1 **Cost-effectiveness of public health strategies for COVID-19 epidemic control**

2 **in South Africa: a microsimulation modelling study**

3

4 Krishna P. Reddy, MD[1,2,3]

5 Fatma M. Shebl, PhD[1,3]

6 Julia H. A. Foote, BA[1,3]

7 Guy Harling, ScD[4,5,6,7]

8 Justine A. Scott, MPH[1]

9 Christopher Panella, BA[1]

10 Kieran P. Fitzmaurice, BS[1]

11 Clare Flanagan, MPH[1]

12 Emily P. Hyle, MD[1,3,8,9]

13 Anne M. Neilan, MD[1,3,8,10]

14 Amir M. Mohareb, MD[1,3,8]

15 Prof. Linda-Gail Bekker, MBChB[11]

16 Richard J. Lessells, PhD[12]

17 Andrea L. Ciaranello, MD[1,3,8,9]

18 Prof. Robin Wood, DSc[11]

19 Prof. Elena Losina, PhD[3,13,14,15]

20 Prof. Kenneth A. Freedberg, MD[1,3,8,16,17]

21 Pooyan Kazemian, PhD[1,3]*

22 Mark J. Siedner, MD[1,3,5,8]*

23

24 * PK and MJS contributed equally to this work.

25

26

27

28 **Affiliations**

29 [1] Medical Practice Evaluation Center, Massachusetts General Hospital, Boston, MA, USA

30 [2] Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston,

31 MA, USA

32 [3] Harvard Medical School, Boston, MA, USA

33 [4] Department of Epidemiology and Harvard Center for Population & Development Studies,

34 Harvard T.H. Chan School of Public Health, Boston, MA, USA

35 [5] Africa Health Research Institute, KwaZulu-Natal, South Africa

36 [6] Institute for Global Health, University College London, London, UK

37 [7] MRC/Wits Rural Public Health & Health Transitions Research Unit (Agincourt), University of

38 Witwatersrand, South Africa

39 [8] Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA, USA

40 [9] Harvard University Center for AIDS Research, Cambridge, MA, USA

41 [10] Division of General Academic Pediatrics, Massachusetts General Hospital, Boston, MA, USA

42 [11] Desmond Tutu HIV Foundation, University of Cape Town, Cape Town, South Africa

43 [12] KwaZulu-Natal Research Innovation and Sequencing (KRISP), College of Health Sciences,

44 University of KwaZulu-Natal, Durban, South Africa

45 [13] Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

46 [14] Orthopedic and Arthritis Center for Outcomes Research (OrACORe), Department of

47 Orthopedic Surgery, Brigham and Women's Hospital, Boston, MA, USA

48 [15] Policy and Innovation eValuation in Orthopedic Treatments (PIVOT) Center, Department of

49 Orthopedic Surgery, Brigham and Women's Hospital, Boston, MA, USA

50 [16] Division of General Internal Medicine, Massachusetts General Hospital, Boston, MA, USA

51 [17] Department of Health Policy and Management, Harvard T.H. Chan School of Public Health,

52 Boston, MA, USA

53

54   **Corresponding Author**

55   Krishna P. Reddy, MD, MS

56   Medical Practice Evaluation Center

57   Massachusetts General Hospital

58   100 Cambridge Street, Suite 1600

59   Boston, MA 02114

60   USA

61   Phone: +1 617-726-1993

62   Fax: +1 617-726-4120

63   Email: kpreddy@mgh.harvard.edu

64

65   **Keywords:** COVID-19, cost-effectiveness, resource-limited setting, South Africa, resource

66   allocation

67

68   **Running title:** Cost-effectiveness of COVID-19 interventions in South Africa

69

70   **Abstract Word Count:** 299

71

72   **Main Text Word Count:** 3,493

73

74   **ABSTRACT**

75   **Background**

76   Healthcare resource constraints in low and middle-income countries necessitate selection of

77   cost-effective public health interventions to address COVID-19.

78

79   **Methods**

80   We developed a dynamic COVID-19 microsimulation model to evaluate clinical and economic

81   outcomes and cost-effectiveness of epidemic control strategies in KwaZulu-Natal, South Africa.

82   Interventions assessed were Healthcare Testing (HT), where diagnostic testing is performed

83   only for those presenting to healthcare centres; Contact Tracing (CT) in households of cases;

84   Isolation Centres (IC), for cases not requiring hospitalisation; community health worker-led Mass

85   Symptom Screening and molecular testing for symptomatic individuals (MS); and Quarantine

86   Centres (QC), for household contacts who test negative. Given uncertainties about epidemic

87   dynamics in South Africa, we evaluated two main epidemic scenarios over 360 days, with

88   effective reproduction numbers (R_e) of 1·5 and 1·2. We compared *HT, HT+CT, HT+CT+IC,*

89   *HT+CT+IC+MS, HT+CT+IC+QC,* and *HT+CT+IC+MS+QC*, considering strategies with

90   incremental cost-effectiveness ratio (ICER) <US$3,250/year-of-life saved (YLS) cost-effective.

91   In sensitivity analyses, we varied R_e, molecular testing sensitivity, and efficacies and costs of

92   interventions.

93

94   **Findings**

95   With R_e 1·5, *HT* resulted in the most COVID-19 deaths over 360 days. Compared with *HT*,

96   *HT+CT+IC+MS+QC* reduced mortality by 94%, increased costs by 33%, and was cost-effective

97   (ICER $340/YLS). In settings where quarantine centres cannot be implemented,

98   *HT+CT+IC+MS* was cost-effective compared with *HT* (ICER $590/YLS). With R_e 1·2,

99   *HT+CT+IC+QC* was the least costly strategy, and no other strategy was cost-effective.

4

100   *HT+CT+IC+MS+QC* was cost-effective in many sensitivity analyses; notable exceptions were

101   when R_e was 2·6 and when efficacies of ICs and QCs for transmission reduction were reduced.

102

103   **Interpretation**

104   In South Africa, strategies involving household contact tracing, isolation, mass symptom

105   screening, and quarantining household contacts who test negative would substantially reduce

106   COVID-19 mortality and be cost-effective. The optimal combination of interventions depends on

107   epidemic growth characteristics and practical implementation considerations.

