Received: 19 February 2021 | Accepted: 3 June 2021

DOI: 10.1111/ppa.13418

Plant Pathology WILEY

ORIGINAL ARTICLE

Performance of dual and triple fungicide premixes for managing soybean rust across years and regions in Brazil: A meta-analysis

Jhonatan P. Barro[1] | Kaique S. Alves[1] | Cláudia V. Godoy[2] | Alfredo R. Dias[3] | Carlos A. Forcelini[4] | Carlos M. Utiamada[5] | Edson R. de Andrade Júnior[6] | Fernando C. Juliatti[7] | Fernando J. Grigolli[8] | Heraldo R. Feksa[9] | Hercules D. Campos[10] | Ione C. P. V. Chaves[11] | Ivan P. Araújo Júnior[12] | João Mauricio T. Roy[13] | José Nunes Júnior[14] | Luana M. R. Belufi[15] | Luciana C. Carneiro[16] | Luís H. C. P. Silva[17] | Marcelo G. Canteri[18] | Marcio M. Goussain Júnior[19] | Marina Senger[20] | Maurício C. Meyer[2] | Moab D. Dias[21] | Mônica A. Müller[12] | Mônica C. Martins[22] | Mônica P. Debortoli[23] | Nédio R. Tormen[23] | Silvânia H. Furlan[24] | Tiago F. Konageski[25] | Valtemir J. Carlin[26] | Wilson S. Venâncio[27] | Emerson M. Del Ponte[1]

[1]Departamento de Fitopatologia, Universidade Federal de Viçosa, Viçosa, MG, Brazil
[2]Embrapa Soja, Londrina, PR, Brazil
[3]Fundação Chapadão, Chapadão do Sul, MS, Brazil
[4]Universidade de Passo Fundo, Passo Fundo, RS, Brazil
[5]Tagro, Londrina, PR, Brazil
[6]Instituto Mato-Grossense do Algodão, Cuiabá, MT, Brazil
[7]Universidade Federal de Uberlândia, Uberlândia, MG, Brazil
[8]Fundação MS, Maracaju, MS, Brazil
[9]Fundação Agrária de Pesquisa Agropecuária, Guarapuava, PR, Brazil
[10]Universidade de Rio Verde, Rio Verde, GO, Brazil
[11]Santa Cruz do Sul, Santagro, RS, Brazil
[12]Fundação Mato Grosso, Rondonópolis, MT, Brazil
[13]Centro de Pesquisa Agrícola Copacol, Cafelândia, PR, Brazil
[14]Centro Tecnológico para Pesquisas Agropecuárias, Goiânia, GO, Brazil
[15]Fundação Rio Verde, Lucas do Rio Verde, MT, Brazil
[16]Universidade Federal de Goiás, Jataí, GO, Brazil
[17]Agro Carregal, Rio Verde, GO, Brazil
[18]Universidade Estadual de Londrina, Londrina, PR, Brazil
[19]Assist Consultoria e Experimentação Agronômica Ltda, Campo Verde, MT, Brazil
[20]3M Experimentação Agrícola, Ponta Grossa, PR, Brazil
[21]Universidade Federal do Tocantins, Gurupi, TO, Brazil
[22]Círculo Verde Assessoria Agronômica e Pesquisa, Luís Eduardo Magalhães, BA, Brazil
[23]Instituto Phytus, Santa Maria, RS, Brazil
[24]Instituto Biológico, Campinas, SP, Brazil
[25]Rural Técnica Experimentos Agronômicos Ltda, Querência, MT, Brazil
[26]Agrodinâmica, Tangará da Serra, MT, Brazil
[27]Universidade Estadual de Ponta Grossa, Ponta Grossa, PR, Brazil

Correspondence
Emerson M. Del Ponte, Departamento de Fitopatologia, Universidade Federal de Viçosa, Viçosa, MG, Brazil.
Email: delponte@ufv.br

Funding information
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; Fundação de Amparo à Pesquisa do Estado de Minas Gerais, Grant/Award Number: APQ-03945-16; Conselho Nacional de Desenvolvimento Científico e Tecnológico, Grant/Award Number: PQ-306857/2015-4

Abstract

Soybean rust in Brazil is currently controlled with several commercial fungicide premixes composed of demethylation inhibitors (EPOXiconazole, CYPRoconazole, PROThioconazole, TEBUconazole), quinone-outside inhibitors (AZOXystrobin, TriFLoXystrobin, PYRAclostrobin, PICOxystrobin), and succinate demethylation inhibitors (BENZovindiflupyr, BIXaFen, FLUXapyroxad). Here, we summarize the performance of eight premixes evaluated in 177 cooperative trials conducted in 46 locations across 10 states from 2015 to 2020. All fungicide treatments were sprayed three times starting at R1/R2. Percentage control ($\overline{C}$, %), from back-transforming meta-analytic estimates of the log of the ratio, ranged from 56.2% (PICO + CYPR) to 76.8% (BIXF + TFLX + PROT). Estimates of mean yield difference ($\overline{D}$, kg/ha) between fungicide-treated and untreated plots were greatest for BIXF + TFLX + PROT (1,080) followed by PICO + BENZ (1,010), PYRA + EPOX + FLUX (981.5), AZOX + BENZ (910), TFLX + PROT (891), PICO +TEBU (682), TFLX + CYPR (646), and PICO + CYPR (600). Significant declines in both $\overline{C}$ and $\overline{D}$ in as little as 4 years were detected for AZOX + BENZ (35.3%; 550 kg/ha) and PICO + BENZ (15.5%; 359.8 kg/ha). Variance in $\overline{D}$ was reduced by the inclusion of baseline severity as covariate. In trials where baseline disease was ≥70%, yield was 250 kg/ha greater compared to areas with low baseline disease. Disease control and yield response were generally greater in the south-east, where the frequency of profitable scenarios was 30% higher on average than in the north-west. Results of this meta-analysis are critical for supporting decisions during planning of fungicide programmes.

KEYWORDS
chemical control, *Phakopsora pachyrhizi*, profitability, severity

1 | INTRODUCTION

Soybean rust (SBR), caused by the fungus *Phakopsora pachyrhizi* (Goellner et al., 2010; Li et al., 2010), is one of the most economically important diseases of soybean (*Glycine max*). First reported in Brazil in 2001 (Yorinori et al., 2005), SBR can lead to severe yield losses (80%–90%) according to literature reports based on experimental research data (Dalla Lana et al., 2015; Delaney et al., 2018; Godoy et al., 2016a).

The overall risk of soybean rust has decreased over the years in Brazil due to the wider adoption of cultural practices that have helped to delay the disease onset. These practices include the adoption of early-maturing cultivars, early sowing to allow a second summer crop (maize, cotton, or dry-beans), and (law-enforced) adoption of soybean-free periods between soybean seasons, which aims to reduce early-season inoculum (Godoy et al., 2016a). To date, major dominant resistance genes have been mapped in at least seven independent loci (*Rpp1* to *Rpp7*) on the soybean genome but a limited number of SBR-resistant soybean cultivars are commercially available (Childs et al., 2018). In the absence of SBR-resistant cultivars, farmers have relied on sequential fungicide applications to avoid losses in the presence of the disease (Beruski et al., 2020; Dalla Lana et al., 2018).

In Brazil, demethylation inhibitor (DMI) fungicides were the first to be widely used to control SBR, either as a single active ingredient (a.i.) or amended with quinone outside inhibitors (QoI), the most common dual mixture for almost a decade. After 2013, succinate dehydrogenase inhibitor (SDHI) fungicides have become an option in SBR management, being used as dual or triple mixtures (Godoy et al., 2016a). Recommendations of these fungicides have been based on beneficial results demonstrated by independent academic or industrial research, as well as on the annual reports by the national network of cooperative fungicide trials (CFTs) coordinated by the anti-rust consortium (Consórcio Antiferrugem) (Godoy et al., 2016a).

The CFTs for soybean rust have been conducted in Brazil since 2004/05 (Godoy et al., 2016a). These standardized trials have contributed critical knowledge for establishing effective fungicide programmes as well as providing information for responding to the emergent issue of fungicide resistance. The CFT summaries are disseminated widely in technical reports (Godoy et al., 2015, 2016b, 2017a, 2018a, 2019, 2020). The original intent of the CFTs was not to create a regional recommendation for fungicide programmes because the sequential sprays of the same fungicide, a standard in the CFTs, are usually tested in late-season planted crops, when inoculum is available. Indeed, the use of sequential sprays of the same active ingredient is not encouraged due to fungicide resistance issues (Hollomon, 2015). However, evaluation of fungicide efficacy data under disease-conducive environments is important to establish future spray programmes as well as to compare and monitor fungicide performance over time and space (Dalla Lana et al., 2018).

Continuous investigation of fungicide efficacy is essential to minimize development of fungicide resistance, and even more critical when their use is continued after reports of reduction of efficacy. Temporal and spatial changes, usually a decline in time, are dependent on (a) which chemical is used and how they are deployed (space and time) and (b) the capability of the pathogen to adapt and build resistant populations (Hollomon, 2015). Indeed, significant temporal decline in the efficacy of fungicides used in SBR control has been reported after at least four years of fungicide use. These fungicides include three single-a.i.: azoxystrobin, cyproconazole, and tebuconazole; and three dual premixes: azoxystrobin + cyproconazole, picoxystrobin + cyproconazole, and pyraclostrobin + epoxiconazole (Dalla Lana et al., 2018). This decline in fungicide performance has been linked to the reports of resistance in Brazilian *P. pachyrhizi* populations to DMI and QoI fungicides (Klosowski et al., 2016; Schmitz et al., 2013). For instance, mutations at the *cyp51* gene in isolates collected during the 2010 growing season were associated with increased EC_{50} for epoxiconazole, metconazole, and tebuconazole (Schmitz et al., 2013). Additionally, the occurrence of the F129L substitution, caused by target site mutations at the *CYTB* gene, was linked to a reduction in fungal sensitivity to QoIs (Klosowski et al., 2016). More recently, a mutation in the *SdhC* gene, which is known to reduce fungal sensitivity to SDHI fungicides, was also detected (Simões et al., 2018).

Whether the triple mixtures continue to be effective and economical over the years would be best understood by a comprehensive analysis of multiple trials. Hence, further analyses that combine multiple season data and focus on estimating not only the means, but also the uncertainty and factors explaining variation, may provide additional insights into the disease management strategy. Meta-analysis has become standard in plant pathology to summarize the effect of treatments on plant disease management (Barro et al., 2019; Edwards-Molina et al., 2018; Machado et al., 2017; Scherm et al., 2009) including effect of year on both fungicide efficacy and yield response over time (Dalla Lana et al., 2018).

