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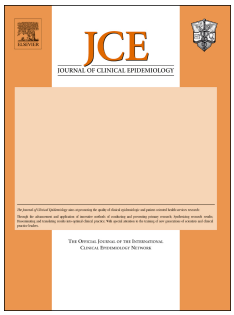

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An evaluation of the eCOVID19 Recommendation Map identified diverging Clinical and Public Health guidance

Zil H. Nasir,[a,b] Dominik Mertz,[a,c] Robby Nieuwlaat,[a] Nancy Santesso,[a,b] Tamara Lotfi,[a,b] Ashley Motilall,[a,b] Lorenzo Moja,[d] Lawrence Mbuagbaw,[a,e] Miloslav Klugar,[f,g] Alexis F. Turgeon,[h,i] Joseph L. Mathew[j], Carlos Canelo-Aybar,[k,l] Kevin Pottie,[m] Omar Dewidar,[n] Miranda W. Langendam,[o] Alfonso Iorio,[a,c] Gunn Elisabeth Vist,[p] Joerg J. Meerpohl,[q,r] Signe Flottorp,[p,s] Tamara Kredo,[t,u] Thomas Piggott,[a,b] Micayla Mathews,[a,b] Amir Qaseem,[v] Derek K. Chu,[a,c] Peter Tugwell,[n,w] Jitka Klugarová,[f,g], Harrison Nelson,[x] Heba Hussein,[y] Jozef Suvada[z], Ignacio Neumann,[a,aa] Holger J. Schünemann[a,b,c,r,ab] for the eCOVID-19 recommendations map Collaborators

a. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton (ON), Canada
b. Michael G. DeGroote Cochrane Canada and GRADE Centre, McMaster University, Hamilton (ON), Canada
c. Department of Medicine, McMaster University, Hamilton (ON), Canada
d. Department of Biomedical Sciences for Health, University of Milan, Italy
e. Biostatistics Unit/The Research Institute, St Joseph's Healthcare, Hamilton (ON), Canada
f. Czech National Centre for Evidence-Based Healthcare and Knowledge Translation (Cochrane Czech Republic, Czech EBHC: JBI Center of Excellence, Masaryk University GRADE Center), Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic
g. Institute of Health Information and Statistics of the Czech Republic, Palackého náměstí 4, 128 01 Prague 2, Czech Republic
h. Department of Anesthesiology and Critical Care Medicine, Division of Critical Care Medicine, Université Laval, Québec City (QC), Canada
i. Population Health and Optimal Health Practices Research Unit, CHU de Québec – Université Laval Research Center, Québec City (QC), Canada
j. Postgraduate Institute of Medical Education and Research, Chandigarh, India
k. Iberoamerican Cochrane Centre - Department of Clinical Epidemiology and Public Health, Biomedical Research Institute Sant Pau (IIB Sant Pau), Barcelona, Spain
l. CIBER de Epidemiología y Salud Pública (CIBERESP), Spain
m. Bruyere Research Institute, Centre for Studies in Family Medicine, Western University, London (ON), N6A 3K7, Canada
n. School of Epidemiology and Public Health, University of Ottawa, Canada; Bruyere Research Institute, Ottawa, Canada
o. Amsterdam University Medical Centers, location Academic Medical Center, University of Amsterdam, Amsterdam Public Health research institute, Meibergdreef 9, 1105AZ, Amsterdam, The Netherlands

p. Norwegian Institute of Public Health, P. O. Box 222 Skøyen, 0213 Oslo, Norway
q. Institute for Evidence in Medicine, Medical Center & Faculty of Medicine, University of Freiburg, Freiburg, Germany
r. Cochrane Germany, Cochrane Germany Foundation, Freiburg, Germany
s University of Oslo, P.O. Box 1130 Blindern 0318, Oslo, Norway
t. Cochrane South Africa, South African Medical Research Council, Cape Town, South Africa
u. Division of Clinical Pharmacology, Department of Medicine, and Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University, Cape Town, South Africa
v. American College of Physicians, Philadelphia, Pennsylvania, USA
w. Department of Medicine, University of Ottawa, Ottawa (ON), K1H 8M5, Canada
x. Faculty of Health Sciences, Queen's University, 18 Barrie Street, Kingston (ON), K7L 3N6, Canada
y. Department of Oral Medicine and Periodontology, Faculty of Dentistry, Cairo University, Cairo, Egypt
z. Departments of Science and International Studies, St. Elizabeth University of Public Health and Social Science, Bratislava, Slovak Republic
aa. Department of Internal Medicine, Pontificia Universidad Catolica de Chile, Avenida Libertador General Bernardo O'Higgins 340, Santiago, Chile
ab. Dipartimento di Scienze Biomediche Humanitas University, Milan, Italy

Corresponding author: Holger Schünemann, Michael G DeGroote Cochrane Canada and McMaster GRADE centres; Department of Health Research Methods, Evidence and Impact, McMaster University, HSC-2C, 1280 Main St West; Hamilton, ON L8N 3Z5, Canada; Tel: +1 9055259140 E-mail: schuneh@mcmaster.ca

Abstract:

Objective: To describe divergence between actionable statements issued by COVID-19 guideline developers catalogued on the "COVID-19 Recommendations and Gateway to Contextualization" platform.

Study Design and Setting: We defined divergence as at least two comparable actionable statements with different explicit judgements of strength, direction or subgroup consideration of the population or intervention**.** We applied content analysis to compare guideline development methods for a sample of diverging statements and to evaluate factors associated with divergence.

Results: Of the 138 guidelines evaluated, 85 (62%) contained at least one statement that diverged from another guideline. We identified 223 diverging statements in these 85 guidelines. We grouped statements into 66 clusters. Each cluster addressed the same population, intervention, and comparator group or just similar interventions. Clinical practice statements were more likely to diverge in explicit judgment of strength or direction compared to public health statements (Cramer's V = 0.7, Fisher's exact test; P <0.001). Statements were more likely to diverge in strength than direction. Date of publication, utilized evidence, interpretation of evidence, and contextualization considerations were associated with divergence.

Conclusion: More than half of the assessed guidelines issued at least one diverging statement. This study helps understanding the types of differences between guidelines issuing comparable statements and factors associated with their divergence.

Keywords: COVID-19, Divergence, Discordance, GRADE, Guidelines, Recommendations

Running Title: An evaluation of the eCOVID19 Recommendation Map identified diverging Clinical and Public Health guidance

Abbreviations:

ACTT-1: Adaptive COVID-19 Treatment Trial (ACTT-1)

ADOLOPMENT: Adopt, Adapt, De Novo Synthesis

ACOEM: American College of Occupational and Environmental Medicine

CDC: Centers for Disease Control and Prevention

COVID-19: The Coronavirus Disease 2019

ECDC: European Centers for Disease Control and Prevention

EtD: Evidence to Decision

GRADE Grading of Recommendations, Assessment, Development and Evaluation

IDSA: Infectious Disease Society of America

IPC: Infection Prevention and Control

NIH: National Institute of Health

NICE: National Institute of Health Care Excellence

PICO: Population Intervention Comparator Outcome

PHAC: Public Health Agency of Canada

WHO: World Health Organization

RecMap: Recommendation Map

SPSS: Statistical Package for the Social Sciences

SSC Surviving Sepsis Campaign

What is new?

What this adds to what is known:

We have developed a new concept, termed divergence, to describe differences in the explicit conclusions or subgroup considerations in clinical and public health guidelines issuing comparable statements and assessed factors associated with their differences.

Key findings:

Divergence was observed in 62% of our included guidelines for the management of COVID-19. Overall, we observed a similar frequency of guidelines diverging in explicit judgements and subgroup considerations but a higher frequency of statements diverging in strength than in direction of the recommended action. We identified associations between differences in methodological and contextualization factors and divergence.

What is the implication, what should change now:

Divergence associated with context-specific considerations can lead to more equitable outcomes between regions with diverse resources. Divergence associated with differences in other methodological steps, may contrarily compromise the overall quality and rigour of the guideline development process. Guideline users may choose to appraise differences in methods, use of evidence, and context-specific criteria to decide which diverging statement is appropriate for their setting.

1.0 Introduction

We have developed a digital platform (COVID-19.recmap.org) classifying and presenting actionable statements published in guidance documents for the management of COVID-19.[1] Alongside each actionable statement issued on this recommendation map (RecMap), we extracted explicit judgements of strength and direction and considerations such as Evidence-to-Decision (EtDs) frameworks when issued by guideline authors to catalogue advice about COVID-19. We noted important discrepancies of the content of the RecMap that may confuse users.

Discrepancies can exist between how those synthesizing and presenting research evidence interpret it. This can lead to confusion amongst evidence users. Studies have specifically evaluated discordance in the results and conclusions of systematic reviews answering equivalent research questions.[2,3] To select between discording reviews, Jadad and colleagues created a decision tool for stakeholders to apply when making clinical or policy decisions which incorporated a comparison of the search strategy and metanalytical processes used for each review.[2] Moja and colleagues utilized this decision tool to examine how frequent duplicate systematic reviews give different results and factors contributing to their discordance.[3] The term discordance has similarly been used in guideline development work to describe differences between the strength of recommendations and their certainty of evidence.[4] Although there is generally agreement among guideline developers, a different concept relates to scenarios when developers create recommendations or other actionable statements[5] that do not align with those from other guideline developers. We define this as divergence of actionable statements. This divergence can lead to confusion among users of recommendations if divergence is unexplained. The primary objective of this study was to

explore the explicit judgements or subgroup considerations of comparable actionable statements on the RecMap that are associated with divergence. Our secondary objective was to investigate factors associated with this divergence.

2.0 Methods

2.1 General approach

There are two classifications of divergence in our study. The first classification is any explicit difference in judgements that influence the strength or direction of two or more actionable statements (Divergence based on guideline developer judgement). When grouping this type of divergence, we used the PICO model to formulate a condition where statements in different guidelines addressed the same population (P) to judge whether a specific intervention (I) or comparator (C) intervention should be implemented. The second classification is any difference within subgroups of the recommendation's target population or in specific elements, e.g., variation in frequencies, dosages, units, or time intervals, of an otherwise similar intervention (Divergence based on subgroup considerations). Examples of the classifications and subclassifications of divergence can be found in **Table 1.**

