

# Combining Rapid Antigen Testing and Syndromic Data Improves Sensitivity and Specificity in Real-World COVID-19 Detection

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## 1. Abstract (288 words)

### *Background*

The majority of the world's population live in low- and middle-income countries (LMICs) where access to gold-standard diagnostics like RT-PCR is often limited. Rapid antigen testing (RAT) and syndromic diagnosis are two alternative, inexpensive and easy-to-deploy surveillance methods but there are concerns that they lack the sensitivity and specificity to effectively guide practice.

### *Methods*

Bangladesh's Institute of Epidemiology Disease Control And Research (IEDCR) identified potential COVID-19 patients in Dhaka using syndromic surveillance.

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A sample ( $n = 1172$ ) of these patients was tested using RAT and syndromic data were collected. Models were fit to predict RT-PCR status using the RAT data, the syndromic data, and the two combined. Model performance was measured using predictive power and classification performance under three epidemiological scenarios: “Agnostic,” “Rising Cases” and “Low-Level Cases.”

### *Findings*

Combined data models yielded equal or improved performance over syndromic- and RAT-only models across all three epidemiological scenarios and when compared as more generic prediction and classification engines. In the “Rising Cases” scenario, which most closely represents the current situation in many LMICs, the combined data model false negative rate is 26.2012339 percentage points lower than that of the RAT only model. Although the syndromic only model matches the combined models false negative rate, its false positive rate is 30.8213341 percentage points higher.

### *Interpretation*

A few accurate tests may be less useful at the population level than many more imperfect ones. Small, scalable improvements in the accuracy of mass-deployed but imperfect tests can then make a very big difference for pandemic control.

We demonstrate that such improvements can be achieved by statistically utilising complementary strengths and weaknesses across two imperfect diagnostics, we can greatly improve the detection of COVID-19.

### *Funding*

The Bill and Melinda Gates Foundation and the Wellcome Trust.

## **2. Introduction (1080 Words)**

Identification and isolation of COVID-19 cases remains key to the pandemic response across the globe. The faster and more accurately we can identify cases, the more effectively we can provide clinical care, reduce transmission of infection and develop population-level interventions. RT-PCR testing has rapidly become the default, gold-standard test for COVID-19 in applied settings (although see [1]) due to its high sensitivity and specificity for COVID-19 [3]. Most of the world’s population, however, live in low- and middle-income countries (LMICs) where the laboratory facilities needed to carry out RT-PCR tests are often scarce and hard to reach [5], and the majority of patient diagnosis and support comes from telemedicine or community support teams (CSTs) composed of local volunteers with basic training. COVID-19 diagnosis worldwide, therefore, must be made accessible using inexpensive methods that can be carried out locally [7].

An increasingly popular alternative to RT-PCR is rapid antigen testing (RAT) [8]. Like RT-PCR, these tests have high specificity for COVID-19 while being less expensive, easier to implement, and faster [9]. For RT-PCR testing, patients must travel to a designated site or have officials visit their home in enhanced personal protective equipment. Then, invasive nasopharyngeal swabs must be taken. In contrast, RATs can be conducted on nasal swabs, completed

71 in the home with minimal PPE, and results are available in 30 minutes. RATs  
72 can be taken by persons with limited training, thus decreasing the time and  
73 expense associated with identifying cases. Together, these traits make RATs an  
74 appealing alternative to RT-PCR, however, concerns have been raised that the  
75 lower sensitivity of RAT [10] leads to more false negative diagnoses.

76 Another diagnostic that has been used since the start of the pandemic  
77 is symptom-thresholding [11]. Here, a patient presenting with a fever and  
78 one or more symptoms is treated as a COVID-19 positive patient. The main  
79 advantage of this approach is the ease of implementation. As with RAT, symptom-  
80 thresholding is faster, cheaper and less invasive than RT-PCR. Unlike RAT,  
81 symptom-thresholding can be scaled immediately at the onset of a pandemic,  
82 however, it is also reliant on thresholds developed then. These thresholds were  
83 necessarily drawn from clinical intuition, rather than data, often for different  
84 variants and populations than they are now applied to. Consequently, the  
85 relationship between the thresholds and the true COVID-19 status is often weak,  
86 with low specificity leading to a very large number of false positive diagnoses. A  
87 natural extension, therefore, is syndromic modelling. In this approach, rather  
88 than using a set of pre-determined thresholds, a range of symptomatic and risk  
89 factor data (such as age and gender ) are collected and then a sub-sample of  
90 patients is tested using RT-PCR for validation [12]. These data are used to fit a  
91 model that allows more accurate prediction of how likely a patient is to have  
92 COVID-19 through the identification of COVID-19 syndromes [14].

