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Review: How have population-level non-pharmaceutical interventions [NPIs] to reduce SARS CoV-2 transmission been related in time to the reproduction number (R) and have countries used measures of R in making decisions about the application of these interventions?

Date: 01 May 2020 Version: 006-01

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Rapid Review Question: How have population-level non-pharmaceutical interventions [NPIs] to reduce SARS CoV-2 transmission been related in time to the reproduction number (R) and have countries used measures of R in making decisions about the application of these interventions?

Dr You Li (you.li2@ed.ac.uk); Prof Harish Nair (Harish. Nair@ed.ac.uk); Prof Harry Campbell (harry.campbell@ed.ac.uk); Durga Kulkarni; Rima Nundy; Alice Harpur; Marshall Dozier

Sub-question 1:
How did the reproduction number (R) for COVID-19 change over time in relation to population-level non-pharmaceutical interventions [NPIs] to reduce SARS CoV-2 transmission?
(Lead authors: You Li, Alice Harpur)

Sub-question 2:
What parameters were considered by countries in making decisions about lifting of population-level non-pharmaceutical interventions [NPIs]?
(Lead Authors: Durga Kulkarni and Rima Nundy)

Sub-question 1: How did the reproduction number (R) for COVID-19 change over time in relation to population-level non-pharmaceutical interventions [NPIs] to reduce SARS CoV-2 transmission?

Background

A number of NPIs to reduce SARS CoV-2 transmission were introduced in countries affected by COVID-19, such as school closure, public events ban, social distancing and lockdown. The basic reproduction number or R_0, is used to measure the average number of people who would catch a disease from a single infected person. R_0 can change over time with interventions being introduced to reduce transmission by changing patterns of social mixing in the population. The time-varying "R_0", which is often referred to as "R" or "R_t", is defined by the expected number of secondary cases arising from a primary case infected at time *t*. R is an important parameter for assessing whether current interventions appear to be effective, or whether additional interventions are required. If R remains below one, then the epidemics will die out eventually; if R is above one, sustained epidemics are expected. Therefore, it is important to review the change of R over time in relation to these NPI decisions.

Method

We included UK and several countries in Europe in this review. We collected the timeline of the NPIs that were adopted by each country. We grouped these interventions into four categories for better comparison, namely school closure, public events ban, social distancing and lockdown [which generally includes these measures plus additional restrictions on movement]. For each country, we grouped the timeline into different stages based on timing of introduction of these interventions in each country. We considered the stage where no interventions were introduced as the baseline.

We collected estimates of R from public websites and publications (see key references 1-6 below). For each country, we calculated the percentage of reduction in R measured immediately before and after the application of each of the individual interventions. Additionally, based on the daily R estimates from the LSHTM model [2], we plotted the change over time in R for each country.

Results

Estimates of R at each stage following introduction of an intervention are presented in **Table 1**. Reduction in R by each intervention was presented in **Figure 1**. Changes in R over time based on the LSHTM model are presented in **Figure 2**. The key findings are summarised as follows:

- The model by Imperial College London [1] and the model by LSHTM [2] provided estimates of R in most of the countries.
- The Imperial model calculated backwards from the deaths observed over time to estimate transmission that occurred several weeks prior whereas the LSHTM model was based on confirmed COVID-19 cases (see details in Appendix 1). Both models were subject to variations in testing (and reporting) practices over time. (detailed comparisons in **Appendix 2**)

- The estimates of R varied substantially in the two models (particularly at baseline) but tended to converge over time (after implementation of lockdown) as more data became available.
- R was shown to be reduced by all interventions, with lockdown contributing to most of the reduction (median reduction in R: 68% by Imperial model; 26% by LSHTM model), followed by public events ban (44% by Imperial model and 25% by LSHTM model), social distancing (6% by Imperial model; 18% by LSHTM model) and school closure (1% by Imperial model; 8% by LSHTM model). (**Figure 1**). It should be noted that different sequence and time periods of application [and possible interaction effects] make strict comparisons of relative effect of interventions uncertain and potentially misleading and results should be interpreted in the light of this.
- A separate study by LSHTM based on survey of over 1350 participants reported 73% reduction in the average daily number of contacts observed per participant (after lockdown) thereby reducing R from 2.6 prior to lockdown to 0.62 (95% confidence interval [CI] 0.37 - 0.89) after the lockdown (Appendix 3). [3]
- By enforcing lockdown, most countries managed to reduce R to less than 1.
- LSHTM provide current R estimates using nowcasting and forecasting. Nowcast refers to estimation based solely on the currently reported cases. There is a 10-day lag in nowcast estimate dates due to the lag in confirmation and reporting. Forecast refers to estimation based on both the currently reported cases and predicted cases (Appendix 4).
- Based on a range of sources, the latest R estimated for UK is in the range 0.62-0.9.

