Acta Biomed 2023; Vol. 94, N. Supplement 3: e2023190 DOI: 10.23750/abm.v94iS3.14565

ORIGINAL ARTICLE

Innovative Covid-19 diagnostics and testing strategies in Italy, Denmark, UK, Israel and Sweden: a comparative analysis including tests, incidence and mortality

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Abstract. *Background and aim*: Detecting SARS-CoV-2 remains a critical component in the global effort to control COVID-19, particularly with the emergence of variants. Since the outbreak, diagnostic techniques have evolved to meet different contexts and needs. *Methods:* In this study, we analyzed the use of these techniques in five countries (i.e. Italy, Denmark, the United Kingdom, Sweden, and Israel) based on their specific national testing and contact tracing strategies. We also examined the number of tests performed per week, the positivity rate of tests, and the mortality rate in these populations during the same time periods. These countries were chosen based on the directives of the consortium involved in the CORONADX project. *Results:* During the three-year period under review, Italy and Denmark adopted large-scale testing strategies over a long period of time, with different results: in Italy an average of 4.5% of the population adhered to diagnosis, in Denmark 21%, while Israel reached 6.5%. The UK prioritised mass testing for short periods, outperforming the other countries with 1,882,596,198 total swabs and an average adherence of 28.1% of the population. Despite this, it recorded the highest number of deaths related to COVID-19 (211,155), with a lethality rate of 0.87%, second only to Sweden with 0.88%, where the average adherence to diagnosis was 1.7% of the population. Significant are the data for Israel, where as deaths increased, so did testing ($r = 0.62$, $p < 0.001$). *Conclusions:* To control future outbreaks it's fundamental satisfying the need for effective testing strategies and government communication, equitable healthcare access, and education in public health and hygiene principles. (www.actabiomedica.it)

Key words: SARS-CoV-2, Covid-19, test, CORONADX, strategy, policy, contact tracing, cases, deaths

Introduction

An outbreak of severe viral pneumonia emerged in Wuhan, Hubei, China in December 2019 (1). Upon deep sequencing analysis of lower respiratory tract samples, a novel coronavirus was identified and named "Severe Acute Respiratory Syndrome coronavirus type 2" (SARS-CoV-2) (2). Since then, this enveloped, single-stranded, positive-sense RNA virus has spread over the world, causing the extremely contagious "Coronavirus disease 19" (COVID-19) (3). From the outset, the Director-General of the World Health Organization (WHO) outlined the importance of testing as the backbone of the COVID-19 response, urging all countries to prioritize testing (4).

Table 1. Main COVID-19 diagnostics options: targets, specimens, purposes, performances, strengths and limitations (8-14).

	RT-qPCR	**Rapid Antigen-Detecting Tests**	**Serological tests**
Target	Viral RNA	Viral Antigen Proteins	Antibodies (IgG, IgM) targeting Spike protein
Specimens	Nasopharyngeal, oropharyngeal, or nasal swabs	Nasopharyngeal, oropharyngeal, or nasal swabs	Blood sample
Purposes	Detect ongoing infection	Detect ongoing infection	Detect ongoing or past infection / previous vaccination
Diagnostic performances	Highest sensitivity, highest specificity (Gold Standard)	High specificity, variable sensitivity according to the viral load and replication cycle	High specificity, variable sensitivity according to the stage of the infection
Potential use	Diagnostic	Diagnostic	Research studies
Limits	Need for specialized operators, accredited laboratories, time-consuming	Lower diagnostic performances compared to RT-qPCR	Cannot be used to determine whether an individual is currently infected or has been previously vaccinated

Tests for COVID-19 can be categorized into three main groups: molecular swab tests, rapid antigenic tests, and serological tests (Table 1) (5).

Both the WHO and ECDC have endorsed molecular tests as the "gold standard" for COVID-19 diagnosis (6). These techniques combine nucleic acid amplification tests (NAATs) with real-time reverse transcription PCR (RT-qPCR) to amplify viral RNA from respiratory tract samples obtained through nasopharyngeal, oropharyngeal, or nasal swabs. However, these tests have practical limitations such as the need for trained operators, accredited laboratories, and time-consuming processing (7).

Furthermore, it should be noted that the aforementioned diagnostic tools have been made available diachronically, with varying availability throughout the pandemic's various stages. As a result, testing policies have developed over time: Table 2 provides a quick synopsis of the history of Main COVID-19 Diagnostic Devices.

In order to address the growing demand for COVID-19 testing and expand testing capacity, there has been a need for tests that meet not only sensitivity and specificity criteria but also rapid testing characteristics that can facilitate their use in specific contexts, in order to develop mass-testing (15) Point of Care Tests (POCT), specifically Rapid Antigen-Detecting (RAD) tests detect SARS-CoV-2 proteins produced during replication in respiratory secretions or oral fluid/saliva in few minutes (16-18). Other advantages of these tests include their ease of use regardless of location, even at home or outside of healthcare facilities, and their lack of specialized staff, training, or medical instruments.

Serological antibody tests, on the other hand, can detect the presence or level of specific antibodies in the blood, which may suggest a previous infection or vaccination. However, these tests have significant variation in terms of sensitivity and specificity (19), and cannot estabilish whether an individual is currently infected or immune to the virus, as per the recommendations of the ECDC (20).

As a result of the high commercial demand for reliable diagnostic tests, and subsequent commercialization of a vast array of tests highly heterogenous in terms of diagnostic performance and reliability, the European Commission has published a searchable database of available data for commercial in vitro diagnostic (IVD) tests that are CE-marked, including analytical and clinical sensitivity and specificity (21). By April 8th, 2023, a total of 283 medical devices have been recorded, and an increasing number of in-house lab-developed tests with performance data in scientific papers are reviewed and updated regularly.

Following the launch of the global SARS-CoV-2 vaccination campaign and the subsequent emergence of Variant of Concern (22) (i.e. clear evidence indicating a significant impact on transmissibility, severity,

Table 2. Evolution of main COVID-19 Diagnostics Devices.