JMC: Not  
an official  
term

93 It is worth highlighting at this point that in resource-limited settings there is  
94 very limited provision for testing of asymptomatic cases, despite their important  
95 role in disease transmission [15] . Even while focusing solely on symptomatic  
96 patients, syndromic modelling is a complex and nuanced task. Disease syndromes  
97 can change between populations, when new variants emerge, and as other diseases  
98 become more or less common [16]. These changes can make syndromic models  
99 generalise poorly. For example, if another disease for which loss of smell is  
100 a symptom becomes common, loss of smell is no longer strongly indicative of  
101 COVID-19. Similarly, if everyone who presents has a cough, regardless of their  
102 COVID-19 status, then coughing will show no relationship with COVID-19  
103 (even if the two are strongly related in the general population). Furthermore,  
104 symptoms do not always occur in isolation, some, like loss of smell and loss of  
105 taste, are strongly related. Unfortunately, the majority of syndromic modelling  
106 methods currently used do not account for these complexities. Even where they  
107 can, at least partially, be accounted for, the many types of common respiratory  
108 disease generally means that syndromic modelling still tends to have quite low  
109 specificity [16].

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110 Moderate to poor sensitivity and specificity are problematic in diagnostics but  
111 may be tolerable depending on their scale and impact given the local situation.  
112 Low specificity means a patient is likely to be told they have COVID-19 when  
113 they do not (a high false positive rate), leading to patients unnecessarily self-  
114 isolating and receiving support. This is expensive to the individual and to  
115 local public health bodies, reducing available resources for those who need them  
116 [17]. Similarly, low sensitivity means more patients being told they do not have

COVID-19 when they actually do (a high false negative rate), leading to the individual not getting appropriate support or taking action to prevent the disease spreading further [18]. Although the default approach is generally to minimise both misclassification rates (our “Agnostic” scenario below), the true costs of these misclassifications will depend on local context. When the prevalence of the disease is low, false negatives will be correspondingly low and false positives may create local scepticism leading to poor adherence longer term. In this situation (our “Low-Level Cases” scenario), false positives might be more costly than false negatives [17]. If the disease is abundant or increasing rapidly then changes in the false negative rate might have an outsized impact on the pandemic trajectory and thus be more costly, as in our “Rising Cases” scenario. Often the situation will be even more nuanced and a different balance will need to be struck [5].

The “best” diagnostic, therefore, is not a single universal test. The two dominant testing methods available in LMICs when not adapted for the local situation are highly flawed. Relying solely on symptomatic diagnosis will likely overestimate the number of individuals with COVID-19 due to its lack of specificity. Conversely, RATs will give a false impression of control due to the number of positive cases that will be missed. In this paper, we demonstrate that by combining these two testing methods we can utilise their complementary strengths, ameliorate their respective weaknesses, and optimise them for different epidemiological scenarios. We aim to compare the performance of these two testing methods and the combined approach both in terms of general prediction and as diagnostics under three epidemiological scenarios with different misclassification requirements. We show that the optimised combined data models achieve equal-to-much-lower error rates than the next best method in all metrics. We then discuss the role of statistically integrating data from multiple imperfect testing methods in resource limited settings to improve the diagnosis of diseases, particularly COVID-19.

### 3. Methods (965 words)

#### 3.1. Data Collection

Participants included in this study were identified for COVID-19 testing by community support teams (CSTs). Recruitment took place across Dhaka (the capital city of Bangladesh) between 19th May 2021 and 11th July 2021.

Patients were selected for further testing if they had a fever ( $>38^{\circ}\text{C}$ ) at the point of testing and one or more of 14 symptoms associated with COVID-19 (breathing problems, coughing, diarrhoea, fever (ongoing), a headache, loss of taste, loss of smell, muscle pain, red eyes, a runny nose, a sore throat, tiredness, vomiting or a wet cough). If selected, the CSTs collected the patient’s age and gender, and took two nasal swabs.

One swab each was used for rapid antigen testing (RAT) and RT-PCR. The full questionnaire and testing protocols are provided in Appendix XX. Participants provided written informed consent to sample collection and for their results to be analyzed in the study.