Conclusions and implications

- All NPI measures were associated with the reduction of SARS-CoV-2 transmission as measured by R. Lockdown is observed to contribute most and school closure (alone) the least to the reduction.
- Although R is often assumed to have straightforward interpretations in practice, estimating R during an ongoing outbreak is complicated and associated with substantial uncertainty.
- During an ongoing outbreak, a robust estimate of R at time T requires incidence data from times later than T, leading to a delay in obtaining “real-time” R. During the early phase of an outbreak, more uncertainty in R is observed due to varying testing and reporting practices.
- Due to the lack of granularity in data, all R estimates in the report are at national level whereas transmission dynamics might vary by region [and so R would not be able to inform most regional / sub-national decision-making].
- R should be interpreted in the context of limitations on data and modelling assumptions. For this reason, although R is a fundamental infectious disease dynamics metric, decisions on enforcing and lifting NPIs need to balance information from R and other key parameters and cannot not be based on R alone.
- Estimating R for specific sectors (e.g. care homes or hospitals) is extremely challenging given the paucity of underlying data (see appendix 1 for details).

Table 1: Estimates of reproduction number (R) over time corresponding to periods with population-level NPIs to reduce SARS CoV-2 transmission

	Population-level NPIs to reduce SARS CoV-2 transmission					R from Imperial[1]		R from LSHTM[2a]		R from other sources
Country	**School closure**	**Public events ban**	**Social distancing**	**Lockdown**	**Date of start of intervention**	**Incremental change in R (%)**	**Average R**	**Incremental change in R (%)**	**Average R**	**Average R**
UK	No	No	No	No	**Baseline**	—	3.92 (3.47-4.57)	—	1.99 (1.70-2.33)	—
UK	No	No	**Yes**[b]	No	**16/3/2020**	-7	3.66 (3.15-4.1)	-20	1.59 (1.43-1.79)	—
UK	**Yes**	No	Yes	No	**21/3/2020**	-1	3.62 (3.11-4.07)	-9	1.45 (1.31-1.61)	—
UK	Yes	**Yes**	Yes	**Yes**	**24/3/2020**	-82	0.65 (0.53-0.78)	-17	1.20 (1.13-1.29)	0.62 (0.37-0.89)[3]
Austria	No	No	No	No	**Baseline**	—	4.52 (3.57-5.57)	—	1.92 (1.61-2.29)	—
Austria	No	**Yes**	No	No	**10/3/2020**	-44	2.55 (1.82-3.55)	-21	1.51 (1.31-1.73)	—
Austria	**Yes**	Yes	No	No	**14/3/2020**	-1	2.53 (1.81-3.58)	-13	1.32 (1.15-1.50)	—
Austria	Yes	Yes	**Yes**	**Yes**	**16/3/2020**	-70	0.77 (0.65-0.91)	-37	0.83 (0.72-0.95)	—
Czech Rep	No	No	No	No	**Baseline**	—	—	—	1.85 (1.47-2.25)	—
Czech Rep	**Yes**	**Yes**	No	No	**10/3/2020**	—	—	-20	1.48 (1.25-1.71)	—
Czech Rep	Yes	Yes	**Yes**	**Yes**	**16/3/2020**	—	—	-36	0.95 (0.82-1.10)	—
Denmark	No	No	No	No	**Baseline**	—	4.13 (3.29-5.22)	—	1.36 (1.10-1.62)	—
Denmark	No	**Yes**	No	No	**12/3/2020**	-45	2.27 (1.66-3.14)	-7	1.27 (1.08-1.46)	—
Denmark	**Yes**	Yes	**Yes**	No	**13/3/2020**	-4	2.17 (1.6-2.88)	+8	1.37 (1.18-1.58)	—
Denmark	Yes	Yes	Yes	**Yes**	**18/3/2020**	-68	0.7 (0.58-0.84)	-20	1.10 (1.01-1.29)	—