Table 1. Examples of the type of divergence between guidelines

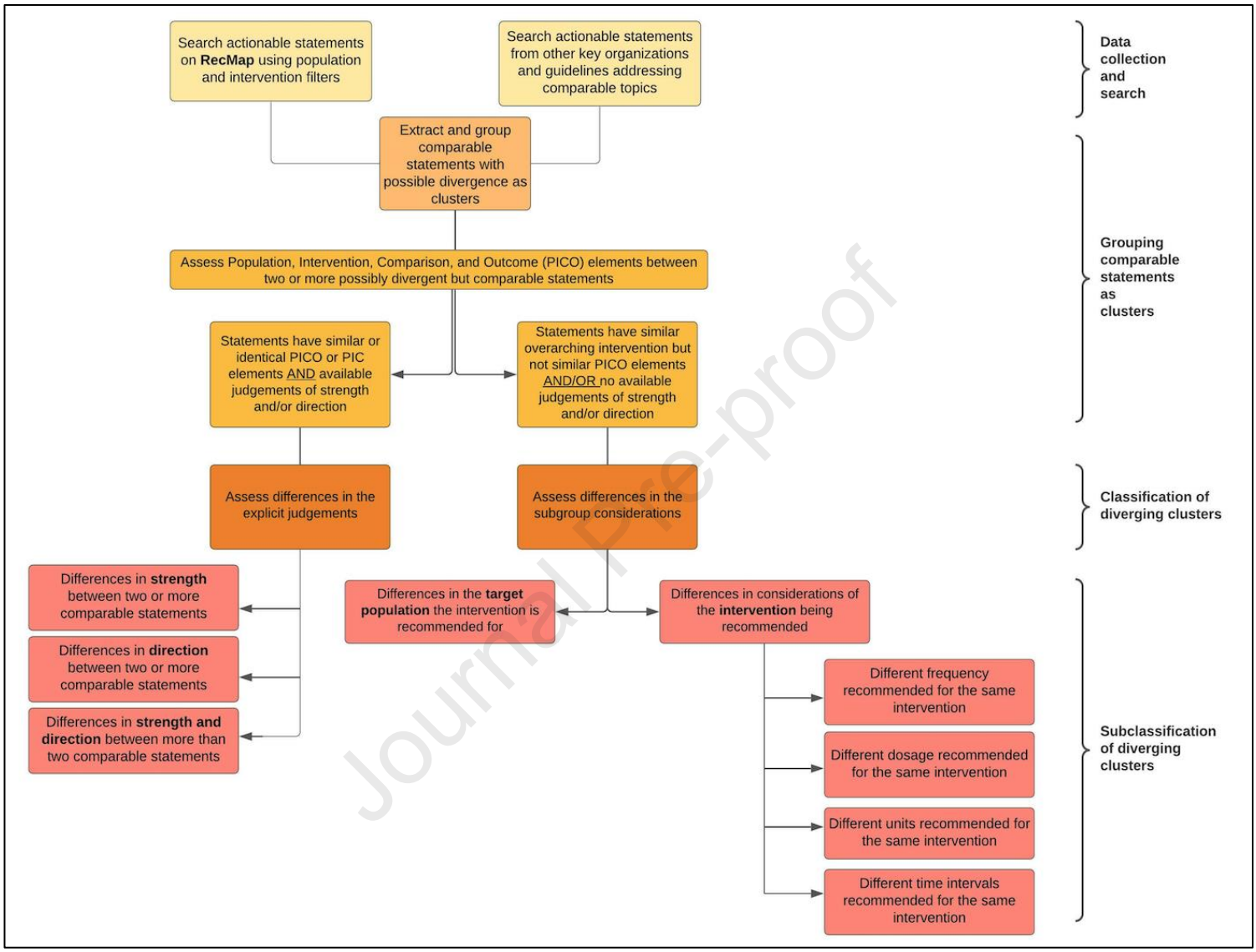
Classification of divergence	Subclassification of divergence	PICO/Intervention	Judgement	Statements from guidelines
Divergence based on guideline developer judgement	Different strength recommended	Gelatin for the acute resuscitation of patients with COVID-19 experiencing shock	Conditional/weak recommendation	**Surviving Sepsis Campaign:** For the acute resuscitation of adults with COVID-19 and shock, we suggest against using gelatin (Jan. 2021)
			Strong recommendation	**World Health Organization:** Do not use hypotonic crystalloids, starches, or gelatins for resuscitation (Jan. 2021)
	Different direction recommended	Bamlanivimab for the treatment of COVID-19 patients	Strong recommendation against the intervention	**Australian National COVID-19 Clinical Evidence Taskforce:** Do not use bamlanivimab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval. (April 2021)
			Recommended in favour of the intervention	**The American College of Occupational and Environmental Medicine:** Bamlanivimab is recommended for the treatment of patients with mild to moderate COVID-19 (Dec. 2020)
Divergence based on subgroup considerations	Population subgroup (different age cut-offs)	The use of facemasks in children in public settings	Not recommended for children younger than two years	**Centres for Diseases Control and Prevention:** Masks should not be put on children younger than two years (April 2021)
			Not recommended for children younger than five years	**World Health Organization:** Children aged five years and under should not be required to wear masks (Dec. 2020)
	Intervention subgroup (different units)	Distancing units between students and teachers in school settings	Recommended one metre distance	**The Technical Advisory Group:** Teachers and support staff should keep at least one metre apart from each other and from students (Sep. 2020)
			Recommended two metres distance	**Office of the Deputy Prime Minister – Ministry for Health:** Keep two metres between staff and students (Aug. 2020)

2.2 Inclusion and exclusion criteria

Figure 1 describes the step- by-step approach we followed. The inclusion criteria for identifying guidance documents to extract relevant recommendations for the RecMap are described in Appendix A.[1] Actionable statements can be divided based on their methodological rigour as formal or informal recommendations **(Appendix A)**.[5] We reviewed both types of statements displayed on the RecMap (COVID19.recmap.org). Our approach to evaluating

divergence was not exhaustive as we included guidelines that were published by key organizations[1] or new actionable statements that could be compared to statements already uploaded to the RecMap through the GRADEpro app **(Appendix A)**. We excluded older versions of updated guidelines, retracted, or archived guidelines at the time of review.

Figure 1: Step-by-step approach to evaluate the classifications and subclassifications of divergence between comparable statements



2.3 Data extraction

2.3.1 Screening: We screened (ZN) and verified (AM) diverging statements published until April 30, 2021, using guidance documents identified for inclusion in the RecMap. For statements already displayed on the RecMap, we applied designated population and intervention filters available for all platform users to group comparable statements for

assessments of divergence. For the remaining documents, we searched for diverging statements in order of guideline topic.

2.3.2 Data extraction: We flagged and subsequently aggregated all diverging statements with the same PICO elements but with different explicit judgements of strength or direction as one type of clusters **(Appendix A)**. We also aggregated actionable statements for the same intervention but with different subgroup considerations as separate clusters**.** For statements with explicit judgements, we coded recommendations on a 4-point ordinal scale using the strength of recommendations as described in the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach **(Appendix A)**.[5,6] When possible, we transformed other grades of recommendations to GRADE in GRADEpro (www.gradepro.org) using a framework applied for the RecMap.[7]

2.4 Statistical analysis

2.4.1 Quantitative analysis: We performed descriptive statistics to assess the frequency of guidelines containing one or more diverging statements from at least one other guideline in our sample. We evaluated the mean and range of diverging statements in our clusters. We conducted a Fisher's exact test to evaluate if there was an observed difference in the type of divergence (i.e., explicit judgement or subgroup consideration) between clinical and public health statements.

2.4.2 Qualitative analysis: We used content analysis to compare differences in guideline development methods between actionable statements grouped in the same cluster. We randomly selected six clusters and purposefully selected an additional six clusters from the World Health Organization (WHO) to achieve information saturation. We developed a

categorization matrix consisting of four major themes using a deductive approach **(Appendix C)** where each theme represented methodological steps in the guideline development process that could be compared between diverging statements. We used Jadad's decision tool[2] and reviewed standardized approaches of guideline development to form themes.[8-10] A single reviewer (ZN) evaluated each guideline in our sample of clusters and recorded information that corresponded with each theme in the matrix. A second reviewer (AM) revised, flagged, and inputted any missing information under each theme for completeness and so all details were available for reproducibility. Any differences between reviewers were noted and resolved through consensus.

3.0 Results

3.1 Summary of guidelines and recommendations

We identified 138 guidelines that allowed us to explore the phenomenon of divergence and explore factors associated with it. Eighty-five (62%) of these guidelines issued at least one diverging statement from another guideline for the same PICO or intervention. We found a total 223 diverging statements in these 85 guidelines that allowed us to evaluate and describe the phenomenon of divergence (out of at least 1330 actionable statements that were available on the RecMap at the time of our evaluation). Ninety-nine (44%) diverging statements were related to clinical interventions and 124 (56%) to public health interventions, respectively. Twenty-four (11%) of these statements used gradings that were readjusted to match GRADE.[7] We observed 115 (52%) statements diverging in explicit judgment of strength or direction and 108 (48%) statements diverging in subgroup considerations of the population or intervention.

3.2 Summary of clusters

We aggregated the 223 statements to 66 clusters. Each cluster represented diverging statements with the same PICO or overarching intervention as described above **(Appendix A)**. Twenty-nine (44%) of the clusters contained clinical interventions and 37 (56%) contained public health interventions **(Table 2)**. The mean number of diverging actionable statements in our clusters was 3.4 (SD: 1.5) and the number of statements per cluster ranged from a minimum of two to a maximum of eight.

Table 2. Summary of diverging recommendation clusters

Overall Summary of Diverging Clusters	(N)	(%)
Number of total diverging clusters	66	100
Number of clinical clusters	29	43.9
Number of non-clinical clusters (i.e., public health)	37	56.1
Summary of Type of Diverging Clusters		
Diverging in the explicit judgment of strength only	19	28.8
Diverging in the explicit judgment of direction only	9	13.6
Diverging in the explicit judgment of strength and direction*	6	9.1
Diverging in subgroup considerations of the population	6	9.1
Diverging in subgroup considerations of the intervention	26	39.4
Summary of Diverging Clusters Across Intervention Groups		
Pharmacological interventions	21	31.8
Other clinical interventions	8	12.1
Infection prevention and control measures	21	31.8
Vaccination-related measures	8	12.1
School-related measures	8	12.1

*At least one recommendation in the cluster diverges in strength, and at least one different recommendation in the same cluster diverges in direction.

3.3 Type of divergence in clusters

Thirty-four clusters diverged in explicit judgment of strength or direction and 32 clusters diverged in subgroup considerations of the population or intervention **(Table 3)**. Of those diverging in judgement, 19 (56%) diverged in strength only and 9 (26%) diverged in direction only. Six (18%) diverged in both, meaning at least one statement diverged in strength and at least one different statement diverged in direction within the same cluster. For clusters diverging in subgroup considerations, 6 (19%) had diverging subgroups for the population and 26 (81%) had diverging subgroups for the intervention.

We found that clinical statements were more often associated with divergence in the judgment of strength or direction whereas public health interventions were associated with divergence in subgroup considerations of the population or intervention (Cramer's V = 0.7, Fisher's Exact Test: 35.8, P<0.001). In our sample, 27 out of 29 (93%) clinical clusters diverged in judgement whereas two diverged in subgroup considerations. Conversely, 81% of the public health clusters diverged in subgroup considerations. Statements for clinical interventions were also more likely to issue explicit judgements of strength or direction whereas statements for public health measures were more likely informal about the strength and direction, which necessitated an assessment of differences in subgroup considerations, likely contributing to our observed differences.

Table 3. Type of divergence within clinical and public health clusters

Health scope	Types of Diverging Clusters					
	Judgement		Subgroup consideration		Total	
	N	%	N	%	N	%
Divergence across overarching health scope						
Clinical Interventions	27	93.1*	2	6.9*	29	43.9
Public Health Interventions	7	18.9†	30	81.1†	37	56.1
Divergence across Intervention groups						
Pharmacological Interventions	19	90.1	2	9.5	21	31.8
Other clinical interventions	8	100.0	0	0.0	8	12.1
Infection Prevention Control measures	5	23.8	16	76.2	21	31.8
Vaccination-related measures	2	25.0	6	75.0	8	12.1
School-Related Measures	0	0.0	8	100.0	8	12.1
Total	**34**	**51.5**	**32**	**48.5**	**66**	**100.0**

* Percentage of the type of diverging clusters within clinical interventions
† Percentage of the type of diverging clusters within public health interventions

3.4 Qualitative findings

Twenty-one guidelines with diverging statements were included in our 12 clusters evaluated for content analysis. We have organized the methodological differences into four major categories **(Table 4)**.