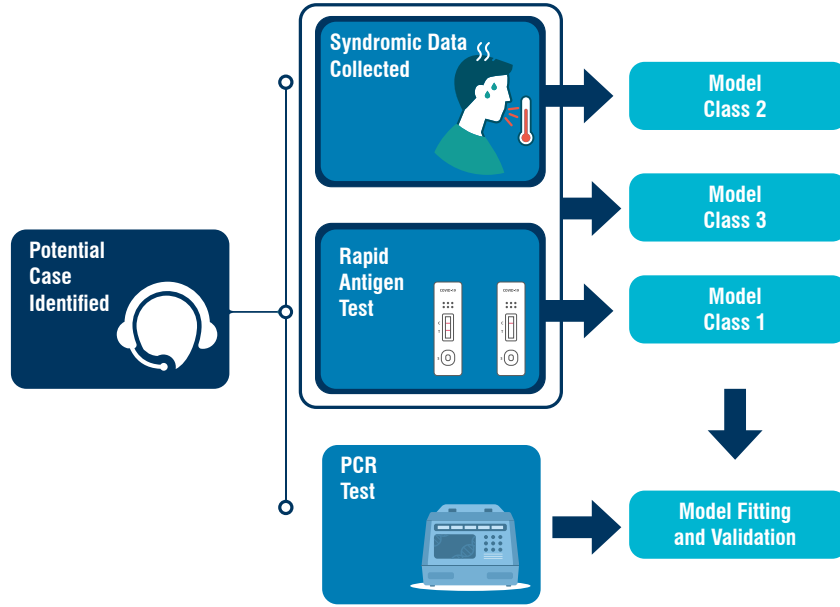


Figure 1: Schematic description of identification of likely COVID-19 patients by community support teams (CSTs), swab collection and model definitions. The teams collected syndromic data (age, gender and presence/absence of 14 predetermined symptoms), and two sets of naso-pharyngeal swabs (one each for Rapid Antigen Testing and RT-PCR). We then used rapid antigen testing (RAT) and syndromic data, two imperfect but inexpensive diagnostics, to generate three model classes: RAT result only in Model Class 1, syndromic data only in Model Class 2, and both RAT result and syndromic data in Model Class 3. The RT-PCR test result is used to train and test each model using temporal cross-validation.

160 *3.2. Modelling*

161 *3.2.1. Structure*

162 We examined the ability of the two imperfect identification methods, syn-  
163 dromic modelling and RAT, to predict the patient’s COVID-19 status when used  
164 separately and together. These combinations define three model classes (Figure  
165 1).

166 Model Class 1 uses only the RAT result. It equates being RAT-positive with  
167 the patient being PCR-positive for COVID-19 (hereafter, PCR-positive), and  
168 being RAT-negative with PCR-negativity.

169 Model Class 2 uses only the syndromic data. For this model, we used a  
170 Bayesian multivariate probit model [19]. The multivariate probit structure allows  
171 the model to account for the binary and correlated nature of the symptoms  
172 while conditioning on the risk factors of age and gender. By using a Bayesian  
173 formulation, we are able to quantify uncertainty in the parameter estimates.

174 Model Class 3 combines the two data sources. We utilise the specificity of RAT  
175 by treating RAT-positive patients as PCR-positive patients. The RAT-negative  
176 patients are modelled using the sensitive syndromic approach using Model Class  
177 2 to capture PCR-positive patients that are missed by the RAT. This approach  
178 leverages the potential different syndromic profiles of PCR-positive patients who  
179 are RAT-positive and -negative, allowing the model to adapt solely to the latter.  
180 The models were fitted to the data using Bayesian inference techniques based on  
181 Hamiltonian Monte Carlo in the Stan programming language [20].

182 *3.2.2. Model Selection*

183 We conducted backwards model selection (starting with the most complex,  
184 biologically plausible model) to identify a subset of models with the highest  
185 predictive power under temporal cross-validation (Figure 2). Reducing the  
186 number of possible models was necessary to reduce computational demand and  
187 reduce the risk of overfitting models to the test scenarios. The large number  
188 of symptoms corresponds to a high number of potential model configurations  
189 (>131 000 for 14 symptoms and two covariates) which might perform well on the  
190 test sets (even under the challenging conditions of temporal cross-validation) but  
191 lack transferability. By first using general predictive power to narrow down the  
192 number of candidate models and then testing those models, we are more likely  
193 to choose models which generalise well to new data. The number of candidate  
194 models used was not pre-determined but it was clear when fitting the models  
195 that there were “jumps” in performance (as defined below) between models  
196 containing five and four symptoms, so the models with one to four symptoms  
197 were used as the candidate models. Zero symptom models were not included  
198 in the analysis as they do not correspond to a feasible policy (with covariates  
199 they would require governments to ask individuals of a given gender and age  
200 as COVID-19 positive, and without covariates they would involve randomly  
201 assigning individuals as COVID-19 positive).