[a] 90% uncertainty range

[b] Bold and underline indicates the change in interventions compared to the previous stage

	Population-level NPIs to reduce SARS CoV-2 transmission					R from Imperial[1]		R from LSHTM[2a]		R from other sources
Country	**School closure**	**Public events ban**	**Social distancing**	**Lockdown**	**Date of start of intervention**	**Incremental change in R (%)**	**Average R**	**Incremental change in R (%)**	**Average R**	**Average R**
France	No	No	No	No	**Baseline**	—	5.03 (4.44-5.70)	—	2.09 (1.53-2.73)	3.31 (3.18-3.43)[4]
France	No	**Yes**	No	No	**13/3/2020**	-44	2.82 (2.15-3.61)	-31	1.44 (1.32-1.61)	—
France	**Yes**	Yes	No	No	**14/3/2020**	-1	2.80 (2.14-3.59)	-3	1.40 (1.28-1.55)	—
France	Yes	Yes	**Yes**	No	**16/3/2020**	-6	2.63 (2.04-3.29)	-4	1.35 (1.25-1.49)	—
France	Yes	Yes	Yes	**Yes**	**17/3/2020**	-68	0.84 (0.73-0.95)	-27	0.98 (0.93-0.85)	0.52 (0.50-0.55)[4]
Germany	No	No	No	No	**Baseline**	—	4.24 (3.62-4.91)	—	2.01 (1.73-2.33)	—
Germany	No	No	**Yes**	No	**12/3/2020**	-6	3.97 (3.33-4.61)	-21	1.58 (1.41-1.79)	—
Germany	**Yes**	No	Yes	No	**14/3/2020**	-1	3.95 (3.31-4.57)	-18	1.29 (1.17-1.43)	—
Germany	Yes	**Yes**	Yes	**Yes**	**22/3/2020**	-82	0.72 (0.60-0.84)	-28	0.93 (0.88-0.97)	1.10 (0.9-1.3)[5]
Italy	No	No	No	No	**Baseline**	—	3.70 (3.36-4.05)	—	1.85 (1.62-2.13)	—
Italy	**Yes**	No	No	No	**5/3/2020**	-1	3.65 (3.21-4.01)	-22	1.45 (1.33-1.63)	—
Italy	Yes	**Yes**	**Yes**	No	**9/3/2020**	-47	1.92 (1.47-2.46)	-8	1.34 (1.23-1.48)	—
Italy	Yes	Yes	Yes	**Yes**	**11/3/2020**	-66	0.65 (0.58-0.73)	-26	0.99 (0.94-1.04)	0.4-0.7[6]
Norway	No	No	No	No	**Baseline**	—	3.83 (2.89-4.9)	—	1.63 (1.33-1.96)	—
Norway	No	**Yes**	No	No	**12/3/2020**	-44	2.15 (1.55-3.15)	-25	1.23 (1.08-1.38)	—
Norway	**Yes**	Yes	No	No	**13/3/2020**	0	2.14 (1.54-3.17)	-1	1.22 (1.09-1.36)	—
Norway	Yes	Yes	**Yes**	No	**16/3/2020**	-7	2.00 (1.50-2.59)	-15	1.04 (0.77-1.17)	—
Norway	Yes	Yes	Yes	**Yes**	**24/3/2020**	-68	0.65 (0.48-0.82)	-26	0.77 (0.64-0.90)	—

