Are DMI+QoI Fungicide Premixes During flowering Worthwhile for Fusarium head blight Control in Wheat? A Meta-analysis

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Abstract

Fusarium head blight (FHB), caused mainly by *Fusarium graminearum*, is best controlled with demethylation inhibitor (DMI) fungicides during flowering. However, the use of premixes of DMI and quinone outside inhibitor (QoI) fungicides to control FHB has increased in Brazil. Data on FHB severity and wheat yields measured in field experiments conducted in Brazil were

gathered from both peer- and non-peer-reviewed sources published from 2000 to 2018. After applying selection criteria, 73 field trials from 35 bibliographic sources were identified, among which 50% of the data were obtained from cooperative network trials conducted after 2011. To be included in the analysis, a DMI+QoI premixes or tebuconazole (TEB) were tested in at least 14 trials and three years. Four premixes met the criteria. Estimates of percent control (and respective 95% confidence interval) by a network model fitted to the log of the treatment means ranged from 44.1% (pyraclostrobin + metconazole applied once; 32.4 to 53.7) to 64.3% (pyraclostrobin + metconazole; 58.4 to 69.3); the latter not differing from TEB (59.9%, 53.6 to 65.3). Yield response was statistically similar for pyraclostrobin + metconazole (532.1 kg/ha, 441 to 623) and trifloxystrobin + prothioconazole (494.9 kg/ha, 385 to 551), and both differed statistically from a group composed of TEB (448.2 kg/ha, 342 to 554), trifloxystrobin + TEB (468.2 kg/ha, 385 to 551), azoxystrobin + TEB (462.4 kg/ha, 366 to 558) and pyraclostrobin + metconazole applied once (413.7 kg/ha, 308 to 518). The two categories of FHB index (7% cut off) and yield (3,000 kg/ha cut off), both in the non-treated check, did not explain the heterogeneity in the estimates. Two sequential sprays of TEB or one spray of pyraclostrobin + metconazole as management choices are likely more profitable than DIM+QoI premixes sprayed twice during flowering considering only the fungicide effects on yield.

Keywords: chemical control; *Fusarium graminearum*, meta-analysis; profitability; systematic review

Fusarium head blight (FHB, or wheat scab), caused mainly by *Fusarium graminearum*, is one of the most economically damaging wheat diseases worldwide, including Brazil (Del Ponte et al. 2015; Goswami and Kistler 2004). FHB-affected wheat crops produce small-sized, shriveled and discolored kernels, which may contain dangerous mycotoxins produced by the fungus (Ponts 2015). The presence of mycotoxins may downgrade grain price or even reject the product at the elevators in countries where maximum limits have been promulgated (ANVISA 2011, 2017; McMullen et al. 2012). In Brazil, model-based estimates of relative losses to wheat yield due to FHB across more than 25 years averaged 10%, ranging from 3 to 25% (Duffeck et al. 2020). The estimates of decadal averages in yield losses were in agreement with reports from field experiments that suggested FHB being of no economic importance prior to the 1990s (Casa et al. 2004; Reis et al. 1996). Multi-toxin surveys in commercial wheat produced in Brazil have shown that trichothecenes, such as deoxynivalenol (DON) and nivalenol, as well as zearalenone, are common contaminants (Del Ponte et al. 2012; Duffeck et al. 2017; Mallmann et al. 2017).

Although several methods have been evaluated for managing FHB, effective and economic control has been achieved with fungicides applied during full flowering in combination with the use of less susceptible cultivars (Mesterházy et al. 2003; Wegulo et al. 2011; 2015; Willyerd et al. 2012). Among them, those of the demethylation inhibitor (DMIs) group have been ranked more consistently as the best options to suppress FHB and DON, but their control efficacy varies among the different active ingredients (Machado et al. 2017; Mesterházy et al. 2011; 2018; Paul et al. 2008). For example, metconazole or prothioconazole, applied solely or mixed together, have provided the highest reduction in FHB and DON than tebuconazole and propiconazole applied alone in the United States (Paul et al. 2008, 2018). In Brazil, a meta-analysis study showed wheat yields numerically higher with two sprays of tebuconazole (+100kg/ha on average), which performed better than propiconazole and carbendazim (Machado et al. 2017). A 28-year simulation study used the meta-analytic estimate of yield gain from a second spray of

tebuconazole (Machado et al. 2017) when linking historical weather, a crop model, a disease model, and a model relating FHB index and yield. The authors of that study showed that the risk of not-offsetting the costs was generally higher for two sprays given the variability in the disease risk in the historical weather for a location in southern Brazil (Duffeck et al. 2020).

Quinone-outside inhbitor (QoIs), also known as strobilurins, are generally not recommended for FHB control due to their lower efficacy than triazoles (Bolanos-Carriel et al. 2020; Feksa et al. 2019; Magan et al. 2002; Pirgozliev et al. 2002). In addition, small reduction, or even an increase, in DON in the grain relative to untreated check plots of wheat in the field treated with the QoI azoxystrobin have been reported (Ellner 2005; Feksa et al. 2019; Mesterhazy et al. 2003; Simpson et al. 2001). The underlying mechanisms leading to the increase in mycotoxin production by QoI are not entirely clear and increases in mycotoxin levels seem to be dependent on the active ingredient. Recently, several QoIs including coumoxystrobin, picoxystrobin, fluoxastrobin, azoxystrobin, fenaminstrobin and pyraclostrobin were associated with DON production by up-regulating the expression of *Tri5* and *Tri6* genes and increasing acetil-CoA production (Duan et al. 2020).