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### 3.2.3. Predictive Performance

We scored the models' predictive power using cross-entropy. Cross-entropy measures the accuracy of models that generate probabilities of binary outcomes, rather than make binary classifications, similar in concept to a mean square error for normally-distributed data, but adapted for binary data [21]. A cross-entropy value close to zero corresponds to high levels of accuracy, with larger values indicating lower accuracy. More details on the model structure and selection process, including code, are available in Appendix XX.

### 3.2.4. Classification Performance

In applied settings, models must often be evaluated on their performance as classifiers rather than just as prediction engines (i.e. their ability to say a patient is COVID-19 positive or negative, not simply the probability the patient might be COVID-19 positive or negative). To generate a classification, a probability threshold must be chosen over which patients are classified as COVID-19 positive.

Classifier performance was compared both generically (using receiver operating characteristic (ROC) curves [22]) and under three epidemiological scenarios (using error terms described in Table 1). We strongly emphasise that generic performance here is only used to show the flexibility of the model classes; the best model for a local situation can only be determined if the relative cost of false positives and false negatives is known.

In Scenario 1, we do not consider epidemiological context but simply minimise false negative and false positive rates equally. We do this by maximising the two correct classification rates both individually and in total, as measured by the harmonic mean (as opposed to the arithmetic mean which would only maximise the rates in total). Scenario 2 corresponds to the current situation in Bangladesh at time of writing (July 2021), with COVID-19 cases beginning to rapidly increase again. Under these circumstances, false negatives are extremely costly relative to false positives due to the exponential growth of the disease. In Scenario 3, the pandemic is not declining but maintaining a steady rate of cases. In this situation, policy-makers may be keen to keep false positive diagnoses low to prevent lockdown fatigue and to keep the workforce active. The requirements in Scenario 2 and 3 were developed in discussion with the Institute of Epidemiology, Disease Control and Research (IEDR), Bangladesh, for illustrative purposes.

## 4. Results (476 words)

Of 1241 subjects surveyed, a total of 1172 subjects had complete data available for the current analyses with the remainder removed due to duplication of barcodes or missing data. The mean age of women participants (47% of the sample) was 37 (SD = 14) years, and for men (53% of the sample) was 36 (SD = 14) years. Participants were identified by the community support teams (CSTs) and drawn from across Dhaka.

Model selection for both Model Class 2 (syndromic data only) and 3 (syndromic and RAT data) showed a marked decline in predictive power at more than

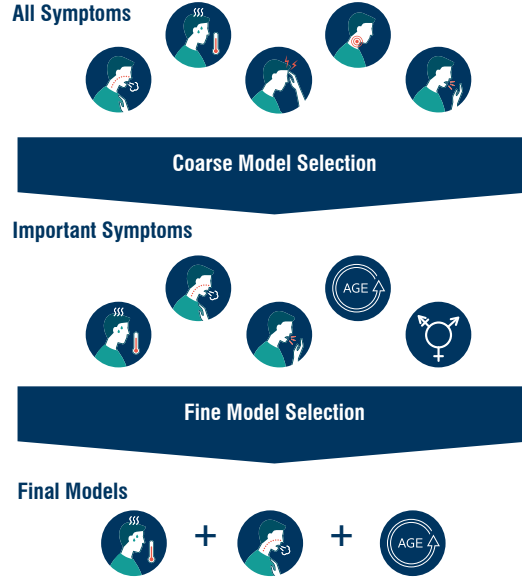


Figure 2: Schematic for rounds of model selection in the multivariate probit component of Model Classes 2 and 3. With 14 symptoms (only 5 shown here for demonstration purposes) and two covariates there are over 131000 possible model combinations. To make exploring these possible models computationally feasible and to reduce the risk of overfitting, we carried out two rounds of model selection. First, the data are divided into temporal cross-validation sets. The multivariate probit connects symptoms to the RT-PCR result through a correlation matrix. In the coarse model selection, the most complex feasible model (all symptoms and covariates) is fit to the training data. The estimated correlations between each symptom and the RT-PCR result are compared for each cross-validation set. The symptoms that have non-zero correlations in a systematic direction (i.e. all positively or all negatively correlated with RT-PCR result) are retained. The process is then repeated on each retained set of symptoms until the four symptoms in each model class with the strongest correlation to RT-PCR result. We then conduct a more exhaustive model selection on all the possible permutations of the four symptoms and two covariates. In this round, each model is fit to training data and used to predict for the test set, and the quality of those predictions is measured using cross-entropy scoring. The cross-entropy score is then used to select the best predictive model for each level of model complexity. Only these final models are then used for classification. This reduces the set of models tested as classifiers from  $>131\,000$  to just four per model class.