	Population-level NPIs to reduce SARS CoV-2 transmission					R from Imperial[1]		R from LSHTM[2a]		R from other sources
Country	**School closure**	**Public events ban**	**Social distancing**	**Lockdown**	**Date of start of intervention**	**Incremental change in R (%)**	**Average R**	**Incremental change in R (%)**	**Average R**	**Average R**
Spain	No	No	No	No	**Baseline**	—	4.54 (3.93-5.33)	—	2.09 (1.81-2.43)	—
Spain	No	No	**Yes**	No	**9/3/2020**	-5	4.32 (3.54-5.13)	-22	1.64 (1.47-1.85)	—
Spain	**Yes**	No	Yes	No	**13/3/2020**	-2	4.25 (3.45-5.06)	-6	1.54 (1.39-1.72)	—
Spain	Yes	**Yes**	Yes	**Yes**	**14/3/2020**	-84	0.67 (0.56-0.77)	-31	1.06 (0.98-1.13)	—
Switzerland	No	No	No	No	**Baseline**	—	3.90 (3.23-4.73)	—	1.86 (1.58-2.19)	—
Switzerland	No	**Yes**	No	No	**13/3/2020**	-45	2.14 (1.64-2.81)	-25	1.39 (1.24-1.56)	—
Switzerland	**Yes**	Yes	No	No	**14/3/2020**	0	2.13 (1.62-2.77)	-6	1.30 (1.15-1.45)	—
Switzerland	Yes	Yes	**Yes**	No	**16/3/2020**	-4	2.04 (1.58-2.55)	-12	1.14 (1.01-1.27)	—
Switzerland	Yes	Yes	Yes	**Yes**	**20/3/2020**	-68	0.65 (0.53-0.76)	-25	0.86 (0.79-0.93)	—

