicide product.  From a cost effectiveness perspective, increasing the total dose in the treatment programme as resistance erodes efficacy, increases the disease control costs. Increased total dose will, however, also decrease the severity of the disease and reduce yield losses. The question is how these two opposing effects of an increased total dose work out on the cost caused by disease.

If the economic optimum dose changes to zero (or close to zero) then terminating use is justified. The addition of an effective mixture partner is likely to change the optimum dose of the fungicide which is in the process of evolving resistance. A further practical consideration is that changing dose has both economic and evolutionary consequences. In the analysis here, we focus on the economic consequences (including the effects of a mixture partner) and comment in the discussion on the evolutionary aspects of adjusting dose according to economic optima.

Using a modelling approach van den Bosch *et al*. (2018) analysed when the total dose in a treatment programme should be increased or decreased when resistance develops. They found that it was often economically justified to increase the total dose until resistance reached levels that precluded effective control. From that point onward, the dose should be sharply reduced. The exception to this rule was found to be when absolute resistance develops (i.e. the fungicide has nil effect against the resistant strain within the range of permitted doses), then the total dose should be decreased from the start of resistance development (where ‘resistance development’ is defined here as an increase in frequency of resistant strains resulting in a measurable change in field performance).

It follows from this previous analysis that when considering the effect of resistance on economics, it is necessary to consider resistance development in its two components: firstly, the size of the difference in sensitivity between resistant and sensitive strains (commonly expressed as a resistance factor), and secondly, the frequency of the resistant strain in the population. Different combinations of these two variables can, for example, result in broadly similar changes to efficacy, but different effects on the economically optimum total dose (van den Bosch *et al.* 2018).

An experimental assessment of whether the total dose in an application programme should increase or decrease when resistance is developing requires a long-term data set stretching from the introduction of a fungicide mode of action onto the market, well into the adjustment phase. The long-term field experiments reported by Blake *et al*. (2018) on wheat septoria tritici blotch (STB, caused by *Zymoseptoria tritici*) provide such a data set.

In the work reported in this article, we used the Blake *et al*. (2018) data to calculate changes in the most cost effective total dose of an application programme (the ‘optimal total dose’), for the time series of dose response curves for example fungicides from three MoA. The calculations were based on average values for wheat grain price, disease-free yield, yield loss coefficient, and untreated disease severity. Only the parameters of the dose response curves, estimated from the experimental data set, changed through time due to selection for resistance. This quantified the effect of selection for resistance on the average trend in the optimal total fungicide dose in the treatment programme. Next, we tested the effect of the year to year variability in the parameters. Does the optimal dose still follow the average trend, or does the year to year variability in the system distort the trends, making it difficult to develop guidance for fungicide treatment programmes? Finally, we consider the current situation around the development of resistance against succinate dehydrogenase inhibitor fungicides (SDHIs) in *Z. tritici*.

There is one key constraint in this analysis which must be accounted for when interpreting the results. This is a retrospective analysis. The dose response curves measured in the field experiments were a consequence of the composition (degree of insensitivity and frequency) of sensitive and resistant strains in the pathogen population in each year. That strain composition was determined substantially by the decisions on fungicide use made in previous years by all growers in the region within which an experiment was conducted. Treatments applied in practice may have differed from those calculated here as being optimal (with the benefit of hindsight). Pesticide usage survey data (https://secure.fera.defra.gov.uk/pusstats/surveys/9099surveys.cfm) provides information on actual fungicide usage and we consider in the discussion the potential effect on pathogen evolution (and hence changes in efficacy) of the differences between calculated and actual treatments.

**Material and Methods**

**The data**

Field experiments were conducted between 1997 and 2018, using two to seven trial sites per year, assessing the efficacy of azoxystrobin (as commercial product ‘Amistar’, Syngenta), prothioconazole (‘Proline’, Bayer) and fluxapyroxad (‘Imtrex’, BASF) against STB. These fungicides are, respectively, a quinone outside inhibitor (QoI), demethylation inhibitor (DMI) and SDHI. The details of the experiments are described in Blake *et al.* (2018), here we give only the information needed as background for the calculations in this paper. The cultivars used for the experiments were all selected for their susceptibility to STB. Blake *et al*. reported data up to 2015 for QoI and DMI fungicides. The same experimental materials and methods were used for subsequent field experiments to 2018. Furthermore, experiments from 2012 to 2018 included fluxapyroxad treatments. The analysis reported here used these additional data, together with the data reported previously.

