Research paper

SARS-CoV-2 transmission risk from asymptomatic carriers: Results from a mass screening programme in Luxembourg

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ABSTRACT

Background: To accompany the lifting of COVID-19 lockdown measures, Luxembourg implemented a mass screening (MS) programme. The first phase coincided with an early summer epidemic wave in 2020.
Methods: rRT-PCR-based screening for SARS-CoV-2 was performed by pooling of samples. The infrastructure allowed the testing of the entire resident and cross-border worker populations. The strategy relied on social connectivity within different activity sectors. Invitation frequencies were tactically increased in sectors and regions with higher prevalence. The results were analysed alongside contact tracing data.
Findings: The voluntary programme covered 49% of the resident and 22% of the cross-border worker populations. It identified 850 index cases with an additional 249 cases from contact tracing. Over-representation was observed in the services, hospitality and construction sectors alongside regional differences. Asymptomatic cases had a significant but lower secondary attack rate when compared to symptomatic individuals. Based on simulations using an agent-based SEIR model, the total number of expected cases would have been 42·9% (90% CI [-0·3, 96·7]) higher without MS. Mandatory participation would have resulted in a further difference of 39·7% [19·6, 59·2].
Interpretation: Strategic and tactical MS allows the suppression of epidemic dynamics. Asymptomatic carriers represent a significant risk for transmission. Containment of future outbreaks will depend on early testing in sectors and regions. Higher participation rates must be assured through targeted incentivisation and recurrent invitation.
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1. Introduction

The COVID-19 pandemic has created an unprecedented public health crisis with a deep impact on health, social life, and the economy. Governments are devising new strategies to limit the impact of the evolving pandemic on their healthcare systems and societies. In the absence of wide-spread immunity, containment strategies are limited to testing and tracing [1-3].

Research in context

Evidence before this study

The COVID-19 pandemic imposes unprecedented challenges to governments and public health officials in containing population-wide transmission of SARS-CoV-2. Mass screening (MS) has been suggested as a means to systematically identify positive carriers including asymptomatic individuals. It was for example applied early on in the pandemic in South Korea and recommended on a national level for the United Kingdom. However, the design and implementation of MS programmes imposes significant logistical, methodological and data analysis challenges. Furthermore, recurrent questions over the effectiveness of such programmes have been posed, especially over the role of asymptomatic carriers in triggering and sustaining infection chains. To accompany the progressive lifting of lockdown measures, Luxembourg implemented a MS programme covering its entire population.

Added value of this study

Our study presents the major results and lessons learned of the implemented population-wide screening programme. Rather than perform MS in a single instance, the test strategy was based on social connectivity within activity sectors. This allowed the programme to build up practicable test capacity while ensuring coverage of specific at-risk sectors at high resolution while the general population was screened at lower resolution. The resolution of the screening was dynamically adjusted based on prevalence in the respective sectors and the population. Based on a participation of 49% amongst the resident population and 22% amongst cross-border workers, the MS allowed identification of 1,099 cases corresponding to 26% of positive cases related to an early summer epidemic wave. We show that a population-wide screening programme is able to affect the epidemic dynamics in close coordination with classical contact tracing.

Importantly, our study highlights that asymptomatic individuals represent a significant risk for transmission.

Implications of all the available evidence

Our study confirms that MS via a pooled rRT-PCR strategy and contact tracing allows the population-wide control of viral transmission. The finding that asymptomatic individuals are similarly infectious as symptomatic patients implies that population-wide containment strategies have to rely on MS to ensure the early breaking of infection chains. Containment of future outbreaks will critically depend on early testing in work sectors and geographical regions. Our analyses, based on the situation and capacities in Luxembourg, imply that a threshold of 150 positive cases per 100,000 per week should trigger the testing of entire groups. Higher participation rates have to be assured through targeted incentivisation and recurrent invitations.

In Spring 2020, it became clear that asymptomatic including pre-symptomatic carriers could transmit the virus [4,5]. Based on the estimated serial interval and incubation period, modelling suggested that up to 44% (25-69%) of transmission occurred just before symptoms appear [6]. This, together with apparent overdispersion [7], drew into question classical pandemic containment strategies. As the population-wide exposure in Luxembourg was estimated to be 2·1% in late April [8], large-scale antibody screening would not have been

efficient and would not have supported mitigation measures including contact tracing. Furthermore, given the large susceptibility for infection, the acquisition of herd immunity was not considered an option.

The Luxembourg Government imposed stringent lockdown measures in mid-March. The gradual easing of restrictions was accompanied by a population-wide SARS-CoV-2 screening programme aimed at pre-emptive breaking of infection chains. Our approach hinged on social connectivity as the key parameter for the stratification of the population, independent of COVID-19 symptoms, or potential contact with infected carriers. The number of expected social interactions defined the testing frequency per activity sector. This design resulted in 'adaptable testing' using differing testing frequencies, which were dynamically adjusted based on prevalence in the respective sectors.

Here we provide a detailed description of the mass screening (MS) programme, analyse the results of the first phase (25th May until 15th September 2020) including contact tracing information and model the impact of the programme on epidemic dynamics. We show that the population-wide screening programme with a participation rate of 49% among residents was able to contain the epidemic dynamics in close coordination with classical contact tracing. According to our data, asymptomatic SARS-CoV-2 carriers are to be considered as infectious as symptomatic individuals. Therefore, the success of MS critically depends on broad participation and incentivisation.

2. Methods

2.1. Logistics

To facilitate the sampling of the entire Luxembourg resident population along with cross-border workers, a pre-analytic workflow with 17 drive- or walk-through sampling stations was established. The analytical capacity reached up to 20,000 tests/day with a turnover of two working days.

2.2. Assay

Real-time reverse transcription polymerase chain reaction (rRT-PCR) was performed using the Fast Track Diagnostics (FTD)^{TM} SARS-CoV-2 single well dual-target (ORF1ab, N gene) assay (Fast Track Diagnostics, Esch-sur-Alzette, Luxembourg) for nucleic acids extracted from oropharyngeal swabs.

