

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

Community support teams in Dhaka, Bangladesh identified potential COVID-19 patients in Dhaka using syndromic surveillance. A sample (n = 1172) of

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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 (IQR: 24, 29) percentage points lower than that of the RAT only model. In the “Rising Cases” scenario, which most closely represents the current situation in many LMICs, the combined data model false negative rate is 26 (IQR: 24, 29) 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 31 (IQR: 29, 34) percentage points higher.

Interpretation

Small, scalable improvements in the accuracy of mass-deployed but imperfect diagnostic methods 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.

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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 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

71 less expensive, easier to implement, and faster but with lower sensitivity [9]. For
 72 RT-PCR testing, patients must travel to a designated site or have officials visit
 73 their home in enhanced personal protective equipment. In contrast, RATs can
 74 be conducted on nasal swabs, completed in the home with minimal PPE, and
 75 results are available in 30 minutes. RATs can be taken by persons with limited
 76 training, thus decreasing the time and expense associated with identifying cases.
 77 Together, these traits make RATs an appealing alternative to RT-PCR, however,
 78 concerns have been raised that the lower sensitivity of RAT [10] leads to more
 79 false negative diagnoses.

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

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

114 Moderate to poor sensitivity and specificity are problematic in diagnostics but
 115 may be tolerable depending on their scale and impact given the local situation.
 116 Low specificity means a patient is likely to be told they have COVID-19 when

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they do not (a high false positive rate), leading to patients unnecessarily self-isolating and receiving support. This is expensive to the individual and to local public health bodies, reducing available resources for those who need them [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.

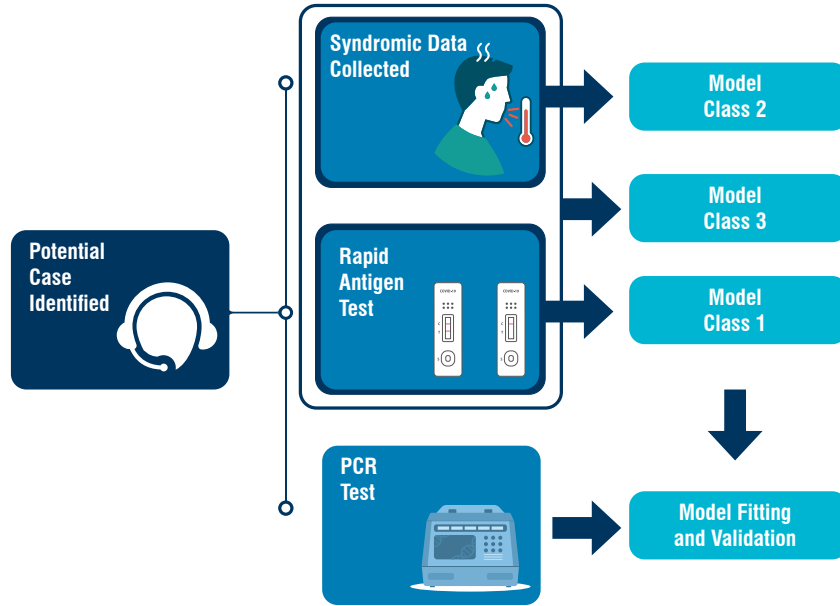


Figure 1: Schematic description of identification of likely COVID-19 patients by community support teams (CSTs), swab collection and model definitions. The teams collected syndromic data (age, gender and presence/absence of 14 predetermined symptoms), and two sets of naso-pharyngeal swabs (one each for 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.

One swab each was used for rapid antigen testing (RAT) and RT-PCR. The full questionnaire and testing protocols are provided in Supplementary 1. Participants provided written informed consent to sample collection and for their results to be analyzed in the study.

3.2. Modelling

3.2.1. Structure

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

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

Find more ways to cite Figure reffig:data-flowchart in this text.