Table 4. Methodological differences between actionable statements in the same cluster

Categories	Clusters
Differences in the date of publication or most recent literature search	3
Differences in the body of evidence for reasons other than the date of publication	6
Differences in the interpretation of evidence and assessments of quality	10
Differences in contextualization considerations including in EtD criteria	4

3.4.1 Differences in the date of publication or most recent literature search

Differences in the date of publication or most recent literature search may explain why some statements omit evidence included in comparable statements from other guidelines. When comparing the Centers for Disease Control and Prevention (CDC), Public Health Agency of Canada (PHAC), and WHO's guidance for cleaning public spaces, we observed differences in the recommended frequency of times surfaces should be cleaned.[11-13] CDC updated their guideline in April 2021 to recommend cleaning most high-touch surfaces in non-healthcare settings once daily based on evidence from Quantitative Microbial Risk Assessment models and other direct studies assessing COVID-19 transmission patterns.[11] In contrast, WHO and PHAC issued their statements in May 2020 and September 2020 respectively. Both guidelines recommended enhanced surface cleaning but do not explicitly state the frequency.[12,13]

3.4.2 Differences in the body of evidence for reasons other than the date of publication

Other guidelines with diverging statements applied different bodies of evidence for reasons other than most recent literature review. One cluster issued diverging statements for delaying the second dose of COVID-19 vaccines that require two complete doses.[14-16] CDC in March, 2021 recognized the limited direct evidence concerning the efficacy and effectiveness of extending the interval beyond 6-weeks to recommend against any further delay.[14] Contrarily, in April, 2021, PHAC recommended delaying the interval by 4-months in the context of limited

vaccine supplies in Canada.[15] Consequently, the National Advisory Committee on Immunization deliberated on whether it was feasible to extend the second dose, so more members of their population are vaccinated. They applied evidence from studies evaluating vaccine effectiveness after one dose and population modelling studies.[15] None of their included studies directly assessed delaying the second dose for a period of 4-months because of insufficient evidence.

3.4.3 Differences in the interpretation of evidence and assessments of quality

Difference in the interpretation and certainty of evidence were evident for remdesivir: WHO issued a conditional recommendation against its use whereas other guidelines issued conditional recommendations favouring its use in patients with moderate to severe COVID-19.[17-24] Most guidelines utilized evidence from the same randomized clinical trials including the ACTT-1[17-24] and WHO Solidarity studies.[17-23] While WHO[17] graded the overall certainty of applied evidence as low, guidelines issued by the National COVID-19 Clinical Taskforce of Australia,[18] Infectious Disease Society of America (IDSA),[19] and National Institute of Health Care Excellence (NICE)[20] graded the certainty of evidence as moderate.

When comparing the balance of effects, WHO concluded there was insufficient evidence to currently prove remdesivir has an effect for patient-important outcomes such as mortality, need for mechanical ventilation, and time to clinical improvement. They balanced this with the high costs, resource requirements, and barriers in low and middle-income countries to recommend against its use.[17] Conversely, the Australian Taskforce concluded that remdesivir has small net benefits or little differences compared to alternative options. This judgement was based on remdesivir's safety profile, probable reduction of death, and probable reduction of serious adverse events.[18] When comparing study outcomes, the Solidarity trial reported no

differences in outcomes of mortality and length of hospital stay.[20] However, the ACTT-1 trial reported improved time to recovery and less percentage of patients progressing to invasive ventilation.[20] Consequently, different interpretation of these studies may be associated with different judgements.

3.4.4 Differences in contextualization considerations including in EtD criteria:

We observed explicit or implicit differences in contextualization considerations **(Appendix C)**. When evaluating CDC's statement on relaxing certain measures for vaccinated travellers, the organization partly considered the American population's values and attitudes towards COVID-19 vaccines in addition to vaccine effectiveness studies.[25] To incentivize vaccination, CDC recommended relaxing certain restrictions for vaccinated populations whereas other organizations acknowledged the limited evidence concerning COVID-19 transmission and its effectiveness to recommend against relaxing restrictions.[26]

Table 5. Simplified Content analysis outcomes of methodological differences within clusters

Organizations	Divergence	Methodological differences between guidelines
Convalescent plasma for the treatment of COVID-19 patients		
Australian Clinical Taskforce; IDSA; NIH; SSC	Strength and direction	**Theme 1: Differences in the date of publication or most recent literature search** • SSC did not use results from RECOVERY trial whereas other organizations did. **Theme 3: Differences in the interpretation of evidence and assessments of quality** • Guidelines had varying gradings of the certainty of evidence.
Gelatin for the acute resuscitation of patients experiencing COVID-19 and shock		
SSC; WHO	Strength	**Theme 3: Differences in the interpretation of evidence and assessments of quality** • Guidelines agree there are unclear benefits. **Theme 4: Differences in contextualization considerations** • Guidelines balanced unclear benefits with high costs.
Immunoglobulins for the treatment of COVID-19 patients		
Australian Clinical Taskforce; NIH;SSC	Strength	**Theme 1: Differences in the date of publication or most recent literature search** • Guidelines applied different evidence based on what was available at the time of publication. **Theme 3: Differences in the interpretation of evidence and assessments of quality**
Ivermectin for the treatment of COVID-19 patients		
Australian Clinical Taskforce IDSA; NIH	Strength and direction	**Theme 2: Differences in the included studies/evidence** • Differences were observed in the included studies between all guidelines. **Theme 3: Differences in the interpretation of evidence and assessments of quality** • All guidelines acknowledged small net benefits and limitations in evidence.
Remdesivir for the treatment of moderate to severe COVID-19 patients		
Australian Clinical Taskforce; ACOEM; IDSA; NIH; NICE; PHAC; SSC; WHO	Direction	**Theme 3: Differences in the interpretation of evidence and assessments of quality** • Differences in certainty of evidence and interpretation of uncertainty were observed between WHO and other guidelines. **Theme 4: Differences in contextualization considerations** • Differences in cost-effectiveness and patient-preferences and values were observed.
Zinc for the treatment of COVID-19 patients		
Australian Clinical Taskforce; NIH	Strength	**Theme 2: Differences in the included studies/evidence** **Theme 3: Differences in the interpretation of evidence and assessments of quality** • Differences were observed in certainty of evidence and interpretation of the uncertainty on statement strength.
Delaying the interval between the first and second dose for COVID-19 vaccines		
CDC; ECDC; PHAC	Subgroup considerations (intervention)	**Theme 2: Differences in the included studies/evidence** **Theme 3: Differences in the interpretation of evidence and assessments of quality** • CDC did not recommend delaying the second dose for more than 6-weeks because of the limited available direct evidence on the effectiveness of the intervention. **Theme 4: Differences in contextualization considerations** • PHAC considered vaccine feasibility concerns to make their statement for the Canadian setting.
Frequency of times to clean surfaces in public settings		
CDC; PHAC; WHO	Subgroup considerations (intervention)	**Theme 1: Differences in the date of publication or most recent literature search** • CDC updated their statement based on availability of new evidence, but other guidelines did not. **Theme 2: Differences in the included evidence/studies**
Minimum age cut-off for wearing facemasks in children' populations		
CDC; PHAC WHO	Subgroup considerations (population)	**Theme 2: Differences in the included evidence/studies** • WHO cited evidence from Influenza studies. CDC cited evidence from single observational study assessing oxygenation levels in children wearing masks. PHAC did not cite explicit evidence.
Mode of birth for pregnant women with COVID-19		
Australian Clinical Taskforce; WHO	Strength	**Theme 2: Differences in the included evidence/studies** **Theme 3: Differences in the interpretation of evidence and assessments of quality** • Guidelines balanced benefits and harms with certainty of evidence to make their final judgements
Rooming mothers with COVID-19 with their newborns after birth		
Australian Clinical Taskforce; WHO	Strength	**Theme 3: Differences in the interpretation of evidence and assessments of quality** • Guidelines balanced benefits and harms with certainty of evidence to make their final judgements
Relaxing certain restrictions for vaccinated travellers/population		
CDC; PHAC; WHO	Direction	**Theme 3: Differences in the interpretation of evidence and assessments of quality** • PHAC and WHO stated there is limited evidence to relax restrictions. CDC considered low rates of asymptomatic infection and possible transmission in vaccinated groups and available data on vaccine effectiveness. **Theme 4: Differences in contextualization considerations** • CDC considered studies on US population attitudes and behaviours towards vaccination.

4.0 Discussion

4.1. Summary of findings

We evaluated the frequency of guidelines containing diverging actionable statements for the management COVID-19 by applying an iterative search, screening and review process using the COVID-19 Recommendations and Gateway to Contextualization RecMap. At the time of evaluation, 62% of the included guidelines contained at least one diverging statement from at least one other guideline. Within these guidelines, we identified 223 total diverging statements. Out content analysis showed differences in methodological factors including date of publication or most recent literature search, utilized evidence, interpretation of evidence and their assessments of quality between guidelines containing comparable diverging statements. We also observed differences in contextualization criteria including judgements of cost-effectiveness and patient values between guidelines. We have developed a meaningful technique for those who need to understand differences between guideline recommendations to categorize the reasons for differences. The results from our study can also be used to clarify misperceptions among decision-makers by promoting transparency in guideline development processes.

4.2 Strengths and limitations

Strengths in our study include the application of a rigorous search strategy to organize actionable statements from guidelines on the RecMap and using two independent reviewers for verification of divergence and content analysis. Nonetheless, we could not quantify the exact number of actionable statements assessed from guidelines not uploaded to the RecMap, but the results suggest that divergence is common and not always explained. Given the large

number of such actionable statements, our approach did not allow evaluating all COVID-19 guidelines or the total number of concordant statements between guidelines, limiting the interpretation of our findings.

4.3 Discussion of quantitative and qualitative findings

4.3.1 Quantitative findings: Overall, we identified a similar frequency of divergence in explicit judgements about the strength and direction and subgroup considerations but a larger frequency of statements diverging in strength than direction. In our assessment, we did not assign direction for statements that did not have explicit judgements. The frequency of statements diverging in direction may be higher than what was suggested in our study if we formulated implicit judgements based on which alternative was selected by organizations in the same cluster. For example, in our cluster for delaying vaccine dosages, CDC and PHAC recommend different time intervals for delaying the administration of the second dose. Because CDC did not explicitly appraise the time intervals that were recommended by PHAC to formulate their judgement, we grouped this cluster as diverging subgroup considerations of the intervention instead of direction despite both organizations recommending alternative intervals.

4.3.2 Qualitative findings: Time constraints, insufficient evidence to inform judgement and additional resource limitations may affect the overall methodological rigour of published guidelines in health emergencies like the COVID-19 pandemic. In some regard, we can attribute divergence associated with differences in the date of most recent literature review and applied evidence to these barriers. Likewise, organizations may have different priorities to update existing statements in their guidelines even when new evidence is available, leading to their

possible omission and subsequently different gradings of certainty or judgement. Nevertheless, these challenges cannot explain divergence between organizations applying equivalent methods and evidence.

4.4 Study implications

4.4.1 Implication for policy and practice: Policy and other decision-makers may choose to utilize our content-analysis themes or adopt existing methods[2,3] by appraising differences in the date of literature review, applied evidence, interpretation of evidence, and context-specific considerations between diverging statements to decide which statements are supported by the best available evidence and will be most appropriate to implement in their setting.