108

109

110   **Funding**

111   National Institutes of Health, Royal Society, Wellcome Trust

112

INTRODUCTION

By early September 2020, 16 countries in sub-Saharan Africa (SSA) had reported over 10,000

COVID-19 cases.[1] High urban density, limited opportunities for physical distancing, and poor

access to hygiene interventions raise the risk of severe epidemics in the region.[2] The existing

public health infrastructure for epidemic response in SSA is also of concern: testing capacity,

surveillance infrastructure, isolation facilities, and intensive care (ICU) services are sparse.[3,4]

Low and middle-income countries (LMICs) are implementing epidemic control programs. The

World Health Organization (WHO) promotes establishment of disease surveillance platforms,

contact tracing, and isolation facilities.[5] Epidemiologic models of these interventions have

generally suggested that their efficacy depends on intervention adherence and transmission

dynamics.[6,7] Yet few studies have included resource costs to examine their cost-effectiveness

and feasibility. Limitations in human resources, public health financing, and healthcare facility

availability necessitate particular attention to these issues in LMICs.

We used a dynamic microsimulation model to compare medical outcomes and costs for a range

of COVID-19 control measures in KwaZulu-Natal, South Africa. Our objective was to inform

policy decision making by projecting clinical and economic outcomes, cost-effectiveness, and

budget impact of alternative control strategies, focusing on those proposed or currently in use in

South Africa. Though the first wave of diagnosed COVID-19 cases in South Africa peaked in

July 2020, this analysis can inform preparation for or response to a resurgence or subsequent

waves.

135   **METHODS**

136   **Analytic Overview**

137   We developed the Clinical and Economic Analysis of COVID Interventions (CEACOV) dynamic

138   state-transition Monte Carlo microsimulation model to reflect COVID-19 natural history,

139   diagnosis, and treatment. We compared six public health intervention strategies (figure S1). In

140   all strategies: (a) testing consists of polymerase chain reaction (PCR) for severe acute

141   respiratory syndrome coronavirus 2 (SARS-CoV-2) on a nasopharyngeal specimen; (b) those

142   awaiting test results are instructed to self-isolate; (c) those severely ill (with dyspnoea and/or

143   hypoxemia), regardless of test result, are admitted to hospital until hospital capacity is reached;

144   (d) those with a negative test result are advised to practice physical distancing and hand

145   hygiene; (e) those with an initial negative test result can present for repeat testing if they

146   develop new or worsening symptoms; (f) those not initially admitted to hospital can be admitted

147   later if they develop severe illness. Unique characteristics of each modelled strategy are:

148

149   1) *Healthcare Testing (HT)*: Approximately 30% of people with mild/moderate COVID-

150   19-like symptoms and all with severe symptoms self-present to a healthcare centre for

151   testing. Those with a positive result and not severely ill are instructed to self-isolate at

152   home.

153

154   2) *Contact Tracing (HT+CT)*: In addition to *HT*, household contacts of COVID-19 cases

155   are tested. Those with a positive result are instructed to self-isolate at home.

156

157   3) *Contact Tracing + Isolation Centre (HT+CT+IC)*: In addition to *HT+CT*, cases who are

158   not severely ill are referred to an isolation centre (IC) offering food, shelter, and basic

159   medical care without supplemental oxygen. They are discharged after 14 days.

160

161   4) *Contact Tracing + Isolation Centre + Mass Symptom Screening (HT+CT+IC+MS)*: In

162   addition to *HT+CT+IC*, community healthcare workers screen the entire population for

163   COVID-19 symptoms every 6 months and refer those with symptoms for PCR testing.

164   Individuals with a positive PCR test but not severely ill are referred to an IC. As a frame

165   of reference, epidemic control measures in South Africa in June 2020 included

166   combinations of HT, CT, IC, and MS.

167

168   5) *Contact Tracing + Isolation Centre + Quarantine Centre (HT+CT+IC+QC)*: In addition

169   to *HT+CT+IC*, household contacts with a negative test result who cannot safely

170   quarantine at home are referred to a quarantine centre (QC) where they receive food

171   and shelter. They are discharged after 14 days, unless they develop COVID-19-like

172   symptoms, in which case they are referred to ICs or hospitals, as available.

173

174   6) *Contact Tracing + Isolation Centre + Mass Symptom Screening + Quarantine Centre*

175   *(HT+CT+IC+MS+QC)*: This is a combination of all measures described above.

176

177 Starting with SARS-CoV-2 infection prevalence of 0·1%, we simulated COVID-19-specific

178 outcomes over 360 days, including daily and cumulative infections (detected and undetected),

179 deaths, resource utilization, and healthcare costs from the health sector perspective without

180 discounting. Outside the model, we calculated the average lifetime years-of-life saved (YLS)

181 from each averted COVID-19 death during the 360-day model horizon, which equated to 16·8

182 life-years (appendix p.5-6). The primary outcome was the incremental cost-effectiveness ratio

183 (ICER), the difference in healthcare costs (2019 US dollars [US$]) divided by the difference in

184 life-years between strategies. We did not include costs beyond the 360-day model horizon.

185 Average non-HIV public health expenditures in South Africa are approximately $600/year per

186 capita;[8,9] including those annual costs over a lifetime yields a lifetime ICER approaching

187   $600/YLS. Therefore, our ICER estimates include healthcare costs during the 360-day model

188   horizon and YLS over a lifetime from averted COVID-19 deaths during the 360-day model

189   horizon. Recognizing no established threshold, we judged an ICER less than $3,250/YLS cost-

190   effective, based on an opportunity cost approach (appendix p.2).[10]

191

192   **Model Structure**

193   *Health States and Natural History*

194   At simulation initiation, each individual is either susceptible to, or infected with, SARS-CoV-2

195   according to age-stratified probabilities (0-19, 20-59, ≥60 years). Once infected, an individual

196   transitions to the pre-infectious latency state. Each individual faces an age-dependent

197   probability of developing asymptomatic, mild/moderate, severe, or critical disease (appendix

198   p.2, table S1, figure S2). Those with critical disease face daily probabilities of death. If they

199   survive, they pass through a recuperation state (remaining infectious) before going to the

200   recovery state. Those in other disease states can transition directly to the recovery state.