INTRODUCTION DATE	TEST	DESCRIPTION
10/01/20	RT-PCR	British Public England has announced that it has a new oral swab-based real-time RT-PCR of Novacyt-Primerdesign (15, 16).
15/01/20	RT-PCR	TestCenter Denmark's PCR test is accredited according by DANAK (Danish quality assurance authority for diagnostic tests) (17).
23/01/20	RT-PCR	Charité University Hospital(German)developed a second RT-PCR, which formed the basis of 250,000 kits distributed by the World Health Organization (18).
05/03/20	RT-PCR	LabCorp was the first among US commercial laboratories to announce the nationwide availability of new RT-PCR-based COVID 19 tests (19).
16/03/20 18/03/20 19/03/20 21/03/20 30/03/20	RT-PCR	Hologic (20) Abbott Laboratories (21) Thermo Fisher Scientific (22) Cepheid (23, 24) LabCorp
02/04/20	Antibody Test	US FDA granted the first EUA for the First American Antibody Test (25).
01/05/20	Antibody Test	Swiss Quotient Limited announced the CE Mark for its MOSAIQ COVID-19 Antibody Test, which had a sensitivity of 100% and specificity of 99.8%, was designed as a specific serological screening (26).
03/05/20	Antigen Test	Swiss Roche received the EUA for a selective ELISA serological test (27).
08/05/20	Antigen Test	US Quidel Corp granted the FDA the first EUA for the antigen test: “Sofia 2 SARS Antigen FIA” (28).
21/05/20	Antigen Test (Thz Spectroscopy)	Israel Ben Gurion University was ahead of its time by presenting the one-minute rapid test with 90% accuracy, based on the “resonance change in the THz spectral range” shown by the coronavirus through THz spectroscopy (29).
06/11/20	Antibody Test	US FDA gave approval GenScript USA Inc’s first serological test that detected neutralizing antibodies from recent or previous infection linked to Sars-cov-2, and issued EUA authorization for the cPass SARS-CoV-2 Neutralization Antibody Detection Kit (30, 31).
06/11/20	Antigen Test	Lucira Health obtained EUA clearance for the first US home rapid molecular diagnostic test, that made available to consumers, the use of the test kit without the need for a healthcare professional, for a rapid 30-minute testing procedure at home. (32, 33)
14/01/21-22/02/21 23/02/21-25/04/21 26/04/21 - 06/06/21 07/06/21- 29/11/21 29/11/21	RT- PCR	Danish SSI - Delta PCR v1.0 Delta PCR v2.0 Delta PCR v3.0 Variant PCR v4.0 Variant PCR v5.0 (34)
11/06/21	Antigen Test	US Innova, SARS-CoV-2 Rapid Qualitative Test approved in UK (35).

and/or immunity that is likely to have an impact on the epidemiological situation), SARS-CoV-2 diagnostic tests were implemented to ensure genomic surveillance, allowing variants to be distinguished according to CDC (23) and WHO defined classifications. Because early diagnosis and reporting can have a significant impact on outbreak control and prevention, the CORONADX project was created as an EU-funded Horizon 2020 project to develop and deliver quick, portable, and cost-effective tools for on-site coronavirus diagnosis, allowing for fast case detection and surveillance. In order to proper design new diagnostic tests, a preliminary assessment of the impact of diagnostic tests and diagnostic policies on the pandemic was considered the cornerstone for adapting diagnostics solutions and properly design new diagnostic options. Therefore, the aim of this study was to compare how COVID-19 diagnostics were used in five different contexts by analyzing specific national testing strategies in Italy, Denmark, UK, Israel and Sweden, and finally to examine the effects in terms of the number of tests performed per day, the percentage of positive tests per day, and mortality rates.

Methods

Testing policies. An electronic search was conducted in the official websites and repositories of the five nations participating in the CORONADX project (i.e. Italy, Denmark, the United Kingdom, Israel, and Sweden). Italian Health Ministry (https://www.salute.gov.it) reconstructed testing policies from 2020 to 2022, Israeli Ministry of Health official statements by its website (https://www.gov.il/en/departments/ministry_of_health/govil-landing-page), Danish Ministry of Health papers (https://sum.dk/english), UK government website (https://www.gov.uk/coronavirus), documents from Public Health Agency of Sweden Trends in contact tracing were obtained from Find Dashboards (https://www.finddx.org/covid-19/).

Testing strategies were classified into four levels (0 to 3), whose working definition is provided as follows:

- Level 0: no specific COVID-19 testing policy;
- Level 1: testing of key groups, such as people presenting specific symptoms such as Influenza-Like-Illness (ILI) and Severe Acute Respiratory Infection, close contacts, high risk groups (25), and the most exposed for working conditions (first and foremost Health Care Workers);
- Level 2: testing of all people presenting any kind of symptoms linked to COVID-19 infection (26);
- Level 3: countries that have adopted Open Public Testing, including asymptomatic persons.

Data about COVID-19. National data about incident cases, COVID-19 associated deaths and performed tests were retrieved from the following official websites: ECDC for Denmark and Sweden (https://www.ecdc.europa.eu/en/covid-19/data), the Italian Ntional Institute for Nuclear Physics (https://covid19.infn.it/) for Italy, UK Health Security Agency (https://coronavirus.data.gov.uk/), and the Israel Ministry of Health for Israel (https://datadashboard.health.gov.il/COVID-19/general).