Fungicides were applied once at proportions 0 (untreated), 0.25, 0.5, 0.75 and 1.0 of the maximum individual product label dose (the maximum dose permitted in each application, referred to in the text as ‘full dose’) in the experiments of 1997 and 1998, and at dose 0, 0.25, 0.5, 1.0 and 2.0 full dose in the experiments from 2001 to 2018. Severity of STB severity (as fraction of the leaf visibly infected) was assessed around 21 and 42 days after the fungicide application. A mean severity score was calculated for leaves representing the protectant efficacy of the fungicide (leaves that had just emerged, or were still to emerge, at the time of the fungicide application) and for leaves representing the curative efficacy of the fungicide (leaves fully emerged 10 days or longer before the fungicide application). Here we use the mean of these two groups of assessments to represent the overall efficacy of the fungicide. At the end of each growing season yield was measured by plot combine (adjusted to 15% moisture content) for all treatments at each trial site.

The data were used to: (i) parameterise the dose response curve, (ii) estimate the disease-free yield, (iii) estimate the disease-induced yield loss coefficient (i.e. the loss per unit severity), and (iv) quantify the untreated disease severity.

(i) *Dose response curve*: Severity data from the trial sites in each year were scaled such that the severity at dose zero, *S*0, equals 1 and then averaged across experimental sites. For each year-fungicide combination dose response curves, the relative severity, *Srel*, as function of fungicide application dose, were fitted, using non-linear least squares, with the equation

(1)

where *S*rel is disease severity, RD is the maximum reduction in the relative severity (at a theoretical infinite dose), *k* is the curvature parameter and *D* the fungicide dose.

(ii) and (iii) *Disease free yield* and *yield loss coefficient*: For each year yield was plotted as a

function of STB severity for all fungicide treatments. A linear relationship between yield and disease severity was fitted to the data

(2)

where *Y* is the yield, *S*, is the disease severity, *Y*0, is the disease-free yield and*L* is the yield loss coefficient.

(vi) *Untreated disease severity*: Measurements of disease severity in the untreated plots, averaged over all experimental sites, were used as estimates of the untreated disease severity, *S*0.

The maximum reduction parameter, *RD*, and the curvature parameter, *k*, of the dose response curve, equation (1), show long term trends in their value due to the selection of fungicide resistant strains in the population. The trends are smoothed to exclude year to year variability due to weather and other environmental variability from our initial calculations. Curves were fitted to the data to smooth out the year to year variability, only retaining the average trend in the changes in *k* and *RD* through time for use in the cost calculations.

**The cost calculation**

The total cost, *CT*, a grower incurs due to disease is the sum of (i) the cost the grower spends on the fungicide applications, *CF*, and (ii) the cost resulting from the disease induced loss of grain yield, *CY*.

(3)

See the left hand chart of Figure 1 for a graphical explanation, in which the costs are plotted as a function of the total dose in the application programme. We consider the situation where the dose of the fungicide under consideration is the same in each of the applications in the spray programme within a year. The total dose in the application programme then is the dose per application, *D*, multiplied by the total number of applications, *N*.

The total cost of the fungicide application programme, *CF*, is the sum of (i) the cost of buying the fungicide and (ii) the cost of fungicide applications

(4)

where *PD* is the price of a full dose of the fungicide and *PA* is the fixed cost of a fungicide application (which includes cost of machinery and labour).