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

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

186 3.2.2. Model Selection

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

206 3.2.3. Predictive Performance

207 We scored the models’ predictive power using cross-entropy. Cross-entropy
 208 measures the accuracy of models that generate probabilities of binary outcomes,
 209 rather than make binary classifications, similar in concept to a mean square error
 210 for normally-distributed data, but adapted for binary data [21]. A cross-entropy
 211 value close to zero corresponds to high levels of accuracy, with larger values
 212 indicating lower accuracy. More details on the model structure and selection
 213 process, including code, are available in Supplementary 2.

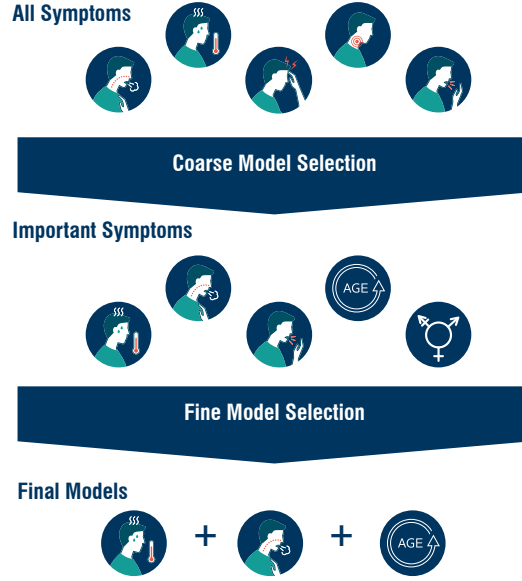


Figure 2: Schematic for rounds of model selection in the multivariate probit component of Model Classes 2 and 3. With 14 symptoms (only 5 shown here for demonstration purposes) and two covariates there are over 131000 possible model combinations. To make exploring these possible models computationally 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

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 (IEDCR), Bangladesh, for illustrative purposes.

4. Results (476 words)

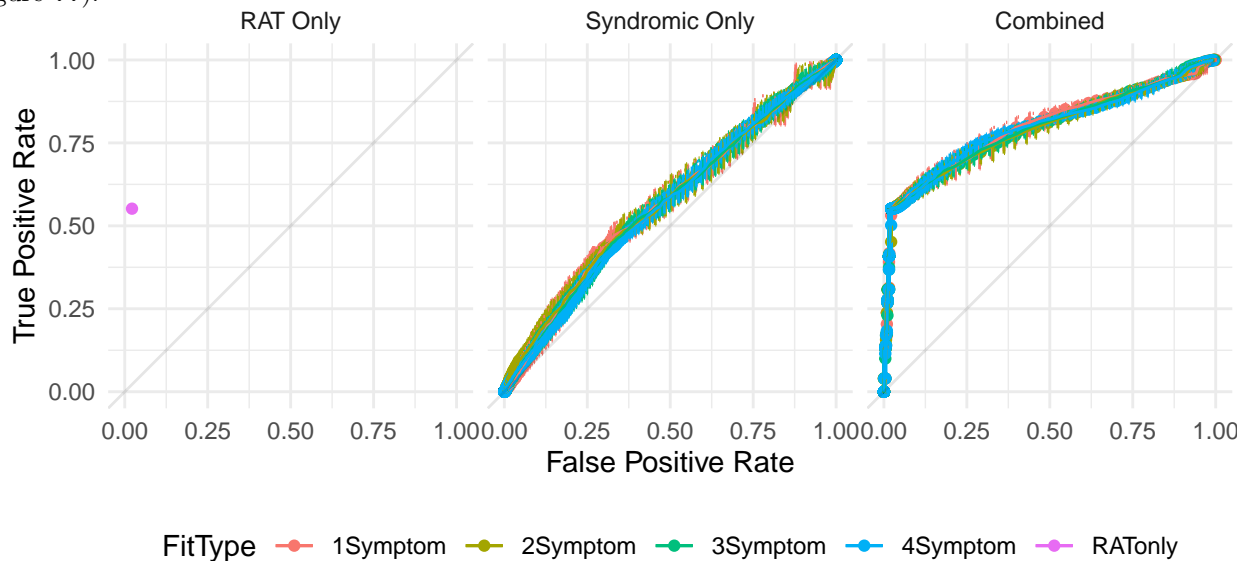
Of 1241 subjects surveyed, a total of 1172 subjects had complete data available for the current analyses with the remainder removed due to duplication