Although recommendations contrary to the use of QoIs to manage FHB, the potential benefits from their use, especially mixed with a DMI, include extended protection against foliar diseases including powdery mildew, tan spot and rusts (Barro et al. 2017; Blandino et al. 2006; Paul et al. 2018; Ransom and McMullen 2008; Willyerd et al. 2012). Studies conducted in controlled conditions have shown that QoIs can alter wheat physiology, resulting in enhanced stress tolerance, increased photosynthesis rate and yield (Blandino et al. 2011; Oerke et al. 2001; Paul et al. 2018). Therefore, the possibility of extending the flag leaf life may result in improved yields especially in disease-conducive environments (Blandino et al. 2011; Wegulo et al. 2011).

In Brazil, DMI+QoI premixes have been evaluated for many years, but a plethora of new data became available after the establishment of an industry-partnered network of cooperative

fungicide trials (CFTs) in 2011 (Santana et al. 2012, 2014, 2016a, 2016b, 2016c, 2019a, 2019b, 2020). Analyses of those data, both at the trial level and all trials combined within a year, do not provide a clear picture whether and under which conditions the use of premixes is justified and profitable for protecting wheat yields. Similar, peer-reviewed studies in the country have shown inconsistent results when QoI-amended premixes were compared to single active ingredients or other premixes. For example, in a four-trial study in Rio Grande do Sul state, significant differences in yield response favored the pyraclostrobin + metconazole compared to metconazole alone in some trials (Spolti et al. 2013). Conversely, in a four-year study in Paraná State, triazole and benzimidazole fungicides performed better than the DMI+QoI premixes with regards to FHB and DON control (Feksa et al. 2019). Similarly, in the United States, studies have reported flowering applications of DMIs as more effective in reducing FHB and DON, but most of the data were based on applications of a QoI alone (Bolanos-Carriel et al. 2020) or DMI+QoI premixes prior to anthesis because they are not recommended during flowering (Paul et al. 2018).

To resolve inconsistencies on treatment effects, meta-analysis is a useful approach to synthesize results from several bibliographic sources, which are selected following a defined criteria, to estimate the significance, size and uncertainty of the effect of a treatment of interest (Madden and Paul 2011; Madden et al. 2016). The method has gained popularity to summarize the effect of treatments in plant disease management, especially for data from uniform fungicide trials, including FHB research (Barro et al. 2019; Dalla Lana et al. 2018; Edwards Molina et al. 2019; Machado et al. 2017; Paul et al. 2008, 2018). This source of data is critical to minimize issues associated with publication bias, or when larger than average effects are more likely to be published (Mueller et al. 2013; Pannucci and Wilkins 2010).

In this study, we combined FHB index and wheat grain yield data gathered from peer- and non peer-reviewed bibliographic sources and CFTs. The final dataset spanned 15 years (2000 to

2018) of experiments conducted at 25 locations in the main wheat-producing regions in southern Brazil. Our objectives were to: 1) obtain meta-analytic estimates of FHB control efficacy and wheat yield response to selected DMI+QoI premixes; 2) test whether at least part of the heterogeneity in treatment effects could be explained by baseline levels of disease or yield; and 3) calculate the profitability of representative fungicide treatments, using meta-analytic estimates, based on the risk of not offsetting the fungicides cost.

Materials and Methods

Data source and criteria for trial and fungicide selection. Data were obtained from both peer and non peer-reviewed articles/reports (hereafter studies) on fungicide efficacy including the CFT-FHB (*Ensaios cooperativos de giberela*). First, a search was conducted in Google Scholar database (https://scholar.google.com.br/) using the following English keywords such as: "wheat", "Fusarium head blight" and "fungicide"; as well as the Portuguese keywords: "trigo", "giberela", "fungicida", "eficácia", because many studies conducted in Brazil were published in the native language and local venues. The publication period in the search was restricted to 2000 to 2018. A total of 50 studies were found (as of March 2020). After duplicate removal (n = 1), 49 studies were scrutinized to check those conforming with the following criteria: a) field trial conducted after 2000 year in Brazil; b) means of FHB index (%) and/or wheat grain yield (kg/ha), together with a measure of sampling variance, reported in tables or charts; c) a non-treated check treatment included for comparison. Forty-two studies did not match the criteria and were excluded. Other sources included the literature section of the studies, abstracts and posters presented at scientific meeting and available in digital format. These were scrutinized and 22 studies were selected. Finally, we used all data available at the annual reports of the *Ensaios cooperativos de giberela* website, totaling six reports (http://www.ensaioscooperativos.net/). The selected studies were further inspected to select the treatments of interest for analysis. To be

included in the meta-analysis, a DMI+QoI premix treatment, as well as DMI for comparison, should have been evaluated in at least 14 trials and during three years, applied either singly or twice during flowering. A total of 113 independent trials (from 35 studies) met the criteria. Screenshots of the tables and graphs from where the data were extracted from the 35 studies used for the analyses are available at https://osf.io/8b3cq/.

Database description. Data from CFTs conducted during an eight-year period (2011 to 2018) constituted the largest portion (50%) of the trials. The remaining trials were obtained from the literature, such as thesis (6%) and extended abstracts or manuscripts (44%) published from 2000 to 2015. The total period encompassed 15 years (2000 to 2018) and the trials were conducted at 25 locations in three states of south of Brazil (RS, PR, and SC). The number of trials differed between the two response variables (FHB index and yield). There were 65 trials for FHB index and 73 trials for yield because FHB index was not obtained in all trials. All experiments were performed as a randomized complete block design with four or five replicates.

Four premixes met the criteria and tebuconazole was included for comparison (Table 1). Most treatments (all trials from the CFTs) were tested with two applications: first spray at the mid- flowering and the following 10 days later. For one premix treatment (PYRA + METC), data were available for one spray (peer-reviewed literature only). This treatment was included in the analysis to compare the single versus two applications of a representative premix (Table 1).