Data were initially retrieved at the national level and pooled as weekly estimates. As United Kingdom (68,138,484 inhabitants by 2023 estimates, with a population density of 270.7 inhabitants/km^2), Italy (58,853,482 inhabitants by 2022 census, 201.3 inhabitants/km^2), Sweden (10,481,937 inhabitants by 2022 census, 25 inhabitants/km^2), Denmark (5,935,619 inhabitants by 2023 estimates, 138.2 inhabitants/km^2), and Israel (9,702,560 inhabitants by 2023 estimates, 440 inhabitants/km^2) are quite heterogeneous not only from a demographic standpoint, but also because of specific COVID-19 related features such as the timing for the implementation of non-pharmaceutical measures aimed at dealing with the SARS-CoV-2 pandemic, as well as their overall extent, we arbitrarily chose to normalize weekly rates in percent values by dividing the point values by the maximum value reported during the entire assessed timeframe (i.e. January 2020 - March 2023).

This timeframe was arbitrarily divided into two phases: the first began with the first reports of COVID-19 cases in Italy, which could be considered the start of the out-of-China COVID-19 pandemic, and continued until July 31st, 2021, the day after the administration of booster doses was authorized in Israel: at that time, all countries in our study had recorded at least 60% administration of one anti-SARS-CoV-2 vaccine. The second phase began on August 1st, 2021 with the first booster doses provided in Israel and ended on March 31st, 2023.

Statistical analysis

Analysis of Variance (ANOVA) was used to compare weekly estimates by participating countries, with Dunnet's multiple comparisons tests used as a post hoc test for the whole of the assessed timeframe. Across the comparisons, Italian estimates were assumed to be the reference category. At last, the association between normalized rates was assessed at country level using Pearson's correlation coefficient (r) and its corresponding p value. All comparisons were carried out using

R 4.0.3 and the packages epiR (v. 2.0.19), EpiReport (v. 1.0.1), and fmsb (0.7.0).

Ethical approval

No ethical approval was needed for this study, as no individual data were identifiable, and only aggregated data were analyzed and presented.

Results

Testing policy

Analysing the first Phase (From first COVID-19 Wave to July 31th, 2021), Denmark was the only country in the study that was able to make testing open for everyone during first COVID-19 wave (Level 3). Italy (28) and Israel (29) permitted open public testing during the second COVID-19 wave, although the latter only for a brief time (30). Sweden (31) and the United Kingdom (32), on the other hand, continued to screen only symptomatic patients (Figure 1). The United Kingdom warrants special consideration because it has been conducting free mass testing programs using lateral flow devices since November 2020 (33). A similar program was implemented in the Italian Region of Alto Adige Südtirol (34), but it was not duplicated at the national level. Vaccination efforts began in December 2020, with Israel serving as a model for their quick rollout. Denmark initiated a major free testing campaign for asymptomatic adults between March and May 2021, with the goal of shifting testing to randomized population checks during the colder months (35).

The target initially envisioned by Danish health authorities during the second Phase (i.e. from first booster administrations to December 31st, 2022) was not met due to the discovery of new Variant of Concern, particularly the Delta Variant (B.1.617.2). A highly contagious SARS-CoV-2 virus strain, it was first detected in India during the early stages of the pandemic (i.e. October 5th, 2020), but it was not until the second half of 2021 that it emerged globally as the leading cause of COVID-19 infection: since late April 2021, the proportion of cases caused by the ancestral Wuhan strain (i.e. Alpha variant) fell from more than 70% to around 42% as of mid-June, with the rise of Delta driving much of that shift, becoming dominant in most of the world

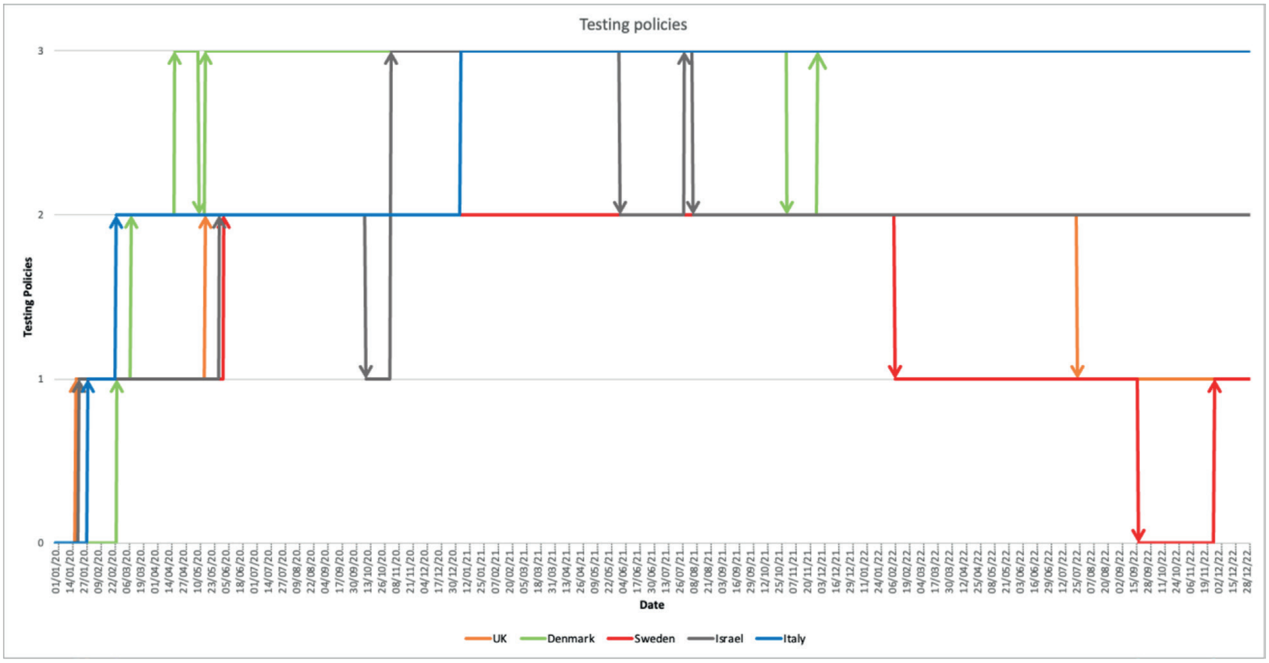


Figure 1. Summary reporting of the testing policies across the whole of the assessed timeframe, i.e. from the first COVID-19 cases reported in Italy (February 2020) to December 31st, 2022, the last available update from the source Authorities.