To save time and costs, an implemented pooling strategy involved mixing the samples from 4 different individuals prior to RNA extraction and re-analysing samples from a positive pool individually a second time [9-15]. Pool size selection for a one-stage pooling strategy was driven by identifying a suitable trade-off between estimated prevalence in asymptomatic SARS-CoV-2 carriers, analytical sensitivity and specificity (both 100% according to the rRT-PCR kit's manufacturer) as well as technical and practical constraints. Given the prevalence of asymptomatic SARS-CoV-2 carriers at 0·3% at the time of implementation and allowing an increase of prevalence to 10% [8], the optimal pool size was determined as four [16]. The pooling strategy presented 100% sensitivity and 100% specificity when compared with individual sample processing (deconvoluted RNA extraction and rRT-PCR testing; Suppl. Note 1). Thus, any uncertainty that may arise from false positives or false negatives was not accounted for in the data analysis.

2.3. Data source and population

All confirmed positive cases of SARS-CoV-2 detected by rRT-PCR were reported on a mandatory basis by the clinical laboratory and were automatically included in the centralised contact tracing management system of the Health Directorate (Ministry of Health, Luxembourg). Once a new positive result was transmitted via secure

electronic reporting to the Health Directorate, the index case was contacted by phone typically on the same day. A health questionnaire including typical COVID-19 symptoms (headaches, myalgia, fever, runny nose, sore throat, cough, loss of smell, diarrhea, etc.) was completed. Positive cases were instructed to self-isolate immediately and avoid contact with other household members. All high-risk contacts which occurred within 48 hours before symptom onset (or before the date of test if asymptomatic) were ordered to self-quarantine. A contact was considered high-risk if there was physical contact or proximity ($<$ 2 meters) to a case for at least 15 minutes without wearing a mask. For each quarantined contact, a laboratory test was automatically prescribed on the 5th day after the date of last contact. If the test was negative, the quarantine ended automatically on the 8th day and was followed by 7 days of self-surveillance. If the test was positive, the person was contacted again as a new positive case thereby starting the contact tracing procedure anew. If the contact did not take a test before the 7th day, the period of quarantine was automatically extended by 7 days to a total of 14 days.

Asymptomatic individuals are those that did not report symptoms at the time of the notification of the positive test result. Thereby, the "asymptomatic" group included individuals who were either presymptomatic or truly asymptomatic. Similarly, symptomatic individuals may have been asymptomatic at the time of sampling, particularly presymptomatic carriers who subsequently developed symptoms.

The COVID-19 surveillance data was linked to the national database managed by General Inspectorate of Social Security using the national identification number. The personal data were available only to the contact tracing team and were transmitted in aggregated, pseudonymised form to the authors.

2.4. Statistical analyses

Two logistic regression models were built to identify the determinants associated with participation in MS (Yes, No) and being tested positive (Yes, No). Models were adjusted for the following variables: gender (Male, Female), 10-year age categories, country of residence (Luxembourg, Belgium, France, Germany, Other), disposable income categories ($<$30k€/year, 30-60k€/year, 60-90k€/year, $\geq$90k€/year), number of total invitations to participate in MS (for the model on participation only), medication use in the past 6 months to treat a chronic condition (Yes, No), and risk population (high-risk, medium risk, general). We computed secondary attack rates (SAR) in three different ways: overall (SAR), in the household (SAR_H) and for close contacts (SAR_{CC}), both for symptomatic and asymptomatic cases. The SAR was defined as the number of contacts who became positive divided by the number of total contacts. SAR_H was defined as the number of contacts who became positive divided by the number of contacts who live in the same place as the positive index case. SAR_{CC} was defined as the number of close contacts who became positive divided by the number of close contacts who were placed in quarantine (the contact had a high-risk interaction with the COVID-19 positive case). For all SAR calculations, the new cases were considered positive contacts if they became positive within five days after the last date of contact with an index case.

To assess the impact of the MS programme on the epidemic dynamics, we developed an agent-based SEIR model similar to Covasim [17], tailored to the situation in Luxembourg. The epidemic model was based on detailed information of the social network considering actual household and workplace compositions obtained from the Luxembourg social security system. It also contained a disease module to integrate hospital data. This detailed description allowed for respecting the age distribution of infected people and considering specific activities as well as the resulting infection risks at workplaces. The testing of symptomatic individuals based on prescription, the testing by MS, and the testing of contacts of index cases were separated in the model and fitted to the observations (Suppl. Note 2).

2.5. Role of the funding source

1) Phase 1 of Large-Scale Testing was mandated by the Luxembourg Government, represented by the Ministry of Higher Education and Research, and the Ministry of Health.
2) Representatives of the Ministry of Higher Education and Research, and the Ministry of Health were involved in the design of this study as well as in the collection, analysis, and interpretation of data and in the writing of the article. Both Ministries approved submission of the manuscript for publication.

3. Results

3.1. Epidemic context

The first wave of the COVID-19 pandemic touched Luxembourg over the months of March and April 2020, followed by a relatively low number of positive cases from end of April onwards, when lockdown measures were gradually lifted (Fig. 1). A second wave started in late June. Although a plateau in the number of positive cases was reached in August, there was another increase in the middle of September when the school vacation period ended (Fig. 1). The first phase of the MS programme ran from 25th May until 15th September 2020 (herein contact tracing data was considered until 24th September). This period coincided with the second epidemic wave.

4. Approach to mass testing

4.1. Design of programme

The testing strategy was designed in an intercalated, three-layered approach: on a first level, we used estimates of exposure to disease and physical proximity to categorize activity sectors into high and medium risk [18,19]. Workers in high-risk sectors were invited every two weeks, resulting in high-frequency testing (Fig. 2A). On a second level, workers and other members of the population in medium-risk sectors were monitored at medium testing frequency by inviting one out of five per week such that individuals in medium-risk sectors were at least invited once (Fig. 2B). Similarly, one in every ten Luxembourg residents in other sectors or the general population was invited at low testing frequency each week to cover an even geographical distribution (Fig. 2C). Consequently, a set of representative cross-sectional cohorts were established. These population- and sector-based tracking cohorts proved essential for the early detection of sector- or region-specific infection clusters. On a third level, we reserved sufficient capacity for tactical targeting of specific population groups that revealed increased prevalences in the level two monitoring approach. If the prevalence in the sector-specific tracking cohorts exceeded 10%, the entire sector was tested; equally, adult members of every household in geographical areas with increased infection rates were invited. In this way, the testing frequencies were dynamically adjusted to maximize the use of available resources without compromising the efficiency of outbreak prevention (Fig. 2C). The established capacity allowed for a maximum test capacity of 10% of residents and cross-border workers per week.