Indeed, divergent recommendations can be based on legitimate contextual reasons. This idea is the core principle behind the GRADE 'adolopment' approach, a process that entails evaluating circumstantial EtD criteria from existing recommendations to decide whether they are appropriate to adopt or adapt in a new context or create new recommendations for better contextualization.[27] Guideline developers can therefore review regional evidence to revaluate judgements of EtD criteria or ultimately change the strength or direction of existing recommendations to reflect the new setting it will be applied. For example, when guideline developers from a low-income region are deciding to adopt or adapt an intervention that is recommended for implementation in a high-income region, they may choose to implement a more cost-effective alternative with similar clinical outcomes instead of the original intervention. This new recommendation will therefore diverge in direction from the original statement but may yield better outcomes in the new setting.

Agreement between guidelines is important in other circumstances. For example, two diverging statements may differ in the direction of the recommendation, and one guideline may issue a strong recommendation. Depending on which alternative option is implemented, inequities could increase between settings if one intervention results in better outcomes than the other. Furthermore, the guideline development process aims to use evidence-informed methods to develop trustworthy statements. Divergence can ultimately affect the quality of these statements, especially when they are associated with the use of outdated evidence, incomplete evidence, or even differences in the interpretation of similar evidence when explanations for these different interpretations are not clarified by guideline authors. In these situations, it would be difficult to justify divergence. This may reduce public trust in the scientific community, which may lead to greater hesitancy to comply with health regulations.[28]

4.4.2 Implications for research: COVID-19 guidelines are being formulated and updated during a period when the evidence to develop actionable statements is constantly evolving. Future studies should assess whether associations of divergence observed in our study are unique to the landscape of the COVID-19 pandemic or observed in other guideline topics. Furthermore, future studies should evaluate if these associations of divergence are linked with causation. If divergence is observed and caused by methodological differences, guideline developers will need to refine their procedures for developing actionable statements. This includes adopting methods, such as living guideline processes[29], to guarantee timely updates of actionable statements to ensure they are supported by the best available evidence.

4.5 Conclusions

We utilized a comprehensive international database to identify and describe differences between comparable statements for COVID-19, a phenomenon that we call divergence. We subsequently examined legitimate and justified methodological differences associated with divergence that can be used to assess causation in future studies.

5.0 Disclosures

5.1 Funding

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5.2 Conflicts of interest

The authors declare no conflicts of interest.

5.3 Acknowledgments

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Appendix A: Completed Methodology

Inclusion and Exclusion criteria:

The RecMap presents actionable statements from guideline literature for the management of COVID-19 at the clinical, policy, and systems level. These include all actionable statements published in guidelines or guidance type documents by key organizations such as the World Health Organization (WHO), Public Health Agency of Canada (PHAC), Centres for Disease Control and Prevention (CDC), European CDC (ECDC), The Association of the Scientific Medical Societies in Germany, National Institute for Health and Care Excellence (NICE), Canadian Task Force on Preventive Health Care (CTFPHC), COVID Network Meta-Analysis Initiative (COVID-NMA), National COVID-19 Clinical Evidence Task Force (Australia), National Institutes of Health (NIH), and the Scottish Intercollegiate Guidelines Network (SIGN).[1] Additionally, the RecMap captures and presents actionable statements from other self-reported guidelines and guideline societies that provide recommendations for COVID-19 by conducting biweekly searches in a list of databases found here.[1] These documents need to meet the criteria of a guideline, which is assessed by two members on the RecMap team.[1] We applied the same inclusion and exclusion criteria as the RecMap to search for diverging statements. Therefore, we excluded all redacted guidelines, archived guidelines, and older versions of updated guidelines by April 30, 2021. We subsequently included all statements uploaded to the RecMap by April 30, 2021. We also reviewed a list of additional guidelines from key organizations or from other guideline literature containing new actionable statements that could be compared to statements already uploaded to the RecMap. These guidelines would otherwise meet the inclusion criteria for the RecMap but were not uploaded at the time of review.

Captured guidelines were reviewed by a member on the team for divergence from February to April 2021. This means there were guidelines captured for the RecMap, that could either be published by a key organization or contain relevant topics at the time of our evaluation for divergence that were not included due to time constraints with the search and upload. Consequently, not all diverging actionable statements and not all guidelines that meet the inclusion criteria for the RecMap have been assessed for this paper.

Types of assessed statements:

Actionable statements on the RecMap and in our study can be classified as formal recommendations and informal recommendations **(Table A1)**. More details about the different classifications and subclassifications of actionable statements can be found here.[2] In general, and for the purpose of this study, formal recommendations are formulated by applying a rigorous guideline development process which entails a literature review to summarize the evidence relevant to the recommendation, an assessment of the quality of that evidence, and an explicit judgement of the recommendations' strength and direction **(Table A2)**.[2] These statements are generally accompanied by Summary of Findings (SoF) tables and evidence-to-decision (EtD) frameworks to transparently summarize and present the evidence to formulate a recommendation.[2] Informal recommendations generally omit some or all the steps in the guideline development process. Hence, the methodology used to produce these statements is often not as rigorous or transparent as that used for formal recommendations. Nonetheless, informal recommendations need to be actionable[2] and can be used by clinicians, policymakers, and program managers to make clinical and public health decisions which is why they were included in our assessment of divergence.

Table A1: Different Classifications of Actionable Statements on the RecMap

Type of Actionable Statement	Explanation of Term
Formal Recommendation	Contain a literature review process, assessment of the certainty of evidence, and provide explicit judgements of the strength and direction
Informal Recommendation	Actionable statements that omit some or all the components of a formal recommendation. They can be further defined as additional guidance statements or good practice statements which have their own subclassifications. For this study, we classified all subclassifications as informal recommendations

Table A2: Grading of the Strength and Direction of Recommendations Based on the GRADE Approach

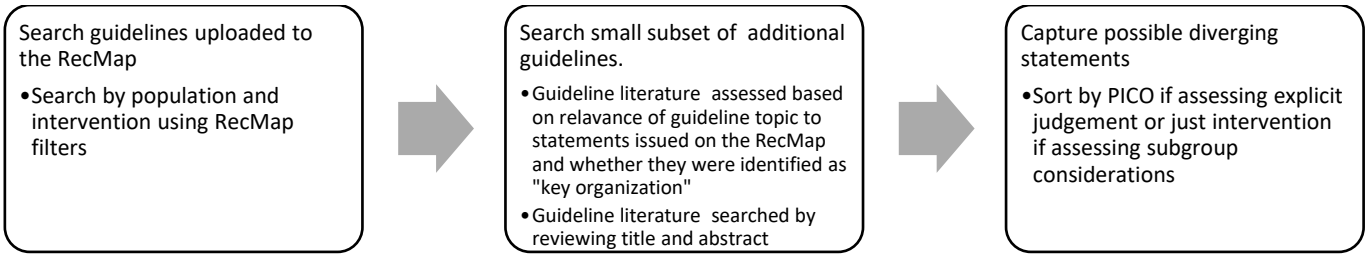
Grading	Recommendation Type
-2	Strong recommendation against the intervention
-1	Conditional/weak recommendation against the intervention
0	Conditional recommendation for either the "intervention or comparator" or recommendation "neither for nor against the intervention"
+1	Conditional/weak recommendation for the intervention
+2	Strong recommendation for the intervention

Search Strategy:

First, we reviewed actionable statements, including formal and informal recommendations from guidelines issued on the RecMap by April 30, 2021. We searched for comparable statements using the population and intervention filters, which is available on the platform to all RecMap users. These filters sort all actionable statements with the same population and intervention codes onto a singular search page. We flagged all potentially divergent statements and captured them in a distinct Excel sheet. Alongside each statement, we extracted the population, intervention, comparator, and outcome groups associated with the actionable statements when they were detailed by guideline authors. If there were no explicit comparator groups, it was assumed to be standard care.

Second, we reviewed actionable statements from guidelines that were not issued on the RecMap but were otherwise published from a key organization or contained topics that were comparable to statements issued on the RecMap. We used key organization websites and an archive of guidance literature organized for the RecMap to search for these documents.[1] We proceeded to sort comparable guidelines by reviewing their title and abstract. Guidelines with similar topics were reviewed together alongside existing actionable statements on the RecMap. Any possibly divergent statement was flagged and inputted on the same Excel sheet as statements flagged directly from the RecMap.

Figure A1: Criteria for capturing guidelines



Classifications of Divergence:

First, we reviewed the PICO elements of each possibly divergent but comparable statements. If comparable statements had similar or equivalent population (P), intervention (I), comparator (C) and at least one outcome (O) group, we grouped them as one type of cluster.

We also included statements that did not explicitly state their assessed outcomes if they shared the remaining PIC elements into the same cluster with statements that had similar PICO elements. Second, we assessed if clusters with the same PICO or PIC elements had explicit judgements of strength and/or direction that can be compared. If they had different explicit judgements, we classified these clusters as divergence in explicit judgements and proceeded to subclassify them as differences in 1) strength, 2) direction, or 3) both. If statements did not have similar PICO or PIC elements or they did not have judgements in strength and/or direction, we proceeded to assess if they had similar overarching interventions. For these statements, we assessed any differences in target population or elements of the same overarching intervention such as frequency, dosage, unit, or interval. Finally, we coded the type of actionable statements, overarching health scope of actionable statements, and the intervention subtype of each group of clusters as nominal data for quantitative analysis **(Table A3)**.

Table A3. Categories for coding actionable statements for quantitative analysis

Categories	Coding Organization for Statements
Type of actionable statement	1. Formal statement **or** 2. Informal statement.
Overarching health scope of the statement	1. Clinical statement **or** 2. Public health statement.
Intervention Subtype	1. Pharmaceutical measure **or** 2. Other clinical measure **or** 3. Infection Prevention and Control (IPC) measure **or** 4. School-related measure **or** 5. Vaccination-related measure.