Therefore, our objectives were to (a) estimate SBR control efficacy and yield response to most commonly used fungicides, including triple premixes, evaluated from 2014/15 to 2019/20 crop seasons across all major soybean regions in Brazil; (b) evaluate whether efficacy and yield response vary over time and across regions; and (c) calculate the profitability of fungicides using the meta-analytic estimates of yield response.

2 | MATERIALS AND METHODS

2.1 | Data source and criteria for fungicide selection

Data were obtained from the CFTs coordinated by the anti-rust consortium (Consórcio Antiferrugem) that have been conducted during the recent six soybean seasons (2014/15 to 2019/20). During this period, 177 independent trials were conducted across 46 locations in 10 Brazilian states (Bahia [BA], Distrito Federal [DF], Tocantins [TO], Goiás [GO], Minas Gerais [MG], Mato Grosso do Sul [MS], Mato Grosso [MT], São Paulo [SP], Paraná [PR], and Rio Grande do Sul [RS]). All data used in this study were published as yearly summaries, where the means of SBR severity (%) and soybean yield (kg/ha) were statistically compared among all evaluated fungicides within the same year (Godoy et al., 2015, 2016b, 2017a, 2018a, 2019, 2020).

In general, the cooperative trials have been conducted following a standard protocol (same experimental design, a common set of treatments, and an SBR-susceptible cultivar planted in the region). These trials are sown later in the season (November to December), depending on the region, to increase the chance of exposure to natural inoculum. Briefly, all plots (minimum 5 m long) were arranged in a randomized complete block design, with four replications. In most trials ($n = 112$), fungicides were applied three times at label rates; while in 65 trials, conducted mainly in 2018/19 ($n = 23$) and 2019/20 ($n = 15$), four sprays were performed. The first application was made between the R1 (beginning of flowering) and R2 (full flowering) growth stages (45–55 days after sowing) with subsequent applications at a 14-day interval. A backpack sprayer pressurized by CO_2, which was calibrated for a volume of at least 120 L/ha, was used to perform the fungicide applications. All weed and insect control practices followed regional recommendations.

In the CFTs, both defoliation and percentage leaf area affected (chlorotic and necrotic area estimated visually and aided by a standard area diagram [Godoy et al., 2006]) are assessed at each of three canopy heights. Disease severity is expressed as mean percentage value for the plot, and considers percentage area affected of remaining leaves and 100% for a defoliated canopy. At least four sampling points (three canopy heights each) are assessed per plot and 10 leaves are examined. The visual assessments were made between R5 (beginning of seed) and R6 (full-seed) growth stages. Yield was obtained by harvesting the central rows (at least 5 m^2) of each plot after full maturity (R8). Grain weight and moisture were measured and crop yield was expressed as kg/ha at 13% moisture.

To be included in the analysis, a fungicide treatment had to be tested in at least 116 trials over all years from 2015 to 2020 and have an untreated control treatment in the same trial. Eight treatments met the criteria, including four DMI + QoI premixes, two QoI + SDHI, and two DMI + QoI + SDHI premixes (Table 1). After treatment selection, SBR severity data were available from 177 trials and soybean yield was available for 175 trials. The states were geographically grouped into the north-western (NW) region ($n = 129$, MT, MS, GO, BA, DF, MG, and TO states) and the south-eastern (SE) region

TABLE 1 Fungicide treatments applied for controlling soybean rust in 177 independent trials from 2014/15 to 2019/20 across 46 locations in 10 Brazilian states (BA, DF, TO, GO, MG, MS, MT, SP, PR, and RS).

Fungicide a.i.	Study code	Commercial name	Dose (L/ha)[a]	Cost ($/ha)[b]
Untreated	CONTROL	—	—	—
Azoxystrobin + benzovindiflupyr	AZOX + BENZ	Elatus	0.2	85
Bixafen + trifloxystrobin + prothioconazole	BIXF + TFLX + PROT	Fox XPRO	0.5	124
Picoxystrobin + benzovindiflupyr	PICO + BENZ	Vessarya	0.6	112
Picoxystrobin + cyproconazole	PICO + CYPR	Aproach Prima	0.3	68
Picoxystrobin + tebuconazole	PICO + TEBU	Horos	0.5	75
Pyraclostrobin + epoxiconazole + fluxapyroxad	PYRA + EPOX + FLUX	Ativum	0.8	115
Trifloxystrobin + cyproconazole	TFLX + CYPR	Sphere Max	0.2	66
Trifloxystrobin + prothioconazole	TFLX + PROT	FOX	0.4	103

[a] Dose for each fungicide.

[b] Overall costs considering commercial prices of the 2019/20 crop season and three applications (operational cost for each application used was $10/ha).

($n = 48$, PR, RS, and SP states). MT ($n = 61$), MS ($n = 26$), GO ($n = 26$), and PR ($n = 35$) were the states with the largest number of trials and accounted for 84% of all trials. Most trials were conducted during the 2016/17 ($n = 36$) and 2017/18 ($n = 34$) soybean seasons.

2.2 | Descriptive analysis

Box plots and scatter plots depicting the means of soybean rust severity (%) and soybean yield (kg/ha) (across years and locations) of the untreated and fungicide-treated plots, as well as the means in the untreated plots within-region and within-year, were used for exploratory analysis (Figure 1). The average efficacy ($100 \times [1 - (\mathrm{Sev}_{\mathrm{Fungicide}}/\mathrm{Sev}_{\mathrm{Control}})]$) across the six most recent seasons, for each fungicide evaluated at each different municipality (latitude and longitude of the centroid) of the 10 Brazilian states was depicted in a map (Figure 2).

2.3 | Network meta-analysis estimates and inconsistency

Data were available at the plot level for all treatments for each variable of interest (SBR severity and soybean yield); these were combined at the trial level for meta-analysis (Madden et al., 2016). An arm-based network model, also known as a two-way unconditional linear mixed model, was fitted directly to the treatment means (log-transformed or untransformed) to obtain control efficacy and yield response (Barro et al., 2019; Machado et al., 2017; Paul et al., 2008). Given the statistical properties of the data (Figure S1), mean SBR severity values were log-transformed, while no transformation was required to obtain the mean difference in yield. The arm-based model can be written as

$$\boldsymbol{Y}_i \sim \boldsymbol{N}\left(\boldsymbol{\mu}, \boldsymbol{\Sigma} + \boldsymbol{S}_i\right) \tag{1}$$

where $\boldsymbol{Y}_i$ is the vector of L (log of the mean SBR severity) or yield (D) for the eight treatments plus the untreated control for the ith study, $\boldsymbol{\mu}$ is a vector representing the mean of $\boldsymbol{Y}_i$ across all studies, $\boldsymbol{\Sigma}$ is a 9 × 9 between-study variance–covariance matrix (for the eight treatments plus the untreated control), and $\boldsymbol{S}_i$ is a within-study variance–covariance matrix for the ith study. $\boldsymbol{N}$ indicates a multivariate normal distribution.

Given the availability of data at the plot level, the within-study variability (sampling variance) of L and D was calculated from the mean square error (MSE) obtained from a linear mixed model fitted to each individual trial, as described (Machado et al., 2017). The within-study variability is required to weight studies based on the inverse function of the sampling variance (Paul et al., 2008, 2010). Maximum-likelihood estimation models were fitted to the data using the *rma.mv* function of the *metafor* package (Viechtbauer, 2010) of R (R Core Team, 2020).

The yield difference ($\overline{D}$) was given by the difference between the estimated means for each fungicide treatment and the estimates for untreated control (Madden et al., 2016). For disease severity, we calculated the differences of the estimated means of the logs (L_{SEV}) between each treatment and the untreated control, which equals the ratio of the two means (Paul et al., 2008). The predicted percentage control ($\overline{C}$) values and their 95% confidence intervals (CIs) were obtained by back-transforming L_{SEV} and the respective upper and lower limits of their 95% CIs as described in Equation 2.

$$\overline{C} = \left[1 - exp\left(L_{\mathrm{SEV}}\right)\right] \times 100 \tag{2}$$

To test for network inconsistency, an important test for multi-arm network meta-analysis (Higgins et al., 2012), we fitted a factorial-type linear model to determine the significance of the treatment × design interaction, evaluated according to the Wald test statistic. The null hypothesis suggests that the network is consistent (Madden et al., 2016; Piepho, 2014). Ten different designs (here design refers to the set of treatments in the trial) were found in the trials reporting both SBR severity and yield response (Table S1).