242 of barcodes or missing data. The mean age of women participants (47% of the
 243 sample) was 37 (SD = 14) years, and for men (53% of the sample) was 36 (SD =
 244 14) years. Participants were identified by the community support teams (CSTs)
 245 and drawn from across Dhaka.

246 Model selection for both Model Class 2 (syndromic data only) and 3 (syn-
 247 dromic and RAT data) showed a marked decline in predictive power at more than
 248 4 symptoms. The covariate gender was dropped for both model classes while
 249 age was dropped in Class 2 but retained in Class 3. The final four symptoms
 250 in order of importance (i.e. the most important symptom was retained in all
 251 of the final 4 models, the least important symptom was only retained in the 4
 252 symptom model) were loss of taste, diarrhoea, vomit and fever for Model Class
 253 2, and fever, wet cough, cough and loss of taste for Model Class 3.

254 In the comparison of model predictive performance, Model Class 1 (RAT
 255 only) performed worst with an out-of-sample cross-entropy of 3.24 (cross-entropy
 256 values further from zero correspond to worse predictive performance). The
 257 median cross-entropy values were between 2.53 and 2.59 for models in Class 2.
 258 Models in Class 3 performed best with cross-entropy values between 1.44 and
 259 1.47 (see Figure 3).

260 Generic model classification performance is shown by their ROC curves
 261 (Figure ??).



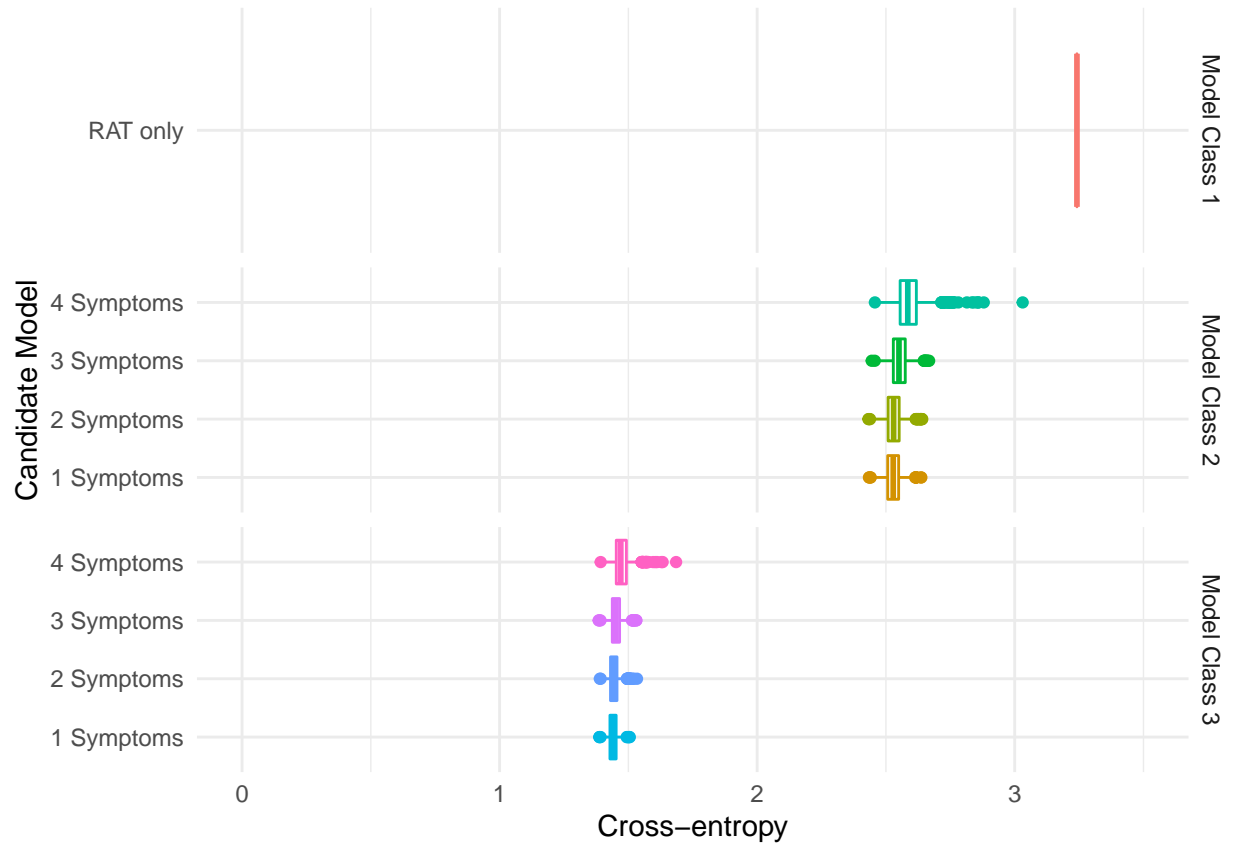
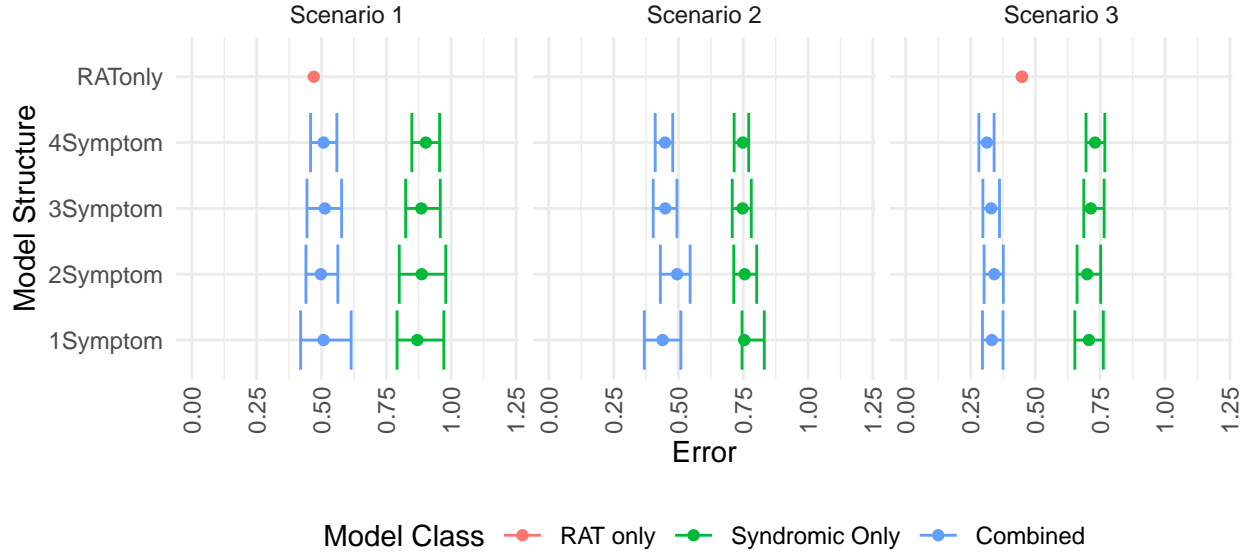


Figure 3: Predictive performance of candidate models. Interquartile ranges for the posterior cross-entropy of the best candidate models at each level of model complexity tested under temporal cross-validation. cross-entropy is a measure of distance from the truth, so values closer to zero indicate better 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).