Appendix A References:

1. Lotfi T, Stevens A, Akl EA, et al. Getting trustworthy guidelines into the hands of decision-makers and supporting their consideration of contextual factors for implementation globally: recommendation mapping of COVID-19 guidelines. J Clin Epidemiol. 2021;135:182-186. doi:10.1016/J.JCLINEPI.2021.03.034
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Appendix B

Table B1: Types of Divergence across intervention clusters:

Cluster	PICO or intervention	Type of Divergence	# of diverging statements in cluster
1	Anakinra for treatment of patients with COVID-19	Population subgroup	4
2	Antibiotics as a prophylactic for patients with mild COVID-19	Strength	2
3	Antipyretics strategies for patients with COVID-19	Strength	2
4	Bamlanivimab for treating patients with COVID-19	Direction	4
5	Baricitinib for treatment of patients with COVID-19	Intervention subgroup	2
6	Colchicine for treatment of patients with COVID-19	Direction	3
7	Convalescent plasma for treatment of patients with COVID-19	Strength and direction	5
8	Crystalloids vs. colloids for acute resuscitation of adults with COVID-19 and shock	Strength	2
9	Dexamethasone for hospitalized patients on supplemental oxygen	Strength	5
10	ECMO for patients with COVID-19 and refractory hypoxemia	Direction	2
11	Gelatin for acute resuscitation of adults with COVID-19 and shock	Strength	2
12	Heparin for treatment of critically ill patients with COVID-19	Strength	4
13	Hydroxychloroquine for treatment of patients with COVID-19	Strength and direction	8
14	Immunoglobulin for treatment of patients with COVID-19	Strength	3
15	Ivermectin for treatment of patients with COVID-19	Strength and direction	3
16	Nitric Oxide in mechanically ventilated adults with COVID-19	Strength	2
17	Norepinephrine as a first-line agent for patients with COVID-19 and shock	Strength	2
18	Higher PEEP Strategy for mechanically ventilated adults with COVID-19	Strength	4
19	Prone positioning in non-intubated patients with COVID-19	Strength and direction	4
20	Prone positioning in intubated patients with COVID-19	Strength	4
21	Pulmonary vasodilator for ventilated adults with COVID-19 and ARDS	Strength	2
22	Remdesivir for moderate to severe patients with COVID-19	Direction	8
23	Remdesivir for severe to critical patients with COVID-19	Strength and Direction	3
24	Sarilumab for treatment of patients with COVID-19	Strength	2
25	Serologic testing for diagnostics of current COVID-19 infection	Strength	4
26	Tocilizumab for treatment of patients with severe or critical COVID-19	Strength and direction	7
27	Vitamin C for treatment of patients with COVID-19	Direction	2
28	Vitamin D for treatment of patients with COVID-19	Direction	2
29	Zinc for treatment of patients with COVID-19	Strength	2
30	Alcohol percentage required for disinfecting surfaces	Intervention subgroup	3
31	Antibody testing for lab confirmation purposes	Intervention subgroup	5
32	AstraZeneca vaccine for adults	Population subgroup	4
33	Breastfeeding practices for mothers with COVID-19	Strength	5
34	Broader contact tracing	Population subgroup	3
35	clean surfaces in public settings (frequency)	Intervention subgroup	3
36	Cohorting classrooms during COVID-19 outbreak	Intervention subgroup	3
37	Cohorting suspected patients together in hospitals	Direction	3
38	Delaying interval for the second dosage of COVID-19 vaccines	Intervention subgroup	3
39	Discarding face mask after extended use in hospital settings	Intervention subgroup	2
40	Distancing b/w students and teachers in schools	Intervention subgroup	6
41	Hand hygiene practices (percentage of alcohol-based hand rub)	Intervention subgroup	4
42	Isolating COVID-19+ children from schools	Intervention subgroup	3
43	Masking practices for vaccinated groups	Intervention subgroup	2
44	Use of Face masks in children in public settings	Population subgroup	2
45	Use of Face masks in children in school settings	Population subgroup	7
46	Mode of Birth for COVID-19 mothers (standard vs. alternative)	Strength	2
47	N95 masks for treating non-ventilated patients in hospital settings	Direction	4
48	Patient criteria for discharge	Intervention subgroup	3
49	Physical distancing units for long-term care staff	Intervention subgroup	2
50	Physical distancing units in hospitals	Intervention subgroup	3
51	Physical distancing units in schools	Intervention subgroup	7
52	PPE use for adult staff members in schools	Intervention subgroup	4
53	PPE use for long term care home staff members	Intervention subgroup	2
54	Quarantining close contacts	Population subgroup	3
55	Quarantining period for travellers after returning from travel	Intervention subgroup	3

56	Reduced restrictions for travellers who are vaccinated	Direction	3
57	Quarantining time requirements for vaccinated individuals	Intervention subgroup	2
58	Reuse of medical masks in hospital settings	Intervention subgroup	3
59	Rooming COVID-19 positive mothers with their newborns in the hospital	Strength	2
60	School activity closures during COVID-19	Intervention subgroup	4
61	School closure requirements during COVID-19	Intervention subgroup	3
62	Self-monitoring symptom requirements for healthcare workers	Intervention subgroup	2
63	Social distancing measure requirements for vaccinated populations	Intervention subgroup	3
64	Vaccinating Immunocompromised groups with COVID-19 vaccines	Intervention subgroup	3
65	Vaccinating lactating women with COVID-19 vaccines	Strength	3
66	Vaccinating pregnant women with COVID-19 vaccines	Intervention subgroup	5

Table B2: Captured guideline organizations or panels with diverging actionable statements

1. American Academy of Pediatrics
2. American Association for Clinical Chemistry
3. American College of Occupational and Environmental Medicine
4. American College of Rheumatology
5. American College of Obstetricians and Gynecologists
6. Australian National COVID-19 Clinical Taskforce
7. Australian Technical Advisory Group on Immunization
8. Brazilian Association of intensive care medicine etc.
9. Centres for Disease Control and Prevention
10. CHEST Panel
11. Dutch Working Party on Antibiotics
12. Department of Education and Skills
13. European Association for Hemophilia
14. European Alliance of Associations for Rheumatology
15. European Centres for Disease Control and Prevention
16. European Academy of Allergy and Clinical Immunology
17. French Pediatric Society
18. Infectious Disease Society of America
19. Indian Academy of Pediatrics
20. Indian Society of Critical Care Medicine
21. National Advisory Committee on Immunization
22. National Health Service
23. National Institute of Healthcare and Excellence
24. National Institute of Health
25. Pan American Health Organization
26. Panel of Latin American Experts by Roche Diagnostics
27. Public Health Agency of Canada
28. Office of the Deputy Prime Minister – Ministry for Health
29. Rapid Review Group
30. Spanish Association of Pediatrics
31. Surviving Sepsis Campaign
32. Technical Advisory Group (UNICEF and WHO)
33. UK Department of Education
34. US Environmental Protection Agency
35. World Health Organization

Appendix C

Table C1: Simplified version of content analysis extraction

Guideline	Methods	Date	Included studies	Main outcomes assessed	Certainty of evidence	EtD Criteria, applied evidence, and contextualization considerations	Conflicts and disagreements
1. Convalescent Plasma for the treatment of COVID-19							
Australian guidelines for the clinical care of people with COVID-19	GRADE	Update: 21/4/2021	9 RCTs	15	Moderate	**Balance of effects:** No difference between intervention and standard care for incidence of death, requirement of mechanical ventilation or non-invasive ventilation, or discharge from hospital **Certainty of evidence:** Moderate due to serious imprecision for mortality due to wide confidence intervals and non-invasive ventilation due to reliance on a single study. Certainty was high for invasive mechanical ventilation and number of patients discharged from hospital **Values and preferences:** substantial variability is expected or uncertain – panel believes some patients may prefer to wait due to uncertainty of benefits and harms ratio while others opt for treatment **Resources:** Important issues or potential issues not investigated **Equity:** Important issues or potential issues not investigated **Acceptability:** Important issues or potential issues not investigated **Feasibility:** Important issues or potential issues not investigated	No reported conflicts
Surviving Sepsis Campaign Guidelines on the Management of Adults with	GRADE	First update: 29/1/2021	4 RCTs	2	Low	**Is the problem a priority?** Yes **Balance of effects:** Probably favours the comparison – no clear evidence of benefits,	Small conflict disclosures 88% of guideline panel members agreed with the recommendation

Coronavirus Disease 2019 (COVID-19) in the ICU: First Update						unclear adverse effects, and low-quality evidence **Desirable effects:** trivial (or small) **Undesirable effects:** trivial (or small) **Quality of evidence:** Low due to serious indirectness, serious imprecision, and high risk of bias **Values:** Probably no important uncertainty or variability – trade-off between mortality and adverse events but most patients would value improved survival, so variation is likely small **Resources required:** moderate costs (moderate to large costs) **Equity:** Probably reduced due to increase in required resources and low supplies **Acceptability:** Probably no [not acceptable] **Feasibility:** Probably yes [Feasible]	but 12% think they should issue no recommendation because of insufficient evidence
Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19	GRADE	Updated guideline: 14/4/2021 Literature search: 31/3/2021	11 RCT and one large (n=20,000) single-arm registry study	5	Low	No EtD table has been completed. **Desirable effects (benefits):** Failed to show or exclude benefits or detriment effects on mortality from RCT evidence for hospitalized patients. May not reduce need for mechanical ventilation in hospitalized patients. **Undesirable effects:** 4 trials could not exclude an increase in mild-to-serious adverse events for hospitalized patients but low certainty of evidence. Other adverse events reported in safety study **Certainty of evidence:** low due to concerns with risk of bias and imprecision in hospitalized patients. **Conclusions:** Additional research is needed to determine	COI ensured no potentially relevant conflicts for most of the panel. Chairs have no conflicts

						whether there is a benefit or the treatment and if treatment effects are based on severity and timing of disease course.	
National Institute of Health – Coronavirus Disease 2019 (COVID-19) Treatment Guideline	NIH grading system	Guideline update: 27/4/2021 Recommendation update: 21/4/2021	11 trials and 1 retrospective study	5-6	Strong evidence based on one or more RCT with no severe limitations	No EtD criteria completed **Benefits:** No significant differences in primary endpoint and did not meet secondary endpoints in RECOVERY trial. Data from other randomized clinical trials have not demonstrated efficacy for treating hospitalized patients **Undesirable effects:** Infrequent serious adverse reaction and consistent with risks associated with plasma infusions for other indications **Conclusions:** Results from adequately powered, well-designed and well-conducted RCT are needed to determine role of convalescent plasma in treatment of hospitalized patients	Financial disclosure between panel members
2. Gelatin for the acute resuscitation of patients with COVID-19 experiencing shock							
Surviving Sepsis Campaign Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU – Original and First Update documents reviewed	GRADE	First update: 29/1/2021 Last literature search: March 2020	Systematic review of 69 RCTs (n=30,020) – 6 trials assessed use of gelatin (n=1698)	1	Low	No EtD completed **Benefits:** Unclear – No statistically significant difference in all-cause mortality between alternatives **Cost-effectiveness:** Costs of gelatin is higher than alternative options like crystalloids **Rationale:** Panel based recommendation on indirect evidence. Balanced absence of benefits and higher costs to make recommendation against the intervention	Small conflict disclosures
World Health Organization – Clinical Management of COVID-19 Patients: Living Guidance, 25 January 2021	GRADE	25/01/2021	1 systematic review and 1 previous guideline for management of sepsis and septic shock	1	No certainty of evidence	No EtD completed **Rationale:** The effects of gelatin are unclear, but they are more expensive than crystalloids (alternative option)	No conflicts of interest were identified

3. Immunoglobulins for the treatment of COVID-19							
Australian guidelines for the clinical care of people with COVID-19	GRADE	21/4/2021	1 Random placebo controlled double-blind clinical trial	2	Very low	**Undesirable effects:** Important harms (well-known side effects of the intervention): Side effects include flu-like symptoms, dermatologic side effects, arrhythmia, hypotension, and transfusion-related acute lung injury **Certainty of the evidence:** Very low for all outcomes due to very serious impression (reliance on single study) and serious risk of bias (missing data) **Values and preferences:** substantial variability is expected or uncertain (regarding benefits to harm ratio): Some patients may prefer to wait while others may be more willing to opt for treatment **Resources:** Important issues, or potential issues not investigated **Equity:** Important issues, or potential issues not investigated **Acceptability:** Important issues, or potential issues not investigated **Feasibility:** Important issues, or potential issues not investigated **Rationale:** Because of limited evidence and significant concerns of harms, IG should not be used outside the context of trials with ethical approval	No reported conflicts
National Institute of Health – Coronavirus Disease 2019 (COVID-19) Treatment Guideline	Other approach but grading modified to GRADE	Update: 27/4/2021 Literature review: 17/07/2020	No included studies	No outcomes assessed	No certainty of evidence	No EtD completed **Rationale:** Unclear whether theoretical effects will benefit patients with COVID-19. **Study Limitations:** The results of the included study are difficult to interpret because of important limitations in the study design.	Financial disclosure between panel members