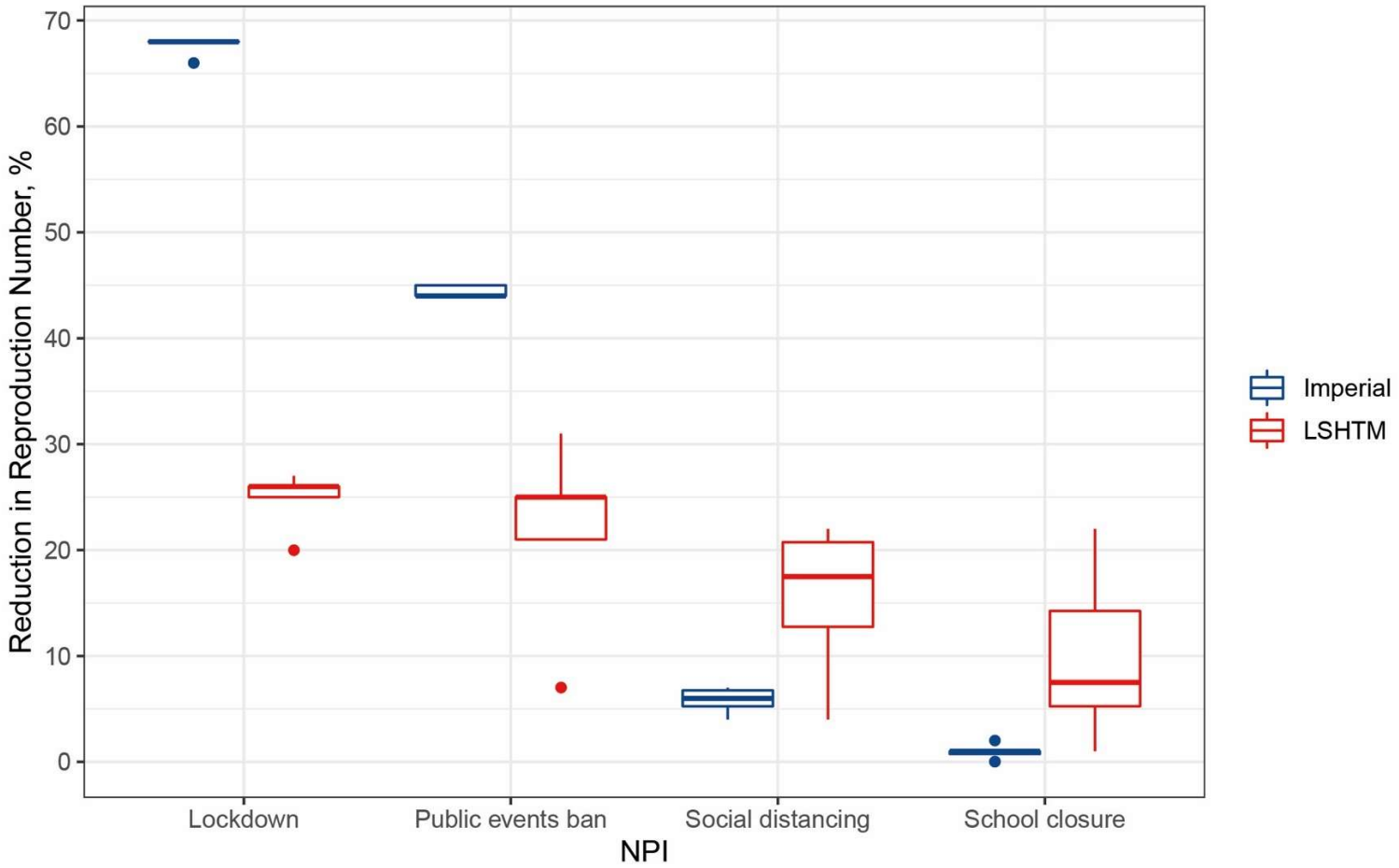

Figure 1. Observed reduction in reproduction number (R) by each NPI among 10 European countries [based on comparison of R estimates for periods immediately before and after the date of intervention introduction]**.** In each country, only NPIs that were separately introduced (i.e. not introduced with another NPI simultaneously) were included. Dots are outliers. The results were based on the following assumptions: 1. Sequence of NPIs did not modify reduction in R; 2. Time periods of NPIs did not modify reduction in R; 3. Definitions for each NPI were comparable among countries. [*Different sequence and time periods of application, and possible interaction effects, make strict comparisons of relative effect of interventions uncertain and potentially misleading and results should be interpreted in the light of this].*