shortly before the emergence of the even more contagious Omicron Variant (B.1.1.529). The failure of mass screening tests in Denmark just before the winter season 2021 demonstrated how reinfection was probable, and decreasing tests would have been a bad idea: Denmark agreed to publish a document on testing on December 6th, 2021 (36) with a return to the open public testing policy. Sweden lifted most anti-COVID-19 restrictions by February 6, 2022, with RT-qPCR reserved for small groups. On April 1, 2022, the UK government announced the end of free testing for the general public, limiting the tests to key categories (37). During the second phase, Italy never changed its Open Public testing strategy. As the pandemic progressed, the government attempted to ensure that testing was available to everyone, regardless of financial circumstances, and provided funding for testing in both the public and commercial sectors. Testing was also available everywhere, including drive-throughs, hospitals, GP ambulatories, and at home with home-kits or USCA, units of doctors authorized to monitor patients' infectious and health condition. The Italian government approved the use of COVID-19 rapid antigen tests in the general population, beginning with their usage in airports and ports for individuals crossing borders. The Italian Health Ministry also issued guidelines for their use, including recommendations on who should be tested, how frequently testing should be done, and how the tests should be performed and interpreted. Furthermore, the government was involved in the establishment and implementation of COVID-19 testing requirements for certain sectors such as healthcare and education. For example, the government has mandated frequent testing for healthcare staff and students, and has provided funding to support these efforts. It also imposed travel restrictions to prevent the entry of additional COVID-19 cases. Anyone entering Italy from outside the country must provide a COVID-19 test that was negative within 48 hours of arrival. Travelers from high-risk nations must additionally undergo a 10-day quarantine upon arrival in Italy. In 2021, the Italian Health Ministry changed its testing guidelines to include recommendations for testing people who have recently traveled to areas with high COVID-19 transmission levels.

In terms of contact tracing policies (Figure 2), the analyzed countries took a quite disparate approach, considering three levels of tracing activity: no tracing, restricted tracing, and complete tracing. Surprisingly,

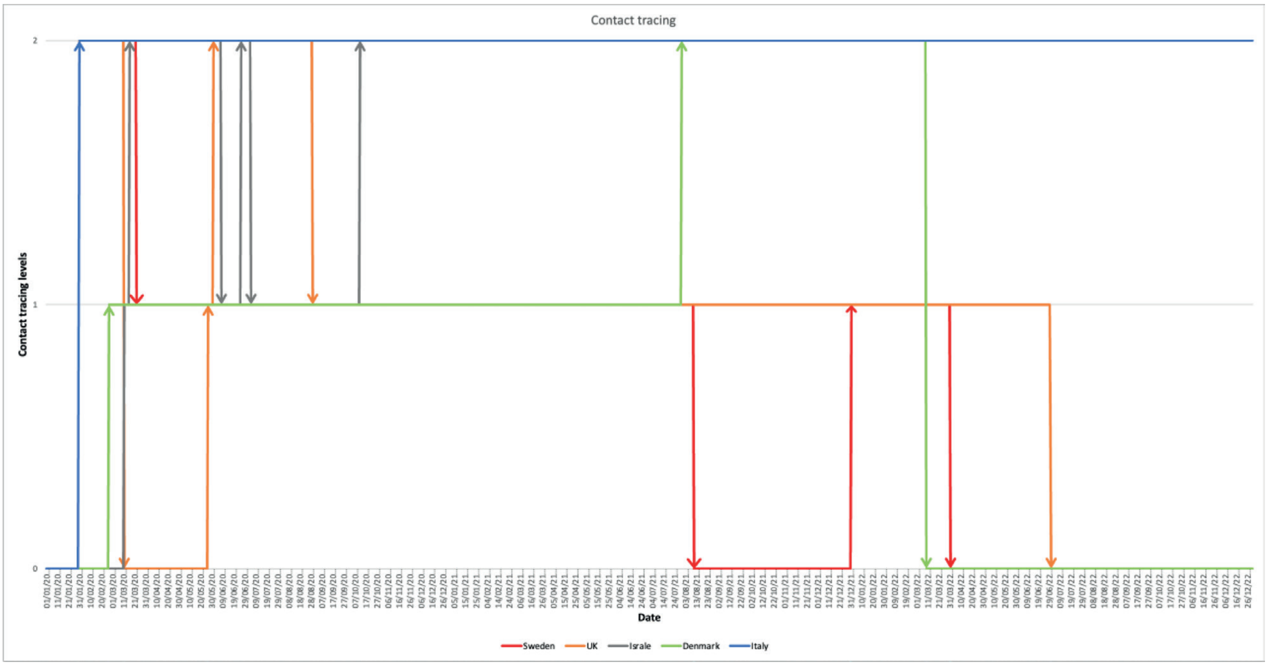


Figure 2. Summary reporting of the contact tracing policies across the whole of the assessed timeframe, i.e. from the first COVID-19 cases reported in Italy (February 2020) to December 31st, 2022, the last available update from the source Authorities.

Italy was the only country to sustain high contact tracing levels over both phases. During the first phase, Israel alternated between a broad spectrum tracking and a more limited approach in a few cases, eventually establishing a more comprehensive tracing in later stages until it was discontinued, whereas other countries (such as Denmark, the United Kingdom, and Sweden) only performed a more limited tracing in the

Table 3. Summary of the COVID-19 statistics in the 5 CORONADX countries (2020 – 2023).