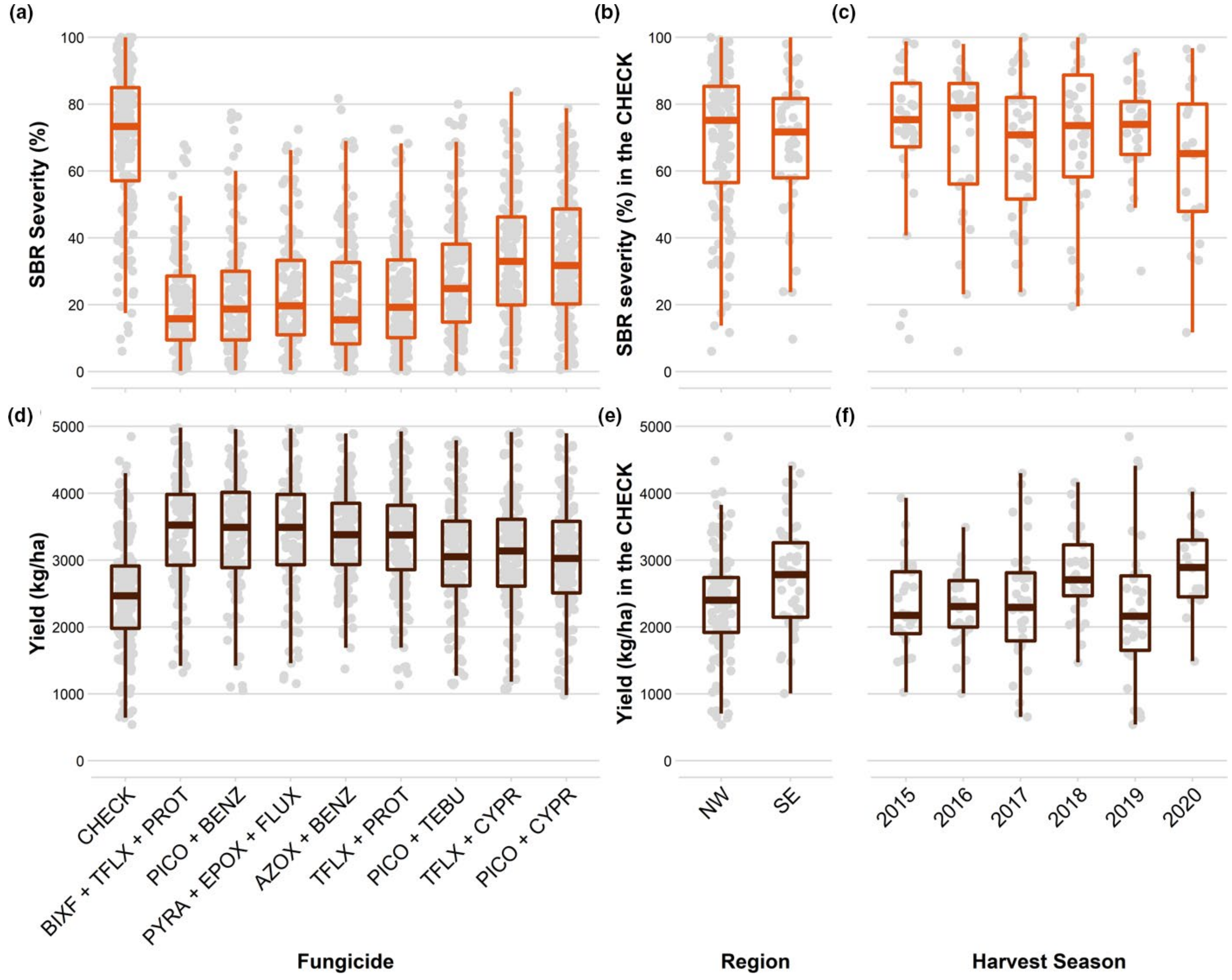

FIGURE 1 Box plots depicting the means of soybean rust (SBR) severity (%) and soybean yield (kg/ha) (across years and locations) of the untreated and fungicide-treated plots (a,d); and the means of the same variables in the untreated plots within-region (b,e) and within-year (c,f), measured from a set of 177 field trials conducted from 2014/15 to 2019/20. Geographic regions defined in our study were: north-western (NW) states (Bahia [BA], Distrito Federal [DF], Tocantins [TO], Goiás [GO], Minas Gerais [MG], Mato Grosso do Sul [MS], and Mato Grosso [MT]), and south-eastern (SE) states (Paraná [PR], Rio Grande do Sul [RS], and São Paulo [SP]) of Brazil. 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 for information on the fungicide treatments [Colour figure can be viewed at wileyonlinelibrary.com]

2.4 | Analysis of moderator effects

The network model (Equation 1) was expanded to include either a categorical or continuous moderator variable that could explain at least a portion of the heterogeneity of the effects across trials (Madden et al., 2016). The expanded model (Paul et al., 2010) is given by

$$Y_i \sim N\left(\mu + \delta_i,\ \Sigma + S_i\right) \qquad (3)$$

where δ_i is the vector representing the moderator variable effect for the *i*th study and all other terms are as defined previously.

Year as a continuous moderator variable was included in the model to evaluate whether there was a significant trend of decline in fungicide efficacy and yield response over time. Years 2015–2020 were transformed to integers (0–6) prior to fitting the model (Dalla Lana et al., 2018). Differences in regression intercept and slopes obtained from the relationships between the years and L_{SEV} and/or $\overline{D}$ between each fungicide treatment and the untreated control were used to predict L_{SEV} and $\overline{D}$ as well as the upper and lower limits of their 95% CI (Dalla Lana et al., 2018). Predicted percentage control ($\overline{C}$) was obtained by back-transforming L_{SEV} and the respective upper and lower limits of their 95% CIs as explained previously (Equation 2).

With regard to categorical variables, we created a baseline for SBR severity based on the median of the mean values in the untreated control. The trials were divided into two groups, representing low (<70% SBR severity, $n = 100$) and high (≥70% SBR severity,

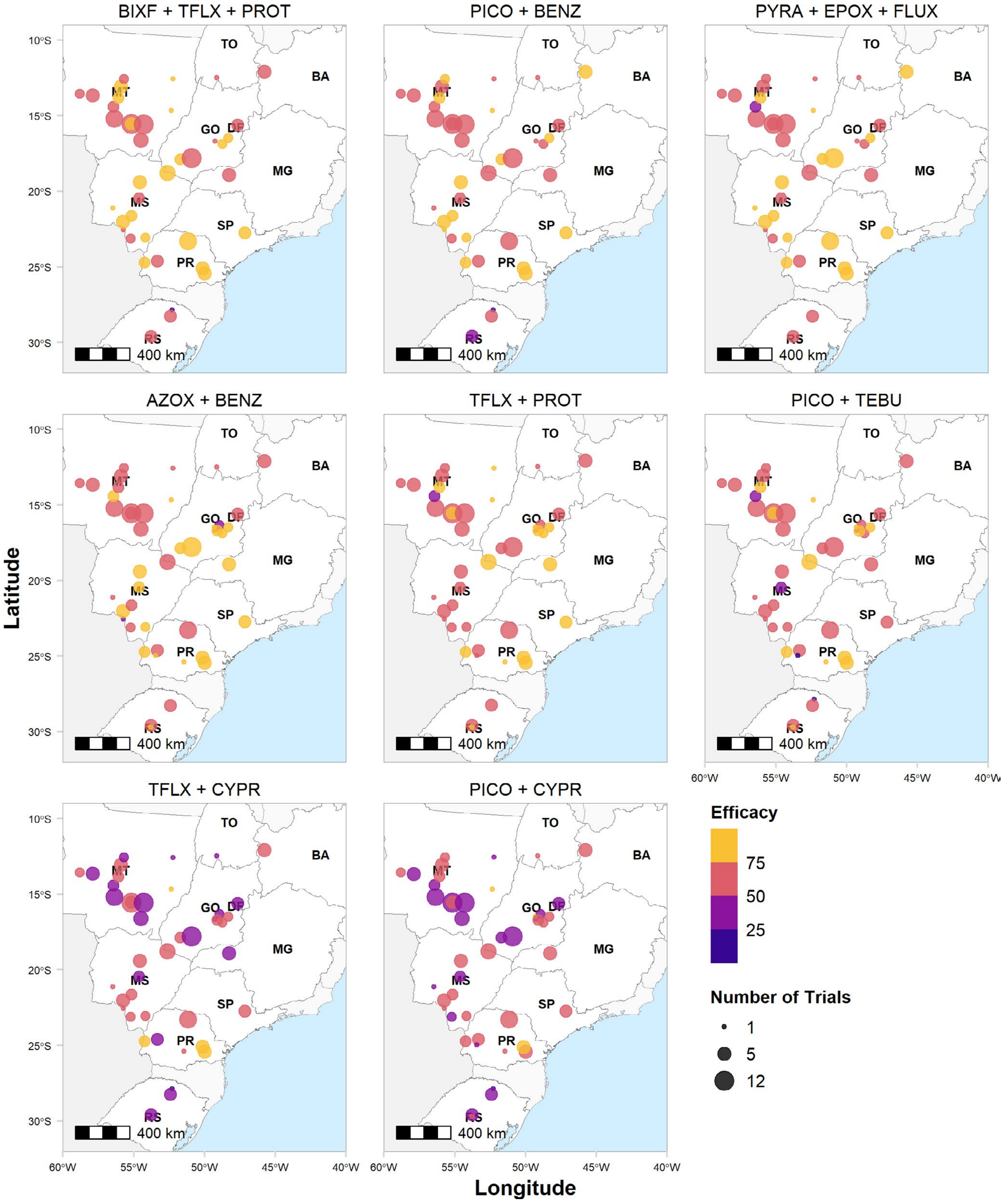

FIGURE 2 Geolocation of the 46 municipalities across 10 states of Brazil where 177 fungicide evaluation trials were conducted from 2014/15 to 2019/20. Dots represent mean percentage efficacy for the eight selected fungicides in each location, with their colour indicating the value. The size of the circle is proportional to the number of trials conducted in each location. See Table 1 for complete information of the evaluated fungicides [Colour figure can be viewed at wileyonlinelibrary.com]

$n = 75$) disease scenarios. Finally, we created an additional categorical variable based on geographical region where trials were grouped into the NW region (MT, MS, GO, BA, DF, TO, MG; $n = 126$) and the SE region (PR, RS, SP; $n = 49$), as mentioned previously. Linear contrasts were used to estimate the mean effect sizes and their standard errors and 95% CIs for each level of the categorical moderator (Madden et al., 2016).

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 log response ratio for SBR severity and differences in mean yield (Paul et al., 2008).

2.5 | Economic analysis

We calculated the distribution of profits provided by each fungicide separately for the NW and SE region, according to the respective estimates of yield return. The product of yield gain (D, kg/ha) and soybean price (S_P, US\$/kg) was used to calculate the income (I, US\$/ha). The profit of each fungicide × region combination was calculated by subtracting the application costs (A_c, US\$/ha; fungicide cost + operational cost) from the income. To obtain the distribution of profits, we ran 40,000 simulations for each fungicide × region scenario. The yield gain (D) was assumed normally distributed $D \sim N(\mu, \sigma)$, μ being the estimated mean yield gain $\overline{D}$ and σ the standard error of $\overline{D}$ [$SE(\overline{D})$]. For fungicides that had a significant decline in yield gain detected in the meta-regression, we used the $\overline{D}$ value corresponding to the more recent year. Soybean price, defined according to values received during two recent seasons (2018/19, 2019/20; AGROLINK, 2020), was assumed to be uniformly distributed between US\$0.25/ha and US\$0.35/ha, that is $S_P \sim \mathrm{Uniform}(0.25, 0.35)$. The application costs for each fungicide were also considered uniformly distributed between 5% above and below the overall cost x, that is $A_c \sim \mathrm{Uniform}(0.95x, 1.05x)$. Overall costs in 2019/20 crop season, including the operational cost for each application (total of three applications) as US\$10/ha, are described in Table 1.