4.2. Invitations and participation

The initial sets of invitations were sent out between 25th May and 27th July. The strategy critically depended on participation upon invitation, as the system was entirely based on a voluntary basis.
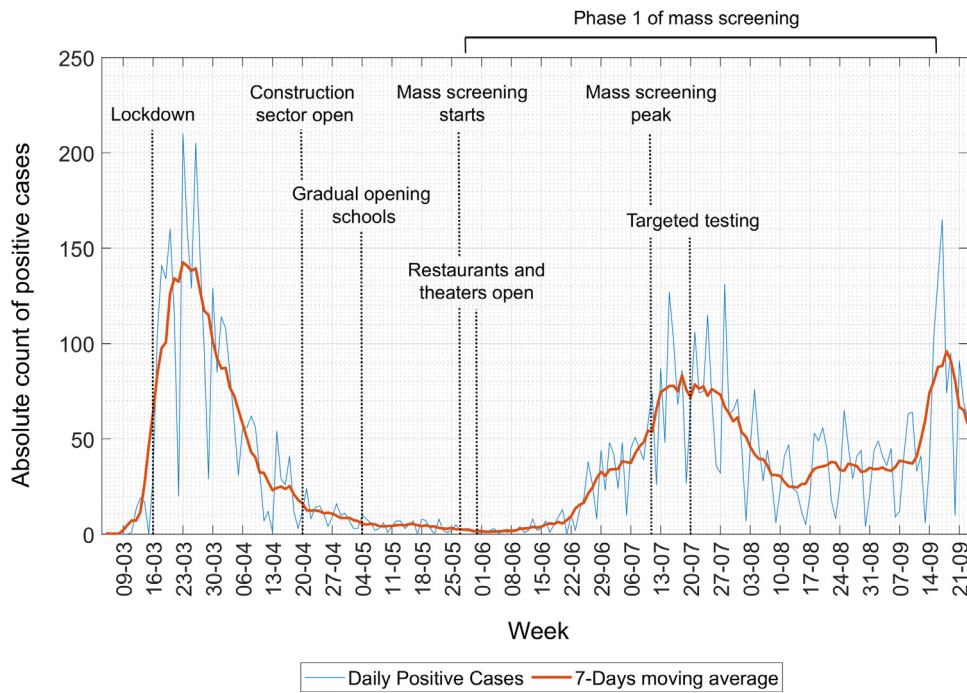
Fig. 1. Epidemic curve for COVID-19 in Luxembourg.

Invitations to residents and cross-border workers were sent out by postal mail (Suppl. Figure 1). Addressees were able to make an appointment via an online portal or by telephone, at one of the 17 test stations strategically distributed around the country. Compliance was very high, as 95% of the individuals who made an appointment were tested. Among the residents, 307,751, i.e. 49% of the population, took part in the MS, whereas among the cross-border workers, participation was 22·5% (87,198 individuals). A total of 566,320 tests was performed based on a total of 1,436,000 invitations, which corresponds to 69·7% of all tests performed between 25th May and 15th September and to an overall response rate of 39·4%. Participation in the programme differed markedly based on socio-demographic factors (Suppl. Note 3).

4.3. Contact tracing

The MS uncovered 850 index cases with an additional 249 cases resulting from contact tracing (Table 1). This corresponds to 26% of positive cases related to the epidemic wave. Among the index cases, 567 (67%) reported symptoms at the time of being informed of their positive test result (these may have been presymptomatic at the time of the test), whereas 283 (33%) were asymptomatic. Symptomatic cases were slightly older (mean=36·8 years) than asymptomatic individuals (34·2 years, Wilcoxon test $p < 0.0001$). Around 53% of all cases were diagnosed in men. rRT-PCR Cq-values were higher in asymptomatic cases (mean Cq=30·2) compared to symptomatic cases (mean Cq=28·9, Wilcoxon test $p < 0.0001$).
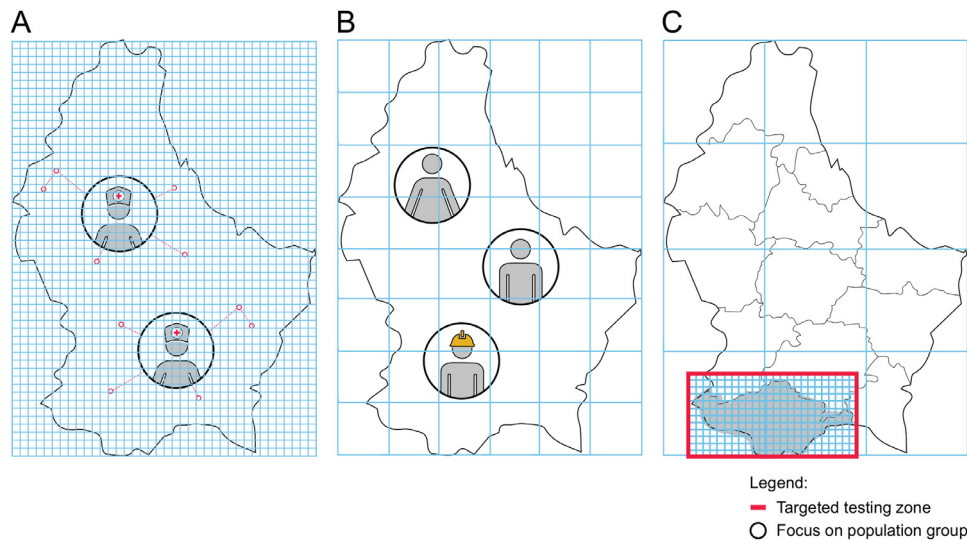

Fig. 2. Strategic and tactical mass testing.