Table 1: For each epidemiological scenario there is a requirement and a performance criterion. The requirement refers to a base level of performance the model must achieve; in general this will be a maximum acceptable error rate of some kind. These requirements were determined in discussion with members of the Institute of Epidemiology, Disease Control and Research, Ministry of Health, Bangladesh (IEDCR). The requirement determines a probability threshold for each model which most closely meets that requirement. The performance criterion is then used to determine which model performs the 'best' given that the requirement has been met.

| Scenario Name     | Requirement                           | Performance Criterion (Error) |
|-------------------|---------------------------------------|-------------------------------|
| 1 Agnostic        | Maximise correct classification rates | Sum of error rates            |
| 2 Rising Cases    | Max. 20% false negative rate          | False negative rate           |
| 3 Low-Level Cases | Max. 20% false positive rate          | False positive rate           |

4 symptoms. The covariate gender was dropped for both model classes while age was dropped in Class 2 but retained in Class 3. The final four symptoms in order of importance (i.e. the most important symptom was retained in all of the final 4 models, the least important symptom was only retained in the 4 symptom model) were loss of taste, diarrhoea, vomit and fever for Model Class 2, and fever, wet cough, cough and loss of taste for Model Class 3.

In the comparison of model predictive performance, Model Class 1 (RAT only) performed worst with an out-of-sample cross-entropy of 3.24 (cross-entropy values further from zero correspond to worse predictive performance). The median cross-entropy values were between 2.53 and 2.59 for models in Class 2. Models in Class 3 performed best with cross-entropy values between 1.44 and 1.47 (see Figure 3).

Generic model classification performance is shown by their ROC curves (Figure 4).

Scenario specific classification performance is shown in Figure 5. Across all three scenarios (defined in Table 1), the best models in Class 3 performed equally well or better than the other two model classes. In Scenario 1 ("Agnostic"), models in Classes 1 and 3 performed equally well (overlapping posterior interquartile ranges) and distinctly better (no overlap in posterior interquartile range) than models in Class 2. In Scenario 2 ("Rising Cases"), Model Class 1 failed to meet the requirement and so was excluded, and Model Class 3 once again outperformed Class 2. In Scenario 3 ("Low-Level Cases"), Model Class 2 once again performed worst, and Model Class 3 achieved the lowest error, with Model Class 1 falling in between the two (closer to Class 3 than 2). For Classes 2 and 3 across all the scenarios the number of symptoms made relatively little difference within the final four candidate models in terms of median performance, although the more complex models have higher precision. It should be noted that the candidate models are chosen as a result of a selection process and performed much better than more complex models (i.e. those with 5 or more symptoms) or