3 | RESULTS

3.1 | Meta-analytic estimates of control efficacy and yield response

There was considerable variation in SBR severity and yield in the untreated plots across seasons, regions, and locations/trials (each dot in Figure 1 represents a single trial). Disease severity in the untreated plots ranged from 6.12% to 100% (median 72.5%). Median severity was higher (75%) in the NW than in the SE (69%) (Figure 1b). Across growing seasons, the highest (78.9%) and the lowest (65.2%) median SBR severities in the untreated control were recorded in the 2015/16 and 2019/20 seasons, respectively (Figure 1c).

Baseline yield ranged from 541 to 4,848 kg/ha (median = 2,501 kg/ha) across the trials. The median yield was lower in the NW (2,404 kg/ha) than in the SE (2,816 kg/ha) (Figure 1e). The highest median yield (2,890 kg/ha) was observed in 2019/20 and the lowest (2,160 kg/ha) in the 2018/19 crop season (Figure 1f). As expected, lower SBR severity and higher yield was observed in the fungicide treatments compared with the untreated control (Figure 1a–1d).

Overall estimates of percentage control efficacy ($\overline{C}$) ranged from 56.2% to 76.8% across the premixes. Triple premix BIXF + TFLX + PROT reduced SBR severity by at least 76% on average and linear contrasts showed that it was significantly different from all other treatments ($p < 0.05$). PICO + BENZ (74%), AZOX + BENZ (72.7%), PYRA + EPOX + FLUX (72.2%), and TFLX + PROT (71.9%), each with a percentage control greater than 70%, were not statistically different from each other ($p > 0.11$) but were significantly different from all other treatments ($p < 0.05$). PICO + TEBU (66%) was significantly different ($p < 0.0001$) from the two least effective fungicides TFLX + CYPR (57.8%) and PICO + CYPR (56.2%), which did not differ from each other ($p = 0.27$) (Table 2). The difference in percentage control efficacy between the most and least effective fungicide was 20.6 percentage points. The Wald test determined that network consistency was significantly affected by the study design ($p < 0.0001$).

The mean estimates of yield difference ($\overline{D}$) between fungicide-treated and untreated plots ranged from 600 to 1,080 kg/ha among the double and triple premixes (Table 3). Yield response values above 1,000 kg/ha were estimated only for BIXF + FLX + PROT (1,080 kg/ha) and PICO + BENZ (1,010 kg/ha), which differed statistically ($p = 0.03$) based on linear contrasts. PICO + BENZ did not differ statistically from PYRA + EPOX + FLUX (981.5 kg/ha; $p = 0.24$). AZOX + BENZ (910 kg/ha) and TFLX + PROT (891 kg/ha), were not statistically different ($p = 0.48$) from each other but were significantly different from all other treatments. PICO + TEBU (682 kg/ha), TFLX + CYPR (646 kg/ha) and PICO +CYPR (600 kg/ha), were statistically different from each other and all other treatments ($p < 0.05$) (Table 3). The difference between the highest and lowest estimated yield means was 480 kg/ha. The Wald test for the treatment ×design interaction showed that the network was inconsistent ($p < 0.001$). In general, there was a linear pattern in the relationship between control efficacy and yield difference. As shown previously, the most effective in reducing disease severity and leading to the greatest mean yield response was the triple premix BIXF + TFLX + PROT. Again, the two least effective fungicides in reducing disease severity and protecting yield were TFLX + CYPR and PICO + CYPR (Figure 3).

3.2 | Effect of year on control efficacy and yield response

The increase in log response ratio for disease severity (L_{SEV}), and consequently reduction in $\overline{C}$ (from back-transforming L_{SEV}), predicted per unit time based on the intercepts and slopes of network meta-regression models using year as a continuous covariate, varied among fungicides. The slope was statistically different from zero ($p < 0.0001$) for only the two QoI + DHI premixes (Table 4).

TABLE 2 Overall means and respective confidence intervals of log response ratio of soybean rust (SBR) severity (L_{SEV}) and calculated percentage control ($\overline{C}$) of SBR relative to untreated control provided by eight fungicides evaluated in 177 independent trials conducted across 46 locations in 10 Brazilian states (BA, DF, TO, GO, MG, MS, MT, SP, PR, and RS) over six growing seasons (2015–2020)

				Effect size			SBR control (%)	
Fungicide[a]	*n*[b]	*k*[c]	L_{SEV}	*SE*	$[CI_L, CI_U]$[d]	*p*	$\overline{C}$	$[CI_L, CI_U]$[d]
BIXF + TFLX + PROT	4	115	−1.4612	0.0504	[−1.5601, −1.3624]	<0.0001	76.80	[74.39, 78.98]
PICO + BENZ	4	116	−1.3482	0.0520	[−1.4501, −1.2463]	<0.0001	74.02	[71.24, 76.54]
AZOX + BENZ	5	144	−1.3017	0.0541	[−1.4078, −1.1956]	<0.0001	72.79	[69.74, 75.53]
PYRA + EPOX + FLUX	4	115	−1.2812	0.0468	[−1.3730, −1.1895]	<0.0001	72.23	[69.56, 74.66]
TFLX + PROT	6	166	−1.2719	0.0462	[−1.3624, −1.1814]	<0.0001	71.96	[69.31, 74.39]
PICO + TEBU	5	149	−1.0793	0.0418	[−1.1613, −0.9973]	<0.0001	66.01	[63.11, 68.69]
TFLX + CYPR	5	143	−0.8651	0.0375	[−0.9385, −0.7916]	<0.0001	57.89	[54.68, 60.88]
PICO + CYPR	6	169	−0.8268	0.0338	[−0.8932, −0.7605]	<0.0001	56.25	[53.25, 59.06]

AZOX, azoxystrobin; BENZ, benzovindiflupyr; BIXF, bixafen; CYPR, cyproconazole; EPOX, epoxiconazole; FLUX, fluxapyroxad; PICO, picoxystrobin; PYRA, pyraclostrobin; TEBU, tebuconazole; TFLX, trifloxystrobin.

[a] See Table 1 for complete information on the evaluated fungicides.

[b] Number of crop seasons that each fungicide was evaluated.

[c] Number of trials in which each fungicide was evaluated.

[d] Upper and lower limits of the 95% confidence interval around L_{SEV} and $\overline{C}$.

TABLE 3 Overall means and respective confidence intervals of unstandardized difference in soybean yield ($\overline{D}$) between fungicide-treated and untreated plots for eight selected fungicide treatments evaluated in 177 independent trials conducted across 46 locations in 10 Brazilian states (BA, DF, TO, GO, MG, MS, MT, SP, PR, and RS) during six growing seasons (2015–2020)

			Yield response (kg/ha)			
Fungicide[a]	*n*[b]	*k*[c]	$\overline{D}$	*SE*	$[CI_L, CI_U]$[d]	*p*
BIXF + TFLX + PROT	4	116	1080.01	40.91	[999.81, 1160.20]	<0.0001
PICO + BENZ	4	118	1010.92	38.58	[935.29, 1086.55]	<0.0001
PYRA + EPOX + FLUX	4	116	981.51	38.93	[905.20, 1057.82]	<0.0001
AZOX + BENZ	5	145	910.62	38.27	[835.60, 985.64]	<0.0001
TFLX + PROT	6	169	891.03	32.08	[828.15, 953.91]	<0.0001
PICO + TEBU	5	154	682.11	28.97	[625.32, 738.89]	<0.0001
TFLX + CYPR	5	146	646.43	25.37	[596.69, 696.16]	<0.0001
PICO + CYPR	6	175	600.39	25.26	[550.86, 649.91]	<0.0001

AZOX, azoxystrobin; BENZ, benzovindiflupyr; BIXF, bixafen; CYPR, cyproconazole; EPOX, epoxiconazole; FLUX, fluxapyroxad; PICO, picoxystrobin; PYRA, pyraclostrobin; TEBU, tebuconazole; TFLX, trifloxystrobin.

[a] See Table 1 for complete information of the evaluated fungicides.

[b] Number of crop seasons that each fungicide was evaluated.

[c] Number of trials that each fungicide was evaluated.

[d] Upper and lower limits of the 95% confidence interval around $\overline{D}$.

AZOX + BENZ showed the greatest relative reduction in percentage control (35.3 percentage points) from the first season (2014/15; 83.6%) compared to the last season (2019/20; 48.3%). PICO + BENZ showed a reduction of 15.5 percentage points in efficacy between 2016/17 (78.5%) and 2019/20 (63%) seasons. The other six fungicides showed a relatively stable efficacy over the years, including the two new triple premixes BIXF + TFLX + PROT (75.9%–75.6%) and PYRA + EPOX + FLUX (73.2%–68.1%) evaluated from 2016/17 to 2019/20 (Figure 4).

Similarly, slopes for $\overline{D}$ over time were statistically different from zero ($p < 0.0001$) for only AZOX + BENZ and PICO + BENZ (Table 4). The greatest reduction in yield response (550 kg/ha), after predicting

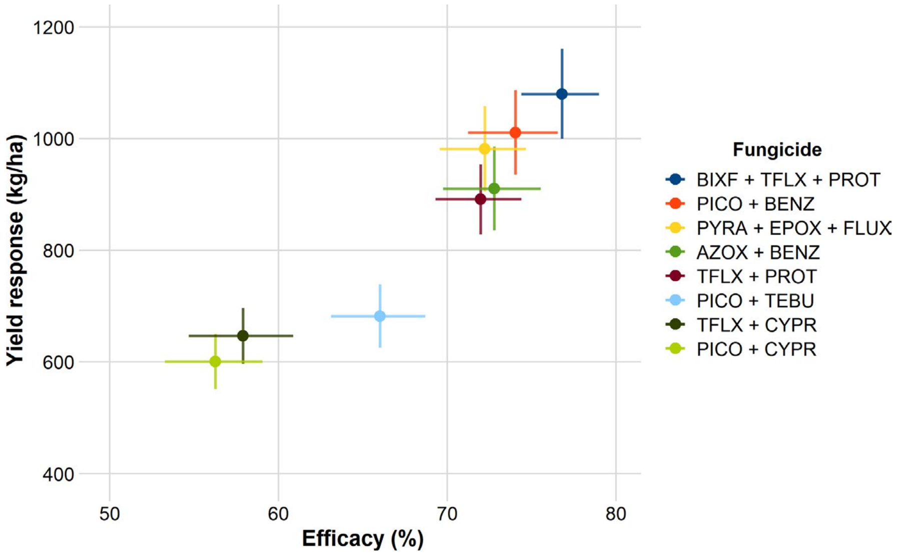

FIGURE 3 Relationship between percent reduction of soybean rust (SBR) and yield response relative to untreated control, for eight fungicides evaluated across 177 independent field trials in Brazil from 2014/15 to 2019/20. Bars show the upper and lower limits of 95% confidence intervals around point estimates for both responses. See Table 1 for complete information of the evaluated fungicides [Colour figure can be viewed at wileyonlinelibrary.com]

$\overline{D}$ for each year using the intercepts and slopes obtained from network meta-regression models, was observed for AZOX + BENZ (1,161 kg/ha in 2014/15 compared with 611 kg/ha in 2019/20). For PICO + BENZ, a reduction of 359.8 kg/ha was observed during the four-year period in which the premix was evaluated (1,096.7 kg/ha in 2016/17 compared with 736.9 kg/ha in 2019/20; Figure 5).