	Italy	**Denmark**	**Sweden**	**Israel**	**U.K.**
Total Population (2020)	59.438.851	5.831.404	10.353.442	9.215.100	67.081.000
Last available estimates (year)	58,853,482 (2022)	5,935,619 (2023)	10,481,937 (2022)	9,702,560 (2023)	68,138,484 (2023)
Inception of testing campaign (date)	31/01/2020	27/02/2020	31/01/2020	23/01/2020	20/01/2020
Inception of NPI measures (date)	23/02/2020	03/03/2020	25/03/2020	17/03/2020	13/03/2020
Total tests performed	270,074,524	122,650,248	17,636,529	59,553,626	1,882,596,198
2020 (No./tot, %)	26,598,607 (9.8%)	6,535,240 (5.3%)	3,063,242 (17.4%)	7,798,269 (13.1%)	62,501,074 (3.3%)
2021 (No./total tests, %)	113,538,999 (42.0%)	95,106,382 (77.5%)	10,614,620 (60.2%)	36,439,118 (61.2%)	972,623,542 (51.7%)
2022 (No./total tests, %)	122,699,762 (45.4%)	20,820,726 (17.0%)	3,797,253 (21.5%)	14,899,135 (25.0%)	847,471,582** (45.0%)
2023* (No./total tests, %)	7,237,156 (2.7%)	187,900 (0.2%)	161,414 (0.9%)	417,104 (0.7%)	N.A.
Test per people (%)	4.5%	21.0%	1.7%	6.5%	28.1%
Total cases reported (No./total population, %)	25.695.311 (42.23%)	3.408.493 (58.45%)	2.701.687 (26.09%)	4.814.034 (52.24%)	24.311.933 (36.24%)
2020 (No./tot, %)	2.083.689 (8.11%)	161.230 (4.73%)	437.300 (16.19%)	419.660 (8.72%)	2.563.565 (10.55%)
2021 (No./total cases, %)	3.897.739 (15.17%)	622.472 (18.26%)	877.400 (32.47%)	962.277 (19.99%)	10.878.102 (44.74%)
2022 (No./total cases, %)	19.187.010 (74.67%)	2.604.737 (76.42%)	1.363.768 (50.48%)	3.381.613 (70.24%)	10.568.649 (43.47 %)
2023* (No./total cases, %)	526.873 (2.05%)	20.054 (0,59%)	23.219 (0.86%)	50.484 (1,05%)	301.617 (1,24%)
Total deaths reported	189,089	8,379	23,861	12,400	211,155
2020 (No./tot, %)	73,604 (38.92 %)	1,256 (14.98%)	9,616 (40,31 %)	3,336 (26,90 %)	75,239 (35,63 %)
2021 (No./tot, %)	63,643 (33.65 %)	2,000 (23.86 %)	5,719 (23,96 %)	4,923 (39,70 %)	74,688 (35,37 %)
2022 (No./tot, %)	47,545 (25.14 %)	4,526 (54.01 %)	6,952 (29.13 %)	3,805 (30.68 %)	50,941 (24.12 %)
2023* (No./tot, %)	4,297 (2.27%)	597 (7.12)	1,574 (6.59 %)	336 (2.70 %)	10,287 (4,87 %)
Case Fatality Ratio (2020 – 2023) (%)	0.74%	0.25%	0.88%	0.26%	0.87%
Mortality Rate (2020 – 2023) (%)	0.32%	0.14%	0.23%	0.13%	0.31%

Note: * = January 1st, 2023 to March 31st, 2023. ** = data available until May 19th, 2022.

first phase, which was substantially lifted during the second phase.

Epidemiological data

As demonstrated in Table 3, the UK has completed the most tests (1,882,596,198) since the outbreak began, despite available series interrupts with May 19th, 2022. Even though Italy has a total population substantially comparable to that of the UK, between 2020 and 2023 total tests accounted to less than 15% of overall British estimates (i.e. 270,074,524). Despite the fact that Denmark has a population that is roughly one-tenth that of Italy, approximately 122,650,248 tests were performed (i.e. 45% of all Italian samples), which is nearly 8 times more than those performed in Sweden, a country with a population that is nearly double that of Denmark. In total, over 59 million tests were conducted in Israel alone. In other words, the UK did 28.1 tests per 100 people, compared to 21.0 per 100 people in Denmark, 6.5 per 100 people in Israel, 4.5 per 100 people in Italy, and 1.7 per 100 people in Sweden.

The majority of SARS-CoV-2 registered cases occurred in Italy (No. 25.695.311), followed by the United Kingdom (No. 24.311.933), Israel (No. 4.814.034), Denmark (No. 3.408.493), and Sweden (No. 2.701.687). In other words, SARS-CoV-2 had infected more than half of the total population of Denmark (58.5%) and Israel (52.2%), a sizable proportion of the total population of Italy (43.2%), the United Kingdom (36.2%), and just 26.1% of the Swedish population. The corresponding crude annual incidence rates were 19.5% in Denmark, 17.4% in Israel, 14.4% in Italy, 12.1% in the United Kingdom, and 8.7% in Sweden. Surprisingly, the vast majority of instances were reported in Italy (74.7%), Denmark (76.4%), and Israel (70.2%) in 2022, while Sweden had a proportion of 50.5%. In contrast, most of UK cases (44.7%) were reported in 2021 rather than 2022 (43.4%).

During the same time period, the UK (211,155 deaths), Italy (189,089), Sweden (23,861), Israel (4,923), and Denmark (2,000) had the highest number of deaths, with a case fatality ratio ranging from 0.88% in Sweden to 0.87% in the UK, 0.74% in Italy, 0.26% in Israel, and 0.25% in Denmark.

Figure 3a shows normalized incidence rates. As demonstrated, the peak for incident cases in all CORONADX countries occurred in the fourth quarter of 2021 and the first months of 2022, following the rise of the VOC "omicron." Interestingly, two additional peaks were observed in both the United Kingdom and Israel in the initial weeks of 2021 and throughout the autumn months of 2021.No substantial differences were reported across the assessed countries, as the mean difference with the reference country (i.e. Italy) was estimated to 0.92% (95%CI -3.78 to 5.62, p = 0.970) for Sweden, 0.85% (95%CI -3.86 to 5.56, p = 0.977) for Denmark, 0.82% (95%CI -3.84 to 5.48, p = 0.979) for Israel, and 1.87% (95%CI -2.78 to 6.53, p = 0.723) for the UK.