To calculate the cost due to disease induced yield loss, *CY*, we first need to discuss how the dose response curves from the one application programme of our data set discussed above can be used to calculate the severity reduction of a programme with more than one application. Paveley *et al*. (2003) showed that successive fungicide applications in a spray programme have a joint action which follows a multiplicative survival model. The relative severity remaining after *N* applications can, therefore, be calculated as giving

(5)

Multiplying the disease severity in an untreated crop, *S0*, with the relative severity remaining after the fungicide application programme, *Srel N*(*D*), gives the disease severity remaining. The yield loss coefficient, *L*, is the fraction of the yield lost resulting from one unit of disease severity. Multiplying *L* and *SrelN*(*D*) thus gives us the fraction of yield lost to disease. Multiplying this with the disease-free yield, *Y0*, gives the total yield, in tonnes per ha, lost to disease. The total cost due to disease induced yield loss, *CY*, thus is given by

(6)

where *PY* is the price of one tonne grain. Combining equations (3), (4) and (6) we find

(7)

Using equation (7) we can plot the total cost to disease as function of the total dose in the fungicide application programme. Figure 1 shows an example for prothioconazole in 2004 for all possible combinations of total dose applied as 1, 2, 3 or 4 applications. Note that the curve of the one application programme ends at a total dose of 1 as that is the maximum individual dose. Similar arguments hold for the two, three and four application programmes. In the case of prothioconazole in 2004 the most cost effective total dose, ‘the optimal dose’, is found in the two application programme (the dot in figure 1).

*Mixing partners*: DMI and SDHI fungicides are generally used in mixtures with other fungicides with a different mode of action. To study the effect of a mixing partner on the optimal dose for the fungicide under consideration we extend equation (7) to include as mixing partner chlorothalonil and a rate of 1.0L/ha, which is equivalent to 0.5 of a full label dose. We assume that the efficacy of the mixing partner is stable during the period of our analysis. The cost of the fungicide application increases with the costs to buy the mixing partner, but does not change the cost of application. Thus

(8)

where the sub-script *M* refers to the mixing partner. The literature on simple models describing the joint action of pesticides was summarised by Paveley et al. (2003). Different types of models have their proponents and critics, but there is general consensus that multiplicative survival models are appropriate where mixture components have different modes of action. We thus assume the mixing partner and the fungicide under consideration have multiplicative action and get

(9)

*Mean economic cost and risk aversion:*  First we calculate the mean cost due to disease as described above, using the mean disease severity that develops when no fungicides are used, averaged over all experiments available. A grower using the optimal total dose resulting from this calculation will on average over years have the lowest costs due to disease. However, the grower will in some years suffer a large loss due to an exceptionally high level of disease developing. Growers may be willing to use higher dosages as ‘insurance’ against these infrequent years. This is termed ‘risk aversion’ and the effect on optimal treatment dose has been discussed by te Beest *et al*. (2013). Here we assume a grower aims to protect against the once in 5 year largest epidemics. This is introduced into the calculations by using the mean untreated disease severity of the 20% largest severities in our data set.

**Results**

*The parameter estimates*: The fit of the dose response curve equation (1) to the data was generally very good with 28 of the 33 fits with R2 values ≥0.95 (all dose response charts shown in supplementary materials I). The fit of the yield loss relationship (2) was generally good with 15 of the 20 fits with an R2 larger than 0.85. We thus conclude that a linear relationship between disease severity and yield loss is sufficient for our data set. (all yield loss charts shown in supplementary materials II).

There was no significant relationship between the disease-free yield, *Y0*, and time. The same holds for the yield loss coefficient, *L*, and the untreated disease severity, *S0*, (see supplementary materials IV) supporting the use of the average value of these parameters for initial calculations. There is a significant trend between wheat grain price and time (see supplementary materials IV). Therefore, we have calculated mean wheat prices for each fungicide separately over the years for which dose response curve experiments were done. The fitted trends of the dose response curve parameters with time were used as they also exclude the year to year variability. The effect of the year to year variability in all these parameters and the effect of the trend in the wheat price on the optimal total dose are analysed and described separately for the longest data set, i.e. on prothioconazole.

There was no significant relationship between the mean yield, *Y*0, and the disease loss coefficient, *L*. This allows us to use the mean values of these parameters and calculate the product for equations 6, 7 and 9 without introducing bias.