201   "Recovered" individuals pose no risk of transmission and are assumed immune from repeat

202   infection for the simulation duration. All simulated individuals advance through the model

203   simultaneously to capture infection transmission dynamics. To validate our natural history

204   assumptions, we compared model-projected COVID-19 deaths with those reported in KwaZulu-

205   Natal (appendix p.4).

206

207   *Transmission*

208   Individuals in asymptomatic, mild/moderate, severe, critical, or recuperation states of COVID-19

209   may transmit infection to susceptible individuals at state-dependent daily rates. The number of

210   daily infections is a function of the proportion of susceptible people in the population, the

211   distribution of disease states among those with COVID-19, and interventions that influence

212   transmission (appendix p.3).

213

214   *Testing and Interventions*

215   PCR testing specifications include sensitivity, specificity, time from testing to result, and

216   cost. Interventions influence testing probability (e.g., CT and MS), infection transmission rate

217   (e.g., IC and QC), and costs.

218

219   *Resource Utilization*

220   Individuals with severe or critical disease are referred to hospitals and ICUs, respectively. If

221   those resources are not available, the individual receives the next lower available intervention,

222   which is associated with a different mortality risk and cost (e.g., if a person needs ICU care

223   when no ICU beds are available, s/he receives non-ICU hospital care).

224

225   **Model Calibration**

226   We populated CEACOV with COVID-19 natural history data from published literature (table

227   1). We used estimates of the basic reproduction number (R_0) and viral shedding duration in

228   various disease states to calculate transmission rates. We then calibrated transmission rates to

229   construct an effective reproduction number (R_e) corresponding to South African estimates in

230   May 2020, after implementation of physical distancing and lockdown policies (appendix p.4).[11]

231

232   **Input Parameters**

233   *Cohort Characteristics*

234   We defined cohort demographic characteristics using 2019 population estimates (table 1).[12] In

235   KwaZulu-Natal, 40.26% were aged 0-19 years, 51.48% were 20-59 years, and 8.26% were over

236   60 years. Day 0 of the model represents a provincial 0·1% prevalence (approximately 11,000

237   individuals) of active SARS-CoV-2 infection, with the remainder of the population susceptible to

238   infection.

10

239

Natural History

For those newly infected with SARS-CoV-2, average pre-infectious latency was 2·6 days. Table S1 indicates duration in each state, age-dependent probability of developing severe or critical disease, and age-dependent mortality for those with critical disease.

Transmission

We stratified transmission rates by disease state (table 1). We adjusted transmission rates to reflect R_e=1·5.[11] Given uncertainty over R_e, both in the past and future, we also simulated alternative epidemic growth scenarios with lower (1·1 or 1·2) or higher (2·6) R_e (appendix p.4).

Testing and Interventions

In the base case, we assumed a 70% sensitivity, 100% specificity, and five days to PCR result return and action across all active infection states.[13] We defined the probability of undergoing testing based on the health state and intervention strategy in place (table S2, appendix p.7). Given limited data about the precise efficacy of each intervention for reducing SARS-CoV-2 transmission rates (e.g., IC), we made assumptions about efficacies and varied them in sensitivity analysis. Ongoing transmission after diagnosis was reduced by 50% from HT alone and by 95% when HT was combined with ICs or QCs (table S2).

Resource Utilization and Costs

The maximum capacity of hospital and ICU beds was 26,220 and 748 per 11 million people, as reported for KwaZulu-Natal (table 1).[14] We assumed that IC and QC beds were available to all who needed them. We applied costs of PCR testing, contact tracing, and mass symptom screening, as well as daily costs of hospitalisation, ICU stay, and IC/QC stays based on published estimates and/or cost quotes obtained in KwaZulu-Natal (appendix p.6).

265

Resource Utilization and Budget Impact Analysis

267 We conducted resource utilization and budget impact analysis from a combined public/private

268 health sector perspective for KwaZulu-Natal (population 11 million). We projected the total

269 resources, including testing, hospital/ICU beds, and IC/QC beds, that would be used in each

270 intervention strategy. IC/QC beds are offered to those who meet criteria, and we assumed in the

271 base case that all offered would be used. In budget impact analysis, we projected total and

272 component healthcare costs associated with each strategy over 360 days and compared them

273 with the 2019 KwaZulu-Natal Department of Health budget of \$3·12 billion.[15] Because ICU care

274 is relatively expensive and mostly in the private sector, we also considered costs exclusive of

275 ICU care.

276

Sensitivity Analysis

278 We conducted one-way sensitivity analysis by varying key parameters across plausible ranges

279 to determine the impact on clinical and cost projections (table 1, table S2). To extrapolate to

280 other settings, we limited hospital and ICU bed availability to the average numbers in SSA

281 countries (22,275 and 371 per 11 million people).[16] We performed multi-way sensitivity analysis

282 in which we varied parameters influential in one-way sensitivity analysis, including reducing

283 IC/QC efficacy and costs to reflect the impact of home-based isolation and quarantine

284 strategies.

285   **RESULTS**

286   For an epidemic with R_e=1·5, we projected that *HT* would result in the most COVID-19

287   infections and deaths, most life-years lost, and lowest costs over 360 days (table 2, figures S3-

288   S4). *HT+CT+IC+MS+QC* provided the greatest clinical benefit and was cost-effective (ICER

289     $340/YLS) (figure 1). *HT+CT+IC+MS+QC* decreased life-years lost by 94% and increased costs

290   by 33% compared with *HT*. All other strategies resulted in higher costs while providing less

291   clinical benefit than *HT+CT+IC+MS+QC*. In settings where quarantine centres cannot be

292   implemented, *HT+CT+IC+MS* was the cost-effective strategy (ICER $590/YLS compared with

293   *HT*).