When dealing with the performed tests (Figure 3b), a rapid increase in all estimates were reported in all of the assessed countries. In all countries, a sustained increase for performed tests was reported by the first semester of 2021 (i.e. VOC "delta"), and particularly in Denmark. Overall, the main peak was consistently identified in all countries between the last weeks of 2021 and the first ones of 2022. Assuming Italian estimates as the reference group, a mean difference of 10.37% (95%CI 2.99 to 17.75) was reported with Sweden (p = 0.003), and of 24.18% (95%CI 17.02 to 31.34) with Israel (p < 0.001), while no significant differences were reported with Denmark (mean difference 7.19%, 95%CI -0.36 to 14.73, p = 0.067), and United Kingdom (mean difference 5.52%, 95%CI -1.64 to 12.69, p = 0.175).

Regarding reported death rates (Figure 3c), visual inspection identified two early peaks in Italy, Sweden and United Kingdom during the first months of 2020 (i.e. the "First wave"), with a second peak at the end of the summer season 2020 (i.e. the beginning of the "second wave"). Since January 2021 (i.e. the start of global vaccination campaign), normalized death rates radically decreased in all of the assessed countries until the peak reported by Israel by the autumn of 2021. A third peak that only involved Israel, Denmark, and Sweden (all of them reporting a normalized rate comparable to that of the first wave) was reported during the first half of 2022, during the emergence of VOC "omicron".