Surviving Sepsis Campaign Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU – Original and First Update documents reviewed	GRADE	First update: 29/1/2021 Original guideline and rationale: March 2020	6 indirect studies	2	Very low	No EtD completed **Desirable effects:** No data on efficacy is available but unlikely to have biological effect **Undesirable effects:** Rarely but can be associated with increased risk of adverse effects for anaphylactic reactions, aseptic meningitis, renal failure, thromboembolism, hemolytic reactions, transfusion-related lung injury or other late reactions	Some conflicts disclosed
4. Ivermectin for the Treatment of COVID-19							
Australian guidelines for the clinical care of people with COVID-19	GRADE	21/4/2021	11 RCTs	19	Very low	**Balance of effects:** small net benefits or little differences between alternatives – uncertain benefits and common side effects **Desirable effects:** Significant uncertainty whether ivermectin is more effective and safer than standard care in treating patients with COVID-19 **Undesirable effects:** Common side effects such as diarrhoea, nausea, and dizziness **Certainty of the evidence:** low for mortality, invasive mechanical ventilation, adverse or serious adverse events, discharge from hospital, admission to ICU and clinical improvement due to very serious imprecision. Very low for other outcomes **Values and preferences:** Substantial variability is expected or uncertain – some patients may prefer to wait while others may be more willing to opt for treatment **Resources:** Important issues, or potential issues not investigated	No reported conflicts

						Equity: Important issues, or potential issues not investigated **Acceptability:** Important issues, or potential issues not investigated **Feasibility:** Important issues, or potential issues not investigated	
Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19	GRADE	Updated guideline: 14/4/2021 Literature search: 2/8/2021	5 RCT and 2 non-randomized studies	4	Very low	No EtD completed **Benefits:** very uncertain evidence but might decrease mortality. There are also trends of increased symptom resolution and viral clearance in in-patients. **Harms:** Unable to exclude potential for adverse events **Risk of bias:** certainty of evidence of treatment of ivermectin for hospitalized and non-hospitalized patients to be very low due to concerns with risk of bias and imprecision Concerns about publication bias, as the available evidence consisted mostly of positive trials of smaller size.	COI ensured no potentially relevant conflicts for most of the panel. Chairs disclosed no conflicts
National Institute of Health – Coronavirus Disease 2019 (COVID-19) Treatment Guideline	Other approach but grading modified to GRADE	Guideline update: 27/4/2021 Statement update: 11/2/2021	7 clinical trials and 3 retrospective studies	4-5 outcomes	Significant limitations in studies	No EtD completed **Benefits:** Some clinical trials showed no benefits or worsening outcomes. Others showed shorter time to resolution of disease manifestations, greater reduction in inflammatory marker levels, shorter time to viral clearance, and lower mortality rates **Adverse effects:** Well-tolerated but adverse effects may include dizziness, pruritis, nausea, or diarrhea. Neurological adverse effects reported for other treatments. **Limitations:** Most of the included studies had incomplete information and significant methodological limitations: small sample size, various doses and schedules, open-label studies, patients receiving various concomitant medications, severity not well described, and outcome	Financial disclosure between panel members

						measures not always clearly defined	
5. Remdesivir to treat patients with moderate to severe patients with COVID-19							
Australian guidelines for the clinical care of people with COVID-19	GRADE	21/4/2021	4 RCTs (n=7333) Majority of evidence from WHO SOLIDARITY and ACTT-1 trials (n=5451 and n=1062)	13	Moderate	**Benefits and harms:** small net benefit, or little difference between alternatives – Remdesivir probably reduces incidence of death, has an acceptable safety profile, and may reduce incidence of serious adverse events for patients not on invasive ventilation. **Certainty of evidence:** Moderate for death at day 28 due to serious imprecision from wide CI, for discharge from hospital due to reliance on a single study, and for serious adverse events, time to recovery and time to clinical improvement due to non-blinding of patients and personnel. Low certainty for remaining outcomes **Preference and values:** no substantial variability expected - consumer panel believes most informed patients would agree with the recommendation and opt for this treatment **Resources:** Important issues, or potential issues not investigated- No issues around opportunity costs in the Australian context **Equity:** Important issues, or potential issues not investigated – may affect equity based on geographic area **Acceptability:** No important issues with the recommended alternative – treatment is probably acceptable to both patients and clinicians **Feasibility:** Important issues, or potential issues not investigated	No reported conflicts
American College of Occupational and Environmental Medicine -	Literature review	Originally published: 8/04/2020 Update: 14/12/2020	3 RCTs, 1 open labelled RCT, 1 case series, and 1	4+	Low	No EtD completed **Benefits:** Reportedly shorter ICU stay, possible improved survival **Rationale:** One high-quality clinical trial (Wang 2020)	Panel declare no relevant conflict of interests

			post-hoc analysis			suggested lack of clinical efficacy and non-significant trends towards earlier clinical improvement. ACTT-1 trial showed modest efficacy (shorter ICU stay and earlier clinical improvement). None of the RCTs showed statistically improved survival. ACTT-1 trended towards improved survival. SOLIDARITY showed lack of efficacy **Harms:** invasive, minimal adverse effects and high costs of the intervention were considered	
Infectious Disease Society of America Guidelines on the Treatment and Management of Patients with COVID-19	GRADE	Section update: 8/4/2021 Literature review: 3/11/2020	3 RCTs	~6	Moderate	No EtD completed **Benefits**: Pooled analysis failed to show benefits for mortality for patients with SpO2 <94%. Some studies show trend towards greater clinical improvement at 28 days, shorter median time to recovery in post-hoc analysis, and decreased need for mechanical ventilation. **Harms:** Patients treated with remdesivir do not appear to experience greater SAEs than those not receiving remdesivir **Other considerations:** Overall certainty of evidence was moderate for hospitalized patients with SpO2 <94% due to imprecision.	
National Institute of Health - Coronavirus Disease 2019 (COVID-19) Treatment Guidelines	Literature review or evidence synthesis	Guideline update: 27/04/2021 Last section update: April 21, 2021	3 RCTs and 2 other randomized trials	4+	No certainty of the evidence. Overall grading: Moderate recommendation for the statement based on other randomized trials or subgroup analyses of randomized trials	No EtD Completed **Rationale:** In ACTT-1 trial, intervention associated with improved time to recovery for participants requiring oxygen supplementation. Lower percentage of patients progressed to mechanical ventilation/high-flow oxygen or ECMO in one trial. Post hoc analysis of death by day 29 conferred substantial survival benefits in people in this subgroup. SOLIDARITY trial reported no difference in rate of in-hospital deaths, no difference in patients who progressed to invasive mechanical ventilation or in length of hospital stay. Biases in SOLIDARITY trial (open-label	Financial disclosure between panel members

						trial is less well-suited to ass time to recovery and it was known that remdesivir was being administered by clinicians and patients.) Overall, based on results of ACTT-1 study, panel recommends remdesivir as treatment option	
National Institute of Care Excellence – COVID-19 Rapid Guideline: Managing COVID-19	GRADE	25/03/2021	4 RCTs but majority of evidence from WHO SOLIDARITY and ACTT-1 trials	13	Moderate	**Benefits and harms:** small net benefits, or little difference between alternatives: For people not receiving IMV, greater trends towards lower all-cause mortality. Treatment also has acceptable safety profile and may reduce incidence of serious adverse events. **Certainty of the evidence:** Moderate for death due to serious imprecision from wide CI, moderate for people needing ventilation and discharge from hospital because of reliance from single study, and moderate for serious adverse events, time to recovery and to improvement because of non-blinding. Low for other outcomes **Values and preferences:** Substantial variability is expected or uncertain – Panel inferred that in view of probable mortality benefits, most would choose remdesivir **Resources:** Important issues, or potential issues not investigated – panel raised concerns about opportunity costs and possibly diverting resources / fewer resource limitations overall in the UK healthcare context **Equity:** Important issues, or potential issues not investigated – Absence of evidence in community setting however, unlikely to be used outside the hospital **Acceptability:** Important issues, or potential issues not investigated – Potential deterring factor is evidence is only moderate. Anticipated that people who do not require invasive mechanical ventilation	Conflicts recorded according to 2019 NICE conflicts of interest policy

						would choose to have remdesivir **Feasibility:** Important issues, or potential issues not investigated – widespread use of remdesivir is an indicator of feasibility	
Public Health Agency of Canada: Clinical Management of Patients with COVID-19	GRADE	Update: 17/08/2020	1 major RCT (ACTT-1)	1+	No certainty of the evidence	No EtD Completed **Benefits:** Data from ACTT-1 trials show shorter median time to recovery observed for patients with severe COVID-19 not on mechanical ventilation	No information
Surviving Sepsis Campaign Guidelines on the Management of Adults with Corona virus Disease 2019 (COVID-19) in the ICU: First Update	GRADE	First update: 29/1/2021	4 major RCTs and other studies	4	Moderate	**Is the problem a priority:** yes **Desirable effects:** Moderate – Meta-analysis shows reduction in risk of 28-day mortality and reduction in adverse events and time to clinical improvement and recovery **Undesirable effects:** Trivial – No clear undesirable effects and all point estimates are in favour of remdesivir **Certainty of evidence:** moderate for mortality, serious adverse events, and time to clinical improvement. Low for time to clinical recovery across all hospitalized patients **Balance of effects:** Favours the intervention – moderate benefits and no clear harms, moderate quality of evidence, and consistent values and preferences **Values:** Probably no important uncertainty or variability **Resources required:** Moderate costs **Equity:** Don't know – Although likely it will increase equity, costs might offset some benefits therefore the equity is unclear **Acceptability:** Probably yes – the intervention is acceptable to key stakeholders	During completion of the EtD framework, the majority of the panel (92.6%) agreed on this recommendation 3 panel members disagreed, eventually 2 of them agreed on the final wording of the recommendation