294

295   With R_e=1·2, *HT+CT+IC+QC* was cost-saving compared with *HT* (table 2). *HT+CT+IC+MS+QC*

296   resulted in 48% fewer life-years lost but was not cost-effective (ICER $27,590/YLS) compared

297   with *HT+CT+IC+QC*. *HT+CT+IC* was the least costly strategy in settings where quarantine

298   centres cannot be implemented, and other strategies were not cost-effective compared with

299   *HT+CT+IC*.

300

301   Regarding resource utilization, with R_e=1·5, *HT* resulted in the highest peak daily use of hospital

302   beds (table 3). Compared with *HT*, *HT+CT+IC+MS+QC* increased cumulative PCR test usage

303   by 2.6 times (though with lower peak daily PCR use) and reduced peak daily hospital bed use

304   by 86% (due to fewer cumulative infections), while requiring 12,380 IC beds and 18,140 QC

305   beds at peak daily use. Only the *HT+CT+IC+MS, HT+CT+IC+QC,* and *HT+CT+IC+MS+QC*

306   strategies maintained peak daily ICU bed demand below provincial capacity.

307

308   With R_e=1·2, compared with *HT*, *HT+CT+IC+MS+QC* increased cumulative PCR test usage by

309   4.1 times and reduced peak daily hospital bed use by 66%, while requiring 1,860 IC beds and

310   3,480 QC beds at peak daily use. All strategies except *HT* maintained peak daily ICU bed

311   demand below capacity.

312

313   Over 360 days, for an epidemic with R_e=1·5, PCR testing contributed 9-27% to overall costs,

314   depending on the strategy (figure 2). In strategies with QCs, these centres contributed 26-30%

315   to overall costs. In strategies without QCs, ICU care was the largest contributor to costs, ranging

316   from 38-71%. Costs exclusive of ICU care were $125 million (*HT*), $413 million

317   (*HT+CT+IC+MS*), and $461 million (*HT+CT+IC+MS+QC*), reflecting approximately 4%, 13%,

318   and 15% of the 2019 KwaZulu-Natal Department of Health budget. CT and MS together

319   contributed ≤10% and ICs contributed 22-31% to overall costs in strategies in which they were

320   used. For an epidemic with R_e=1·2, costs exclusive of ICU care were $71 million (*HT*), $159

321   million (*HT+CT+IC+MS*), and $167 million (*HT+CT+IC+MS+QC*), reflecting 2%, 5%, and 5% of

322   the 2019 KwaZulu-Natal Department of Health budget.

323

324   In sensitivity analyses, results were similar to the base case (i.e., *HT+CT+IC+MS+QC* remained

325   cost-effective) when varying costs of CT and MS (table S3) and hospitalisation (table S4);

326   varying PCR sensitivity and time to result (table S5) and PCR cost (table S6); and varying

327   availability of hospital and ICU beds (table S7). When PCR sensitivity increased to 90%, both

328   *HT+CT+IC+MS* (ICER $440/YLS) and *HT+CT+IC+MS+QC* (ICER $1,660/YLS) used resources

329   efficiently.

330

331   Conversely, our projected ICERs changed meaningfully in a model with R_e=2·6 – resource

332   requirements increased substantially, making *HT+CT+IC+MS+QC* no longer cost-effective

333   (ICER $25,040/YLS), and all strategies had ICERs above our cost-effectiveness threshold

334   compared with *HT* (table S8). The pattern of results with R_e=1·1 was similar to that with R_e=1·2

335   (table S8). When the efficacies of CT and MS to detect infections were halved from the base

336   case values, *HT+CT+IC+MS+QC* was no longer cost-effective (ICER $5,930/YLS) (table S9).

337   When the efficacy of ICs/QCs for transmission reduction was decreased from 95% to 75%,

338   *HT+CT+IC+MS+QC* was not cost-effective ($12,490/YLS) (table S10). When the IC/QC costs

339   decreased, *HT+CT+IC+MS+QC* became more favourable in terms of cost-effectiveness, and it

340   remained cost-effective when IC/QC costs were double those of the base case (table S11).

341

342   In a multi-way sensitivity analysis that varied CT/MS efficacy and reduced IC/QC efficacy and

343   cost to assess lower-cost but potentially lower-efficacy home-based IC and QC programs,

344   *HT+CT+IC+MS+QC* or *HT+CT+IC+QC* were cost-effective in nearly all scenarios in which

345   CT/MS efficacy for case detection was double that of the base case efficacy (figure S5). When

346   CT/MS efficacy for case detection was half that of the base case efficacy, strategies involving

347   quarantine centres were less likely to be cost-effective. If quarantine centers were not an option,

348   then *HT+CT+IC+MS* was cost-effective in most scenarios (figure S6).

349

350 **DISCUSSION**

351 Public health strategies combining contact tracing, isolation of those with confirmed COVID-19,

352 community-based mass symptom screening, and quarantine of household contacts of confirmed

353 cases will substantially reduce infections, hospitalisations, and deaths while efficiently using

354 healthcare resources in KwaZulu-Natal, South Africa. We estimate that a strategy combining all

355 interventions would cost an additional $340 per year-of-life saved, which compares favourably

356 with the cost-effectiveness of many established public health interventions in South Africa,

357 including tuberculosis diagnostic testing[17] and cervical cancer screening.[18] In scenarios in which

358 implementation of quarantine centres cannot be accomplished, a strategy of contact tracing,

359 isolation centres, and mass symptom screening would be cost-effective.

360

361 Notably, the cost-effectiveness of strategies was sensitive to epidemic growth conditions. We

362 conducted sensitivity analyses intended to generalize to other settings with resource

363 constraints, to epidemics at varying degrees of acceleration (including published estimates in

364 South Africa[11,19]), and with varying intervention costs.[20] With low epidemic growth (R_e 1·1-1·2),

365 *HT+CT+IC+QC* was the optimal strategy; QCs remained cost-effective but adding MS was not

366 cost-effective. With high epidemic growth (R_e 2·6), when the epidemic outpaced control

367 measures and costs increased substantially, no combination of the modelled interventions was

368 cost-effective compared with *HT* alone.