*QoI*: Figure 2 clearly shows the evolution of resistance reflected in the field dose response curves with a decreasing curvature parameter, *k*, and increasing asymptote, 1-*RD*. Some residual activity remains even where the proportion of the pathogen population containing the G143A mutation, conferring resistance to QoIs is close to 100%, resulting in an asymptote value of around 0.8-0.9. This is possibly associated with effects on germ tube extension observed following QoI treatment (Kildea *et al*., 2010)).

In agreement with previous work (te Beest *et al*., 2013; van den Bosch *et al.,* 2017), Figure 3 shows that the optimal total dose is larger for risk averse growers than for growers aiming at the lowest mean cost due to disease. As expected, the optimal total dose decreases when a mixing partner is added in both the mean economic gain and the risk averse case (Figure 3). All optimal azoxystrobin treatment programmes use two applications per growing season.

As resistance develops, the optimal QoI dose increases initially. The rate of increase in the optimal dose is higher in the risk averse case than in the mean economic gain case. The increase in the optimal total dose in the application programme is much smaller in the mixture than with solo use. After 2003-2004, resistance had increased to such a high frequency of highly insensitive strains that the cost effectiveness of the fungicide is compromised. This results in a sharply decreasing optimal dose and after 2006 not using the fungicide for control of STB is the most cost effective.

*DMI*: The decrease of the curvature parameter and the increase of the asymptote of the prothioconazole dose response curves is more gradual than those of azoxystobin (Figure 2). The decrease of the curvature parameter from a value of around 4 to around 1 took 5 years for azoxysrtobin and 11 years for prothioconazole. A similar difference in the rate of change is seen in the asymptote, with an increase in azoxystobin from 0.4 to 0.8 in 10 years, and an increase from 0.2 to 0.4 taking 18 years in prothioconazole.

The optimal total dose increases when resistance develops (Figure 3). As for azoxystobin the optimal dose increases more sharply in the risk averse case and the increase in optimal dose is considerably smaller in the case where mixtures were included in the calculations. The treatment programme with the optimal total dose has two applications in most cases. The exception is in the risk averse, solo use case, where after 2005 a three applications treatment programme becomes optimal.

The figures show that in recent years the optimal dose of prothioconazole treatments is stabilising. For the mixtures case the optimal dose is tending to decrease, whereas in the solo use case the optimal dose is still increasing slightly.

*SDHI*: Contrary to the azoxystobin and the prothioconazole cases, the curvature parameter, *k*, of fluxapyroxad seems to increase between 2012 and 2015 after which it starts to decrease. Control in 2012 may have been affected by adverse weather conditions for fungicide application, although there is no clear evidence that this affected DMI performance in the same experiments. The rate of decrease in *k* is comparable to that of azoxystobin, with a decrease from 5 to 2 in about 5 years. The rate of decrease is considerably faster than in the prothioconazole case. The asymptote increases monotonically in agreement with the azoxystobin and prothioconazole cases. Again, the rate of increase is comparable to that of azoxystobin and faster than that of prothioconazole.

Due to the initial increase in the curvature parameter, the optimal total dose in the treatment programme initially decreases. After 2015 the optimal dose increases. As with the other fungicides the optimal total dose increases faster and to a greater extent in the risk averse case and increases to a much lower extent when mixtures are used.

*A closer look at the optimum dose of fluxapyroxad* (Figure 4): For the year 2015 the optimal total dose of fluxapyroxad used solo was 0.80 of the maximum permitted individual dose, with a cost due to disease of £112/ha. In 2018 the optimal total dose had increased to 1.14 with a cost to disease of £169/ha. Applying the optimal dose of 2015 to the circumstances of 2018 (i.e. not increasing dose in response to resistance) the grower would be faced with a cost to disease of 175 £/ha, a difference of 6 £/ha or 4% compared to applying the 2018 optimum dose of 1.14.

*The effect of parameter variability*: Figure 5 shows the optimal dose of prothioconazole when the year to year variability in the dose response curve parameters, *RD* and *k*, the wheat grain price, *PY*, the disease-free yield, *Y0*, the yield loss coefficient, *L* and the untreated disease severity, *S0* are taken into account. The drawn line in the curve is the optimal total dose calculated using mean parameters values as shown in Figure 3 (mean economic gain and solo use). Including the year to year variability in all parameters introduces considerable variability in the optimum dose, but does not obscure the clear trend in the optimal dose as calculated previously on the basis of constant parameter values.