Meta-analytic model. Estimates of the control efficacy and yield response were obtained from fitting an arm-based network model, also known as two-way unconditional linear mixed model, to the data. In this approach, the model is fitted directly to data on treatment means (absolute or log-transformed) (Machado et al. 2017; Madden et al. 2016; Paul et al. 2008) and not to the pairwise differences of treatments, known as contrast-based models. While means of FHB index were log-transformed, no transformation or standardization was required to obtain the mean absolute difference in yield, given the statistical properties of the data (Supplementary Fig. S1). The arm-based model can be written as Equation 1:

$$Y_i \sim N(\mu, \textstyle\sum + S_i) \tag{1}$$

where Y_i is the vector of L (log of the means of yield or FHB index) or absolute yield for the six treatments plus the non-treated check for the ith study, μ is a vector representing the mean of Y_i across all studies, $\sum$ is a 7 x 7 between-study variance-covariance matrix (for the seven treatments, including the non-treated check), and S_i is a within-study variance-covariance matrix for the ith study. N indicates a multivariate normal distribution.

The within-study variability (sampling variance) of L and D was calculated from the reported coefficient of variation (CV) or the mean square error (MSE); the latter when the data were available at the replicated plot level, as described (Machado et al. 2017; Paul et al. 2008, 2010). An unstructured (*UN*) matrix $\sum$ was used, given its better fit to the data than other structures such as heterogeneous compound symmetry (*HCS*) (*data not shown*). Maximum likelihood estimation models were fitted to the data using the *rma.mv* function of *metafor* package (Viechtbauer 2010) of R (R Core Team 2019).

To express the model estimates in more intuitive responses such as percent FHB control ($\overline{C}$) and percent yield increase ($\overline{Y}$) we calculated the differences of the estimated means of the logs ($\overline{L}_{IND}$ and $\overline{L}_{YLD}$) which equals the ratio of the two means (Paul et al. 2008). The $\overline{C}$ and $\overline{Y}$ values and their 95% confidence intervals (CIs) were obtained by back-transforming $\overline{L}_{IND}$ and $\overline{L}_{YLD}$ and the respective upper and lower limits of their 95% CIs as described in Equations 2 and 3.

$$\overline{C} = (1 - (\exp(\overline{L}_{IND}))x100) \tag{2}$$

$$\overline{Y} = ((\exp(\overline{L}_{YLD}) - 1)x100) \tag{3}$$

The yield difference ($\overline{D}$) was calculated directly after model fitting by subtracting estimated means of fungicide treatment and non-treated check (Madden et al. 2016).

When performing a multi-arm network meta-analysis, assessment of the inconsistency or the extent to which different sources of evidence are compatible is an important component (Higgins et al. 2012). The most important source is known as "design inconsistency" for which a design-by-treatment interaction provides a useful general framework for investigating inconsistency (Higgins et al. 2012; Madden et al. 2016; Piepho et al. 2014). We used a factorial-type ANOVA model to determine the significance of the *treatment × design* interaction, evaluated based on the Wald test statistic. The null hypothesis suggests that the network is consistent (Madden et al. 2016; Piepho et al. 2014). Eleven different designs (here design refers to the set of treatments in the trial) were found in the trials reporting both FHB index and yield response.

Analysis of moderator effects. The model was expanded to include categorical or continuous moderator variables that could explain, at least portion of, the heterogeneity of the effects across trials (Madden et al. 2016). As categorical variables, we created baselines for FHB disease index and wheat grain yield based on the median of the mean values in the non-treated check. The FHB index class was split into two groups, or baselines, representing low (<7% FHB index) and high (≥7% FHB index) disease scenarios. This threshold (7% FHB index) has been used to separate low from moderate FHB epidemic levels in Brazil (Del Ponte et al. 2005), which is close to the 10% FHB index used in the United States to define an epidemic case (De Wolf et al. 2003). The baseline yield was defined as low as 3,000 kg/ha (and elsewhere) based on the median yield in the non-treated check plot. As continuous moderators, FHB index in the non-treated check and year were included in the model; the latter to check whether there was any trend of decline in fungicide efficacy over time (Dalla Lana et al. 2018).

The moderator variables were included in the model and tested using a Wald-type chi-square test to determine if the moderator variables directly affected the differences in logs of FHB index and the non-transformed yield values (Paul et al. 2008).

Economic risk and profitability of fungicides

With the estimates of mean yield difference ($\overline{D}$) and the respective between-study variance (τ) obtained from the meta-analysis, we calculated the risk probability (P_{loss}) of not offsetting the costs of fungicide plus application (F_C) as described in Equation 4 used in previous studies (Barro et al. 2019; Machado et al. 2017; Paul et al. 2008):

$$P_{loss} = 1 - \Phi(\overline{D} - \frac{\frac{F_C}{W_P}}{\sqrt{\tau}}) \tag{4}$$

where Φ is the cumulative standard-normal function, W_P is the wheat price, and F_C is the fungicide costs (product + application).

Based on the meta-analysis results, three treatments were selected for comparison: the best performing premix (PYRA + METC) applied once or twice was compared with TEBU applied twice. For each fungicide treatment, 25 combinations were simulated (five W_P x five F_C), totaling 125 scenarios. For the calculations, we used an exchange rate as of July 2020 ($5.2 BRL = $1 USD) and a central value of fungicide price practiced in the 2019/20 cropping season. The total costs (fungicide + operational cost of $10 USD/ha) for each fungicide treatment were: PYRA + METC = $50 USD/ha (the half for one spray); and TEBU = $35 USD/ha. The central value for wheat price (160 U$/ton) was obtained from the data gathered at the AGROLINK database for three wheat-producing states (Rio Grande do Sul, Paraná, and Santa Catarina) (AGROLINK 2020). Tile plots of the probability classes of not offsetting on fungicide costs were produced for each fungicide.