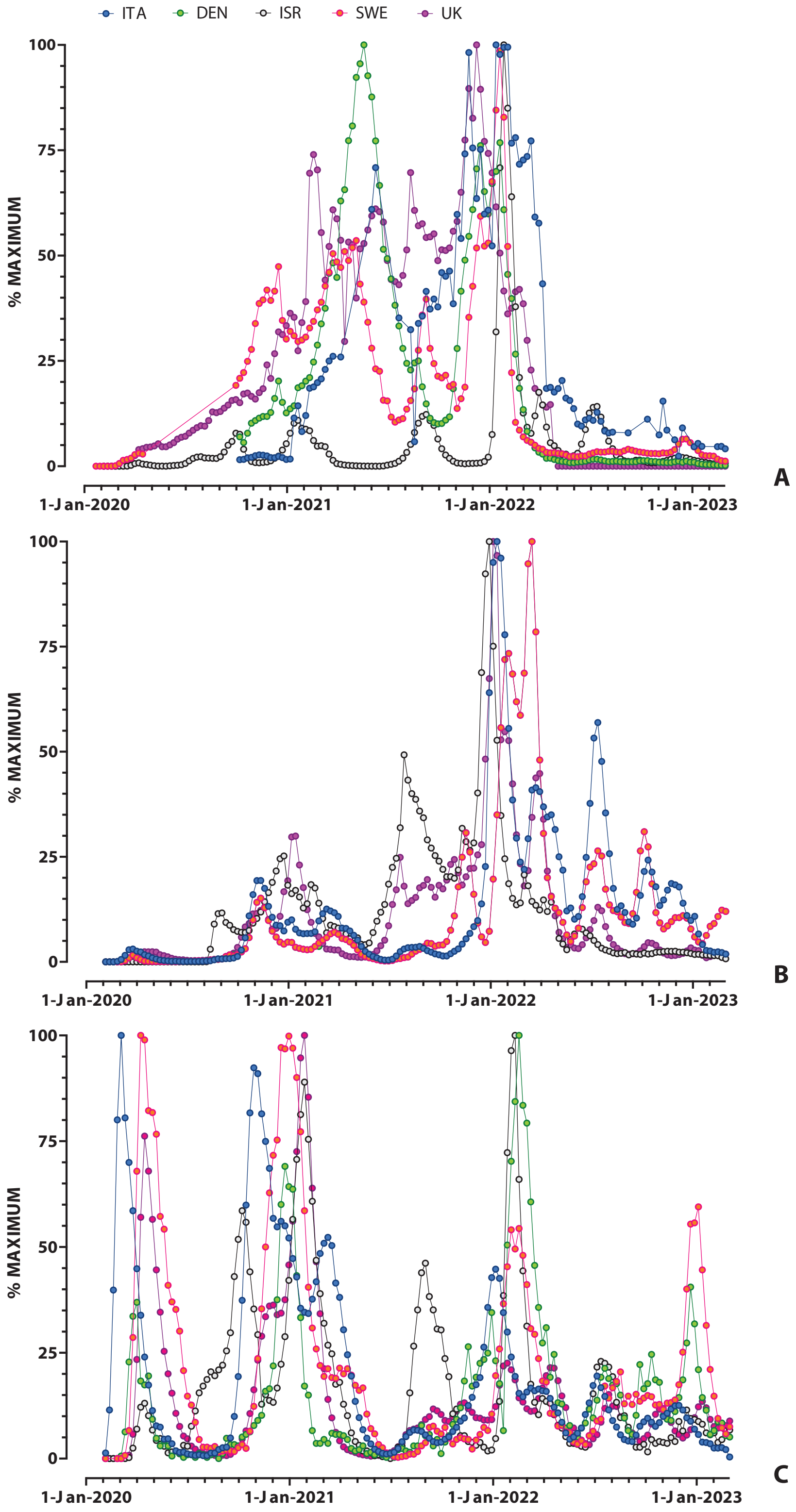


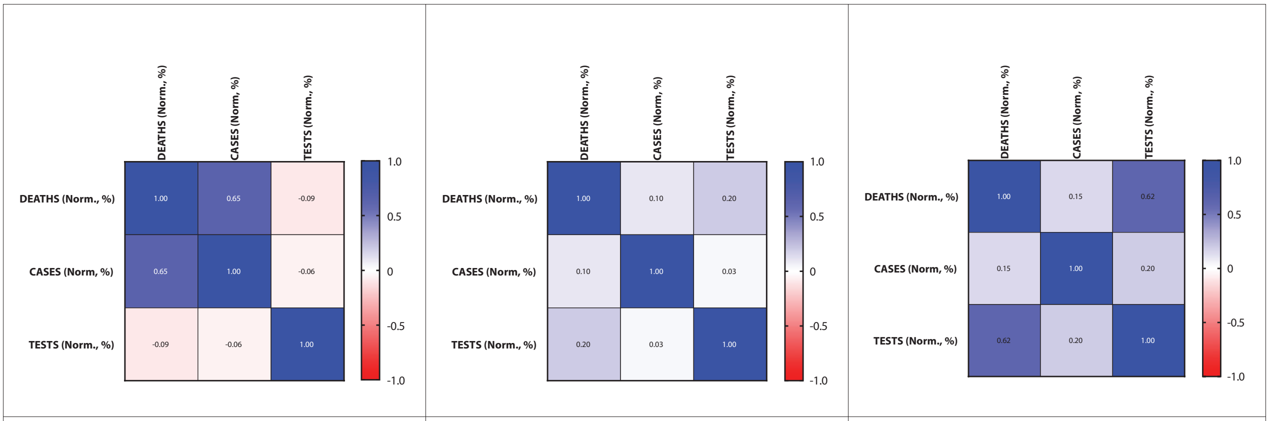
Figure 3. Time trend of weekly tests (a), incident cases (b), and reported deaths (c) associated with COVID-19 in Italy, Denmark, Israel, Sweden, UK, since the inception of the SARS-CoV-2 pandemic. All values are normalized as 100% value by maximum weekly estimate.

Table 4. Correlation of the weekly estimates for deaths, cases and total tests, all of them normalized as 100% values by the maximum weekly estimate (Pearson's r value with their corresponding 95% Confidence Intervals; p value).

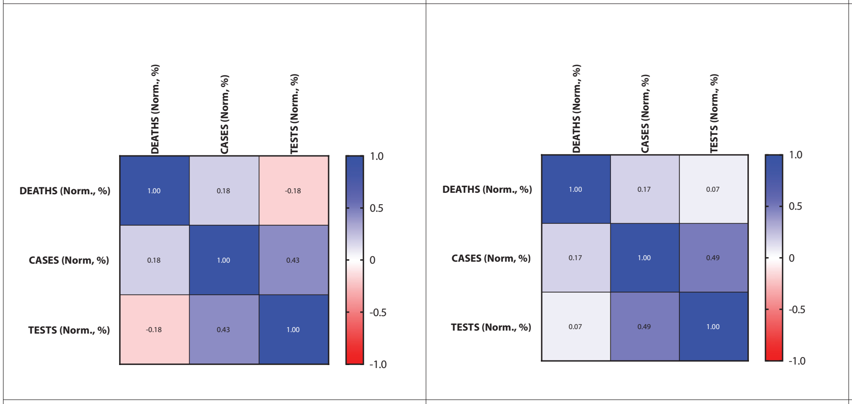
	Deaths (Norm., %)	**Cases** (Norm., %)	**Tests** (Norm., %)
Denmark			
Deaths (Norm., %)	-	**0.181 (0.547; 0.730)** **< 0.001**	-0.176 (-0.261; 0.083) 0.305
Cases (Norm., %)	**0.181 (0.547; 0.730)** **< 0.001**	-	0.428 (-0.233; 0.113) 0.491
Tests (Norm., %)	-0.176 (-0.261; 0.083) 0.305	0.428 (-0.233; 0.113) 0.491	-
Sweden			
Deaths (Norm., %)	-	0.097 (-0.059; 0.248) 0.224	**0.198 (0.032; 0.353)** **0.020**
Cases (Norm., %)	0.097 (-0.059; 0.248) 0.224	-	0.032 (-0.137; 0.199) 0.712
Tests (Norm., %)	**0.198 (0.032; 0.353)** **0.020**	0.032 (-0.137; 0.199) 0.712	-
Israel			
Deaths (Norm., %)	-	0.147 (-0.005; 0.293) 0.058	**0.615 (0.511; 0.702)** **< 0.001**
Cases (Norm., %)	0.147 (-0.005; 0.293) 0.058	-	**0.196 (0.045; 0.338)** **0.011**
Tests (Norm., %)	**0.615 (0.511; 0.702)** **< 0.001**	**0.196 (0.045; 0.338)** **0.011**	-
Italy			
Deaths (Norm., %)	-	**0.181 (0.029; 0.324)** **0.020**	-0.176 (-0.361; 0.022) 0.081
Cases (Norm., %)	**0.181 (0.029; 0.324)** **0.020**	-	**0.428 (0.252; 0.577)** **< 0.001**
Tests (Norm., %)	-0.176 (-0.361; 0.022) 0.081	**0.428 (0.252; 0.577)** **< 0.001**	-
United Kingdom			
Deaths (Norm., %)	-	**0.171 (0.019; 0.315)** **0.027**	0.068 (-0.085; 0.218) 0.382
Cases (Norm., %)	**0.171 (0.019; 0.315)** **0.027**	-	**0.494 (0.370; 0.601)** **< 0.001**
Tests (Norm., %)	0.068 (-0.085; 0.218) 0.382	**0.494 (0.370; 0.601)** **< 0.001**	-

As for incident cases, non-significant differences were reported across the sampled countries, as the mean difference with the Italian figures was estimated to -2.77% (95%CI -8.48 to 2.94, p = 0.578) for Sweden, 4.10% (95%CI -1.64 to 9.84, p = 0.239) for Denmark, 2.55% (95%CI -3.12 to 8.23, p = 0.639) for Israel, and 5.12% (95%CI -0.55 to 10.80, p = 0.090) for the United Kingdom.