The data points between 2001 and 2010 mostly fall below the curve for the mean parameter values (drawn line) and above that curve after 2010. This is caused by the significant trend in the wheat grain price, with low prices early in the time series and higher prices later in the time series. This is clearly shown when only the year to year variation in the grain price was taken into account. Year to year variations in the disease-free yield, *Y0*, had little effect on the optimum dose. All other parameters contributed to the overall year to year variation in optimal dose.

**Discussion**

Using a long-term data set on the efficacy of fungicides for the control of *Z. tritici* on wheat in the UK, we have investigated whether the total dose in a fungicide application programme should be increased or decreased when resistance develops. Our criterion of assessment in this analysis was purely economic: the cost due to disease (the sum of the cost of the fungicide application programme and the cost due to yield losses induced by the remaining disease). Our results clearly show, for ‘solo’ applications of a single MoA, that to achieve the smallest cost to disease the total dose of a treatment programme should be increased initially as efficacy declines. This is found for all fungicides, azoxystobin, prothioconazole and fluxapyroxad, analysed, which might be characterised as representing, ‘single step’, ‘slow multi-step’ and ‘fast multi-step’ development of resistance. This result implies that, initially, increasing the total dose increased control and the resulting decreased yield loss outweighed the increased cost of fungicide. When resistance levels become high the optimal total dose decreases, as is shown in the azoxystobin case, implying that the additional control no longer outweighs the additional costs. The same is seen if we extrapolate the optimal total dose for prothioconazole into the future, by extrapolating the trends in the curvature and the asymptote parameters (results not shown).

Fungicides are usually applied in mixtures of two or more MoA in the UK (Garthwaite et al., 2016). Chlorothalonil was used in this analysis as an example mixture partner for each of the single-site acting MoA being studied. This multi-site acting fungicide was chosen because its efficacy is well quantified and has remained unchanged over the period of the field experiments reported by Blake *et al*. (2018), thus avoiding confounding changes in the optimal dose of one mixture partner by changes in efficacy of the other partner. In all cases, for the DMI, QoI and SDHI fungicides being studied, the effect of adding chlorothalonil as a mixture partner was to ameliorate the increase in optimal dose seen in the early stages of resistance development. The subsequent decrease in optimal dose to zero, seen in the QoI case, occurred in the solo and mixture treatments. As efficacy erodes, the mixture partner provides an increasing proportion of the disease and yield loss reduction; so the presence of a mixture partner reduces the size of the efficacy reduction, which causes the optimum dose to fall.

These findings using chlorothalonil are generalizable to other possible mixture partners to some degree. The same effect of the mixture partner (on the economically optimal dose of the single-site acting fungicide) would be found for any other mixture partner of the same efficacy, regardless of its cost or MoA. More or less effective mixture partners than chlorothalonil would increase or decrease, respectively, the difference in the optimum dose compared with the solo optimum. In farm practice, the availability of effective mixture partners may be constrained by pesticide regulation removing active substances from use or by resistance reducing their efficacy (the latter being a particular risk for single-site acting mixture partners). The analysis shows, from a purely economic perspective, that the most effective mixture partner available will have the greatest benefit to stabilising the optimum dose.

The analysis was retrospective. The changes in dose response curves were influenced by the treatments actually applied in the UK during the study period, and not by the treatments we analyse as being optimal. This limitation needs to taken into account in the interpretation of our findings. For example, the comparison between the solo and mixture treatments for the QoI case could be interpreted (probably erroneously) to mean that use of mixture shortens the life of a MoA. The calculations show only how the optimal dose changes given the dose response curves as measured in the field. In the QoI example, the year in which the financial benefit from QoI use becomes zero is earlier for the mixture than the solo, due to the control provided by the mixture partner. A similar effect is also predicted for DMI and SDHIs if the observed decline in performance continues. In practice, there is good evidence that the use of mixture partners slows selection for resistant strains (van den Bosch *et al.,* 2014b). Part of the reason for the short life of the QoIs may have been due to their use solo in the early years following their introduction. The use of mixtures would therefore be expected to slow the rate at which efficacy declines, prolonging effective life. It remains to be analysed what the net effect is of the evolutionary and economic effects of a mixture partner.