The frequencies of invitations resulted in (A) high-frequency testing for high-risk sectors and (B) medium-frequency testing for medium-risk sectors. (C) The prevalence in the population was monitored at low testing frequency and targeted invitations were sent in the case of regional flare-ups.

Table 1
Characteristics of index cases identified through mass screening.

Characteristics		With symptoms (N=567)		Without symptoms (N=283)		Total (N=850)		P value
		N	%	N	%	N	%	
Sex	Female	278	49	125	44·2	403	47·4	0·18*
	Male	289	51	158	55·8	447	52·6	
Age (in years)	0-9	12	2·1	26	9·2	38	4·5	<0·0001*
	10-19	65	11·5	49	17·3	114	13·4	
	20-29	131	23·1	55	19·4	186	21·9	
	30-39	120	21·2	43	15·2	163	19·2	
	40-49	118	20·8	35	12·4	153	18	
	50-59	80	14·1	52	18·4	132	15·5	
	≥60	41	7·2	23	8·1	64	7·6	
Country of residence	Belgium	16	2·8	10	3·5	26	3·1	0·39*
	Germany	4	0·7	3	1·1	7	0·8	
	France	52	9·2	17	6	69	8·1	
	Luxembourg	495	87·3	253	89·4	748	88	
Period (in weeks)	25 − 28	101	17·8	49	17·3	150	17·6	<0·0001*
	29	105	18·5	36	12·7	141	16·6	
	30	93	16·4	36	12·7	129	15·2	
	31	77	13·6	43	15·2	120	14·1	
	32 - 33	31	5·5	31	11	62	7·3	
	34	24	4·2	8	2·8	32	3·8	
	35	22	3·9	13	4·6	35	4·1	
	36	43	7·6	9	3·2	52	6·1	
	37	54	9·5	21	7·4	75	8·8	
	38	17	3	37	13·1	54	6·4	
		Mean	STD	Mean	STD	Mean	STD	
Age (in years)		36·8	15·3	34·2	18·9	35·9	16·6	<0·0001#
rRT-PCR Cq values		28·9	5·3	30·2	5·1	29·3	5·3	<0·0001#

* Chi-square test
\# Wilcoxon test

The 850 index cases resulted in 7,909 contacts. After the removal of redundancy, 6,074 were further considered (Fig. 3). Each index case resulted in an average of 8·3 contacts (range 1-101) and in a mean of 0·7 (SD=1·1) subsequent positive contacts. The positive index cases with no symptoms infected slightly fewer contacts than the symptomatic individuals (Wilcoxon test, p<0·0001) whereby 0·6 (SD=1) and 0·7 (SD=1·1) positive contacts resulted per index case with contacts from asymptomatic and symptomatic cases, respectively. Thereby, cases which were asymptomatic on the day of the positive result overall had a significant but lower secondary attack rate compared to those who were symptomatic (SAR=0·02 (SD=0·09) versus SAR=0·04 (SD=0·12), p<0·0001). This was reflected in households (SAR$_H$=0·05 (SD=0·18) versus SAR$_H$=0·10 (SD=0·24), p<0·0001) as well as for close contacts (SAR$_{CC}$=0·02 (SD=0·11) versus SAR$_{CC}$=0·05 (SD=0·16), p<0·0001). Infections were mostly linked to travel to a foreign country (31·4%), the household setting (23·2%), or the work environment (20%).

Overall, there were more contacts in the "asymptomatic" than in the "symptomatic" group (8·5 vs 8·2, Wilcoxon test p<0·0001). The difference between the date of the positive result for the index case and the date of last contact was higher in the "asymptomatic" group (4·36 days) compared to the other (1·86 days; Wilcoxon test, p<0·0001). A total of 84·6% of the contacts declared by the asymptomatic individuals were high-risk contacts (placed into quarantine).
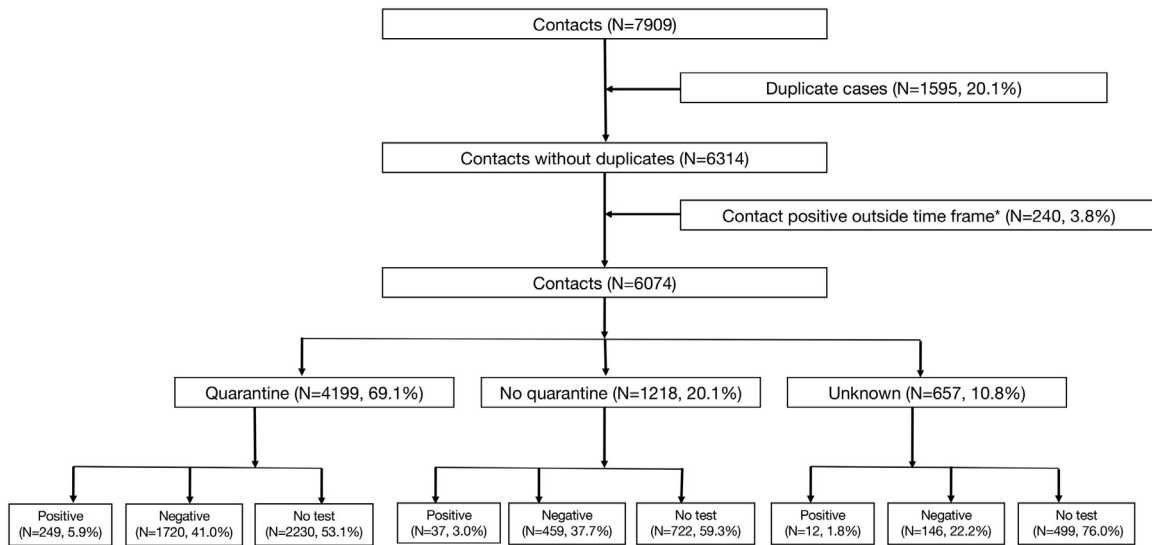
* Contact should be positive between 2 and 14 days after the date of contact with the positive case