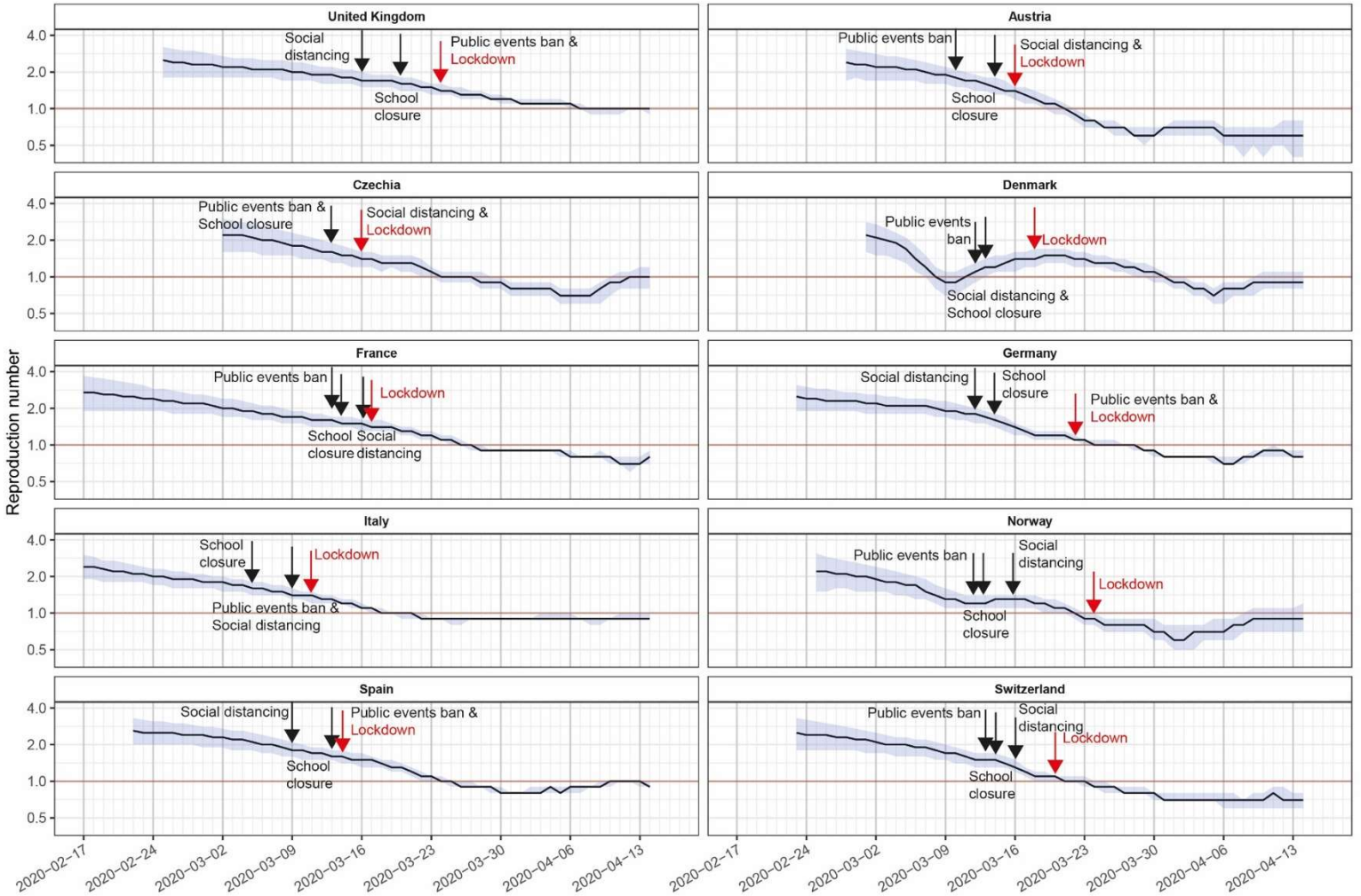

Figure 2. Changes in reproduction number (R) over time.[c] Estimates of R from LSHTM model [2]. Shaded areas denote 90% confidence interval.

[c] The impact of NPIs on R in this figure may not be a substantial because of change in population behaviour prior to official order for implementation of NPI, short time intervals between new intervention, and reduction of R in response to NPI is not immediate.

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Sub Question 2: What parameters were considered by countries in making decisions about lifting of population-level non-pharmaceutical interventions [NPIs]?

Aim:
This rapid review addresses whether countries considered time-varying "R0", often referred to as "R" or "Rt", and/or other parameters in making decisions about lifting NPI restrictions.

Methods:

We searched Government websites, Health ministry websites, newspaper articles and press releases for evidence of R in guiding exit strategies in pre-selected countries or regions. We searched evidence from Austria, the Czech Republic, Denmark, Germany, Italy, Norway, Spain, Finland, Hongkong and Wuhan, China.

We simultaneously looked at the latest available R estimates from the Government (where available) and estimates from the London School of Hygiene and Tropical Medicine (LSHTM) model which tracks R over time to explore any evidence of correlation between these values and decision-making. We analysed data on lifting of NPIs by grouping these into categories in relation to actions on schools, non-essential stores, offices, social distancing measures and on mandated/recommended use of face masks.

Results:

Our key findings include:

- Other than Denmark and Norway, no other national Government seems to have referenced R in the announcement of controlled re-opening. Germany referenced epidemiological data from the Robert Koch Institute which included R estimates.
- When R estimates and their 90% confidence intervals estimated by the LSHTM on April 12, 2020 are looked at, the estimates are close to 1, except Austria reporting a value as low as 0.6.
- For Denmark, Hongkong and Norway the R measured by Governments was <1 (see Table 1) at the time of announcements of lifting NPIs . However, Hongkong still decided to extend its restrictions by a further 14 days to 04th May 2020.
- All countries studied in this review have used different exit strategies (applying interventions in different sequences) but the commonality has been a phased cautious approach rather than a sudden lifting of all restrictions and continued bans on public gatherings.

Conclusions:

It remains unclear if the R values were the drivers or one of the contributors to the decision-making regarding exit strategies in these countries. A phased approach to lifting of restrictions has been used by all countries.

Limitations of this review:

Countries like Italy and Germany have separate national and state-wise or regional guidelines depending on the regional severity of affection and resource availability. It is observed that regional guidelines are sometimes contradictory to the national guidelines. This rapid review does not consider these regional estimates and measures.
Several Government websites had pages in local languages and information might have been missed owing to language barrier.