Results

FHB index and yield data at the trial level. FHB index in the non-treated check plots of the studies ranged from 0.08 to 92.2% (median 7.4%) with no evident pattern of significant variation associated with season or state (Fig. 1; Supplementary Fig. S1). Over the years, the highest (36.8%) and the lowest (3.8%) median FHB index in the untreated check were recorded in the 2000 and 2008 seasons, respectively (Fig. 1A). Similarly, baseline yield ranged from 67 to 6,048 kg/ha (median 2,993 kg/ha) across the trials. Baseline yields were generally higher in Paraná state (median 3,358 kg/ha) than Rio Grande do Sul and Santa Catarina states combined (median 2,838 kg/ha). There was a general trend of decreased FHB index and increased yield in the fungicide treatments compared with the untreated check (Fig. 1A,B).

Percent FHB control. Percent control efficacy, obtained from back-transformation of the estimated differences of the log-transformed FHB index in the fungicide-treated and non-treated plots, ranged from 44.1 to 64.3%. Two sprays of PYRA + METC or TFLX + PROT reduced FHB index by at least 60% and did not differ significantly between them ($P > 0.42$), neither to TEBU (59.8%), but differed ($P < 0.05$) from AZOX + TEBU (58.7%). The latter did not differ significantly from TEBU ($P = 0.41$) and TFLX + TEBU (58.4%; $P = 0.85$). All fungicides differed from PYRA + METC applied once, which showed the least level of control (44.1%) (Table 2). The absolute difference in percent control efficacy between the most and least effective fungicide was 20.2 percentage points. The Wald test for the treatment × design interaction showed that the network was consistent ($P = 0.49$).

Yield response. The mean estimates of yield difference ($\overline{D}$) between fungicide-treated and the non-treated plots ranged from 413.7 to 532.1 kg/ha among the premixes and tebuconazole. Yield response values as high as above 500 kg/ha were estimated only for PYRA + METC applied twice (532.1 kg/ha), which did not differ from TFLX + PROT (494.9 kg/ha) ($P = 0.2398$). These were followed by TFLX + TEBU (468.2 kg/ha), AZOX + TEBU (462.4 kg/ha), TEBU (448.2 kg/ha) and PYRA + METC$_{1X}$ (413.7 kg/ha) (Table 3). The difference between the higher and lower estimated yield means was 118.4 kg/ha. Similarly, the estimated mean of the relative yield ($\overline{Y}$) was higher (>15%) for PYRA + METC and TFLX + PROT. These were followed by AZOX + TEBU (14.74%), TEBU (14.68%), TFLX + TEBU (14.66%), and PYRA + METC$_{1X}$ (12.97%) (Table 3). The Wald test for the treatment x design interaction showed that the network was consistent ($P = 0.99$).

In general, the pattern of the relationship between control efficacy and yield differences was consistent. The fungicides leading to the greatest mean disease control and yield response were PYRA + METC and TFLX + PROT. Although TEBU performed similarly to TFLX + TEBU and AZOX + TEBU in control efficacy (~59%), yield response was slightly lower, 20 to

14.2 kg/ha, than TFLX + TEBU and AZOX + TEBU, respectively. Again, PYRA + METC$_{1X}$ provided the least yield response.

Effect of moderator variables. The categories of FHB index and wheat grain yield as baselines did not affect FHB index or yield ($P > 0.05$). Similarly, FHB index as continuous in the non-treated check did not affect yield ($P = 0.2757$) and year did not affect FHB index ($P = 0.8672$), suggesting no decline in fungicide efficacy over time.

Probability of breaking even on fungicide cost. The probability of loss (P_{loss}), or not-offsetting the costs, was generally low ranged from 38.8 to 52.8%. For an average benefit-cost scenario (central tile in the plot) P_{loss} ranged from 41.6 to 43.2%, regardless of the treatment. P$_{loss}$ values increased to around 50% for higher fungicide costs and low wheat price for the selected treatments. TEBU applied twice or PYRA + METC applied once were more likely to be profitable ($P_{loss} < 45\%$) in a higher number of scenarios than the QoI-amended premix applied twice (Fig. 2).

Discussion

Quantitative summaries of the effect of DMIs applied alone or in mixture with other DMIs have been made available using data from several studies conducted during the last decades (Machado et al. 2017; Paul et al. 2008, 2010). However, just recently the performance of premixes, including one QoI for controlling FHB, have been studied more extensively and summarized in other studies that combined data from multiple trials (Bolanos-Carriel et al. 2020; Feksa et al. 2019; Paul et al. 2018; Spolti et al. 2013). In Brazil, there has been an increasing interest, mainly by the industry, in testing the performance of DMI+QoI premixes for FHB management. In fact, only a handful of studies testing DMI+QoI premixes conducted prior to

2011 were found in our review; most of the trials being tested in the industry-partnered CFT network (Santana et al. 2012, 2014, 2016a, 2016b, 2016c, 2019a, 2019b, 2020).

Our results showed that two premixes, PYRA + METC and TFLX + PROT, applied at flowering and 10 days later, provided the greatest level of control and yield response, at least numerically. However, their performance did not differ statistically from TEBU, a more affordable option included for comparison and for which the estimates in our study were similar to those obtained in the previous study using the same dataset (Machado et al. 2017).

