Article

Mass Screening for SARS-CoV-2 uncovers significant transmission risk from asymptomatic carriers

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Abstract

Background To accompany the lifting of COVID-19 lockdown measures, Luxembourg implemented a mass testing programme. The first phase coincided with an early summer epidemic wave.

Methods High-throughput rRT-PCR was performed using a validated pooling strategy. The sampling infrastructure allowed the testing of the resident and cross-border worker populations. Test strategy was based 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 Sensitivity and specificity of the test protocol were 100%. The tests covered 49% of the resident and 22% of the cross-border worker populations. The programme identified 850 index cases with an additional 249 cases resulting from contact tracing, corresponding to 26% of positive cases of the epidemic wave. Enrichment in positive cases was observed in the services (11·4% increase over the mean prevalence), hospitality (8·6%) and construction (6·6%) sectors alongside regional differences. Strikingly, cases that were asymptomatic on the day of the positive result had a similar secondary attack rate in the household compared to those who were symptomatic. Based on simulations using a tailored agent-based SEIR model, the total number of expected cases would have been 39·1% higher without the mass screening programme. Mandatory participation would have resulted in a further difference of 41·4%.

Interpretation The implementation of strategic and tactical mass testing for SARS-CoV-2 allows the breaking of nascent infection chains and the suppression of epidemic dynamics. Asymptomatic carriers are at least as infectious as symptomatic patients. Containment of future outbreaks will critically depend on early testing in sectors and geographical regions. Higher participation rates must be assured through targeted incentivisation and recurrent invitation.

Funding This project was funded by the Luxembourg Ministries of Higher Education and Research, and Health.

Keywords: Asymptomatic; contact tracing; COVID-19; mass screening; rRT-PCR; SARS-CoV-2

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 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 mass screening 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 mass screening 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 mass screening 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 screening meshes were 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 mass screening 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 contain the epidemic dynamics in close coordination with classical contact tracing. Importantly, our study highlights that asymptomatic individuals were at least as infectious as symptomatic patients.

Implications of all the available evidence

Our study confirms that mass screening 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 mass screening 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 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.

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]

In Spring 2020, it became clear that asymptomatic including presymptomatic carriers could transmit the virus.[4,5] Based on the estimated serial interval and incubation period, modeling 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. Relying on herd immunity was deemed unrealistic as population-wide exposure in Luxembourg was estimated to be 2·1% in late April,[8] so that population-wide antibody surveys were not considered meaningful.

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 'grid testing' using differing mesh sizes, which were dynamically adjusted based on prevalence in the respective sectors.

We show that the population-wide screening programme with a participation rate of 49% was able to contain the epidemic dynamics in close coordination with classical contact tracing. According to our data, asymptomatic SARS-CoV-2 carriers are as infectious as symptomatic carriers. Therefore, the success of mass screening critically depends on broad participation and incentivisation.

Methods

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.

Assay

Real-time reverse transcription polymerase chain reaction (rRT-PCR) was performed using the Fast Track Diagnostics (FTD)™ 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, a pooling strategy involved mixing the samples from four different individuals prior to RNA extraction and re-analyzing a positive pooled sample individually a second time.[9-15] The pooling strategy presented 100% sensitivity and 100% specificity (Suppl. Note 1).

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 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 date of test if asymptomatic) were encouraged 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. 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.

Statistical analyses

The prevalences of SARS-CoV-2 infections were calculated using the *normcdf* function in Matlab.

Two logistic regression models were built to identify the determinants associated with participation in mass screening (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, ≥90k€/year), number of total invitations to participate in mass testing (for the model on participation only), medication use in the past 6 months to treat a chronic condition (Yes, No), risk population (high-risk, medium risk, general). We also computed secondary attack rates (SAR) in the household (SAR_H) and for close contacts (SAR_{CC}), both in symptomatic and asymptomatic cases. 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 put under quarantine (the contact had an high-risk interaction with the COVID-19 positive case), according to the definition of a close contact used by the CDC[16].

To assess the impact of the mass testing program 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 (Suppl. Note 2).

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 report. Both Ministries have approved submission of the manuscript for publication.

Results

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 (Figure 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 (Figure 1). The first phase of the mass screening program 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.

Design of programme

The testing strategy was designed in an intercalated, 3-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, creating a theoretical mesh-size of one (Figure 2A). On a second level, workers and other members of the population in medium-risk sectors were monitored by inviting one out of five per week such that individuals in medium-risk sectors were at least invited once (Figure 2B). Similarly, one in every ten Luxembourg residents in other sectors or the general population was invited each week to cover an even geographical distribution (Figure 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 infection rates in the level 2 monitoring approach. If the incidence 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 test mesh sizes were dynamically adjusted to maximize the use of available resources without compromising the efficiency of outbreak prevention (Figure 2C). The established capacity allowed for a maximum test capacity of 10% of residents and cross-border workers per week.

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. 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 mass screening, whereas among the cross-border workers, participation was 22·5% (87,198 individuals). A total of 566,320 tests was performed, which is equivalent to 69·7% of all tests performed between 25th May and 15th September. Participation in the programme differed markedly based on socio-demographic factors (Suppl. Note 3).

Characteristics of cases and contacts

The mass screening 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).