As shown in Table 4 and Figure 4, a positive correlation between incident cases and reported deaths



A. Denmark **B.** Sweden **C.** Israel



D. Italy **E.** United Kingdom

Figure 4. Correlation matrix of the weekly estimates for deaths, cases and total tests in Denmark (a), Sweden (b), Israel (c), Italy (d) and United Kingdom (e), all of them normalized as 100% values by the maximum weekly estimate (Pearson's r value).

associated with a diagnosis of COVID-19 was reported in Denmark (r = 0.648, 95%CI 0.547 to 0.730, $p < 0.001$), Italy (r = 0.181, 95%CI 0.029 to 0.324, p = 0.020), and United Kingdom (r = 0.171, 95%CI 0.019 to 0.315, p = 0.027). On the contrary, a positive correlation between performed tests and deaths was reported in Sweden (r = 0.198, 95%CI 0.032 to 0.353, p = 0.020), and Israel (r = 0.615, 95%CI 0.511 to 0.702, $p < 0.001$), while a positive correlation between performed tests and incident cases was identified in Israel (r = 0.196, 95%CI 0.045 to 0.338, p = 0.011), Italy (r = 0.428, 95%CI 0.252 to 0.577, $p < 0.001$), and United Kingdom (r = 0.494, 95%CI 0.370 to 601, $p < 0.001$). No significant negative correlation was found.

Discussion

Our study has stressed huge heterogeneities across the various countries included in the CORONADX project in terms of testing policies as well as epidemiological features. In fact, such differences may be only partially explained in terms of timely response to the diachronous nature of the COVID-19 pandemic, rather reflecting the underlying cultural attitude to this unprecedent stressor. While Italy was the first to apply lockdown measures, a systematic testing program was not launched until the end of January. Interestingly, despite the NPI tactics employed in the UK and Italy were basically similar, at least in Phase 1 of the pandemic, the UK surpassed Italy and other examined countries in terms of testing done. However, these efforts seemingly did not lead to a better control of the pandemic neither to better epidemiological features, as suggested by the estimates for COVID-19 related mortality and case fatality ratio. In other words, a more aggressive approach did not mean a better containment of the pandemic, neither in early nor in later stages as suggested by the univariate correlation analyses between tests performed, incident cases and reported deaths. The positive correlation we were able to stress across the various countries should be in fact conveyed rather as a crude correlation (i.e. higher the infection rates across the general population, greater the number of performed tests) than in causal terms. Interestingly enough, our analyses hints towards a limited value for the early diagnosis of pauci- and asymptomatic cases, whose role in the spreading of the pandemic, particularly in early stages, has been often stresses, and that were therefore addressed as a promising target for mass-scale testing campaign. In this regard, the experience from Italian province of Südtirol had guaranteed an early warning about the reliability of this approach from a Public Health point of view, and in fact the National level did not follow this innovative approach envisioned from the local Health Authorities. On the other hand, the radically opposite approach from Sweden, where the testing policies led to less than 1.7 tests per 100 inhabitants compared to the 28.1 per 100 inhabitants from UK, 21 per 100 inhabitants from Denmark, 6.5 per 100 inhabitants for Israel, and 4.5 per 100 inhabitants for Italy, was associated with the highest case fatality ratio (0.88% vs. 0.87% in UK, 0.74% in Italy, 0.26% in Israel, and 0.24% in Denmark).

From a Public Health Point of view, out study has stressed several potential strengths and limitations in the testing policies across the CORONADX Countries. First of all, the coordination between Government and regions was inconsistent across the various countries. In Denmark, TestCenter Denmark (TCDK) (38), was established for coordination between government and regional test sites, while Italy (39) and Sweden (40) suffered from decentralization of the healthcare system and conflicting strategies between regions. Reasonably, a more focused approach allowed Denmark to perform more targeted interventions that in turn contributed to the better features in terms of CFR when compared to other countries.

Second, we reported an inconsistent attention on minorities groups. In Israel, at the beginning there was a lack of attention given to minority groups such as the ultra-Orthodox Jewish community and Arab population. In both communities, not only testing campaigns but even the implementation of NPI was particularly difficult to achieve, for both cultural and political reasons and both communities have been acknowledged as hot points for new COVID-19 outbreaks in later stages of the pandemic (41).

Despite its potential interest, our study is affected by several limitations. Firstly, our study relies on data provided by National Authorities, whose quality has been often questioned. Moreover, our data are affected by several interruption in the time series, and all our estimates should be therefore cautiously acknowledged as representative of the whole of the pandemic.

Conclusions

Comparison between countries outlined some necessities for the future, first of all editing national and regional testing strategies to control next epidemics, by allocating the available resources (in this case diagnostic devices) in the specific settings, ensuring appropriate roles for the parts involved and identifying the coordinator between healthcare system, government and laboratories infrastructures; Government role in creating trust among general population, with good communication, transparency in statements and data sharing. Another pillar is guaranteeing access to healthcare for all people, without social distinctions, focusing on vulnerable minority groups in view of their unique characteristics, needs, culture and behaviors. At last, teaching everyone the importance of education in public health and hygiene principles.

Funding: CORONADX Project (H2020). Contract No: 101003562.

Ethic Committee: No ethical approval was needed for this study, as no individual data were identifiable, and only aggregated data were analyzed and presented.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors contribution: P.M., M.S., L.G., A.O., C.R., C.S. provided substantial contributions to the conception and design of the study, acquisition of the data, or analysis and interpretation of the data; 2) P.M., M.S., L.G., A.O., C.R., C.S. drafted the article or revised it critically for important intellectual content; and 3) P.M., M.S., L.G., A.O., C.R., C.S. gave the final approval of the version to be published.

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Received: 08 April 2023
Accepted: 06 June 2023

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