Our estimates of control efficacy for the premix PYRA + METC (64%) were very close to the efficacy reported other recent studies, not included in our analysis, such as a two-year study (62%) conducted in the north of RS state, Brazil (Bonfada et al. 2019) and a four-year study (64.5%) conducted in the south of Paraná (Feksa et al. 2019). In the latter, the premixes were applied following pathogen inoculation, differing from our dataset from natural epidemics. Moreover, three DMI+QoI premixes (TFLX + PROT, TFLX + TEBU and PYRA + METC) in that study were evaluated in curative (post-inoculation) sprays, which were less effective than preventative application (pre-inoculation), corroborating previous findings (Spolti et al. 2013). Conversely, the authors reported that DMIs or carbendazim fungicides alone provided a better control efficacy (>70%) compared to DMI+QoI premixes in all growing seasons when taking both preventative and curative applications into account (Feksa et al. 2019). Their findings corroborate the evidence of a superior performance of a single best DMI (metconazole) compared to the PYRA + METC premix in the United States (Paul et al. 2018). However, in US study the applications of the DMI+QoI premixes were not made during flowering, but at the heading stage, in some cases followed by one spray of DMI at flowering. This may explain in part the lower efficacy (41.8%) (Paul et al. 2018) compared with estimates in our study for sprays of the premix at and after flowering (64%).

Apart from the differences due to time relative to growth stage, the generally lower efficacy in DMI+QoI premixes compared with some DMIs alone or in premix, reported in some studies, has been associated with the reduced rate of DMI, which is known to be more highly effective fungicide against *F. graminearum* (Edwards et al. 2001; Paul et al. 2018). In our analysis, however, the rate of TEBU alone was the same (200 g/L) as in the two premixes (TFLX + TEBU and AZOX + TEBU) and did not affect control efficacy as well as yield response. Similarly, Dardis and Walsh (2000) also reported comparable levels of FHB control when testing AZOX + MET and TFLX + METC with the corresponding DMI pair alone. Bonfada et al. (2019) reported similar control efficacy and yield response between PYRA + METC and single-DMI METC, both applied at anthesis and seven days later. In Italy, Blandino et al. (2006) reported greater control efficacy of the premix AZOX + TEBU (79%) compared to TEBU(64%) with applications made at mid-anthesis.

Yield benefits from the use of DMI+QoI premixes for FHB control on wheat grain yields has been linked to a broad spectrum of protection, due to the different modes of action, that could be extended to foliar diseases, especially under high disease pressure conditions (Bolanos-Carriel et al. 2020; Blandino et al. 2011; Spolti et al. 2013; Wegulo et al. 2011). For instance, Blandino et al. (2006) reported a 8.7% increase in yield by applying AZOX+TEBU compared to two DMIs applied alone (tebuconazole and prochloraz). Those reports agree with our findings of yield response for PYRA + METC being greater than TEBU (83.8 kg/ha). Information on the presence and intensity of foliar diseases was not available in the primary studies used in our analysis. However, the two groups of trials representing low or high baseline yield may be indicative of conditions that are more or less favorable for foliar diseases. When tested as moderator, we failed to reject the hypothesis that yield response is not influenced by the baseline yield. This result agrees with a previous meta-analysis on the effect of tebuconazole,

propiconazole and benzimidazole fungicide to control FHB in wheat, for which the estimates were not affected by disease pressure (Machado et al. 2017).

Using the means and respective uncertainty of the estimates in a benefit-cost risk analysis, the one-time (full flowering) spray of PYRA + METC was generally of lower risk of loss (not offsetting costs) than two sprays of this mixture or TEBU applied twice. The economic benefit from an additional spray of tebuconazole for FHB control has been questioned in previous studies. However, caution is needed because only yield protection, not mycotoxin reduction, which can contribute to economic loss in some situations, was not taken into account in those studies, as well as in our current study (Duffeck et al. 2020; Machado et al. 2017).

Results of our profitability analysis using data representative of specific experimental conditions - two sequential sprays of the same commercial fungicide, suggest that some DMI+QoI premixes can be as effective and affordable as tebuconazole in reducing FHB index and increasing wheat grain yield. This is important information for grower making more informed decisions to manage FHB economically. Current recommendations vary across the main wheat regions. In general, one spray of a DMI+QoI, premix at flowering has become standard practice, but two sprays are common in production situations that target high yield and quality such as in southern PR State (Feksa et al. 2019). Preliminary data from the CFTs has shown benefits from adding a third active ingredient (carbendazim) in the mixture (Santana et al. 2019a, b, 2020) and more data will become available in the near future to confirm this.

Another important outcome of systematic reviews is the possibility to identify knowledge gaps (Koricheva and Gurevitch 2014; Nakagawa et al. 2017). Our study shows clearly the need to invest resources on the analysis of DON data. The limited number of studies testing the effect of DMI+QoI premixes, both from published and CFT sources, reporting DON data (Baseggio et al. 2017; Bonfada et al. 2019; Feksa et al. 2019; Spolti et al. 2017) prevents us from obtaining reliable estimates of mycotoxin reduction or accumulation for large databases as elsewhere (Paul

et al. 2018). Thus far, there is very limited evidence of the effect of one or two applications of premixes, during flowering period, on FHB, yield and DON, which are composed of different combinations of QoIs and DMIs that can act differently (Blandino et al. 2006; Feksa et al. 2019; Paul et al. 2018; Zhang et al. 2009).

Data availability statement

All data, including graphical work, were processed and analyzed with R version 3.6.0 (R Core Team 2019). Scripts were prepared in R Markdown and organized as a research compendium available at https://osf.io/ge7ux/. A website was generated to better visualize the scripts where all data and analyses are documented, reproducible and openly available https://git.io/JUDyk

Author's contribution

JPB analyzed the data and wrote the manuscript. MRD and FJM contributed to the literature review and writing. FMS, DL, CCS, CAS, DFC, WSV, LJD, CWG, PK, HRF conducted the

trials and contributed data and comments on the manuscripts. EMD conceptualized the work, conducted the analysis and wrote the manuscript.

Conflict of interests

The authors declare that they have no conflict of interests.

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Table 1. Fungicide treatments applied for controlling Fusarium head blight in wheat, evaluated in 73 fungicide trials conducted from 2000 to 2018 across three Brazilian states (PR, RS and SC).

