Evaluation of a predictive model for suspected **drug-drug interactions** in **routine signal detection**

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Background

Reports in VigiBase, the WHO global database of individual case safety reports, often concern multi-drug users at risk of drug-drug interactions, and should be valuable for finding interaction signals. A dedicated signal detection algorithm, *vigiRank for Interactions*[1], has been developed at Uppsala Monitoring Centre.

Aim

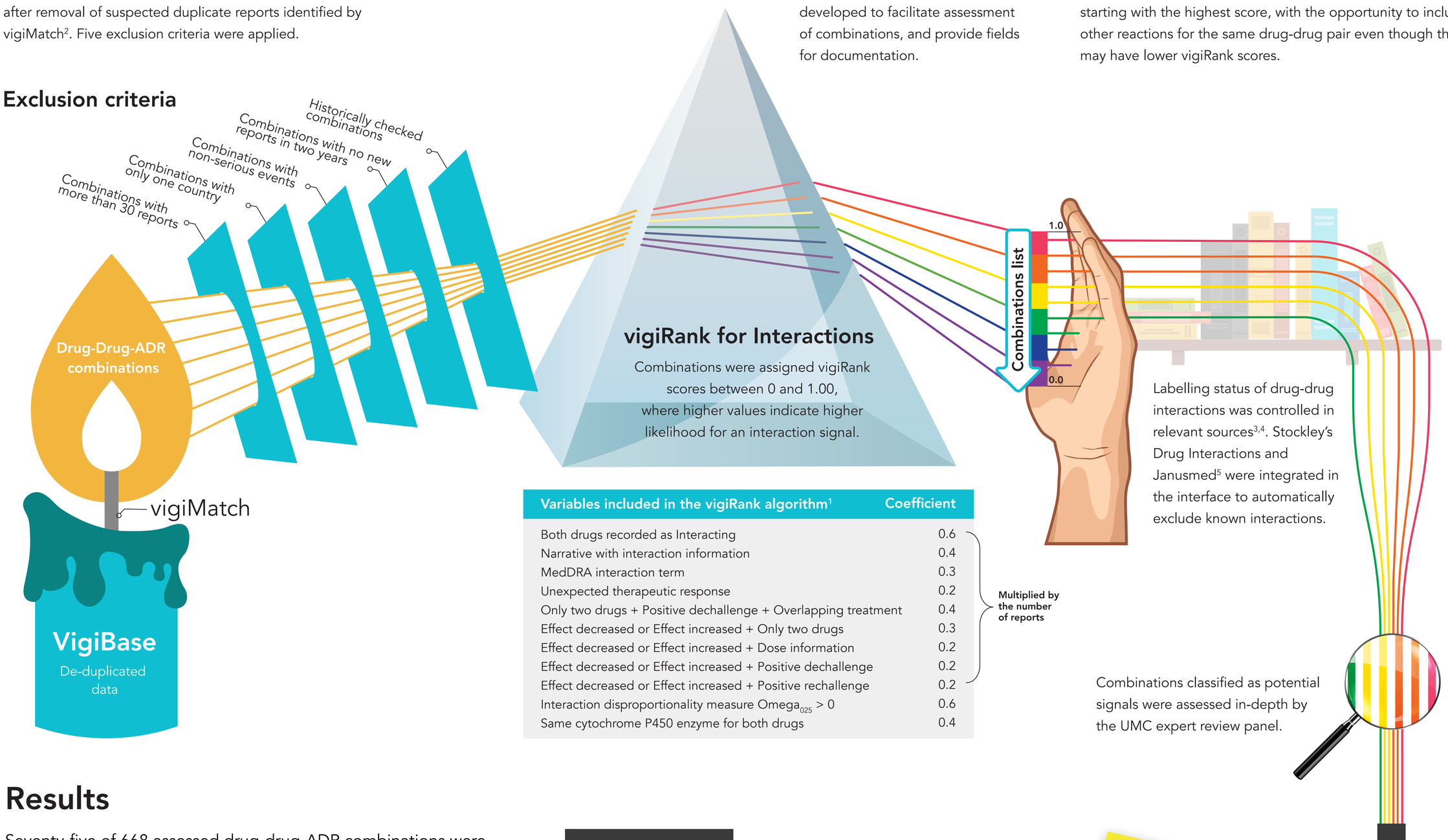
To apply and evaluate vigiRank for Interactions in routine signal detection.

Methods

Statistical screening and filtering

Drug-drug-ADR combinations were retrieved from VigiBase after removal of suspected duplicate reports identified by vigiMatch[2]. Five exclusion criteria were applied.

Exclusion criteria



Manual assessment

A Microsoft Access interface was developed to facilitate assessment of combinations, and provide fields for documentation.

Combinations were assessed manually in vigiRank order, starting with the highest score, with the opportunity to include other reactions for the same drug-drug pair even though they may have lower vigiRank scores.

Labelling status of drug-drug interactions was controlled in relevant sources[3,4]. Stockley's Drug Interactions and Janusmed[5] were integrated in the interface to automatically exclude known interactions.

Combinations classified as potential signals were assessed in-depth by the UMC expert review panel.

Variables included in the vigiRank algorithm[1]	Coefficient
Both drugs recorded as Interacting	0.6
Narrative with interaction information	0.4
MedDRA interaction term	0.3
Unexpected therapeutic response	0.2
Only two drugs + Positive dechallenge + Overlapping treatment	0.4
Effect decreased or Effect increased + Only two drugs	0.3
Effect decreased or Effect increased + Dose information	0.2
Effect decreased or Effect increased + Positive dechallenge	0.2
Effect decreased or Effect increased + Positive rechallenge	0.2
Interaction disproportionality measure $Omega_{025} > 0$	0.6
Same cytochrome P450 enzyme for both drugs	0.4

Multiplied by the number of reports

Results

Seventy-five of 668 assessed drug-drug-ADR combinations were selected for further review, representing eight potential signals, where some included several similar combinations. Another eight combinations were decided to be kept under review, and 585 were dismissed. Of the latter, 246 were non-suggestive of an interaction and 209 concerned known interactions. Among the potential signals 75% (6/8) had vigiRank scores in the range 0.90 to 1.00 compared to 33% (219/668) among all assessed combinations. All potential signals concerned drugs with a first report in VigiBase year 2003 or earlier. Of the six potential signals assessed in-depth so far, three have been confirmed as signals.

Conclusions

Signals of drug-drug interactions can be identified in VigiBase using a predictive algorithm to direct clinical review. There were no newly marketed drugs among the detected potential signals. Examples of obstacles were lack of sufficient information on many reports, and remaining duplicates. Effectiveness of exclusion criteria will be further evaluated in future UMC signal screenings.

References

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Disclosure

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