3.3 | Region effect on control efficacy and yield response

Based on the Wald test ($p < 0.0001$), the expanded model including the categorical moderator variable region differed statistically from the simpler model for both disease severity and yield response. Based on linear contrasts, control efficacy in the SE region was statistically higher compared to the NW region for six fungicides (BIXF + TFLX + PROT, PICO + CYPR, PICO + TEBU, TFLX + CYPR, and TFLX + PROT) (Table S2; Figure 6). In the NW region, the lowest mean percentage control for the two treatments whose performance declined over time was determined for AZOX + BENZ (28%) and PICO + BENZ (51%) at the municipalities of Cabeceira do Apa (MS) and Diamantino (MT), respectively (Table S3; Figure 2). For the SE region, the lowest efficacies estimated for AZOX + BENZ and PICO + BENZ, were determined in the southernmost state, RS, in Itaara (57%) and Erebango (16%) (Figure 2).

Similarly, yield response from the use of fungicides was generally higher in the SE than in the NW, except for the premix PICO + BENZ. There was a statistical difference in $\overline{D}$ between regions for four fungicides (PICO + CYPR, PICO + TEBU, TFLX + CYPR, and TFLX + PROT), with yield responses ranging from 130 to 203 kg/ha (Table S2; Figure 6).

3.4 | Effect of baseline disease on yield response

The expanded model including the categorical interaction term (baseline severity) differed statistically from the simpler model based on the Wald test ($p < 0.05$), meaning that severity in the untreated control treatment explained at least a portion of the variability in yield response. In general, $\overline{D}$ was greater in high-disease than in low-disease scenarios, with differences ranging from 107 kg/ha (PICO + TEBU) to 250 kg/ha (PICO + BENZ) among treatments (Table 5).

3.5 | Economic analysis

Overall, all fungicides were profitable, but especially the triple premix BIXF + TFLX + PROT, with medians profits of \$186.05/ha and \$230.68/ha for the NW and the SE regions, respectively (Figure 7). The lowest profit levels were obtained by AZOX + BENZ, with median value of \$73.39/ha and \$55.48/ha for NW and SE regions, respectively. Two dual premixes, AZOX + BENZ and PICO + BENZ, which were the only treatments whose performance declined over time, were the only treatments yielding negative 0.025 quantiles in their profit distributions (Figure 7). Overall, the more profitable scenarios were observed for the SE region, approximately 30% superior than in the NW region.

4 | DISCUSSION

The present study updates critical information for managing soybean rust with fungicides with data gathered during the past six growing seasons (2014/15 to 2019/20) across the main soybean-producing states in Brazil. On average, we found the best performing and most consistent fungicide premix to be the three-group mixture (BIXF + TFLX + PROT), while the poorest performing ones were two QoI + DMI dual mixtures (TFLX + CYPR and PICO + CYPR). In addition, a statistically significant decline in performance was detected for two dual premixes of QoI + SDHI fungicides (AZOX + BENZ and PICO + BENZ). Finally, we found generally greater levels of SBR control in the SE region and in trials with conditions favourable

TABLE 4 Regression parameters (intercept and slope) for the temporal change in log response ratio for soybean rust (SBR) severity (L_{SEV}) and absolute yield ($\overline{D}$) for each fungicide treatment relative to the untreated control from a meta-analytical model with year as a continuous moderator variable ($p < 0.05$)

			SBR severity (log scale)			Yield response (kg/ha)		
Fungicide[a]	First Season[b]	Parameter	L_{SEV}	$[CI_L, CI_U]$[c]	p	$\overline{D}$	$[CI_L, CI_U]$[c]	p
AZOX + BENZ	2014/15	Intercept	−1.808	[−1.981, −1.634]	<0.0001	1161.6	[1039.3, 1283.9]	<0.0001
		Slope	0.229	[0.167, 0.292]	<0.0001	−109.8	[−153.7, −66.0]	<0.0001
PICO + BENZ	2016/17	Intercept	−1.901	[−2.166, −1.635]	<0.0001	1336.6	[1175.4, 1497.8]	<0.0001
		Slope	0.181	[0.101, 0.260]	<0.0001	−119.9	[−171.6, −68.1]	<0.0001
BIXF + TFLX + PROT	2016/17	Intercept	−1.432	[−1.694, −1.170]	<0.0001	1025.1	[840.0, 1210.2]	<0.0001
		Slope	0.003	[−0.074, 0.082]	0.922	8.8	[−49.8, 67.4]	0.769
PYRA + EPOX + FLUX	2016/17	Intercept	−1.436	[−1.681,−1.191]	<0.0001	1055.0	[876.6, 1233.4]	<0.0001
		Slope	0.058	[−0.015, 0.132]	0.119	−37.8	[−94.1, 18.3]	0.186
TFLX + PROT	2014/15	Intercept	−1.361	[−1.523, −1.199]	<0.0001	927.5	[815.3, 1039.7]	<0.0001
		Slope	0.037	[−0.018, 0.093]	0.190	−15.6	[−55.0, 23.7]	0.436
PICO + TEBU	2014/15	Intercept	−1.106	[−1.254, −0.958]	<0.0001	627.3	[527.8, 726.7]	<0.0001
		Slope	0.004	[−0.051, 0.060]	0.878	30.4	[−5.7, 66.7]	0.099
TFLX + CYPR	2015/16	Intercept	−0.917	[−1.072, −0.761]	<0.0001	655.3	[561.5, 749.1]	<0.0001
		Slope	0.024	[−0.026, 0.074]	0.354	−4.8	[−37.2, 27.6]	0.772
PICO + CYPR	2014/15	Intercept	−0.841	[−0.960, −0.722]	<0.0001	619.3	[530.8, 707.7]	<0.0001
		Slope	0.006	[−0.034, 0.047]	0.742	−7.9	[−39.1, 23.1]	0.615

AZOX, azoxystrobin; BENZ, benzovindiflupyr; BIXF, bixafen; CYPR, cyproconazole; EPOX, epoxiconazole; FLUX, fluxapyroxad; PICO, picoxystrobin; PYRA, pyraclostrobin; TEBU, tebuconazole; TFLX, trifloxystrobin.

[a] See Table 1 for complete information of the evaluated fungicides.

[b] First season in which the fungicide was tested in the SBR uniform fungicide trial.

[c] Upper and lower limits of the 95% confidence interval around L_{SEV} and $\overline{D}$.

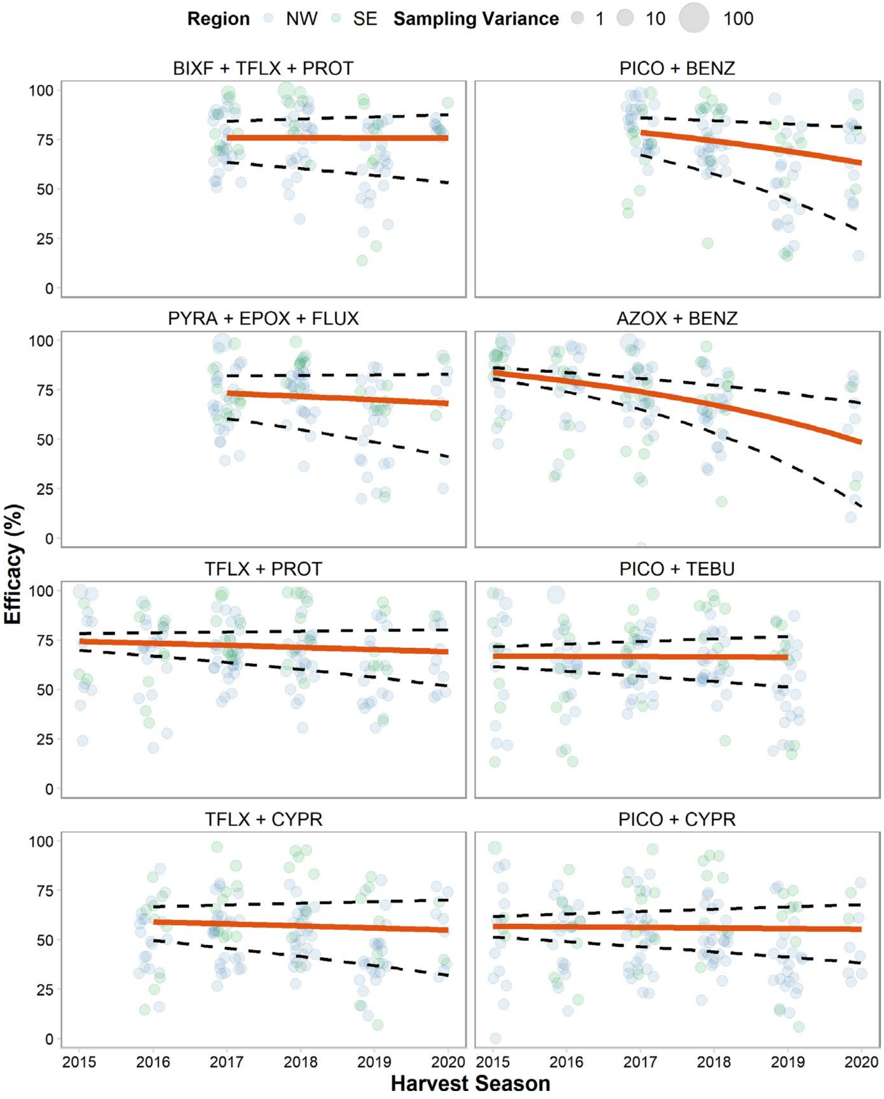

FIGURE 4 Yearly variation of efficacy (percentage control) for eight selected fungicide treatments applied three times during the season for the control of soybean rust. Solid (mean) and dashed (95% confidence intervals) lines are the predictions from back-transforming the log response ratio for each year based on the intercepts and slopes (Table 4) of network meta-regression models using year as a continuous covariate. Each dot represents the observed efficacy in an individual trial, coloured according to the two geographic regions defined in our study: north-western (NW) states (Bahia [BA], Distrito Federal [DF], Tocantins [TO], Goiás [GO], Minas Gerais [MG], Mato Grosso do Sul [MS], and Mato Grosso [MT]), and south-eastern (SE) states (Paraná [PR], Rio Grande do Sul [RS], and São Paulo [SP]). See Table 1 for detailed information on the fungicide treatments [Colour figure can be viewed at wileyonlinelibrary.com]

for severe epidemics (where severity in the untreated control was greater than 70%).