Fungicide a.i.	n[a]	Study code	Commercial name	Sprays[b]	Dose[c]
Non-treated	73	CHECK	-	-	-
azoxystrobin + tebuconazole	25	AZOX + TEBU	Azimut	2	0.50
pyraclostrobin + metconazole	23	PYRA + METC$_{1X}$	Opera Ultra	1	0.75
pyraclostrobin + metconazole	66	PYRA + METC	Opera Ultra	2	0.75
trifloxystrobin + prothioconazole	41	TFLX + PROT	FOX	2	0.50
trifloxystrobin + tebuconazole	36	TFLX + TEBU	Nativo	2	0.75
tebuconazole	25	TEBU	Folicur	2	0.75

[a] Number of trials that each fungicide was evaluated.
[b] Number of applications: first spray at the beginning of flowering (25% to 50%) and the following 10 days apart.
[c] Dose (L/ha) for each fungicide.

Table 2. Overall means and respective confidence intervals of log response ratio ($\bar{L}$) and calculated percent control ($\bar{C}$) of Fusarium Head Blight (FHB) relative to non-treated check provided by six fungicides evaluated during 15 years (2000 to 2018) across 65 studies conducted in three Brazilian states (PR, RS and SC).

		Effect Size					FHB control (%)		
Fungicide[a]	k[b]	$\bar{L}$	SE($\bar{L}$)	CI_L[c]	CI_U[c]	*P value*	$\bar{C}$	CI_L[c]	CI_U[c]
PYRA + METC	60	-1.0299	0.0774	-1.1815	-0.8783	<0.0001	64.29	58.44	69.31
TFLX + PROT	42	-0.9845	0.0821	-1.1454	-0.8235	<0.0001	62.63	56.11	68.19
TEBU	14	-0.9137	0.0742	-1.0592	-0.7682	<0.0001	59.89	53.61	65.32
AZOX + TEBU	25	-0.8844	0.0775	-1.0363	-0.7326	<0.0001	58.70	51.93	64.52
TFLX + TEBU	40	-0.8768	0.0799	-1.0334	-0.7202	<0.0001	58.38	51.33	64.42
PYRA + METC$_{1X}$	16	-0.5816	0.0966	-0.7710	-0.3921	<0.0001	44.09	32.43	53.74

[a] See Table 1 for complete information of the evaluated fungicides.
[b] Number of trials that each fungicide was evaluated.
[c] Upper (CI_U) and lower (CI_L) limits of the 95% confidence interval around $\bar{L}$ and $\bar{C}$.

Table 3. Overall means and respective confidence intervals of unstandardized difference in wheat grain yield ($\overline{D}$) between fungicide-treated and non-treated plots, and percent yield increase ($\overline{Y}$) for selected fungicide treatments evaluated during 15 years (2000 to 2018) across 73 studies conducted in three Brazilian states (PR, RS and SC).

Fungicide[a]	k[b]	Effect size					Yield Return (%)		
		$\overline{D}$	SE($\overline{D}$)	CI_L[c]	CI_U[c]	P value	$\overline{Y}$	CI_L[c]	CI_U[c]
PYRA + METC	70	532.08	46.40	441.14	623.02	<0.0001	17.17	14.30	20.11
TFLX + PROT	45	494.99	45.09	406.60	583.38	<0.0001	16.21	13.14	19.37
TEBU	25	448.20	54.04	342.27	554.13	<0.0001	14.68	11.24	18.22
AZOX + TEBU	25	462.43	48.92	366.53	558.32	<0.0001	14.74	11.54	18.02
TFLX + TEBU	40	468.24	42.43	385.08	551.41	<0.0001	14.66	11.92	17.46
PYRA + METC$_{1X}$	23	413.72	53.66	308.53	518.90	<0.0001	12.97	9.70	16.35