DHC: out-of sample vs test set cross-entropy

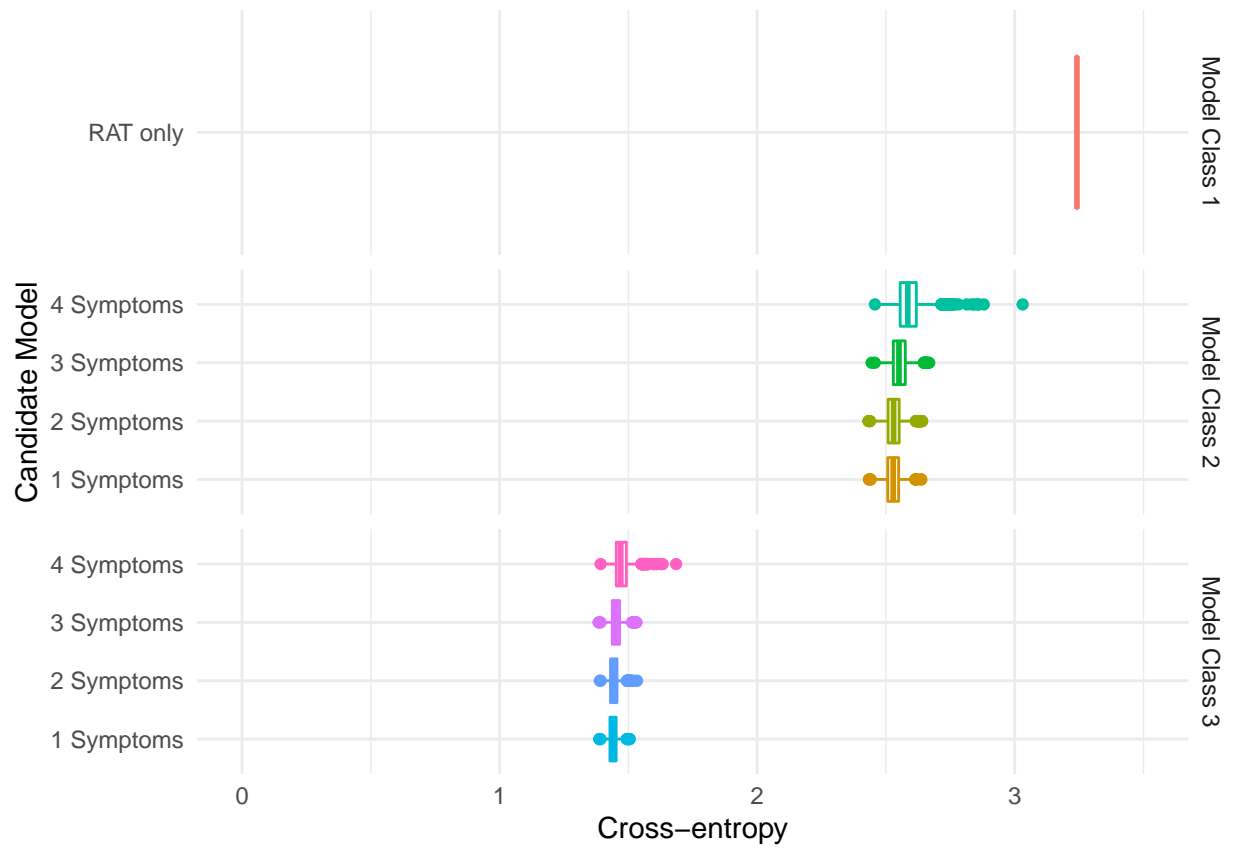


Figure 3: Predictive performance of candidate models. Interquartile ranges for the posterior cross-entropy of the best candidate models at each level of model complexity tested under temporal cross-validation. cross-entropy is a measure of distance from the truth, so values closer to zero indicate better models. The intermediate complexity models perform best at prediction, although performance is similar across all the models within each model class (1: rapid antigen testing (RAT) only; 2: syndromic data only; and 3: combined RAT and syndromic data).

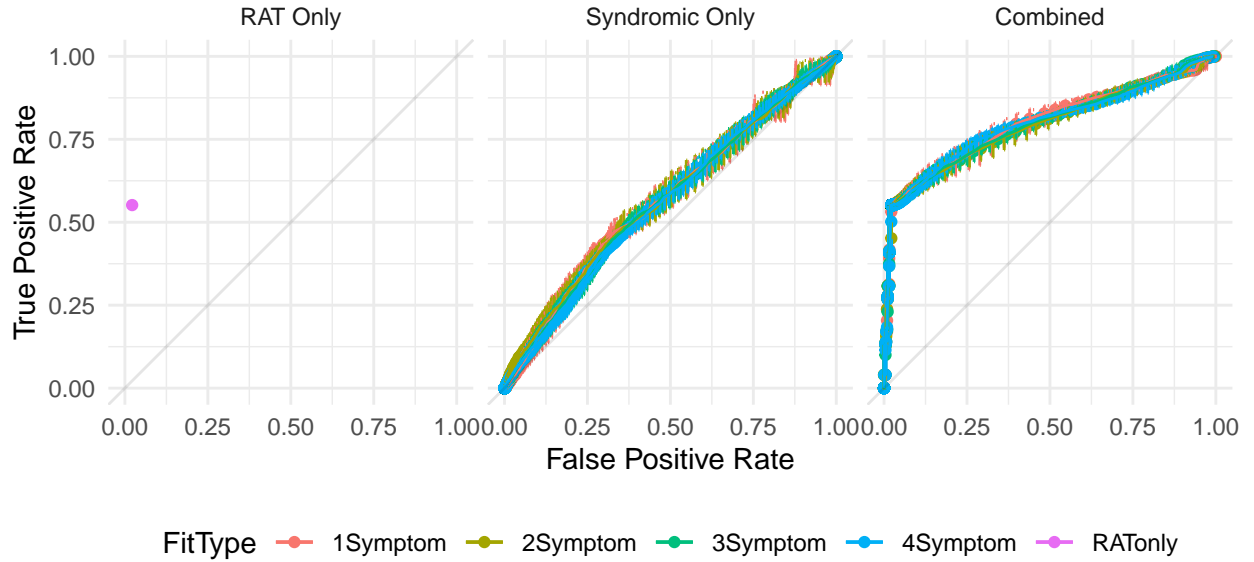


Figure 4: Receiver operating characteristics for rapid antigen testing (RAT) only approach (Model Class 1) and posterior median and interquartile range ROC for Class 2 (syndromic data only) and 3 (syndromic and RAT data) models. These curves demonstrate the performance of the model for any hypothetical scenario as defined by the axes (as opposed to Figure 5 which demonstrates model performance in specific epidemiological scenarios which are realisations of a single point in this space).