369

370 Our model parameters and specifications were selected for their relevance to LMICs. Our

371 estimates are based on the population structure of KwaZulu-Natal, with a median age of 25

372 years (compared with 38 years in the USA), and thus are likely to reflect epidemic scenarios in

373 LMICs with similarly young age structures. We chose intervention scenarios based on prior work

374 supporting their efficacy for epidemic control, WHO recommendations, and particular relevance

375 to settings with limitations in formal healthcare infrastructure.[5–7] We did not limit the PCR testing

376   availability – so that the total number of tests needed and associated costs could be estimated –

377   and peak PCR use reached approximately 10,000-15,000 tests/day in the optimal strategies,

378   marginally above established capacity in KwaZulu-Natal during the recent surge.[21] We specified

379   the model to reflect the number of available hospital and ICU beds in KwaZulu-Natal,[14] and

380   results were similar when we further restricted bed availability to that elsewhere in SSA.[16]

381   Contact tracing and community-based screening have been frequently used for case-finding in

382   LMICs.[22] Many SSA countries are thus theoretically poised to implement such interventions

383   through established networks of community health workers. Finally, isolation centres, which are

384   likely to require the greatest investment in new infrastructure, have been implemented

385   successfully in response to Ebola epidemics in West Africa and the Democratic Republic of

386   Congo, where healthcare resources are among the lowest in the world.[23] South Africa has

387   rapidly implemented and expanded COVID-19 related services in recent months, but further

388   scale-up would be required to meet demand in some of our modelled scenarios.[21,24]

389

390   Isolation centres in our model are designed as housing facilities for people with confirmed

391   COVID-19 who do not require hospital-level care but cannot safely isolate at home. We

392   estimated that their use reduces ongoing transmission after a confirmed diagnosis from 50% (in

393   the *HT* strategy) to 5%. They are likely to be most effective in areas with high household density

394   and limited capacity for in-home isolation, as is the case for many urban centres in SSA.

395   Quarantine centres, which include optional housing for contacts who test negative and cannot

396   safely distance during the latency period, have also been proposed for interrupting epidemic

397   spread and were implemented in the early phases of the COVID-19 response in China. They

398   were effective in our model at reducing the deleterious impact of the epidemic and were cost-

399   effective in many modelled scenarios.

400

401 Importantly, there are critical social and human rights considerations to implementation of

402 isolation and quarantine in many settings, due to trade-offs between public health benefits and

403 civil liberties.[25] In our model, both interventions are provided optionally for those who cannot do

404 so safely at home, but we conservatively included costs to reflect needs should they be used.

405 We also considered the use of home-based isolation and quarantine in a multi-way analysis that

406 reduced efficacies and costs of both. We found that isolation and quarantine remained cost-

407 effective in some lower efficacy scenarios, particularly if their costs were also reduced. On

408 balance, from a public health perspective, our findings support use of quarantine centres in

409 areas with individual and community support for their use.

410

411 Our model should be interpreted within the context of several limitations. We did not account for

412 heterogenous mixing within the population. Instead, we assumed that contact patterns were

413 random, as commonly done in infectious disease models. We assumed that the age-adjusted

414 prevalence of non-communicable co-morbidities in South Africa would be similar to that in in the

415 US and that age would be the primary driver of COVID-19 outcomes as demonstrated in

416 multiple settings.[26–28] In line with most published studies, we conservatively assumed no

417 modifying effect of HIV on the severity of COVID-19, though additional data are needed from

418 HIV-endemic countries to support this.[28,29] If the high prevalence of non-communicable diseases

419 and/or HIV in South Africa does worsen COVID-19 outcomes compared with resource-rich

420 settings, then the benefit of public health interventions in terms of years-of-life saved and cost-

421 effectiveness will likely be greater than our estimates. Nonetheless, in extending projections

422 beyond the 360-day model horizon, we accounted for South Africa-specific mortality rates in our

423 calculations of life expectancy and years-of-life lost. It will be crucial to consider how resources

424 and interventions implemented in response to COVID-19 will impact available resources for

425 other regional healthcare priorities. We did not include lifetime costs of healthcare beyond

426 COVID-19 or of sequelae among the recovered, and we did not account for impacts of COVID-

427   19 interventions on other economic sectors. As with all modelling exercises, our estimates are

428   determined by assumptions of input parameters. We selected COVID-19 clinical parameters

429   based on the published literature, which are largely derived from high-income settings.

430   Intervention efficacy estimates were hypothesized based on other model parameters, existing

431   literature where available, or expert opinion if no data were available. Recognizing a lack of

432   empiric data for some of these estimates, we focused our sensitivity analyses on varying those

433   for which data was lacking. Finally, costing data were derived from the literature and direct cost

434   estimates from local suppliers in KwaZulu-Natal and therefore might not reflect costs in other

435   contexts nor full implementation and scale-up costs. Nonetheless, our primary findings and

436   policy conclusions were largely consistent across a range of costing estimates.

437

438   We recommend that policymakers consider contact tracing, isolation of confirmed cases, mass

439   symptom screening, and quarantine of household contacts of cases to address COVID-19

440   epidemic control efficiently. Where quarantine centres are not feasible – for example, due to

441   budget constraints or lack of public support – a strategy that includes the other interventions

442   would still provide clinical benefit in an economically efficient manner.

443 **AUTHOR ROLES**

444 All authors contributed substantively to this manuscript in the following ways: study and model

445 design (all authors), data analysis (KPR, FMS, JHAF, GH, KPF, KAF, PK, MJS), interpretation

446 of results (all authors), drafting the manuscript (KPR, MJS), critical revision of the manuscript

447 (all authors) and final approval of submitted version (all authors).

448

449 **CONFLICTS OF INTEREST AND FINANCIAL DISCLOSURES**

450 The authors have no conflicts of interest or financial disclosures.

451

452 **DATA SHARING STATEMENT**

453 This modelling study involved the use of published or publicly available data. The data used and

454 the sources are described in the manuscript and appendix. No primary data were collected for

455 this study. Model flowcharts are in the appendix.

456

457 **ACKNOWLEDGMENTS**

468 **REFERENCES**

469 1 Xu B, Kraemer MUG, Xu B, *et al.* Open access epidemiological data from the COVID-19

470   outbreak. *Lancet Infect Dis* 2020; **20**: 534.