Fig. 3. Flowchart detailing numbers of contacts resulting from the 850 identified index cases.
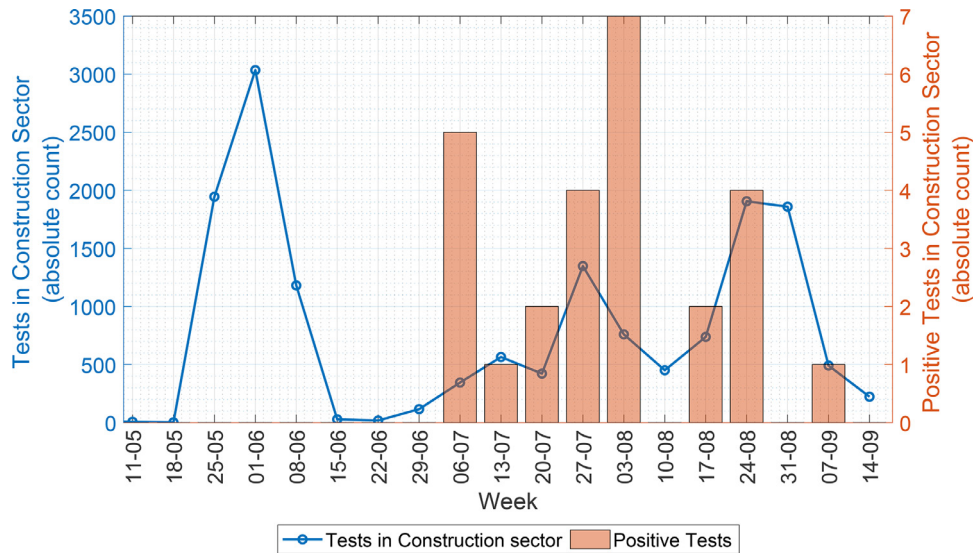
Fig. 4. Testing in the construction sector since its reopening.

In contrast, 73·8% of the contacts declared by the symptomatic individuals were high-risk contacts (also placed into quarantine; Chi-square test, p<0·0001).

With regards to factors associated with being tested positive (Suppl. Table 1), we observed no difference in relation to sex (OR 0·92 [0·76-1·09] for women compared to men). People who worked in the medium- and high-risk sectors had greater odds for being tested positive (OR 1·41 [1·12-1·78] and 2·24 [1·77-2·85], respectively). Individuals with a disposable household income of less than 30k€/year had the highest odds of being tested positive (OR 1·87 [1·53-2·28] when compared to people with 30k€-60k€/year). When compared to people between 30-39 years old, age groups of 20-29 (OR 1·93 [1·39-2·68]), 40-49 (OR 1·77 [1·27-2·46]) and 50-59 (OR 1·46 [1·03-2·08]) had greater odds of being tested positive, whereas no difference was observed for people aged 60-69 (OR 0·86 [0·54-1·38]) or 70-79 (OR 0·53 [0·27-1·04]), and lower odds were observed for extreme age groups, such as individuals ≤9 years old (OR 0·35 [0·20-0·61]) or ≥80 years old (OR 0·37 [0·15-0·91]).

4.4. Prevalence in specific sectors and regions

Over the course of the testing of the high- and medium-risk sectors, the prevalence was not evenly distributed according to the assumed risk and period covered (Suppl. Note 4, Suppl. Table 2, Suppl. Figure 3, Suppl. Figure 4). For instance, enrichment in positive cases was observed in the services sector (classified among the general population; 11·4% increase over the mean prevalence), hospitality (high-risk; 8·6%) and the construction sector (medium-risk; 6·6%). Moreover, we observed regional differences (33·7% for the canton of Esch-sur-Alzette versus 21·1% for Luxembourg). In addition, the prevalence for individuals from different income categories was not evenly distributed (Suppl. Note 5, Suppl. Figure 5).

4.5. Tactical interventions

Sector- and region-specific prevalences were monitored in accordance with the programme design. At the end of April-beginning of May, specific working sectors received invitations as part of the gradual reopening. As it was the first to be reopened, the entire construction sector was invited on 25th May. However, the higher number of tests did not result in higher number of positive cases in that sector (Fig. 4). During the subsequent epidemic wave, the prevalence in the construction sector was significantly higher than in the other sectors (as an increase of 6·6%, or 1,390 cases per 100,000 inhabitants over the entire period versus 5·7%, or 698 per 100,000 on average, in other sectors; this corresponds to an incidence rate ratio (IRR) of 1·99, (95% CI [1·94,2], p < 0·00001)). The peak in prevalence was reached on 24th July with 87·7 infected individuals in the construction sector per 100,000 inhabitants. Consequently, this sector was again invited for testing. The number of tests increased and showed two more peaks during the weeks starting 27th July and 24th August, the latter corresponding to the end of the collective holidays in this sector. However, by late August, the second epidemic wave had peaked, which is reflected in the declining numbers of positive cases identified in the construction sector (Fig. 4, Suppl. Figure 6). The services and
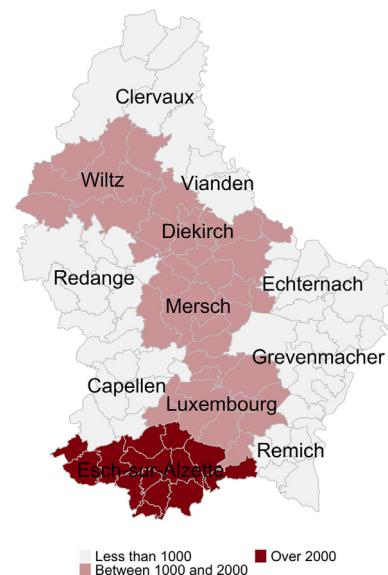