273 simpler models (with no symptoms but an intercept and covariates) in terms of  
 274 cross-entropy and ROC, indicating they would likely also perform worse in these  
 275 scenarios.

## 276 5. Discussion (815 words)

277 We have demonstrated that combining rapid antigen tests (RATs) with  
 278 syndromic modelling yields better identification of COVID-19 cases than either  
 279 diagnostic in isolation. These gains in performance are mirrored across metrics of  
 280 prediction, generic classification and scenario-specific classification. The biggest  
 281 improvement is seen in Scenario 2 (“Rising Cases”) which was developed around  
 282 the current situation in Bangladesh (see Table 1 where the pandemic is once  
 283 again accelerating. In this scenario, the combined data model (Model Class 3)  
 284 false negative rate is 26 percentage points lower than that of the RAT only model  
 285 (Model Class 1). Although the syndromic only model (Model Class 2) matches the  
 286 combined models false negative rate, its false positive rate is 31 percentage  
 287 points higher.

288 In a country where there are currently 15 000 new cases being identified  
 289 every day, these improvements are non-trivial, representing tens of thousands of  
 290 daily cases that would otherwise be missed. Furthermore, this boost in diagnostic

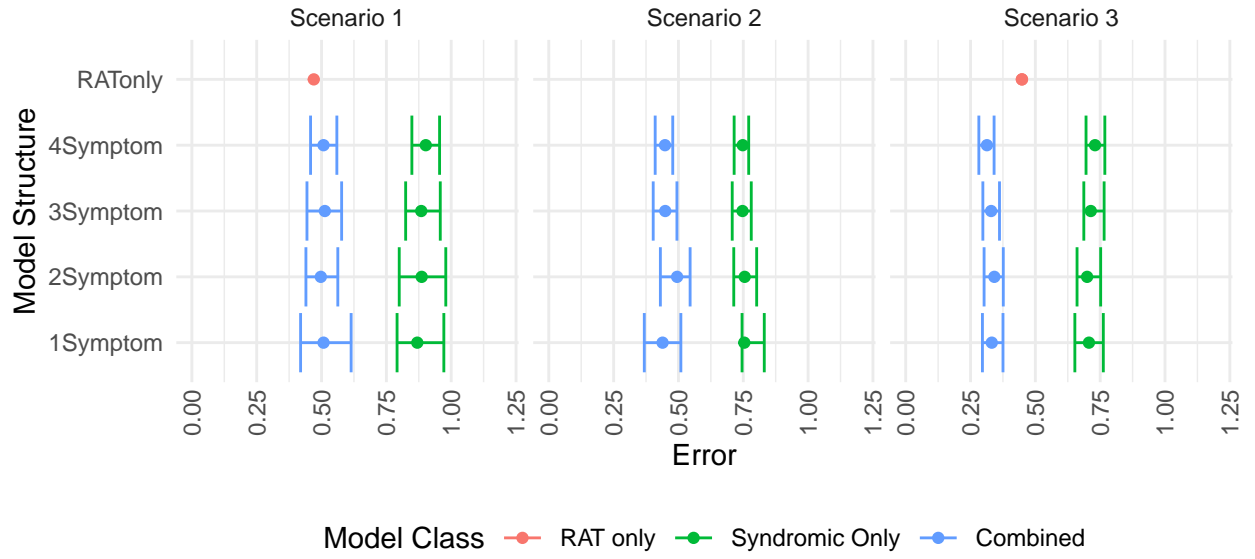


Figure 5: Performance of models under each scenario measured by posterior median and interquartile range for errors defined in Table 1. Low errors correspond to better model performance. There is no error rate defined for the Model Class 1 (RAT only model) in Scenario 2 as the model failed to meet the requirement for that scenario (making the error functionally infinite).

291 performance is achieved with data that are already being collected in Bangladesh  
292 and other low- and middle- income countries (LMICs). Outwith developing and  
293 rerunning the models presented in this paper, these improvements are essentially  
294 cost-free and eminently scalable.