471 2 Johnstone-Robertson SP, Mark D, Morrow C, *et al.* Social mixing patterns within a South

472   African township community: implications for respiratory disease transmission and control.

473   *Am J Epidemiol* 2011; **174**: 1246–55.

474 3 Siedner MJ, Gostin LO, Cranmer HH, Kraemer JD. Strengthening the detection of and early

475   response to public health emergencies: lessons from the West African Ebola epidemic. *PLoS*

476   *Med* 2015; **12**: e1001804.

477 4 Gilbert M, Pullano G, Pinotti F, *et al.* Preparedness and vulnerability of African countries

478   against importations of COVID-19: a modelling study. *Lancet* 2020; **395**: 871–7.

479 5 World Health Organization. COVID-19 Strategic Preparedness and Response Plan:

480   Operational planning guidelines to support country preparedness and response. 2020;

481   published online Feb 12. https://www.who.int/docs/default-source/coronaviruse/covid-19-

482   sprp-unct-guidelines.pdf?sfvrsn=81ff43d8_4 (accessed June 24, 2020).

483 6 Hellewell J, Abbott S, Gimma A, *et al.* Feasibility of controlling COVID-19 outbreaks by

484   isolation of cases and contacts. *Lancet Glob Health* 2020; **8**: e488–96.

485 7 Peak CM, Childs LM, Grad YH, Buckee CO. Comparing nonpharmaceutical interventions for

486   containing emerging epidemics. *Proc Natl Acad Sci* 2017; **114**: 4023–8.

487 8 Basu S, Wagner RG, Sewpaul R, Reddy P, Davies J. Implications of scaling up

488   cardiovascular disease treatment in South Africa: a microsimulation and cost-effectiveness

489   analysis. *Lancet Glob Health* 2019; **7**: e270–80.

490 9 Global Burden of Disease Health Financing Collaborator Network. Spending on health and

491   HIV/AIDS: domestic health spending and development assistance in 188 countries, 1995-

492   2015. *Lancet* 2018; **391**: 1799–829.

493   10 Edoka IP, Stacey NK. Estimating a cost-effectiveness threshold for health care decision-

494   making in South Africa. *Health Policy Plan* 2020; **35**: 546–55.

495   11 National Institute for Communicable Diseases. The Initial and Daily COVID-19 Effective

496   Reproductive Number (R) in South Africa. 2020; published online May 27.

497   https://www.nicd.ac.za/wp-content/uploads/2020/05/The-Initial-and-Daily-COVID-19-

498   Effective-Reproductive-Number-R-in-South-Africa-002.pdf (accessed June 24, 2020).

499   12 Statistics South Africa. Mid-year population estimates 2019.

500   http://www.statssa.gov.za/publications/P0302/P03022019.pdf (accessed Sept 7, 2020).

501   13 National Institute for Communicable Diseases. COVID-19 Testing Summary. 2020; published

502   online May 23. https://www.nicd.ac.za/wp-content/uploads/2020/05/NICD-COVID-19-Testing-

503   Summary_-Week-21-2020-007.pdf (accessed June 24, 2020).

504   14 National Department of Health, South Africa. COVID-19 Public Health Response. 2020;

505   published online April 10. https://sacoronavirus.co.za/2020/04/11/covid-19-public-health-

506   response/ (accessed June 24, 2020).

507   15 Province of KwaZulu-Natal, Department of Health. Annual Performance Plan 2019/20-

508   2021/22. 2019. http://www.kznhealth.gov.za/app/APP-2019-20.pdf (accessed June 24,

509   2020).

510   16 Craig J, Kalanxhi E, Hauck S. National estimates of critical care capacity in 54 African

511   countries. Public and Global Health, 2020 DOI:10.1101/2020.05.13.20100727.

512   17 Reddy KP, Gupta-Wright A, Fielding KL, *et al.* Cost-effectiveness of urine-based tuberculosis

513   screening in hospitalised patients with HIV in Africa: a microsimulation modelling study.

514   *Lancet Glob Health* 2019; **7**: e200–8.

515   18 Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, *et al.* Cost-effectiveness of cervical-cancer

516   screening in five developing countries. *N Engl J Med* 2005; **353**: 2158–68.

517   19 Centre for the Mathematical Modelling of Infectious Disases, London School of Hygiene and

518   Tropical Medicine. COVID-19 Estimates for South Africa. 2020; published online June 22.

519   https://epiforecasts.io/covid/posts/national/south-africa/ (accessed June 24, 2020).

520   20 Siedner MJ, Harling G, Reynolds Z, *et al.* Social distancing to slow the US COVID-19

521   epidemic: Longitudinal pretest-posttest comparison group study. *PLoS Med* 2020; **17**:

522   e1003244.

523   21 National Institute for Communicable Diseases, South Africa. COVID-19 Testing Summary.

524   NICD. 2020; published online March 2. https://www.nicd.ac.za/wp-

525   content/uploads/2020/08/COVID-19-Testing-Summary-Week-34-2020.pdf (accessed Sept 2,

526   2020).

527   22 Shapiro AE, Variava E, Rakgokong MH, *et al.* Community-based targeted case finding for

528   tuberculosis and HIV in household contacts of patients with tuberculosis in South Africa. *Am*

529   *J Respir Crit Care Med* 2012; **185**: 1110–6.

530   23 Legrand J, Grais RF, Boelle PY, Valleron AJ, Flahault A. Understanding the dynamics of

531   Ebola epidemics. *Epidemiol Infect* 2007; **135**: 610–21.

532   24 Abdool Karim SS. The South African response to the pandemic. *N Engl J Med* 2020; **382**:

533   e95.

534   25 Blendon RJ, Koonin LM, Benson JM, *et al.* Public response to community mitigation

535   measures for pandemic influenza. *Emerg Infect Dis* 2008; **14**: 778–86.

536   26 Lewnard JA, Liu VX, Jackson ML, *et al.* Incidence, clinical outcomes, and transmission

537   dynamics of severe coronavirus disease 2019 in California and Washington: prospective

538   cohort study. *BMJ* 2020; **369**: m1923.