Fig. 5. Cumulative numbers of cases per 100 000 population, by canton.
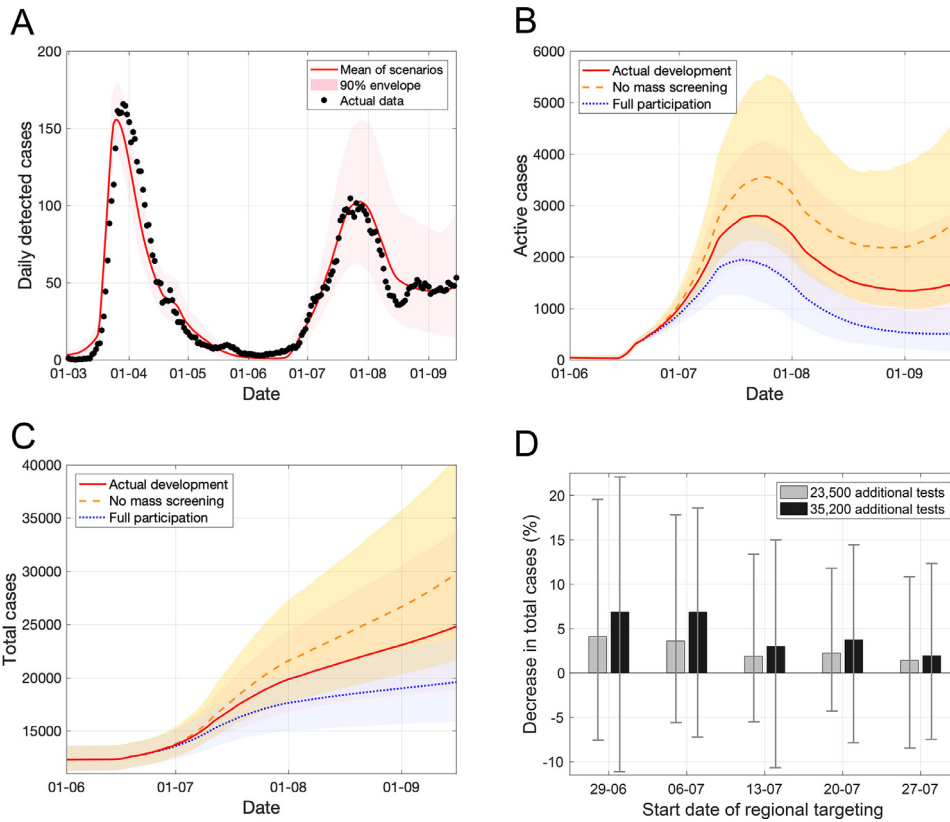
Fig. 6. Impact analysis by agent-based modelling
(A) Daily detected cases from the simulated actual scenario together with 7-day moving average of true data. (B, C) The second wave in terms of active cases (B) and total cases (C) in the actual scenario, a scenario without mass screening, and a scenario with full participation. (D) The effect of trigger date and the numbers of tests in regional targeting in relation to the reduction in total cases.

hospitality sectors also received additional, targeted invitations based on increases in prevalence (Suppl. Note 6).

Based on the population-based monitoring, increases in prevalence were observed in the south-west communes belonging to the canton of Esch-sur-Alzette starting in mid-July (Fig. 5). Between the 1st July and the 20th July, the prevalence in the canton was 327·1 cases per 100,000 inhabitants compared to a mean prevalence of 108·6 cases per 100,000 in all other cantons (IRR 3·01, 95% CI [2·98,3·05], p<0·00001). Based on the observation that the majority of transmissions was occurring in households, each household in the high-prevalence communes of the Esch-sur-Alzette canton received an invitation over one week starting on 27th July (36,197 unique invitations with the exception of households already invited as part of targeted sectors such as services and hospitality).

4.6. Impact analysis

To assess the impact of MS on the epidemic dynamics, we used an agent-based SEIR model tailored to the situation in Luxembourg in terms of implemented measures and detected cases identified by classical prescription, MS and contact tracing (Fig. 6A). Based on the calibrated model, the effect of the MS was quantified [20] by comparing the projected number of active cases for the actual development scenario with 566,320 MS tests performed during the period from 1st June until 15th September to a scenario without any MS and to a setting in which all the 1,436,000 invitations would have been complied with (Fig. 6B). The analysis of the amplitude of active cases highlights that, without the implemented MS, the peak of active cases would have increased by 29·0% and that full participation would have led to a further reduction of 29·4% (Table 2). This positive effect of MS is

Table 2
Impact of mass screening on numbers of cases.

Scenario	Total cases* 25/5-15/09/2020	Peak height (active cases)	Intensive care unit peak occupancy
Actual development	12395 [7350, 20340]	2860 [1873, 4443]	38·2 [15·0, 86·0]
No MS	17248 [10257, 27271] (+42·9%† [-0·3, +96·7])	3602 [2358, 5603] (+29·0% [-14·7, +79·3])	48·5 [26·5, 81·0] (+50·5% [-20·0, +135·9])
Full participation	7258 [4439, 10747] (-39·7% [-59·2, -19·6])	1969 [1290, 2786] (-29·4% [-51·4, -3·6])	14·1 [6·0, 22·0] (-55·4% [-80·5, -15·4])
No sector targeting	13053 [7683, 20264] (+7·9% [-26·4, +63·8])	2971 [1889, 4581] (+7·2% [-31·4, +63·2])	41·1 [14·0, 82·5] (+14·2% [-27·7, +69·3])
No regional targeting	12589 [7683, 20264] (+1·8% [-7·8, +12·2])	2865 [1873, 4443] (+0·1% [0·0, +0·1])	39·1 [15·5, 92·5] (+5·3% [-30·0, +47·1])
No contact tracing for MS cases	15530 [9192, 26933] (+27·3% [-2·0, +77·2])	3378 [2168, 5463] (+20·2% [-10·7, +69·7])	52·1 [20·0, 98·0] (+49·1% [+1·2, +111·8])

* Total number of cases includes both detected and undetected cases.
† Percentages in the table show the difference to the actual development scenario. These are calculated based on the statistics of individual replicates (Suppl. Note 2). MS: mass screening.

also highlighted by the number of total cases (Fig. 6C) which would have been 42·9% higher without the implemented test strategy and full participation would have led to a further reduction of 39·7% (Table 2).