295 The pattern is similar in epidemiological Scenarios 1 (“Agnostic”) and 3  
296 (“Low-Level Cases”), with the combined model class performing performing  
297 equally well or better than the other two classes (Figure 5). These three  
298 scenarios only offer snapshots of performance. An indication of how these models  
299 will perform under any condition can be obtained by comparing the more generic  
300 model performance metrics for prediction and classification (Figures 3 and 4,  
301 respectively). These figures demonstrate both the added flexibility of the more  
302 complex model classes that allow them to be tailored to specific needs and  
303 the need to combine the high-quality but inflexible RAT results with the more  
304 flexible but lower quality syndromic data.

305 The final symptoms chosen through model selection should be interpreted  
306 cautiously. These models were developed for prediction and classification in a  
307 unique sub-population: CST-identified, symptomatic patients. The symptoms  
308 and risk factors retained in the model classes differed, despite these data being  
309 collected over a short time period from the same population. These differences  
310 may point to mechanisms by which CST-identified and RAT-positive patients  
311 differ from other groups. Of particular interest is whether individuals that are  
312 missed by RAT are less infectious, which could be explored by using viral load  
313 measured as Threshold Cycle (Ct) values from the RT-PCR [23].

314 Our methodology has been developed using a large sample size drawn under  
315 field-realistic conditions and has thus developed with the practicalities of mass  
316 deployment in mind. Improving case identification using statistical methods  
317 allows us to update our diagnostic process in real-time, allowing rapid adaptation  
318 to new variants or even new diseases. The modelling frameworks we have used are  
319 also sufficiently flexible to accommodate new data sources (such as background  
320 case numbers) or changes in the local relative costs of false positives and false  
321 negatives.

322 Naturally, these strengths have complementary limitations. Our models  
323 require updating in real-time and can only achieve good performance if the  
324 validation data are of good quality. Similarly, targeting misdiagnosis rates is only  
325 sensible if those rates properly reflect local conditions which can be challenging.  
326 While these limitations should be seriously considered, we believe that the  
327 alternatives simply hide these problems. We choose to make these decisions  
328 explicitly to allow them to be more readily challenged, researched and improved  
329 upon. These challenges represent promising new avenues for impactful research  
330 that improve our understanding of estimating misdiagnosis rate trade offs and  
331 how to translate sample population findings to target populations.

332 We believe that our combined syndromic and rapid antigen testing approach  
333 is the most promising method for large-scale testing in LMICs for COVID-19 at  
334 present. We have demonstrated that these improvements can be impressive in  
335 real-world scenarios, and will have a large impact when scaled to the population  
336 sizes in LMICs. The framework we outline above is readily adapted for other

337 diagnostic problems. Malaria, schistosomiasis, rabies and many other diseases  
338 are all currently monitored either sparsely with gold-standard methods (such as  
339 RT-PCR, autopsies, fluorescent antibody testing) or at a large scale with more  
340 error-prone methods (RATs, blood smears, egg counts, differential diagnosis).

341 The management of global pandemics can only be done with global testing.  
342 While the quest to achieve this using only gold-standard diagnostic methods  
343 is laudable, it is also often impractical. Imperfect diagnostics are frequently  
344 imperfect in different ways, and these differences are ripe for statistical treatment.  
345 What is more, these approaches are often more agile than gold-standard diag-  
346 nostics in situations of flux, for example, in the early stages of new pandemics  
347 or disease strains, when fast responses are essential.  
348 By investing in understanding how to utilise the complementary strengths of  
349 imperfect testing and deploy the limited gold-standard testing available for vali-  
350 dation, we can provide good quality testing at the scale needed to fight infectious  
351 diseases.

## 352 **6. Funding (26 words)**

353 The Bill and Melinda Gates Foundation funded work by FAO (INV-022851),  
354 and University of Glasgow reports funding from Wellcome (207569/Z/17/Z).  
355 The authors declare no competing interests.

## 356 **7. Acknowledgements (69 words)**

357 We would like to thank members of the community support teams in  
358 Bangladesh who have provided essential services throughout the pandemic.  
359 Earlier drafts of this manuscript benefited from the input of Paul Johnson,  
360 Daniel Haydon, Anne-Sophie Bonnet-Lebrun, Luca Nelli, Crinan Jarrett, Rita  
361 Claudia Cardoso Ribeiro, Halfan Ngowo, Heather McDevitt and Gina Bertolacci.  
362 The University of Glasgow COVID-19 in LMICs Group provided the environment  
363 in which to develop this work.

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