To the best of our knowledge there is only one study considering whether the dose of a treatment programme should be increased or decreased when resistance develops. That study (van den Bosch *et al.,* 2017) was a modelling analysis and concluded that for disease severity yield loss relationships that are linear, as in the current case, or for disease yield relationships for which the slope decreases with increasing severity,

1. When absolute resistance develops the total dose should decrease when resistance develops
2. When partial resistance develops the total dose should initially increase when resistance develops.

In that study the QoI case was used as an example of where ‘absolute’ resistance develops. Our data analysis presented here shows that the optimal total dose of azoxystrobin increased initially through time. At first sight this contradicts the earlier theoretical model predictions. However, in that model analysis the resistant strain was represented as being completely resistant to the fungicide, implying that the dose response curve (for a pathogen population with a 100% resistance frequency) was a straight horizontal line, indicating that the fungicide had no residual effect. The field data on azoxystrobin however show that there is a residual effect of the fungicide. Even in 2006-7 when the population consisted virtually only of strains carrying the G143A mutation (Blake *et al*., 2018; Gisi *et al*., 2005; Lucas and Fraaije, 2008) the fungicide still had some effect on disease severity. The data show that the maximum achievable control is about 20%. The model analysis (van den Bosch *et al*., 2017) had shown that for such levels of ‘partial resistance’ or residual effect the dose should increase, initially, when resistance is developing. The data analysis presented here and the previous model study are thus in agreement.

Our calculations were all based around average parameter values and did not include the year-to-year variability that is important in practice. For the prothioconazole data set, which is the longest data set available, we also calculated the optimal dose including all the year-to-year variability in the dose response curve parameters, the yield loss coefficient, the untreated disease severity, the un-diseased yield and the grain price. Including all these sources of variability did not change the overall trend in the optimal dose. If the trend in optimal total dose had been severely distorted or obscured by the seasonal variation, we would have had to conclude that there may be a mean trend but that developing practical guidance for farmers is difficult, if possible at all, due to the effect of variability in the system’s components. That the variability did not obscure the trends implies that guidance can be developed for the adjustment phase of the fungicide resistance development cycle.

The economic analysis showed that the total dose should be increased, initially, to achieve the economic optimum both in the case where a grower aims at maximising mean economic gain and in the case where a grower is risk averse. The conclusion also holds for solo use of the fungicide and for mixture use of the fungicide. However, increasing total dose in a fungicide treatment programme would be expected to increase selection for resistance (van den Bosch *et al.,* 2011, 2014). Increased total dose will thus optimise the within-year economic gain, but may result in higher levels of resistance that are more difficult to control in the following years. There is thus a direct conflict between within-year and longer term economic gains. This conflict is not tractable to analyse using field experiments, but could be explored by further model analysis. It is, however, clear from this analysis that an effective mixture partner minimises the short-term economic driver to increase dose as resistance develops, thus reducing the consequent risk to longer term economics.

The optimum doses calculated here encompass the doses of DMI and SDHI fungicides used in UK wheat crops. Data from surveys in 2016 (Garthwaite et al., 2017; Anon. 2016) gave DMI and SDHI usage averaging 1.91 and 0.88 total dose, respectively (proportions of maximum individual dose). These usage values sit between the optimum doses calculated for that year for solo and mixture treatments, for a risk averse grower. Detailed comparisons between calculated and actual use are not appropriate, as these fungicides are also applied to control other diseases (particularly rusts and fusarium ear blight) in addition to STB.

For the SDHIs to which resistance is developing currently, our results on fluxapyroxad show that the optimal total dose is increasing. For solo use the optimal total dose, for a grower that aims at optimising mean economic gain, increased between 2015 and 2018 from 0.8 to 1.14 full dosages. For mixture use this increase was much smaller, from 0.52 to 0.58. For a grower that is risk averse these figures are 0.96 to 1.44 for solo use and 0.64 to 0.82 for mixture use. Mixture use thus largely removes the economic incentive to increase the total dose. Moreover, the additional reduction in the cost due to disease from increasing the total dose from 0.8 to 1.14 is only 4%. It remains to be seen whether this increase is justified if it is compared to the additional selection for resistance imposed by a higher dose.