[a] See Table 1 for complete information of the evaluated fungicides.
[b] Number of trials that each fungicide was evaluated.
[c] Upper (CI_U) and lower (CI_L) limits of the 95% confidence interval around $\overline{D}$ and $\overline{Y}$.
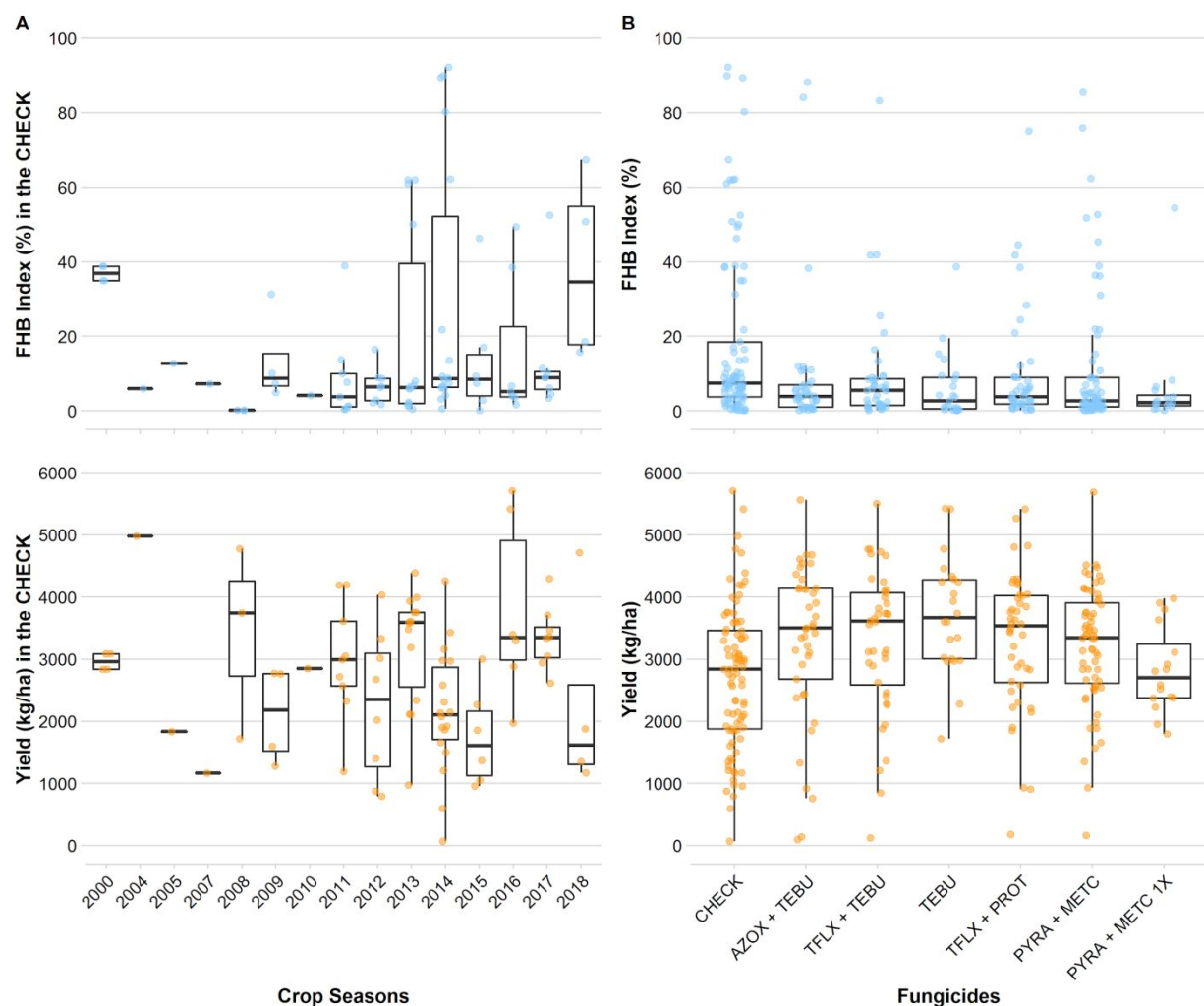
Fig. 1. Box plots for the within-season variation across trials in the nontreated check (**A**), and means for a set of fungicide treatments (**B**) of FHB Index (%) and wheat grain yield (kg ha^{-1}) obtained from 73 trials conducted during 15 years across three Brazilian states (PR, RS and SC). The thick horizontal line inside the box represents the median, the limits of the box represent the lower and upper quartiles, and the circles represent yearly means of each treatment (See Table 1).
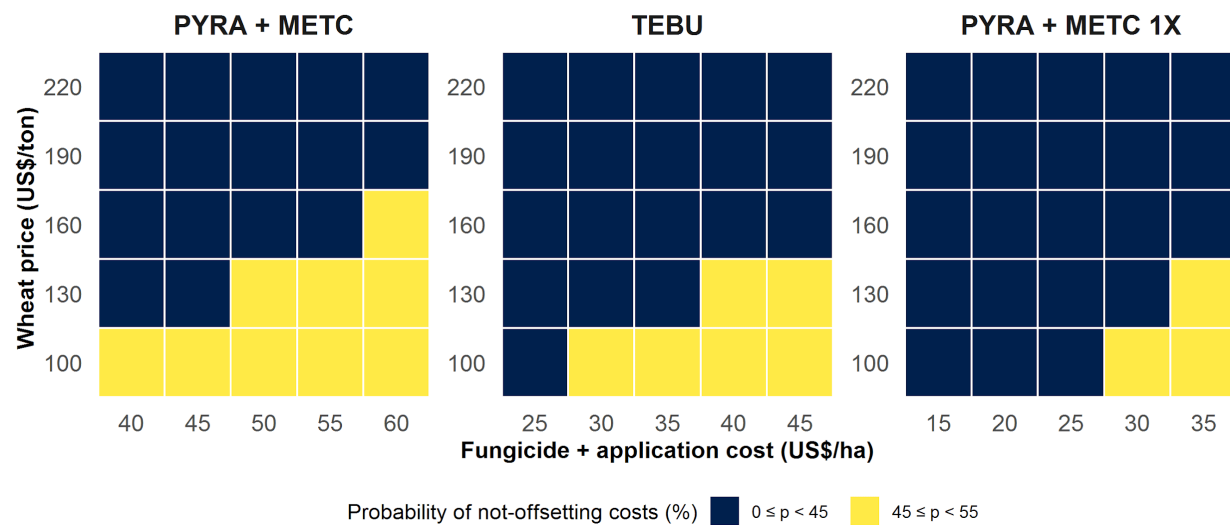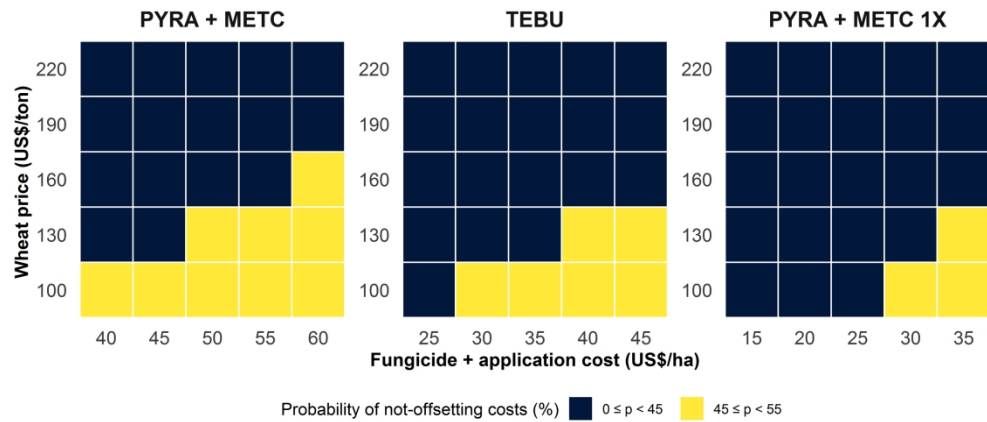
Fig. 2. Probability categories of not-offsetting on fungicide investment for different scenarios of wheat prices and fungicide costs (product price + operational costs [fixed at $10.00 U.S./ha]) for three representative fungicide treatments (see Table 1) applied once (at flowering) or twice (10-days apart) for Fusarium Head Blight control. Probability for each fungicide treatment was calculated using the estimates of the mean difference ($\overline{D}$), and respective between-study variance ($\hat{\tau}$), obtained from meta-analysis of data from 73 studies conducted over 15 years (2000 to 2018) in three Brazilian states.