						Feasibility: Varies – Likely feasible in high-income countries and less feasible in low-income countries (cost, availability, and given intravenously are main concerns)	
World Health Organization: Therapeutics and COVID-19: Living Guideline	GRADE	Statement issued: 20/11/2020	4 main RCTs including ACTT-1, SOLIDARITY, SIMPLE MODERATE, Yang Y	9	Low	**Benefits and harms:** Lack of evidence that remdesivir improved outcomes such as mortality, need for mechanical ventilation, time to clinical improvement etc. Low certainty of evidence does not prove the intervention is ineffective but there is insufficient evidence to confirm that it improves patient-important outcomes **Certainty of the evidence:** Low certainty for all patient important outcomes across benefits and harms, mostly driven by risk of bias and imprecision due to wide CI. **Values:** Substantial variability is expected or uncertain – GDG panel inferred most patients would be reluctant to use remdesivir due to high uncertainty of prioritized outcomes **Resources and other considerations:** Important issues, or potential issues not investigated – Novel therapy require higher certainty of evidence. Panel raised concerns for opportunity costs and the importance of not drawing resources/attention away from best supportive care **Justification:** Panel emphasized evidence of possibly no effect on mortality, need for ventilation, recovery from symptoms and other patient important outcomes. Panel also anticipated variability in patient values and other context factors (resource considerations, accessibility, feasibility, and health equity)	No reported conflicts
6. Zinc for the treatment of COVID-19							
Australian guidelines for the clinical care	GRADE	21/4/2021	3 RCT and 1 systematic review	6	Low	**Benefits and harms:** small net benefits, or little differences between alternatives. (Uncertain whether zinc	No reported conflicts

of people with COVID-19						increases or decreases death, the need for invasive mechanical ventilation, rate of hospitalisation or discharge from hospital, clinical recovery or duration of hospital stay) **Harms:** Common side effects of zinc poisoning include hypotension, pulmonary oedema, diarrhoea, vomiting, jaundice, and oliguria **Values and preferences:** Substantial variability is expected or uncertain **Resources:** Important issues, or potential issues not investigated **Equity:** Important issues, or potential issues not investigated **Acceptability:** No important issues with the recommended alternative **Feasibility:** Important issues, or potential issues not investigated	
National Institute of Health – Coronavirus Disease 2019 (COVID-19) Treatment Guideline	Other approach but grading modified to GRADE	Update: 27/4/2021 Statement update: 21/4/2021	1 multi-center trial, 1 RCT, 1 observational study and 1 multi-center cohort study	No direct outcomes assessed	No certainty of evidence	No EtD completed **Benefits:** Zinc concentrations can impair number of RNA viruses and enhance cytotoxicity. Several clinical trials are investigating the use of clinical supplementation however the doses between trials varies. **Harms:** long-term supplementation can cause copper deficiency with reversible hematologic defects and potentially irreversible neurological manifestations so using above recommended dietary levels is not recommended	Financial disclosure between panel members
7. Masks in children (aged 2 and up vs. aged 5 and up)							
Centres for Disease Prevention and Control – Guidance for wearing masks	Scientific brief: Community Use of Cloth Masks to Control the Spread of	Guideline updated: 19/04/2021	2 studies assessing respiratory function	~3	No certainty of evidence	No EtD completed and informal methods applied Considered appropriate and consistent mask use, high sensitivity to materials, and understanding why masks should not be worn in children younger than 2 years old. No	No information

	SARS-CoV-2					direct evidence supporting age cut-off at this version of scientific update	
Public Health Agency of Canada - Individual and community -based measures to mitigate the spread of COVID-19 in Canada	Possible lit. review	Updated 07/04/2021	No included studies	3	No certainty of evidence	No EtD completed and informal methods applied Considered child's ability to wear mask, care for their mask, and ability to tolerate mask to recommend why masks should not be worn in children younger than 2 years old. No direct evidence supporting age cut-off.	No information
World Health Organization - Mask use in the context of COVID-19	Lit. review	12/01/2020	2 cluster randomized trial from influenza studies, 1 feasibility study for influenza, 1 observational study from influenza studies	2	No certainty of evidence	No EtD completed and informal methods applied Considered children's compliance and difficulty to wear a mask to recommend why masks should not be worn in children younger than 5 years old. No direct evidence to support their statement but indirect evidence from influenza studies. No direct evidence supporting age cut-off.	No information
8. Mode of birth for pregnant women with COVID-19							
Australian guidelines for the clinical care of people with COVID-19	GRADE	21/4/2021	Systematic review (n=655 women and n=666 newborns)	1	Very low	**Benefits and harms:** small net benefits, or little differences between the alternative – recommendation informed by systematic review which showed vertical transmission and newborn infection did not substantially differ by mode of birth. **Certainty of the evidence:** Very low due to reliance in case reports and case series **Values and preferences:** No substantial variability expected – consumer panel believes most women would agree with recommendation as no available evidence suggest harm to mother or newborn. **Resources:** Important issues, or potential issues not investigated – cesarian section would have additional resource implications	No reported conflicts

						Equity: Important issues, or potential issues not investigated **Acceptability:** Important issues, or potential issues not investigated **Feasibility:** No important issues with the recommended alternative	
World Health Organization - Clinical management of COVID-19 patients: Living guidance, 25 January 2021	GRADE	25/1/2021 Systematic review search: 6/10/2020	Living systematic review	1	No certainty of evidence	No EtD Completed **Benefits and harms:** Current studies vary in their rigour about postnatal infections. This limits their interpretation. Pregnant women appear less likely to be symptomatic or show common symptoms. Complications do not seem to increase during third trimester.	No reported conflicts
9. Relaxing certain measures for vaccinated travellers							
Centres for Disease Prevention and Control - Interim Public Health Recommendations for Fully Vaccinated People	Scientific Brief	2/4/2021	Literature review (multiple studies)	5	No certainty of evidence	No EtD completed and informal methods **Benefits and harms:** Evidence suggests vaccinated groups are less likely to have asymptomatic infection and potentially less likely to transmit SARS-CoV-2. **Values and preferences:** Lowering restrictions may increase vaccination in the US population.	No information
Public Health Agency of Canada - COVID-19 vaccinated travellers entering Canada	Possible lit. review	09/04/2021	No included studies	No outcomes assessed	No certainty of evidence	No EtD Completed and informal methods **Certainty of the evidence:** No current evidence to support lifting restriction for vaccinated populations. Current understanding following vaccination and duration of immunity is limited to lift restrictions.	No information
World Health Org: Interim position paper: considerations regarding proof of COVID-19 vaccination for international travellers	Scientific considerations/ Possible lit. review	5/2/2021	No cited studies	5	No certainty of the evidence	No EtD completed and informal methods **Certainty of the evidence:** Critical unknowns of vaccine efficacy and effectiveness in reducing transmission including whether vaccines offer protection against asymptomatic infections, age and population, and contraindications.	No information

10. Delaying the second dose for mRNA vaccines that require two complete doses							
Centres for Disease Prevention and Control: Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States	No clearly reported methods /possible literature review	Updated: 26/3/2021	No cited studies	1	No certainty of the evidence	No EtD completed and informal methods **Certainty of the evidence:** No efficacy date available beyond 6-weeks	No information
European Centres for Disease Prevention and Control: Risk assessment : SARS-CoV-2 - increased circulation of variants of concern and vaccine rollout in the EU/EEA, 14th update	Literature review	15/02/2021	No directly cited studies	2-4	No certainty of the evidence	No EtD completed and informal methods No direct evidence to support their statement for extending intervals to reduce risk of variants but discussion of dosing intervals was provided where overall dosing interval evidence was summarized. **Increasing number of vaccinations:** by Extending vaccine rollout. **Evidence on vaccine effectiveness:** Evidence for vaccine effectiveness is emerging following a single dose.	No information
Public Health Agency of Canada - Extended dose intervals for COVID-19 vaccines to optimize early vaccine rollout and population protection in Canada in the context of limited vaccine supply	Lit. review	4/15/2021	3 Clinical trials, multiple observational studies assessing vaccine effectiveness, internal population modelling studies	8 main outcomes	No certainty of the evidence	No EtD Completed **Vaccine efficacy:** Multiple efficacy studies after one dose show a range of 76-92% efficacy. Most studies assessed duration of 21 days between doses **Vaccine effectiveness:** Maximum duration between doses assessed was 8-weeks. Other multidose vaccine studies show VE 6-months after first dose. For mRNA vaccines, VE varied from 79%-90.4% in included studies **Priming and boosting:** Vaccinology principles support 3-week interval between doses to avoid immune interference	All panel members conduct themselves within PHAC's Policy on Conflict of Interest

						Population impact: Extending interval will allow more people to be vaccinated. **Population modelling studies:** Predicted public health benefits (reducing symptomatic infection, hospitalization, and deaths) after extending interval. Model assumed 90% effectiveness of all vaccines after the first dose and projected highest benefits for reducing severe outcomes after extending interval for 16-weeks. If VE was greater than 65%, then sensitivity analysis predicted a decrease in deaths. **Impact of extending intervals on variants of concern (VOC):** Unknown impact on VOC however, preventing community transmission may decrease chance of its emergence.	
11. Rooming mothers with COVID-19 with their newborns							
Australian guidelines for the clinical care of people with COVID-19	GRADE	21/04/2021	Systematic review (n=666 across 49 studies) and Observational cohort study	1	Very low	**Benefits and harms:** Substantial net benefits of the recommended alternative (e.g., bonding, exclusive breastfeeding, duration of breastfeeding) and no evidence to support separating mother and newborn to prevent transmission. **Certainty of the evidence:** Very low due to reliance on case reports and case series **Values and preferences:** No substantial variability expected - consumer panel believes most woman would agree as there is no available evidence to suggest harm to mother or newborn. **Resources:** Important issues, or potential issues not investigated **Equity:** Important issues, or potential issues not investigated **Acceptability:** Important issues, or potential issues not investigated **Feasibility:** Important issues, or potential issues not investigated	No reported conflicts

World Health Organization: Clinical management of COVID-19 patients: Living guidance, 25 January 2021	GRADE	25/1/2021	No directly cited studies	3-4	No certainty of the evidence	No EtD Completed **Benefits:** mother-infant contact enhances thermoregulation and other physiological outcomes, significantly reduces mortality and morbidity, and improves parental attachment **Benefits and harms:** Several important benefits outweigh potential (and likely mild) harms of COVID-19 transmission to the child	No reported conflicts
12. Frequency of times to clean public surfaces							
Centres for Disease Prevention and Control: Cleaning and Disinfecting Your Facility	Scientific brief/literature review	5/4/2021	quantitative microbial risk assessments	3	No certainty of the evidence	No EtD Completed **Fomite transmission:** Considered low for SARS-CoV-2 compared to direct contact, droplet transmission, or airborne transmission. Unclear of the proportion of cases acquired through transmission. But evidence suggests low frequency of cases. **Surface survival:** surface survival higher in non-porous surfaces **Conclusion:** surfaces are not the main route of transmission	No information
Public Health Agency of Canada: COVID-19: Cleaning and Disinfecting	Possible literature review	Statement updated: 23/09/2020	No directly cited studies	Unknown	No certainty of the evidence	No EtD completed and informal methods **Surface survival:** Evidence suggests COVID-19 virus can live on objects and surfaces from a few hours to days, depending on the type of surface. The length is unknown	No information
World Health Organization: Cleaning and disinfection of environmental surfaces in the context of COVID-19	Literature review	16/05/2020	No directly cited studies	Unknown	No certainty of the evidence	No EtD completed and informal methods **Fomite Transmission:** No evidence for equating risk of fomite transmission to environment outside of hospital	No information

Table C2: Completed Content Analysis Outcomes Analysis Assessing Methodological Differences