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**Supporting information legends:**

SUPPORTING INFORMATION I: Dose response curves and estimated parameter values.

SUPPORTING INFORMATION II: Disease yield relationships.

SUPPORTING INFORMATION III: Untreated disease severity

SUPPORTING INFORMATION IV: Trends in the parameters disease free yield, yield loss coefficient, untreated disease severity and the price of grain.

**Figure legends:**

*Figure 1:*

Cost due to disease as function of the fungicide application dose. *Left-hand figure*: a hypothetical illustration for the cost due to the fungicide treatments and the cost to disease induced yield loss as function of the application dose. The total cost is the sum of these two costs. *Right-hand figure*: the cost to disease (£ per hectare) as function of the total dose in the treatment programme (where 1 dose unit is a maximum individual dose). N is the number of applications in the treatment programme. The dot is the optimal total dose, minimising the cost to disease. The right-hand figure is the example of prothioconazole in 2004.

*Figure 2:*

The time courses of the curvature parameter, *k*, and the asymptote parameter, 1-*RD* for azoxystrobin, prothioconazole and fluxapyroxad (top, middle and bottom row of charts, respectively). The dose response curve is given in equation (1). Dots are parameter values estimated by fitting equation (1) to the data. The vertical lines are error bars, + and - one standard deviation. The drawn lines are fitted functions. The three data points in brackets in the proline graph were excluded on basis of being outliers with the mean more than 5 sd from the fitted line.

*Azoxystrobin:* Both the data for k and for RD are fitted with a logistic function y = a/(1+exp(-(year x0)/b)). For RD, a=0.655±0.108, b=-1.35±0.835, x0=2004±0.878, R2=0.6986. For k, a=6.630±1.740, b=-1.795±1.330, x0=2002.92±1.504, R2 =0.703.

*Prothioconazole:* k= a\*exp(-b\*x) with a=4.349±0.631, b=0.0885±0.020, x=year-2001, R2=0.644. RD= y0+a\*x with y0=0.8268±0.061, a=-0.011±0.0062,x=year-2001 R2=0.158.

Fluxapyroxad: k = y0+a\*x+b\*x^2 with y0=3.567±0.505, a=0.878±0.394, b=-0.181±0.0631, x=year-2012, R2=0.747. RD= y0+a\*x with y0=0.804±0.0527, a=0.0280±0.0146, x=year-2012, R2=0.423.

*Figure 3:*

Time course of the total dose (where 1 = a maximum individual dose) in the application programme that minimises the cost to disease. Left-hand column of charts is for the grower that aims at minimising the long-term costs, right-hand column for a risk averse grower. Top row of charts for azoxystrobin, middle row for prothioconazole and bottom row for fluxapyroxad. Each panel contains a curve for solo use of the fungicide and one for mixture use. The latter represents where a total of one full dose (one maximum individual dose) of chlorothalonil is used in the application programme, split equally between the applications.

*Figure 4:*

Cost to disease (£ per hectare) as function of the total dose (where 1 = a maximum individual dose) in the application programme for fluxapyroxad in the year 2015 and 2018. Only the treatment programmes with 1 and with 2 applications are shown as the maximum allowed number of applications is 2. The dot in the left-hand figure is the optimal total dose in 2015. The right-most dot in the right-hand figure is the optimal total dose in 2018. The leftmost dot is at the position of the optimal total dose in 2015.

*Figure 5:*

The optimal total dose (where 1 = a maximum individual dose) as function of time, showing the effect of year-to-year variability in the model parameters on the optimal total dose. The left-top panel includes the variability of all parameters, the other panels include only the variability of the parameter indicated in the panel. Dots are data for each year, the drawn line is the optimal total dose in the case of using the mean parameter values (as used in the remainder of the analysis presented in this article). The curve is the same as in figure 3, prothioconazole, solo-use in the case of mean economic gain.