In contrast to our previous meta-analysis (Dalla Lana et al., 2018) that used a 10-year data set (up to 2014), we included two triple premixes (BIXF + TFLX + PROT and PYRA + EPOX + FLUX) and four dual premixes (AZOX + BENZ, PICO + BENZ, PICO + TEBU, and TFLX + CYPR) that were not evaluated previously. In the previous study, the dual premix PICO + CYPR (80.2%) performed the best among all fungicides. In our analysis, its efficacy was reduced by 24 percentage points (56% efficacy, on average) compared to the previous period. This difference confirms the trend of significant decline in control efficacy determined previously for this premix after seven years of use (2006/07 to 2013/14; Dalla Lana et al., 2018). Further decline was not detected for PICO + CYPR in our analysis, meaning that the reduced levels have been maintained during the six growing seasons. Also, the large spatial variation in efficacy prevented us from detecting significant trends in fungicide performance over time.

Our results also confirm the consistent good performance of TFLX + PROT over the years, with no decline being detected, on average, during the previous period (Dalla Lana et al., 2018). The higher efficacy of the triple mixture (TFLX + PROT + BIXF) could not be attributed only to the addition of BIXF, because the amount of TFLX and PROT a.i./ha (75 + 87.5) in the triple mixture is higher than in the dual mixture (TFLX 60 + PROT 70). A recent two-year study, not included in our analysis, conducted in the north of RS state (Sacon et al., 2020), reported a 71% efficacy for TFLX + PROT, which was close to our overall estimates (72% efficacy), but both were numerically lower than in the previous meta-analysis (83.6% efficacy; Dalla Lana et al., 2018). Additionally, the authors reported SBR control efficacy for PYRA + EPOX + FLUX (>70%) (Sacon et al., 2020) similar to the estimates reported here (72%).

In general, lower levels of percentage control and yield response were observed for the NW region relative to the SE region, which could be explained by the greater disease pressure on those states, as reported by Scherm et al. (2009). The within-season average number of sprays of fungicides is usually higher in the NW states, so issues with fungicide resistance are more likely to occur (Godoy et al., 2016a). Accordingly, more profitable scenarios were calculated for the SE region. The increased levels of yield return that occurred

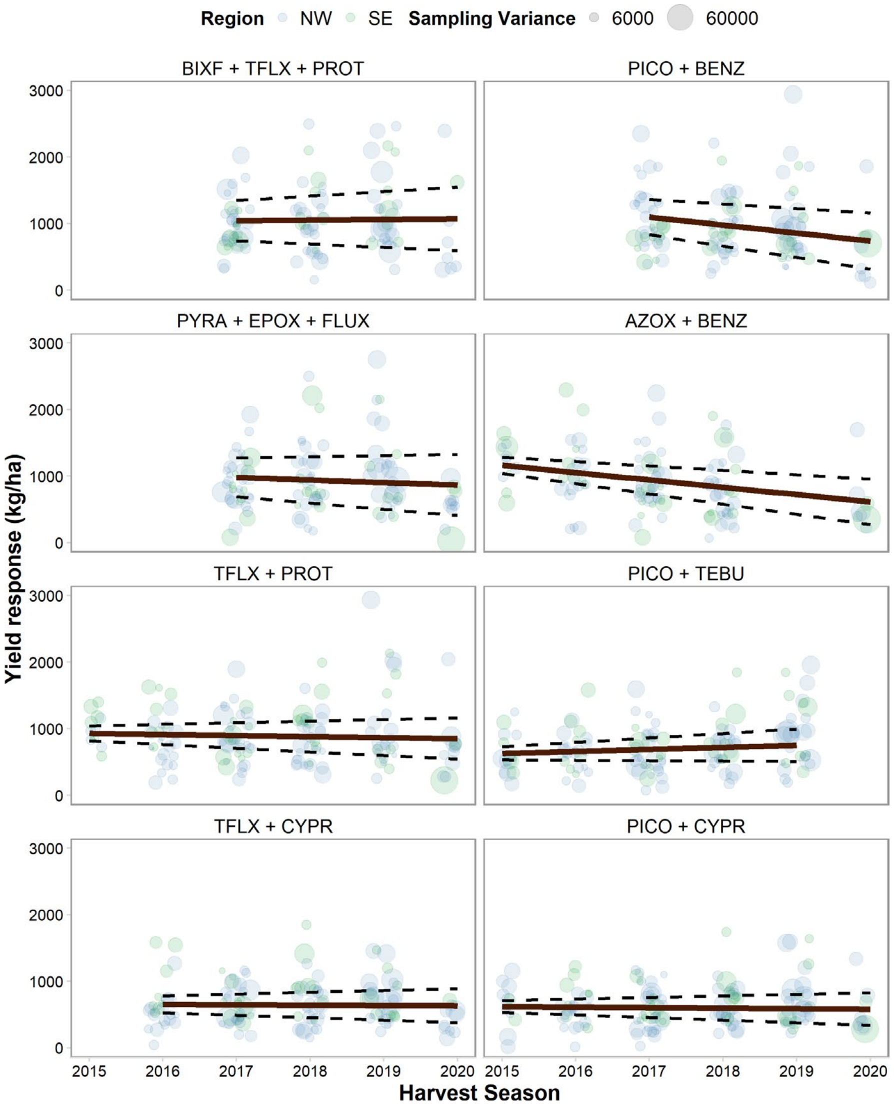

FIGURE 5 Yearly variation in the difference in yield between the fungicide-treated and the untreated plots (yield response) for eight fungicide treatments applied three times during the season for the control of soybean rust. Solid (mean) and dashed (95% confidence intervals) lines represent the predictions from network meta-regression modelling where year was included as a continuous covariate. Each dot represents the observed yield response at each trial coloured according to the two geographic regions defined in our study: north-western (NW) states (Bahia [BA], Distrito Federal [DF], Tocantins [TO], Goiás [GO], Minas Gerais [MG], Mato Grosso do Sul [MS], and Mato Grosso [MT]), and south-eastern (SE) states (Paraná [PR], Rio Grande do Sul [RS], and São Paulo [SP]). See Table 1 for detailed information on the fungicide treatments [Colour figure can be viewed at wileyonlinelibrary.com]

under high disease severity conditions is in agreement with the effect of fungicides on soybean diseases found in previous studies, suggesting greater benefit with increased disease pressure (Barro et al., 2019; Delaney et al., 2018; Edwards-Molina et al., 2018).

The reduction in control efficacy and yield response levels reported here for AZOX + BENZ and PICO + BENZ is possibly linked to reports of *P. pachyrhizi* populations resistant to QoIs (Klosowski et al., 2016) and, more recently, to the SDHIs (Simões et al., 2018). Regarding QoIs, Dalla Lana et al. (2018) reported a decline in the performance of QoIs applied either as a single a.i. or as a premix amended with cyproconazole. The reduction of sensitivity to QoI has been clearly associated with the occurrence of the F129L substitution, caused by target site mutations at the *CYTB* gene, which was first reported in *P. pachyrhizi* isolates collected in 2012/13 and has been increasing in frequency in 2013/14 (Klosowski et al., 2016). Although cross-resistance in the same group occurs, the mutations affect the active ingredients in different ways. For QoIs, the F129L mutation presents a quantitative effect in *P. pachyrhizi*, and affects the performance of azoxystrobin and pyraclostrobin more than other active ingredients, including picoxystrobin, trifloxystrobin, and metominostrobin (Godoy & Meyer, 2020).

Reduction in the sensitivity of *P. pachyrhizi* isolates to SDHIs was first reported in the 2015/16 crop season, linked to a mutation in the *SdhC* gene causing the amino acid substitution C186F (Simões et al., 2018). According to the authors, the C186F mutation was not detected before SDHI market introduction, and the mutation frequency was lower in samples collected from untreated plots compared to SDHI-treated plots in several field trials. Additionally, C186F frequency increased in the 2016/17 season and the mutation was found in *P. pachyrhizi* populations from various and distinct regions in Brazil, accelerating the occurrence of resistance (Simões et al., 2018).

The use of cultivars with resistance genes (*Rpp*) to SBR has been more widely adopted to improve SBR management and to reduce the selection pressure of fungicides (Childs et al., 2018). However, the sole use of resistant cultivars as a management choice has the same limitation as the use of fungicides: the selection of pathogen populations capable of overcoming the *Rpp* genes (Godoy et al., 2016a). Therefore, recent studies have investigated interaction effects of chemical and genetic control (Bahry et al., 2020; Sacon et al., 2020). A two-year study (2016/17 to 2017/18) conducted in Paraná

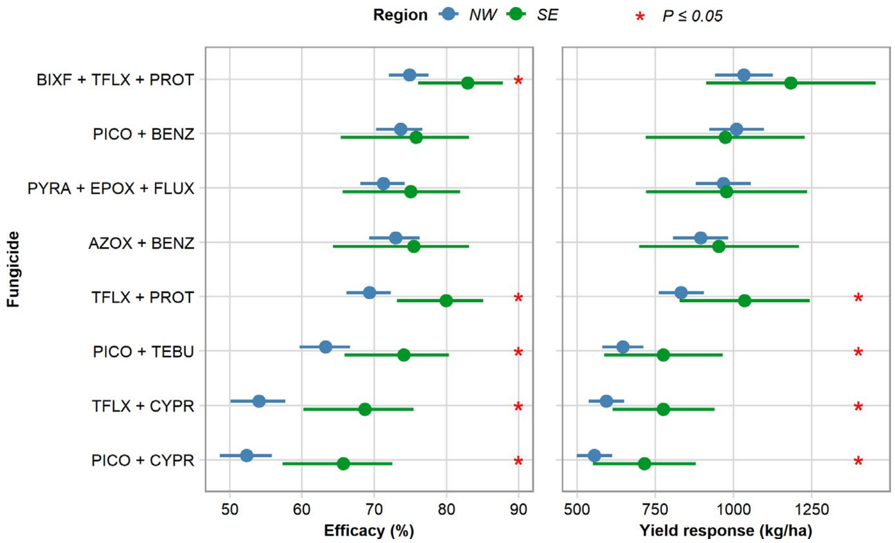

FIGURE 6 Means and respective 95% confidence intervals (error bars) for control efficacy (%) and soybean yield response (kg/ha) provided by fungicide treatments evaluated over years 2015 to 2020 and grouped into two geographic regions defined in our study: north-western (NW) states (Bahia [BA], Distrito Federal [DF], Tocantins [TO], Goiás [GO], Minas Gerais [MG], Mato Grosso do Sul [MS], and Mato Grosso [MT]), and south-eastern (SE) states (Paraná [PR], Rio Grande do Sul [RS], and São Paulo [SP]). The means were calculated using a network meta-analytic model where region was included as covariate. Means shown for control efficacy (%) were back-transformed from log values. See Table 1 for detailed information on the fungicide treatments [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Overall means of soybean yield response ($\overline{D}$) for each fungicide treatment, relative to the untreated control, conditioned (moderator analysis) to two classes of soybean rust severity representing a low (<70% in the untreated control) or high disease pressure (>70% in the untreated control)