539   27 Docherty AB, Harrison EM, Green CA, *et al.* Features of 20 133 UK patients in hospital with

540   covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective

541   observational cohort study. *BMJ* 2020; **369**: m1985.

542   28 Boulle A, Davies M-A, Hussey H, *et al.* Risk factors for COVID-19 death in a population

543   cohort study from the Western Cape Province, South Africa. *Clin Infect Dis* 2020; published

544   online Aug 29. DOI:10.1093/cid/ciaa1198.

545   29 del Rio C. COVID-19 in Persons Living with HIV — What Do We Know Today? *NEJM J*

546   *Watch* 2020; **2020**. DOI:10.1056/nejm-jw.NA52137.

547   30 Yang Y, Yang M, Shen C, *et al.* Evaluating the accuracy of different respiratory specimens in

548   the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections.

549   Infectious Diseases (except HIV/AIDS), 2020 DOI:10.1101/2020.02.11.20021493.

550   31 Wang W, Xu Y, Gao R, *et al.* Detection of SARS-CoV-2 in different types of clinical

551   specimens. *JAMA* 2020; **323**: 1843–4.

552   32 Netcare Hospitals. Netcare Tariffs. 2016. https://www.netcarehospitals.co.za/ (accessed June

553   10, 2020).

554   33 Mahomed S, Mahomed OH. Cost of intensive care services at a central hospital in South

555   Africa. *S Afr Med J* 2018; **109**: 35.

556

557 **TABLES**
558
559 **Table 1. Input parameters for a model-based analysis of COVID-19 intervention strategies in KwaZulu-Natal, South Africa.**

Parameter	Base Case Value (Range)	Source
Cohort Characteristics		
Age distribution, %		12
0-19y	40·26	
20-59y	51·48	
≥60y	8·26	
Natural History		
Proportion in each health state at model start, %		Asm.
Susceptible	99·900	
Infected		
Pre-infectious latency	0·030	
Asymptomatic	0·030	
Mild/moderate disease	0·030	
Severe disease	0·005	
Critical disease	0·005	
Recuperation after critical disease	0·000	
Recovered	0·000	
Transmission		
Probability of onward transmission, daily, stratified by health state*		See Appendix
Asymptomatic	0·1556	
Mild/moderate disease	0·1266	
Severe disease	0·0088	
Critical disease	0·0070	
Recuperation after critical disease	0·0088	
Effective reproductive number (R_e, range)	1·5 (1·1-2·6)	11

560
561
562
563
564

565 **Table 1, continued.**

PCR Testing		
Sensitivity†, nasopharyngeal specimen, % (range)	70 (50-90)	[30,31]
Specificity, nasopharyngeal specimen, %	100	Asm.
Cost, 2019 US$ (range)	26 (13-52)	AHRI
Time to result return and action, days (range)	5 (1-7)	AHRI
Resource Utilization		
Resources available per 11,000,000 people, n		
Hospital beds	26,220	[14]
ICU beds	748	[14]
Isolation centre beds	As needed, no capacity limitation	Asm.
Quarantine centre beds	As needed, no capacity limitation	Asm.
Cost, per person, 2019 US$ (range)		
Hospital bed, daily	165 (83-330)	[32]
ICU bed, daily	2,059 (1,030-4,118)	[33]
Contact tracing/mass symptom screen, per instance	3 (2-6)	AHRI
Isolation centre bed, daily	44 (22-88)	AHRI
Quarantine centre bed, daily	37 (19-74)	AHRI

566

567 COVID-19: coronavirus disease 2019. y: years. Asm.: assumption. PCR: polymerase chain reaction. US$: United States dollars. ICU:

568 intensive care unit. AHRI: Africa Health Research Institute (KwaZulu-Natal, South Africa; personal communication).

569

570 Values indicated are those applied in the base case analyses or, in parentheses, the ranges evaluated in sensitivity analysis.

571 *These values reflect transmission probabilities in a scenario in which R_e is 1·5.

572 †Test sensitivity does not vary by disease stage, except that it is 0% in the pre-infectious latency phase.

Table 2. Model-projected life-years lost, healthcare costs, and cost-effectiveness of COVID-19 intervention strategies in KwaZulu-Natal, South Africa.

Effective reproduction number (R_e)	Strategy	Total life-years lost,* n	Healthcare costs over 360 days, US$[†]	ICER, US$/YLS[‡]
1·5	HT	450,940	437,000,000	--
	HT+CT+IC+MS+QC	27,220	581,000,000	340
	HT+CT	322,970	588,000,000	DOMINATED
	HT+CT+IC+MS	60,930	668,000,000	DOMINATED
	HT+CT+IC	128,890	780,000,000	DOMINATED
	HT+CT+IC+QC	60,190	965,000,000	DOMINATED
1·2	HT+CT+IC+QC	3,890	139,000,000	--
	HT+CT+IC	6,850	141,000,000	DOMINATED
	HT+CT+IC+MS	4,260	183,000,000	DOMINATED
	HT+CT+IC+MS+QC	2,040	190,000,000	27,590
	HT+CT	32,040	276,000,000	DOMINATED
	HT	97,600	393,000,000	DOMINATED

COVID-19: coronavirus disease 2019. ICU: intensive care unit. US$: United States dollars. ICER: incremental cost-effectiveness ratio. YLS: year-of-life saved. HT: healthcare testing. CT: contact tracing within households. IC: isolation centre. MS: mass symptom screen. QC: quarantine centre. DOMINATED: strong dominance, resulting in more life-years lost and higher costs than an alternative strategy.

Strategies are listed in order of ascending costs, per convention of cost-effectiveness analysis. The cost-effective strategy is highlighted in light grey in each R_e scenario. The displayed life-years and costs are rounded, but the ICER was calculated with non-rounded life-years and costs.

*We assumed that each death results in 16·8 life-years lost, on average, based on our derivation (appendix).

[†]This reflects costs to the healthcare sector.