Table 2: Summary of lockdown exit date, estimated reproduction number [R] and exit strategies

Country	Date lockdown ordered	Date lockdown lifted	LSHTM		Government website		Schools re-open	Non-essential stores re-open	Offices resume activity	Social distancing measures lifted	Mask use recommended	Travel Policy
			R Estimate (90% CI)	Date	Estimate (95% CI)	Date						
Austria	16-Mar-20	14-Apr-20	0.6 (0.4 – 0.8)	12-Apr-20	--	--	No	Yes	No	No	Yes	Ban on non-essential travel
Czech Republic	16-Mar-20	20-Apr-20	1 (0.8 – 1.2)	12-Apr-20	--	--	No	Yes	Yes (specific)	Yes (only weddings upto 10 people)	Yes	Ban on non-essential travel
Denmark	18-Mar-20	15-Apr-20	0.9 (0.8 – 1.1)	12-Apr-20	0.6	06-Apr-20	Yes	No	Yes (Private sector)	No	No	Public transport upscaled to facilitate safe work commute in next phase. Advice against non-essential international travel

Country	Date lockdown ordered	Date lockdown lifted	LSHTM		Government website		Schools re-open	Non-essential stores re-open	Offices resume activity	Social distancing measures lifted	Mask use recommended	Travel Policy
			R Estimate (90% CI)	Date	Estimate (95% CI)	Date						
Germany	22-Mar-20	20-Apr-20	0.9 (0.8-1.0)	12-Apr-20	0.9 (0.8-1.1)	15-Apr-20	No	Yes	No	No	No	Ban on non-essential travel
Italy	11-Mar-20	14-Apr-20	0.9 (0.9-1.0)	12-Apr-20	--	--	No	Yes	Yes (Specific production industries)	No	Yes	Ban on non-essential travel
Norway	24-Mar-20	20-Apr-20	1 (0.7 – 1.3)	12-Apr-20	0.7	07-Apr-20	Yes (Day-care)	Yes	No	No	No	Ban lifted on travel to country holiday cabins. Ban on non-essential international travel
Spain	14-Mar-20	13-Apr-20	1 (1 – 1)	12-Apr-20	--	--	No	Yes	Yes	No	Yes	Ban on non-essential travel

Country	Date lockdown ordered	Date lockdown lifted	LSHTM		Government website		Schools re-open	Non-essential stores re-open	Offices resume activity	Social distancing measures lifted	Mask use recommended	Travel Policy
			R Estimate (90% CI)	Date	Estimate (95% CI)	Date						
Finland	16-Mar-20	15-Apr-20	1.1 (0.9-1.3)	12-Apr-20	--	--	No	No	Yes	No	No	15- Apr-2020 (intercity) - only essential travel allowed; 13-May-2020 (International)
Wuhan, China	23-Jan-20	08-Apr-20	1.08 (0.79-1.37)	07-Apr-20		--	No	Yes	Yes	No (public gatherings banned until end April)	Yes	Intercity flights, railways & public transport

Country	Date lockdown ordered	Date lockdown lifted	LSHTM		Government website		Schools re-open	Non-essential stores re-open	Offices resume activity	Social distancing measures lifted	Mask use recommended	Travel Policy
			R Estimate (90% CI)	Date	Estimate (95% CI)	Date						
Hong Kong	26-Jan-20	Extended to 4 May 2020	--	--	0.36 (0.01-1.81)	18-Apr-20	No (end May)	No (early May)	No (early May)	No	Yes	International flights uninterrupted with screening All public transportation uninterrupted

The UNCOVER network is committed to responding quickly and impartially to requests from policymakers for evidence reviews. This document has therefore been produced in a short timescale and has not been externally peer-reviewed.

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Appendix 1. Summary of the three methods to estimate R

- The Imperial College model focuses on modelling the effect of interventions in several European countries.
    - The group used COVID-19 deaths data from ECDC and calculated backwards from the deaths observed over time to estimate transmission that occurred several weeks prior.
    - The group assumed change in R is an immediate response to interventions and each intervention has the same effect on R across countries and over time, except for lockdown, in which a global effect and a country-specific effect were assumed.
    - Estimated R is less likely to reflect its daily change.
- The LSHTM model focuses on modelling changes in R over time on daily basis in different countries worldwide.
    - The group used COVID-19 daily number of cases provided by ECDC and estimated R from the daily number of cases and a specified serial interval distribution.
    - The group estimated daily R with a lag of ~14 days, and forecasted daily R for the recent 14 days.
    - Estimated R is more likely to reflect its daily change.
- The contact survey focuses on understanding the effect of interventions at a certain time point (see Appendix 3 for details).
    - Contact patterns are required in both before and after the interventions for the same population.
    - To calculate R after the interventions, a reference R before the interventions needs to be known.
    - Estimated R only represents the time period that the survey investigates. Multiple surveys are required to monitor changes in R.