Organizations	Divergence	Methodological difference
Convalescent plasma for the treatment of COVID-19 patients		
Australian Clinical Taskforce IDSA NIH SSC	Strength and direction	**Theme 1: Differences in the date of publication or most recent literature search** • The SSC guideline was updated before results from the RECOVERY trial were published whereas the Taskforce, NIH, and IDSA updated their recommendations using direct evidence from the trial • Given the limited evidence at the time of literature review, SSC downgraded certainty of evidence due to serious indirectness in the population and outcomes of interest. They issued a conditional/weak recommendation against its use while awaiting results of large ongoing RCTs and included RCTs were low quality **Theme 3: Differences in the interpretation of evidence and assessments of quality** • The IDSA downgraded the certainty of evidence to low whereas the Taskforce downgraded the certainty of evidence to moderate. IDSA issued a conditional recommendation against the intervention whereas the Taskforce issued a strong recommendation against the intervention for all COVID-19 patients • The NIH guideline did not use the GRADE approach but graded "strong evidence based on one or more RCT with no severe limitations" to recommend against for patients with COVID-19 who do not have impaired immunity and "neither for nor against the intervention" for hospitalized patients who have impaired immunity and out-patients
Gelatin for the acute resuscitation of patients experiencing COVID-19 and shock		
SSC WHO	Strength	**Theme 3: Differences in the interpretation of evidence and assessments of quality** • Both guidelines agree there are unclear benefits of the intervention, but SSC issued a conditional recommendation whereas WHO issued a strong recommendation against the intervention **Theme 4: Differences in contextualization considerations** • WHO and SSC balanced unclear benefits with high costs of the intervention to recommend against the use of gelatin
Immunoglobulins for the treatment of COVID-19 patients		
Australian Clinical Taskforce NIH SSC	Strength	**Theme 1: Differences in the date of publication or most recent literature search** • The Taskforce updated its recommendation using evidence from a single placebo-controlled double blinded clinical trial. This trial was published in October 2020 • SSC and NIH guidelines have not updated their recommendation using the newly available evidence, despite updating their guidelines • SSC's initial guideline acknowledged no data on efficacy. Their updated guideline did not include any changes to their initial recommendation • NIH used evidence from a multicenter retrospective study issued in April 2020. Noting limitations in the current evidence, NIH issued their recommendation based on expert opinion to recommend against its use **Theme 3: Differences in the interpretation of evidence and assessments of quality** • The Taskforce and SSC guidelines acknowledged adverse effects of the intervention; however, the Taskforce issued a strong recommendation due to very low certainty for all outcomes and the uncertainty around the benefits whereas the SSC issued a conditional/weak recommendation against its use
Ivermectin for the treatment of COVID-19 patients		
Australian Clinical Taskforce IDSA NIH	Strength and direction	**Theme 2: Differences in the included studies/evidence** • Differences were observed in the included studies between all guidelines • 3 RCTs were used by all three guidelines and 2 RCTS were used by the Taskforce and IDSA only **Theme 3: Differences in the interpretation of evidence and assessments of quality** • The Taskforce, NIH and IDSA acknowledged small net benefits and limitations in the evidence • The Taskforce issued a strong recommendation and the IDSA issued a conditional recommendation against the intervention

		• The NIH issued a recommendation 'neither for nor against the intervention' because of insufficient evidence. The NIH also listed significant limitations in the available evidence at the time of their literature review
Remdesivir for the treatment of moderate to severe COVID-19 patients		
Australian Clinical Taskforce ACOEM IDSA NIH NICE PHAC SSC WHO	Direction	**Theme 3: Differences in the interpretation of evidence and assessments of quality** • The Taskforce, NIH, NICE, and IDSA assessed certainty of evidence as moderate whereas WHO assessed certainty of evidence as low • WHO concluded there is insufficient evidence to prove remdesivir has effects for patient important outcomes such as mortality, need for mechanical ventilation, and time to clinical improvement. WHO also considered additional resource and cost-constraints across countries. Therefore, they judged that the balance of effects favours the comparison group (standard care) • The Taskforce concluded small net benefits due to probable reduction of death, the safety profile of remdesivir, and probable reduction of serious adverse events for this population • ACOEM also compared desirable and undesirable effects to formulate a conditional recommendation for the intervention but also acknowledged opportunity-costs of intervention • Differences in the interpretation of the ACTT-1 and Solidarity study were observed between WHO and other guidelines. NIH primarily considered results from ACTT-1 study but also assessed results from Solidarity study **Theme 4: Differences in contextualization considerations** • Differences in cost-effectiveness was observed between the Taskforce, NICE and WHO where WHO considered opportunity costs associated with a new intervention whereas the Taskforce and NICE did not consider opportunity costs in the Australian or UK context due to availability of resources • Differences in patient values and preferences were observed where WHO and NICE both agreed that substantial variability is expected whereas the Taskforce did not expect substantial variability. WHO and NICE agreed on patient values and preferences, but issued different directions for their recommendations
Zinc for the treatment of COVID-19 patients		
Australian Clinical Taskforce NIH	Strength	**Theme 2: Differences in the included studies/evidence** • Taskforce used evidence from 3 trials, but the evidence was uncertain for death, need for invasive mechanical ventilation, rates of hospitalization. Two of these studies were also included by NIH • Taskforce included a pilot double-blind safety and feasibility study evaluating high-dose intravenous zinc in hospitalized patients with COVID-19 that was excluded by NIH. Similarly, NIH included an observational and multi-cohort study on the effects of zinc on survival that was excluded by the Taskforce **Theme 3: Differences in the interpretation of evidence and assessments of quality** • Taskforce found low certainty of evidence (insufficient evidence) overall and issued a strong recommendation against its use unless in clinical trials • NIH made a conditional or moderate recommendation against its use unless it's for clinical trials because zinc has not shown to have clinical benefit and may be harmful when increasing doses. Existing trials had limitations in the studies
Delaying the interval between the first and second dose for COVID-19 vaccines		
CDC ECDC PHAC	Subgroup considerations of the intervention	**Theme 2: Differences in the included studies/evidence** • PHAC considered evidence from vaccine studies after one dose • PHAC did not include any direct evidence to support delaying vaccines for 4-months but provided rationale from their population modelling studies which predicted reduction in symptomatic infection, hospitalization, and death under certain circumstances • ECDC did not provide a direct statement or direct evidence concerning how long vaccine dosages should be delayed. They summarized evidence for dosing intervals and pre-print studies evaluating immunity after one dose. The study did not evaluate immunity beyond 21 days. **Theme 3: Differences in the interpretation of evidence and assessments of quality** • CDC did not recommend delaying the second dose for more than 6-weeks because of the limited available direct evidence on the effectiveness of the intervention. **Theme 4: Differences in contextualization considerations**

		• PHAC considered delaying the second dose for 4-months to address feasibility concerns due to shortages of vaccine supplies in the Canadian setting at the time of the statement's publication • ECDC considered extending intervals in their risk assessment for circulation of variants as an option for response
Frequency of times to clean surfaces in public settings		
CDC PHAC WHO	Subgroup considerations of the intervention	**Theme 1: Differences in the date of publication or most recent literature search** • WHO published their statement in June 2020, PHAC published their statement in September 2020 and CDC updated their statement in April 2021 • CDC cited evidence from QMRA and transmission studies whereas PHAC and WHO did not provide details for included evidence. The studies cited by CDC were published after PHAC and WHO issued their guidelines • PHAC excluded descriptions of their methodology or evidence used to formulate the statement but provided rationale regarding COVID-19 unknowns and the virus's ability to survive on surfaces • WHO explicitly stated that COVID-19 transmission has not been conclusively linked to contaminated environmental studies at the time their guideline was issued, and did not cite direct evidence for non-healthcare settings **Theme 2: Differences in the included evidence/studies** • WHO cited indirect evidence, due to the absence of direct evidence available at the time the guidance was published • PHAC updated their guidance on individual and community-based measures to mitigate COVID-19 in April 2021 which included evidence for cleaning and disinfecting surfaces in the home. PHAC did not include this evidence for their statement on cleaning public spaces which has not been updated since September, 2020
Minimum age cut-off for wearing facemasks in children' populations		
CDC PHAC WHO	Subgroup considerations of the population	**Theme 2: Differences in the included evidence/studies** • WHO applied evidence from three separate studies evaluating mask use in children during the Influenza season whereas CDC applied evidence from a single observational study assessing oxygenation levels in children wearing masks • CDC and WHO do not state direct evidence for how the age cut-off was determined but agree masks should not be worn in younger children. The age for cut-off varied • PHAC did not cite any explicit evidence for its statement
Mode of birth for pregnant women with COVID-19		
Australian Clinical Taskforce WHO	Strength	**Theme 2: Differences in the included evidence/studies** • WHO and the Taskforce used evidence from different systematic reviews to formulate their recommendations **Theme 3: Differences in the interpretation of evidence and assessments of quality** • WHO stated current studies on mother-to-child transmission varied in rigor, therefore limiting interpretation of these results. WHO issued a strong recommendation for not changing the mode of birth due to COVID-19 status in their guideline • The Taskforce stated desirable effects outweigh undesirable effects. However, the evidence was limited thus likely resulting in a conditional recommendation
Rooming mothers with COVID-19 with their newborns after birth		
Australian Clinical Taskforce WHO	Strength	**Theme 3: Differences in the interpretation of evidence and assessments of quality** • WHO stated mother-infant contact has many important benefits. They judged that several important benefits outweigh potential (and likely mild) harms of mother-child transmission • The Taskforce also favoured the intervention of rooming (not separating the mother and infant) due to substantial benefits. The certainty of evidence for mother-infant transmission was very low because they primarily relied on case reports and case series. Taskforce also stated there are substantial benefits which favours the intervention. The Taskforce issued a conditional recommendation overall
Relaxing certain restrictions for vaccinated travellers/population		
CDC PHAC WHO	Direction	**Theme 3: Differences in the interpretation of evidence and assessments of quality** • PHAC stated there is no current evidence to support lifting restrictions for vaccinated populations. Likewise, WHO stated critical unknowns of vaccine efficacy and effectiveness to reduce transmission, thus issued recommendations against reducing restrictions

	• Evidence from CDC's scientific brief suggested vaccinated groups are less likely to have asymptomatic infection and are potentially less likely to transmit the virus. **Theme 4: Differences in contextualization considerations** • CDC made their statement considering studies on population attitudes and behaviours towards vaccination in addition to using data evaluating vaccine effectiveness. To increase uptake in the American population, they relaxed some restrictions for vaccinated individuals

Highlights

What this adds to what is known:

We have developed a new concept, termed divergence, to describe differences in the explicit conclusions or subgroup considerations in clinical and public health guidelines issuing comparable statements and assessed factors associated with their differences.

Key findings:

Divergence was observed in 62% of our included guidelines for the management of COVID-19. Overall, we observed a similar frequency of guidelines diverging in explicit judgements and subgroup considerations but a higher frequency of statements diverging in strength than in direction of the recommended action. We identified associations between differences in methodological and contextualization factors and divergence.

What is the implication, what should change now:

Divergence associated with context-specific considerations can lead to more equitable outcomes between regions with diverse resources. Divergence associated with differences in other methodological steps, may contrarily compromise the overall quality and rigour of the guideline development process. Guideline users may choose to appraise differences in methods, use of evidence, and context-specific criteria to decide which diverging statement is appropriate for their setting.

Link: CRediT Author Statement

Zil H Nasir: Conceptualization, Methodology, Validation, Investigation, Writing - Original Draft, Writing - Review & Editing, Project Administration
Dominik Mertz, Robby Nieuwlaat, Nancy Santesso: Methodology, Investigation, Writing - Review & Editing
Tamara Lotfi[1,2]: Methodology, Writing - Review & Editing, Project Administration

Ashley Motillal, Lorenzo Moja, Tamara Kredo[5,6], Miranda W Langendam[7], Alfonso Iorio[1,8], Miloslav Klugar[9,10], Jitka Klugarová[9,10], Ignacio Neumann[1,11], Lawrence Mbuagbaw[1,12], Alexis F. Turgeon[13,14], Kevin Pottie[17-20], Omar Dewidar[17-20], Signe A Flottorp[21,22], Joerg Meerpohl, Peter Tugwell[17-20], Derek Chu, Joseph L Mathew[28], Amir Qaseem[31] Jitka Klugarová,[f,g], Harrison Nelson,[x] Heba Hussein,[y] Jozef Suvada[z]: Methodology, Validation, Investigation, Writing – Review & Editing

Holger J. Schünemann[1,2,5]: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition

Conflict of interest statement

The authors declare no conflicts of interest.