‡The ICER is the difference between two strategies in costs divided by the difference in undiscounted life-years (16·8 YLS per averted COVID-19 death, see appendix p.5-6). We considered a strategy cost-effective if its ICER was less than US$3,250/YLS.[10] When we used life-years discounted 3%/year (12·5 discounted YLS per averted COVID-19 death), cost-effectiveness interpretations were unchanged: in the R_e=1·5 scenario, *HT+CT+IC+MS+QC* remained cost-effective with ICER $460/YLS compared with *HT*; in the R_e=1·2 scenario, *HT+CT+IC+MS+QC* had ICER $37,210/YLS compared with *HT+CT+IC+QC*.

573

574 **Table 3. Model-projected resource utilization of COVID-19 intervention strategies in KwaZulu-Natal, South Africa.**

Effective reproduction number (R_e)	Strategy	Cumulative PCR tests performed over 360 days, n	Peak daily resource use, n				
			PCR tests	Hospital beds (non-ICU)	ICU beds*	Isolation centre beds	Quarantine centre beds
1·5	HT	1,527,450	14,820	4,690	748	--	--
	HT+CT+IC+MS+QC	3,904,230	12,900	640	341	12,380	18,140
	HT+CT	5,951,180	31,050	3,440	748	--	--
	HT+CT+IC+MS	4,639,280	16,930	1,320	715	21,260	--
	HT+CT+IC	4,904,010	19,340	1,930	748	30,510	--
	HT+CT+IC+QC	4,478,770	16,710	1,380	737	26,710	39,470
1·2	HT+CT+IC+QC	2,963,280	9,870	590	363	1,840	3,110
	HT+CT+IC	3,025,260	9,870	590	363	1,620	--
	HT+CT+IC+MS	3,159,950	10,520	570	396	1,510	--
	HT+CT+IC+MS+QC	3,120,800	10,520	570	396	1,860	3,480
	HT+CT	3,647,570	12,450	770	506	--	--
	HT	766,140	4,440	1,680	748	--	--

COVID-19: coronavirus disease 2019. PCR: polymerase chain reaction. ICU: intensive care unit. HT: healthcare testing. CT: contact tracing within households. IC: isolation centre. MS: mass symptom screen. QC: quarantine centre.

Strategies are listed in order of ascending costs as indicated in table 2, per convention of cost-effectiveness analysis. The cost-effective strategy is highlighted in light grey in each R_e scenario.

*The total number of available ICU beds was 748.

575 **FIGURE LEGENDS**

576

577 **Figure 1. Cost-effectiveness efficiency frontier: COVID-19 intervention strategies in**

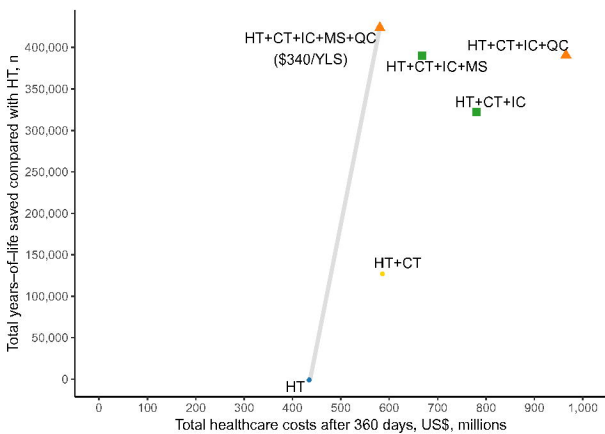578 **KwaZulu-Natal, South Africa.**

579

580 COVID-19: coronavirus disease 2019. HT: healthcare testing. CT: contact tracing within

581 households. IC: isolation centre. MS: mass symptom screen. QC: quarantine centre.

582

583 Model results are shown for an effective reproduction number of 1·5. Strategies that are below the

584 line are dominated – i.e., an inefficient use of resources compared with other strategies. For non-

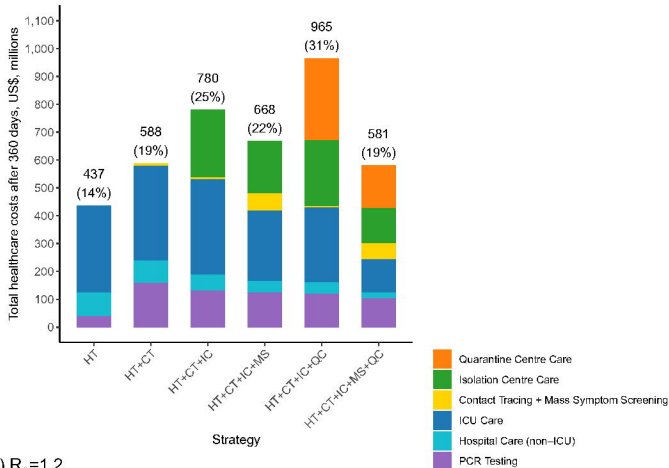585 dominated strategies, ICERs are shown below the strategy label.

586

587

588 **Figure 2. Budget impact analysis: contributors to healthcare costs of COVID-19**

589 **intervention strategies in KwaZulu-Natal, South Africa.**

590

591 SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. COVID-19: coronavirus disease

592 2019. R_e: effective reproduction number. HT: healthcare testing. CT: contact tracing within

593 households. IC: isolation centre. MS: mass symptom screen. QC: quarantine centre.

594

595 Panel A shows results for an epidemic with R_e=1·5, and Panel B shows results for an epidemic

596 with R_e=1·2. The figures show the total and component COVID-19-related healthcare costs, from

597 a health sector perspective, associated with different intervention strategies when applied to the

598 entire KwaZulu-Natal population of 11 million people. The costs are derived from model-generated

599 results. Percentages in parentheses represent the proportion of the 2019 KwaZulu-Natal

600 Department of Health budget.

Total years-of-life saved compared with HT, n (y-axis) vs. Total healthcare costs after 360 days, US$, millions (x-axis)

HT+CT+IC+MS+QC ($340/YLS)

HT+CT+IC+QC

HT+CT+IC+MS

HT+CT+IC

HT+CT

HT

(A) R_e=1.5

(B) R_e=1.2