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Box plots for the within-season variation across trials in the nontreated check (A), and means for a set of fungicide treatments (B) of FHB Index (%) and wheat grain yield (kg ha-1) obtained from 73 trials conducted during 15 years across three Brazilian states (PR, RS and SC). The thick horizontal line inside the box represents the median, the limits of the box represent the lower and upper quartiles, and the circles represent yearly means for each treatment (See Table 1).

Probability categories of not-offsetting on fungicide investment for different scenarios of wheat prices and fungicide costs (product price + operational costs [fixed at $10.00 U.S./ha]) for three representative fungicide treatments (see Table 1) applied once (at flowering) or twice (10-days apart) for Fusarium Head Blight control. Probability for each fungicide treatment was calculated using the estimates of the mean difference (D), and respective between-study variance (τ), obtained from meta-analysis of data from 73 studies conducted over 15 years (2000 to 2018) in three Brazilian states.

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Supplementary Figure for

Are DMI+QoI Fungicide Premixes During flowering Worthwile for Fusarium head blight Control is Wheat? A meta-analysis
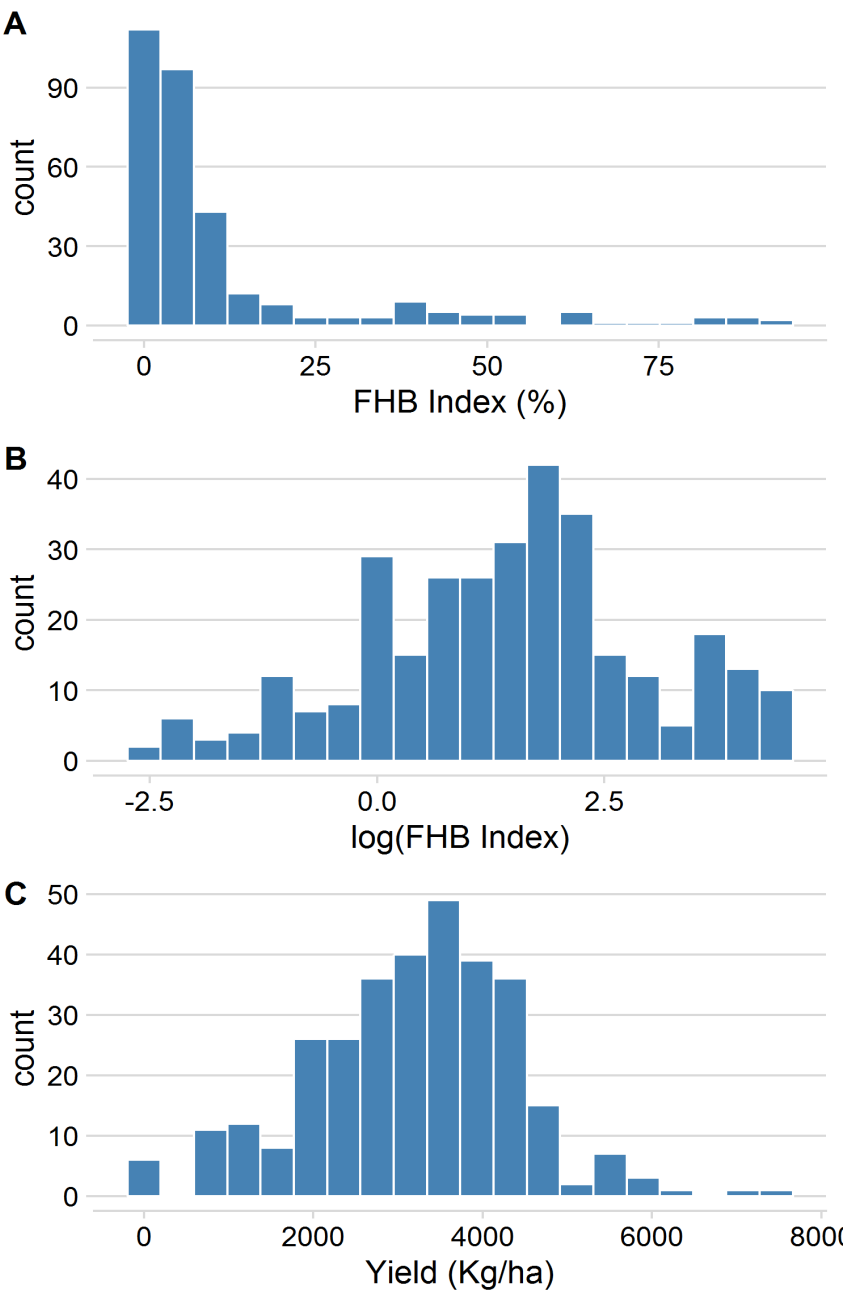
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Fig. S1: Histograms for the distribution of FHB index (**A**) and wheat grain yield (**C**) to check normality; **B**: log-transformed FHB index data for normalizing the distribution and use in the meta-analysis.