We observed that not performing the sector-specific screening moderately increased the amplitude of active cases by 7·2% and the number of total cases by 7·9%. The regional targeting of the high-prevalence communes in the canton of Esch-sur-Alzette during the weeks of 27th July to 7th August increased the number of identified cases by MS by 13·9% [3·4,23·2] in the canton (corresponding to 7·1% [-3·6,17·1] on the country level). Without these additional tests, there would have been only a modest increase in total cases (+1·8%) within the whole country and a 7·9% [-18·5,42·5] increase in the targeted canton during the period from 27th July to 15th September. Simulations of different starting dates and test numbers for the regional targeting (Fig. 6D) reveal that the effect could have been nearly three times greater, had the regional targeting started four weeks earlier.

The synergistic effect of MS and contact tracing was studied by switching off tracing for index cases identified by MS. According to our simulations (Table 2), the impact of mass screening may be reduced by more than half without contact tracing (27·3% [-2·0,77·2] increase in total cases when no contact tracing would have been performed for MS index cases).

5. Discussion

Mass screening for SARS-CoV-2 has been a topic of intense political and societal debate, the rationale for screening asymptomatic individuals having in particular been questioned. In May 2020, the possibility of transmission from asymptomatic carriers was recognised as a possible driver of the pandemic [4,5]. Appropriate measures, such as MS of presymptomatic and asymptomatic individuals, at least in high-risk communities, were recommended [4,5]. Nevertheless, whether asymptomatic carriers play an important role in population-based transmission has remained an essential question. The MS programme implemented in Luxembourg, which coincided with a second epidemic wave, thereby provides a unique test case for assessing the role of asymptomatic carriers and the effectiveness of testing and tracing to break infection chains early on.

Our data show that asymptomatic carriers infect on average the same number of people as symptomatic individuals. The assessment is robust, as the information of a positive carrier being symptom-free was recorded by the contact tracing team once a person was informed about their positive test result. Based on the incubation time of a mean of 4-5 days and given that the test results were communicated to participants within two working days of sample collection, it is highly likely that a significant fraction of individuals did not exhibit any symptoms at the time of testing [4,21]. With the number of asymptomatic carriers estimated to be about four-fold the number of positively tested symptomatic individuals at the end of the first epidemic wave in Luxembourg [8], our data therefore implies that asymptomatic including presymptomatic individuals are an important factor in triggering and sustaining infection chains. Our work indicates that, in Luxembourg and during the period of study, asymptomatic individuals had significant SARs, both in households and amongst close contacts, but these were lower compared to those for symptomatic cases. Further dedicated studies need to focus on possible differences in infectivity and linked SAR between these two groups as well as in other transmission contexts. Nevertheless, our results highlight that classical pandemic containment strategies, such as a consequential identification and isolation of symptomatic patients, cannot work efficiently for COVID-19.

We acknowledge that a potential differential recall bias may exist between asymptomatic and symptomatic cases due to the self-reporting of symptoms as well as the fact that the data are generated for public health surveillance purposes (isolation of cases and quarantining of their contacts) and not for research purposes. This potential bias may have partially affected our results. In addition, no data was collected on low-risk contacts (which were not placed into quarantine) and this could have had an effect on overestimating the SAR. Caution needs to therefore be taken to compare these estimates with other studies which might have used different definitions for at-risk individuals. Nevertheless, further analysis on the comparison and timing of symptoms onset alongside the SAR will soon be possible in Luxembourg.

Based on the sector-specific prevalences, the classification into high- and medium-risk sectors proved appropriate for certain sectors (2,384 and 1,022 invitations per positive case for healthcare and social work, and hospitality, respectively) but not for others (2,810 and 9,095 invitations for pharmacists and police, for 0 and 1 positive case, respectively). Medium-risk and sectors belonging to the general population which should be reclassified as high-risk include the construction and services sectors. Although recurrent invitations increased participation, the overall compliance within the high-risk sectors varied from 60·8% of invitations being complied with amongst preschool and primary teachers to 27·5% in the hospitality sector. Given the differing prevalence and participation rates in the different sectors, it is challenging to assess the relationship between test frequency and prevalence with the present dataset. Future dedicated work is needed to assess sector-specific testing frequencies with respect to their impact on prevalence and possible sector-specific mitigation. Nevertheless, in addition to the ability to deploy test capacity to affected work sectors and regions, broader participation and compliance are essential to enhance the effectiveness of MS. This may be achieved through tailored incentivisation.

Based on our simulations, without the MS programme, the number of cases would have increased substantially (42·9%, (90% CI [-0·3, 96·7])) during the second epidemic wave. Further increase in testing would have been even more impactful, whereby complete participation would have led to a 39·7% [19·6, 59·2] decrease. The impact analysis is based on simulations and is therefore subject to uncertainties as detailed in Suppl. Note 2. A retrospective analysis of sector- and region-specific prevalences highlights that a threshold of 150 positive cases per 100,000 per week should trigger the testing of entire groups (Suppl. Figure 7). A caveat concerns smaller groups whereby these are more prone to noise and, thus, false alarms may be raised. Tactical testing may also be triggered by other early warning signals based on population-level symptomatology or surveillance of wastewater [22-24]. Rapid tactical interventions based on regional prevalence are essential for increasing efficiency.

Further viral pandemics are to be expected, even within this decade [25,26]. As the role of asymptomatic carriers in the transmission of SARS-CoV-2 is becoming more and more recognised [27,28] population-level containment and mitigation strategies need to take this into account. Luxembourg was successful in quickly setting up and implementing such a MS programme, with reliable, high-quality assay material. According to our model, the intensive care unit peak occupancy would have been 50·5% [-20·0, 135·9] higher without MS, whereas full participation would have resulted in a further reduction of 55·4% [15·4, 80·5]. Initial assessments of the economic impact of the lockdown reveal that the loss in gross domestic product per capita and per month of lockdown is approximately €3,200 per Luxembourg resident [29]. The opportunity cost of lockdown is significant compared to the €30 per test. Thereby, the testing of the approximately 635,306 Luxembourg residents and 341,302 cross-border workers represents a public health measure with important socio-economic benefits. A detailed cost-benefit analysis, including comparisons to neighbouring regions and counties, contrasting different non-pharmaceutical interventions including social distancing, mask wearing, and MS would provide decision makers with an objective basis for implementing future measures aimed at the continued mitigation of the spread of SARS-CoV-2. In any case, as evidenced by the early summer epidemic wave, nascent infection chains were rapidly

detected through MS, and effective contact tracing was ensured through the closely controlled testing frequency.