Minimum number of cases required to estimate R

This depends on the model. For the country-specific estimate, the LSHTM model only includes countries if at least 60 cases have ever been reported in a single day. For the region-specific estimate, the LSHTM model only includes regions if at least 40 cases have ever been reported in a single day.

About estimating R in specific sector (e.g. hospitals, care homes)

Estimating R in specific sectors is challenging. For the modelling method, number of cases in each hospital/care home is not sufficient for modelling; combining different hospitals/care homes brings up the issue of heterogeneity. For the contact survey, this requires a reference R for the same setting but such reference R is not available; either contact survey or R from the general population cannot be applied to these sectors due to the differences in susceptibility and contact patterns.

Appendix 2. Comparisons of key assumptions and model properties between Imperial model and LSHTM model*

	Imperial model	LSHTM model	Comment
Data	Based on COVID-19 deaths; then conducted back-wards projection	Confirmed COVID-19 cases	Reported deaths are likely to be more reliable than cases
The model parameter serial interval	*Gamma* (6.5,0.62) — with a mean of 6.5 days	1000 samples from the mean of 4.7 days (95% CrI: 3.7, 6.0) and the standard deviation of 2.9 days (95% CrI: 1.9, 4.9) — with a mean of 4.7 days	Longer serial interval results in higher R, including the baseline R, i.e. R_0.
R and interventions	Changes in R is an immediate response to interventions; Each intervention has the same effect on R across countries and over time.	No assumption (i.e. independent)	The effect of interventions is unlikely to be the same in all countries.
Impact on R of testing and reporting practice	Could not be eliminated although expected to be less compared with models using COVID-19 cases.	Could not be eliminated.	Could be eliminated only if the testing and reporting practice remains constant, which is not the case in reality.

*The key assumptions and model properties included are not meant to be exclusive.
R=reproduction number

Appendix 3. Characteristics and key assumptions for estimating R by contact surveys

- Rationale: R is proportional to the dominant eigenvalue of the contact matrix, assuming that
    - the duration of infectiousness does not change
    - the probability that a single contact leads to transmission does not change
- A reference R, R_{ref} is needed and the corresponding contact matrix needs to be known. In the study by Jarvis et al, R_{ref} is assumed to follow a normal distribution with mean 2.6 and standard deviation of 0.54.
- Reduction in transmission can be estimated independent of R_{ref} by estimating the reduction in contact but the same assumptions in point 1 apply. It does not require number of cases/deaths that are needed by LSHTM or Imperial model.

Appendix 4. Current R estimates by LSHTM

Country	R by "nowcast"	Date	R by "forecast"	Date
United Kingdom	1 (0.9-1)	20-April-2020	0.9 (0.6-1.2)	01-May-2020
Austria	0.9 (0.6-1.2)	20-April-2020	0.9 (0-1.5)	01-May-2020
Czechia	0.7 (0.5-0.9)	20-April-2020	0.6 (0-1.1)	01-May-2020
Denmark	0.9 (0.8-1.1)	20-April-2020	0.9 (0-1.5)	01-May-2020
France	0.7 (0.7-0.8)	20-April-2020	0.6 (0-1.3)	01-May-2020
Germany	0.7 (0.7-0.8)	20-April-2020	0.6 (0.2-0.9)	01-May-2020
Italy	0.8 (0.8-0.9)	20-April-2020	0.8 (0.5-1)	01-May-2020
Norway	0.8 (0.6-1)	20-April-2020	0.7 (0-1.2)	01-May-2020
Spain	0.8 (0.7-0.9)	19-April-2020	0.6 (0.1-1.1)	01-May-2020
Switzerland	0.8 (0.6-0.9)	20-April-2020	0.7 (0.3-1.2)	01-May-2020