Scenario specific classification performance is shown in Figure ???. 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. The median error was 0.470082 for models in Class 1 and Class 3 and between 0.8692795 and 0.9019423 for models in Class 2 (Figure ??). 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. The median errors were between 0.746984 and 0.755422 for models in Class 2, and 0.4387707 and 0.494805 for models in Class 3 (Figure ??). 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). The error in Class 1 was 0.0218039 and the median errors ranged from 0.1946676 to 0.1999916 for Class 2, and 0.1831021 to 0.1989851 for Class 3 (Figure ??). 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 simpler models (with no symptoms but an intercept and covariates) in terms of cross-entropy and ROC, indicating they would likely also perform worse in these scenarios.

5. Discussion (815 words)

We have demonstrated that combining rapid antigen tests (RATs) with syndromic modelling yields better identification of COVID-19 cases than either

290 diagnostic in isolation. These gains in performance are mirrored across metrics of
 291 prediction, generic classification and scenario-specific classification. The biggest
 292 improvement is seen in Scenario 2 (“Rising Cases”) which was developed around
 293 the current situation in Bangladesh (see Table 1 where the pandemic is once
 294 again accelerating. In this scenario, the combined data model (Model Class 3)
 295 false negative rate is 26 (IQR: 24, 29) percentage points lower than that of the RAT
 296 only model (Model Class 1). Although the syndromic only model (Model Class
 297 2) matches the combined models false negative rate, its false positive rate is 31
 298 (IQR: 29, 34) percentage points higher.

299 In a country where there are currently 15 000 new cases being identified
 300 every day, these improvements are non-trivial, representing tens of thousands of
 301 daily cases that would otherwise be missed. Furthermore, this boost in diagnostic
 302 performance is achieved with data that are already being collected in Bangladesh
 303 and other low- and middle- income countries (LMICs). Outwith developing and
 304 rerunning the models presented in this paper, these improvements are essentially
 305 cost-free and eminently scalable.

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

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

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

333 Naturally, these strengths have complementary limitations. Our models
 334 require updating in real-time and can only achieve good performance if the
 335 validation data are of good quality. Similarly, targeting misdiagnosis rates is only

336 sensible if those rates properly reflect local conditions which can be challenging.
337 While these limitations should be seriously considered, we believe that the
338 alternatives simply hide these problems. We choose to make these decisions
339 explicitly to allow them to be more readily challenged, researched and improved
340 upon. These challenges represent promising new avenues for impactful research
341 that improve our understanding of estimating misdiagnosis rate trade offs and
342 how to translate sample population findings to target populations.

343 We believe that combined syndromic and rapid antigen testing approach is the
344 most promising method for large-scale testing in LMICs for COVID-19 at present.
345 We have demonstrated that these improvements can be impressive in real-world
346 scenarios, and will have a large impact when scaled to the population sizes
347 in LMICs. The framework we outline above is adaptable for other diagnostic
348 problems. Malaria, schistosomiasis, rabies and many other diseases are all
349 currently monitored either sparsely with gold-standard methods (such as RT-
350 PCR, autopsies, fluorescent antibody testing) or at a large scale with more
351 error-prone methods (RATs, blood smears, egg counts, differential diagnosis).

352 The management of global pandemics can only be done with testing at
353 scale. While the quest to achieve this using only gold-standard diagnostic
354 methods is laudable, it is also often impractical. Imperfect diagnostics are
355 frequently imperfect in different ways, and these differences are ripe for statistical
356 treatment. What is more, these approaches are often more agile than gold-
357 standard diagnostics in situations of flux, for example, in the early stages of new
358 pandemics or disease strains, when fast responses are essential.

359 By investing in understanding how to utilise the complementary strengths of
360 imperfect testing and deploy the limited gold-standard testing available for
361 validation, we can provide good quality testing at the scale needed to fight
362 infectious diseases.

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