Ethical aspects

The study was presented to the National Research Ethics Committee of Luxembourg (Comité National d'Ethique de Recherche, CNER) which approved the submission (ref. 1120-218).

Data sharing

De-identified data can be made available after review of request. The code for the agent-based model used for the impact analysis is available on Gitlab (doi:https://doi.org/10.17881/q3g1-7a85).

Declaration of Competing Interests

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2021.100056.

References

[1] Gilbert M, Dewatripont M, Muraille E, Platteau JP, Goldman M. Preparing for a responsible lockdown exit strategy. Nat Med 2020;26:643–4.
[2] Editorial. The COVID-19 testing debacle. Nat Biotechnol 2020;38:653.
[3] Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic population. N Engl J Med 2020;382:2302–15.
[4] Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. N Engl J Med 2020;382:2081–90.
[5] Gandhi M, Yokoe DS, Havlir DV. Asymptomatic transmission, the Achilles' heel of current strategies to control Covid-19. N Engl J Med 2020;382:2158–60.
[6] He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020;26:672–5.
[7] Endo A, Abbott S, Kucharski AJ, Funk S. Estimating the overdispersion in COVID-19 transmission using outbreak sizes outside China. *Wellcome Open Res* 2020;5:67.
[8] Snoeck CJ, Vaillant M, Abdelrahman T, et al. Prevalence of SARS-CoV-2 infection in the Luxembourgish population: the CON-VINCE study. medRxiv 2020. doi: 10.1101/2020.05.11.20092916.
[9] Snoeck CJ, Owoade AA, Couacy-Hymann E, et al. High genetic diversity of Newcastle Disease Virus in poultry in West and Central Africa: cocirculation of genotype XIV and newly defined genotypes XVII and XVIII. J Clin Microbiol 2013;51:2250–60.
[10] Abdalhamid B, Bilder CR, McCutchen EL, Hinrichs SH, Koepsell SA, Iwen PC. Assessment of specimen pooling to conserve SARS CoV-2 testing resources. Am J Clin Pathol 2020;153:715–8.
[11] Ben-Ami R, Klochendler A, Seidel M, et al. Large-scale implementation of pooled RNA extraction and RT-PCR for SARS-CoV-2 detection. Clin Microbiol Infect 2020;26:1248–53.
[12] Garg J, Singh V, Pandey P, et al. Evaluation of sample pooling for diagnosis of COVID-19 by real-time PCR: a resource-saving combat strategy. J Med Virol 2020. doi: 10.1002/jmv.26475.
[13] Lohse S, Pfuhl T, Berkó-Göttel B, et al. Pooling of samples for testing for SARS-CoV- in asymptomatic people. Lancet Infect Dis 2020. doi: 10.1016/S1473-3099(20) 30362-5.
[14] Perchetti GA, Sullivan KW, Pepper G, et al. Pooling of SARS-CoV-2 samples to increase molecular testing throughput. J Clin Virol 2020;131:104570.
[15] Regen F, Eren N, Heuser I, Hellmann-Regen J. A simple approach to optimum pool size for pooled SARS-CoV-2 testing. Int J Infect Dis 2020. doi: 10.1016/j.ijid.2020.08.063.
[16] Hanel R, Thurner S. Boosting test-efficiency by pooled testing for SARS-CoV-2-formula for optimal pool size. PLoS ONE 2020;15:e0240652.
[17] Kerr CC, Stuart RM, Mistry D, et al. Covasim: an agent-based model of COVID-19 dynamics and interventions. medRxiv 2020. doi: 10.1101/2020.05.10.20097469.
[18] Office for National Statistics. Employment and labour market. People in work. Employment and employee types. Which occupations have the highest potential exposure to the coronavirus (COVID-19)? https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/articles/whichoccupationshavethehighestpotentialexposuretothecoronaviruscovid19/2020-05-11 (accessed November 4th, 2020).
[19] O*NET Resource Center. O*NET 25.0 Database https://www.onetcenter.org/database.html#individual-files (accessed November 4th, 2020).
[20] Panovska-Griffiths J, Kerr CC, Stuart RM, et al. Determining the optimal strategy for reopening schools, the impact of test and trace interventions, and the risk of occurrence of a second COVID-19 epidemic wave in the UK: a modelling study. Lancet Child Adolesc Health 2020;4:817–27.
[21] Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS- CoV-2 and COVID-19. Nat Rev Microbiol 2020. doi: 10.1038/s41579-020-00459-7.
[22] Segal E, Zhang F, Lin X, et al. Building an international consortium for tracking coronavirus health status. Nat Med 2020;26:1161–5.
[23] Daughton CG. Wastewater surveillance for population-wide Covid-19: the present and future. Sci Total Environ 2020;736:139631.
[24] Farkas K, Hillary LS, Malham SK, McDonald JE, Jones DL. Wastewater and public health: the potential of wastewater surveillance for monitoring COVID-19. Curr Opin Environ Sci Health 2020;17:14–20.
[25] Billington J, Deschamps I, Erck SC, et al. Developing vaccines for SARS-CoV-2 and future epidemics and pandemics: applying lessons from past outbreaks. Health Secur 2020;18:241–9.
[26] Naguib MM, Ellström P, Järhult JD, Lundkvist A, Olsen B. Towards pandemic preparedness beyond COVID-19. Lancet Microbe 2020;1:e185–6.
[27] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020;324:782–93.
[28] Lee S, Kim T, Lee E, et al. Clinical course and molecular viral shedding among asymptomatic and symptomatic patients with SARS-CoV-2 infection in a community treatment center in the Republic of Korea. JAMA Intern Med 2020;180:1447–52.
[29] Beine M, Bertoli S, Chen S, et al. Economic effects of Covid-19 in Luxembourg. First *RECOV*id working notes with preliminary estimates. https://www.liser.lu/documents/RECOVID/RECOVid_working-note_full-1.pdf.