		Yield response (kg/ha)			
Fungicide[a]	**Condition**	k[b]	$\overline{D}$	$[\mathrm{CI}_L, \mathrm{CI}_U]$[c]	p
AZOX + BENZ	High	82	1005.3	[908.0, 1102.5]	0.004
	Low	63	784.5	[539.0, 1029.9]	
BIXF + TFLX + PROT	High	63	1154.1	[1048.4, 1259.9]	0.035
	Low	53	982.7	[717.4, 1248.0]	
PICO + BENZ	High	63	1119.6	[1021.3, 1217.8]	0.001
	Low	55	869.3	[623.0, 1115.6]	
PICO + CYPR	High	100	651.0	[586.5, 715.6]	0.020
	Low	75	533.7	[370.6, 696.7]	
PICO + TEBU	High	93	728.4	[654.4, 802.4]	0.065
	Low	61	621.3	[433.3, 809.3]	
PYRA + EPOX + FLUX	High	61	1088.0	[988.5, 1187.5]	0.002
	Low	55	850.7	[601.6, 1099.8]	
TFLX + CYPR	High	80	707.2	[642.3, 772.1]	0.006
	Low	66	569.6	[406.3, 732.9]	
TFLX + PROT	High	96	956.3	[874.5, 1038.2]	0.017
	Low	73	804.7	[597.9, 1011.5]	

AZOX, azoxystrobin; BENZ, benzovindiflupyr; BIXF, bixafen; CYPR, cyproconazole; EPOX, epoxiconazole; FLUX, fluxapyroxad; PICO, picoxystrobin; PYRA, pyraclostrobin; TEBU, tebuconazole; TFLX, trifloxystrobin.

[a] See Table 1 for complete information of the evaluated fungicides.

[b] Number of trials in which each fungicide was evaluated.

[c] Upper and lower limits of the 95% confidence interval around $\overline{D}$.

state found a significant reduction in SBR severity when combining fungicide treatment (AZOX + BENZ) with a resistant cultivar (TMG 7062; c.72%); slightly less reduction was obtained when fungicide was combined with the highly tolerant cultivar LG 60163 (c.64%) and less still with the susceptible cultivar NA 5909 (c.52.1%) (Bahry et al., 2020). Sacon et al. (2020) also reported higher SBR control applying

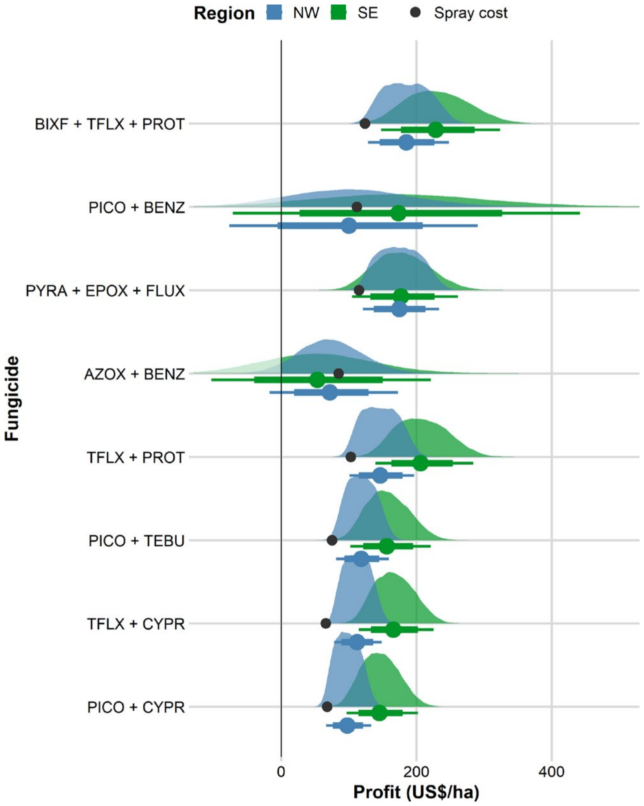

FIGURE 7 Half-eye plots (a density and interval) of profits (40,000 simulation runs) based on the meta-analytic estimate of yield response (kg/ha) for eight fungicide treatments conditioned to two geographic regions: north-western (NW) states (Bahia [BA], Distrito Federal [DF], Tocantins [TO], Goiás [GO], Minas Gerais [MG], Mato Grosso do Sul [MS], and Mato Grosso [MT]), and south-eastern (SE) states (Paraná [PR], Rio Grande do Sul [RS], and São Paulo [SP]) of Brazil, evaluated over six years (2015 to 2020). The profits of each fungicide × region combination were calculated by subtracting costs of sprays (see black dot in the figure for specific cost for the fungicide) from the income ($/ha) given by yield response multiplied by soybean price. Bars show the upper and lower limits of 95% confidence intervals around point estimates. See Table 1 for detailed information on the fungicide treatments and costs [Colour figure can be viewed at wileyonlinelibrary.com]

AZOX + BENZ to resistant cultivars (>80%) compared to a susceptible one (c.56%) in field experiments conducted in northern Rio Grande do Sul state during 2016/17 and 2017/18 growing seasons.

Another ongoing strategy to improve SBR control, as well as reduce the risk of resistance development, is to alternate modes of action and the use of premixes of single-site amended with multisite fungicides (Godoy et al., 2016a). In fact, a recent two-year study (2016/17 to 2017/18) reported significant gain values in SBR control efficacy using TFLX + PROT (14%) and AZOX + BENZ (28%) amended with mancozeb (Netto et al., 2020). Preliminary data from the CFTs have also shown benefits from adding multisite fungicides (Godoy et al., 2016c, 2017b, 2018b). More data will become available in the near future that should be amenable for quantitative estimation of the benefits of multisite fungicides.

In conclusion, the results of our study provide critical information to support decision making in the selection of fungicides that maximize profit and minimize development of fungicide resistance. The continuing evaluation of fungicides in the CFT network is essential and should be encouraged. The results obtained in this study are also useful when choosing the fungicides to be tested in future trials. Finally, the suspension of the registration of noneffective fungicides can help to manage fungicide resistance, which may be partially reversible when the selection pressure of fungicide is removed or minimized (Parnell et al., 2005). For instance, the efficacy of tebuconazole applied as single a.i., which showed the greatest rate of reduction (7.7 percentage points per year) in the previous study (Dalla Lana et al., 2018), has reached increased levels of efficacy during the last crop seasons (Godoy et al., 2020).

ACKNOWLEDGEMENTS

The first and senior author acknowledges the financial support provided by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq/Brazil) for a scholarship and research fellowship (PQ-306857/2015-4), respectively. We also acknowledge the financial support provided by the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (Fapemig/Brazil) for a research grant (APQ-03945-16). All other authors are thankful to their institutions and teams for providing support during the conduction of field experiments and the collection of the data.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

AUTHOR'S CONTRIBUTIONS

J.P.B., K.S.A., and E.M.D. conceived the idea, analysed the data and wrote the manuscript. C.V.G. planned and coordinated the experiments; A.R.D., C.A.F., C.M.U., E.R.A.J., F.C.J., F.J.G., H.R.F., H.D.C., I.C.P.V.C., I.P.A.J., J.M.T.R., J.N.J., L.M.R.B., L.C.C., L.H.C.P.S., M.G.C., M.M.G.J., M.S., M.C.M., M.D.D., M.A.M., M.C.M., M.P.D., N.R.T., S.H.F., T.F.K., V.J.C., and W.S.V. conducted the field trials and shared the data. All authors provided feedback and approved the final manuscript.

OPEN RESEARCH BADGES

The data and R scripts that support the findings of this study are openly available in the Open Science Framework project at https://osf.io/zjfyg/. A website was generated to better visualize the scripts where all data and analyses are documented and reproducible (https://git.io/JtPaY).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the Open Science Framework project at https://osf.io/zjfyg/.

ORCID

Jhonatan P. Barro https://orcid.org/0000-0002-6509-4744
Kaique S. Alves https://orcid.org/0000-0001-9187-0252
Maurício C. Meyer https://orcid.org/0000-0001-5751-1715
Emerson M. Del Ponte https://orcid.org/0000-0003-4398-409X

REFERENCES

AGROLINK. (2020). Cotações. Available at: https://www.agrolink.com.br/cotacoes/ [Accessed 30 January 2020].

Barro, J.P., Meyer, M.C., Godoy, C.V., Dias, A.R., Utiamada, C.M., Jaccoud Filho, D.D.S. et al (2019) Performance and profitability of fungicides for managing soybean white mold: A 10-year summary of cooperative trials. *Plant Disease*, *103*, 2212–2220.

Beruski, G.C., Del Ponte, E.M., Pereira, A.B., Gleason, M.L., Câmara, G.M.S., Araújo Junior, I.P. et al (2020) Performance and profitability of rain-based thresholds for timing fungicide applications in soybean rust control. *Plant Disease*, *104*, 2704–2712.

Carlos, A.B., Leocádio, C., Ângela, A.C., Françoá, S.D.P., Leandro, A.P., Gelson, G. et al (2020) Analysis of combined strategies for the management of Asian soybean rust. *African Journal of Plant Science*, *14*, 297–307.

Childs, S.P., Buck, J.W. & Li, Z. (2018) Breeding soybeans with resistance to soybean rust (*Phakopsora pachyrhizi*). *Plant Breeding*, *137*, 250–261.

Dalla Lana, F., Paul, P.A., Godoy, C.V., Utiamada, C.M., da Silva, L.H.C.P., Siqueri, F.V. et al (2018) Meta-analytic modeling of the decline in performance of fungicides for managing soybean rust after a decade of use in Brazil. *Plant Disease*, *102*, 807–817.

Dalla Lana, F., Ziegelmann, P.K., Maia, A.H.N., Godoy, C.V. & Del Ponte, E.M. (2015) Meta-analysis of the relationship between crop yield and soybean rust severity. *Phytopathology*, *105*, 307–315.

Delaney, M., ArchMiller, A.A., Delaney, D.P., Wilson, A.E. & Sikora, E.J. (2018) Effectiveness of fungicide on soybean rust in the southeastern United States: A meta-analysis. *Sustainability.*, *10*, 1784.

Edwards Molina, J.P., Paul, P.A., Amorim, L., Silva, L.H.C.P., Siqueri, F.V., Borges, E.P. et al (2018) Meta-analysis of fungicide efficacy on soybean target spot and cost-benefit assessment. *Plant Pathology*, *68*, 94–106.

Godoy, C.V., Koga, L.J. & Canteri, M.G. (2006) Diagrammatic scale for assessment of soybean rust severity. *Fitopatologia Brasileira*, *31*, 63–68.

Godoy, C.V. & Meyer, M.C. (2020) Overcoming the threat of Asian soybean rust in Brazil. In: Deising, H.B., Fraaije, B., Mehl, A., Oerke, E.C., Sierotzki, H. & Stammler, G. (Eds.) *Modern Fungicides and Antifungal Compounds*. *IX*, Braunschweig: Deutsche Phytomedizinische Gesellschaft, pp. 51–56.

Godoy, C.V., Seixas, C.D.S., Soares, R.M., Marcelino-Guimarães, F.C., Meyer, M.C. & Costamilan, L.M. (2016a) Asian soybean rust in Brazil: Past, present, and future. *Pesquisa Agropecuária Brasileira*, *51*, 407–421.

Godoy, C.V., Utiamada, C.M., Meyer, M.C., Campos, H.D., Forcelini, C.A., Pimenta, C.B. et al (2016b). *Eficiência de fungicidas para o controle da ferrugem-asiática da soja, Phakopsora pachyrhizi, na safra 2015/16: resultados sumarizados dos ensaios cooperativos*. Circular técnica 119. Londrina, Brazil: Embrapa Soja.

Godoy, C.V., Utiamada, C.M., Meyer, M.C., Campos, H.D., Forcelini, C.A., Pimenta, C.B. et al (2016c). *Eficiência de fungicidas multissítios no controle da ferrugem-asiática da soja, Phakopsora pachyrhizi, na safra 2015/16: resultados sumarizados dos ensaios cooperativos*. Circular técnica 121. Londrina, Brazil: Embrapa Soja.

Godoy, C.V., Utiamada, C.M., Meyer, M.C., Campos, H.D., Lopes, I.O.N., Dias, A.R. et al (2018a). *Eficiência de fungicidas para o controle da ferrugem-asiática da soja, Phakopsora pachyrhizi, na safra 2017/2018: Resultados sumarizados dos ensaios cooperativos*. Circular técnica 138. Londrina, Brazil: Embrapa Soja.

Godoy, C.V., Utiamada, C.M., Meyer, M.C., Campos, H.D., Lopes, I.O.N., Dias, A.R. et al (2018b*). Eficiência de fungicidas multissítios no controle da ferrugem-asiática da soja, Phakopsora pachyrhizi, na safra 2017/18: resultados sumarizados dos ensaios cooperativos*. Circular técnica 144. Londrina, Brazil: Embrapa Soja.

Godoy, C.V., Utiamada, C.M., Meyer, M.C., Campos, H.D., Lopes, I.O.N., Dias, A.R. et al (2019). *Eficiência de fungicidas para o controle da ferrugem-asiática da soja*, Phakopsora pachyrhizi, *na safra 2019/19: Resultados sumarizados dos ensaios cooperativos. Circular técnica 148*. Londrina, Brazil: Embrapa Soja.

Godoy, C.V., Utiamada, C.M., Meyer, M.C., Campos, H.D., Lopes, I.O.N., Dias, A.R. et al (2020). *Eficiência de fungicidas para o controle da ferrugem-asiática da soja*, Phakopsora pachyrhizi, *na safra 2019/2020: Resultados sumarizados dos ensaios cooperativos*. Circular técnica 160. Londrina, Brazil: Embrapa Soja.

Godoy, C.V., Utiamada, C.M., Meyer, M.C., Campos, H.D., Lopes, I.O.N., Forcelini, C.A. et al (2017a). *Eficiência de fungicidas para o controle da ferrugem-asiática da soja, Phakopsora pachyrhizi, na safra 2016/17: Resultados sumarizados dos ensaios cooperativos. Circular técnica 129*. Londrina, Brazil: Embrapa Soja.

Godoy, C.V., Utiamada, C.M., Meyer, M.C., Campos, H.D., Lopes, I.O.N., Forcelini, C.A. et al (2017b). *Eficiência de fungicidas multissítios e produto biológico no controle da ferrugem asiática da soja, Phakopsora pachyrhizi, na safra 2016/17: Resultados sumarizados dos ensaios cooperativos*. Circular técnica 131. Londrina, Brazil: Embrapa Soja.

Godoy, C.V., Utimada, C.M., Meyer, M.C., Campos, H.D., Forcelini, C.A., Pimenta, C.B. et al (2015). *Eficiência de fungicidas para o controle da ferrugem-asiática da soja, Phakopsora pachyrhizi, na safra 2014/15: resultados sumarizados dos ensaios cooperativos. Circular técnica 111*. Londrina, Brazil: Embrapa Soja.

Goellner, K., Loehrer, M., Langenbach, C., Conrath, U., Koch, E. & Schaffrath, U. (2010) *Phakopsora pachyrhizi*, the causal agent of Asian soybean rust. *Molecular Plant Pathology*, *11*, 169–177.

Higgins, J.P.T., Jackson, D., Barrett, J.K., Lu, G., Ades, A.E. & White, I.R. (2012). Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods*, *3*, 98–110.

Hollomon, D.W. (2015) Fungicide resistance: facing the challenge. *Plant Protection Science*, *51*, 170–176.

Klosowski, A.C., May De Mio, L.L., Miessner, S., Rodrigues, R. & Stammler, G. (2016) Detection of the F129L mutation in the cytochrome b gene in *Phakopsora pachyrhizi*. *Pest Management Science*, *72*, 1211–1215.

Li, X., Esker, P.D., Pan, Z., Dias, A.P., Xue, L. & Yang, X.B. (2010) The uniqueness of the soybean rust pathosystem: an improved understanding of the risk in different regions of the world. *Plant Disease*, *94*, 796–806.

Machado, F.J., Santana, F.M., Lau, D. & Del Ponte, E.M. (2017) Quantitative review of the effects of triazole and benzimidazole fungicides on Fusarium head blight and wheat yield in Brazil. *Plant Disease*, *101*, 1633–1641.

Madden, L.V., Piepho, H.-P. & Paul, P.A. (2016) Statistical models and methods for network meta-analysis. *Phytopathology*, *106*, 792–806.

Netto, A., Sacon, D., Gallina, A., Fochesatto, M., Spitza Stefanski, F. & Mendes Milanesi, P. (2020) Use of systemic fungicides combined with multisite to control of Asian rust and soybean yield. *Colloquium Agrariae*, *16*, 101–108.

Parnell, S., Gilligan, C.A. & van den Bosch, F. (2005) Small-scale fungicide spray heterogeneity and the coexistence of resistant and sensitive pathogen strains. *Phytopathology*, *95*, 632–639.

Paul, P.A., Lipps, P.E., Hershman, D.E., McMullen, M.P., Draper, M.A. & Madden, L.V. (2008). Efficacy of triazole-based fungicides for Fusarium head blight and deoxynivalenol control in wheat: a multivariate meta-analysis. *Phytopathology*, *98*, 999–1011.

Paul, P.A., McMullen, M.P., Hershman, D.E. & Madden, L.V. (2010) Meta-analysis of the effects of triazole-based fungicides on wheat yield and test weight as influenced by Fusarium head blight intensity. *Phytopathology*, *100*, 160–171.

Piepho, H.-P. (2014) Network-meta analysis made easy: detection of inconsistency using factorial analysis-of-variance models. *BMC Medical Research Methodology*, *14*, 61.

R Core Team. (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available at: https://www.R-project.org/ [Accessed 25 June 2021].

Sacon, D., Netto, A., Fochesatto, M., Stefanski, F.S., Gallina, A., Milanesi, P.M. & et al (2020). Integration between genetic and chemical control on the progress of Asian soybean rust and yield. *Summa Phytopathologica*, *46*, 198–204.

Scherm, H., Christiano, R.S.C., Esker, P.D., Del Ponte, E.M. & Godoy, C.V. (2009) Quantitative review of fungicide efficacy trials for managing soybean rust in Brazil. *Crop Protection*, *28*, 774–782.

Schmitz, H.K., Medeiros, C.-A., Craig, I.R. & Stammler, G. (2013) Sensitivity of *Phakopsora pachyrhizi* towards quinone-outside-inhibitors and demethylation-inhibitors, and corresponding resistance mechanisms. *Pest Management Science*, *70*, 378–388.

Simões, K., Hawlik, A., Rehfus, A., Gava, F. & Stammler, G. (2018) First detection of a SDH variant with reduced SDHI sensitivity in *Phakopsora pachyrhizi*. *Journal of Plant Diseases and Protection*, *125*, 21–26.

Viechtbauer, W. (2010) Conducting meta-analyses in R with the metafor Package. *Journal of Statistical Software*, *36*, 1–48.

Yorinori, J.T., Paiva, W.M., Frederick, R.D., Costamilan, L.M., Bertagnolli, P.F., Hartman, G.E. et al (2005) Epidemics of soybean rust (*Phakopsora pachyrhizi*) in Brazil and Paraguay from 2001 to 2003. *Plant Disease*, *89*, 675–677.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Barro, J.P., Alves, K.S., Godoy, C.V., Dias, A.R., Forcelini, C.A., Utiamada, C.M., et al (2021) Performance of dual and triple fungicide premixes for managing soybean rust across years and regions in Brazil: A meta-analysis. *Plant Pathology*, 70, 1920–1935. https://doi.org/10.1111/ppa.13418