The 850 index cases resulted in 7,909 contacts. After the removal of redundancy, 6,074 were further considered (Figure 3). Each index case resulted in an average of 8·3 contacts (range 1-101) and in a mean of 0·7 (STD 1·1) subsequent positive contacts. The positive index cases with no symptoms were slightly less infectious than the symptomatic individuals (Wilcoxon test, P<0·0001) whereby 0·6 (STD=1) and 0·7 (STD=1·1) positive contacts resulted per index case from asymptomatic and symptomatic cases, respectively. Cases who were asymptomatic the day of the positive result had a similar secondary attack rate in the household as those who were symptomatic (SAR_H=0·36 (STD=0·70) versus SAR_H=0·38 (STD=0·67), p=0·26) but they had a slightly lower SAR for close contacts (SAR_{CC}=0·15 (STD=0·33) versus SAR_{CC}=0·20 (STD=0·42) respectively, p<0·0001). Infections were mostly linked to foreign travel (31·4 %), the household setting (23·2 %), or the work environment (20 %).

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]).

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 in individuals from different income categories was not evenly distributed (Suppl. Note 5, Suppl. Figure 5).

Tactical interventions

Sector- and region-specific prevalence was 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 (Figure 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 (Figure 4, Suppl. Figure 6). The services and 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 (Figure 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).

Impact

To assess the impact of the mass screening 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, mass screening and contact tracing (Figure 6A). Based on the calibrated model, the effect of the mass screening was quantified[20] by comparing the projected number of active cases for the actual situation with 566,320 mass screening tests performed during the period from 1st June until 15th September under a scenario without any mass screening and a setting in which all the 1,436,000 invitations would have been complied with (Figure 6B). The analysis of the amplitude of active cases highlights that, without the implemented mass screening, the peak of active cases would have increased by 26·9% and that full participation would have led to a further reduction of 30·5% (Table 2). This positive effect of mass screening is also highlighted by the number of total cases (Figure 6C) which would have been 39·1% higher without the implemented test strategy and full participation would have led to a further reduction of 41·4% (Table 2).

We observed that not performing the sector-specific screening moderately increased the amplitude of active cases by 4·3% and the number of total cases by 5·3%. 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 mass screening by 17% in the canton (corresponding to 8·2% on the country level). Without these additional tests, there would have been only a modest increase in total cases (+1·6%) within the whole country and a 4·8% 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 (Figure 6D) reveal that the effect could have been nearly four times greater, had the regional targeting started four weeks earlier.

Discussion

Mass screening for SARS-CoV-2 has been a topic of intense political and societal debate, the rationale for screening asymptomatic individuals having 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 mass screening 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 mass testing 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 symptomatics. 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 4-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. This in turn confirms that classical pandemic containment strategies, such as a consequential identification and isolation of symptomatic patients cannot work efficiently for COVID-19.

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. Therefore, 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 mass screening. This may be achieved through tailored incentivisation.

Based on our simulations and without the mass screening programme, the number of cases would have increased substantially (39·1%) during the second epidemic wave. Further reductions would have been even more impactful, whereby complete participation would have led to a 41·4 % decrease. A retrospective analysis of sector- and region-specific prevalence 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 generated. 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 is 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 mass screening programme, with reliable, high-quality assay material. According to our model, the intensive care unit peak occupancy would have been 45·9 % higher without mass screening, whereas full participation would have resulted in a further reduction of 59·9 %. 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 represented a public health measure with important socio-economic benefits. As evidenced by the early summer epidemic wave, nascent infection chains were rapidly detected through mass testing, and effective contact tracing was ensured through the closely controlled mesh of interconnected cells.

Ethical aspects

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

Contributors

PW designed and supervised the programme, performed data analysis and interpretation, and wrote the manuscript. JZ participated in data analysis and wrote the manuscript. JS contributed to the design and supervision of the programme and contributed to manuscript writing. FG contributed to the design and supervision of the programme and contributed to manuscript writing. LV performed data analysis and interpretation and contributed to manuscript writing. LM performed data analysis and interpretation and contributed to manuscript writing. BR assisted with data cleaning, performed data analysis and interpretation, and contributed to manuscript writing. AA performed the modeling analysis and contributed to manuscript writing. JP performed data cleaning and contributed to manuscript writing. CS performed rRT-PCR validations and contributed to manuscript writing. MO supervised the rRT-PCR validations and contributed to manuscript writing. GF assisted with data cleaning, performed data analysis and interpretation, and contributed to manuscript writing. JM assisted with data cleaning and analysis planning, and manuscript writing. JG performed the modeling analysis and contributed to manuscript writing. AS performed the modeling analysis and contributed to manuscript writing. UN designed and supervised the programme and contributed to manuscript writing.

Declaration of interests

All authors report grants from Luxembourg Ministry of Higher Education and Research, and Ministry of Health during the conduct of the study. Dr. Rodrigues reports working for the Ministry of Higher Education and Research as a public servant, during the conduct of the study. Dr. Snoeck reports that Fast Track Diagnostics provided a few SARS-CoV-2 rRT-PCR kits (RUO) free of charge at the time of evaluation of different commercial assays to be procured by the Luxembourg Government in order to do the mass screening intervention in the country.

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.org/10.17881/q3g1-7a85).

Acknowledgments

The authors are grateful to the Luxembourg Ministry of Higher Education and Research and the Ministry of Health for funding the intervention. PW acknowledges the European Research Council (ERC-CoG 863664).

Niels Juchem from Laboratoires Réunis is acknowledged for assistance with rRT-PCR validations.

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Tables

Table 1: Characteristics of cases and contacts identified through mass screening

Characteristics		**With symptoms (N=567)**		**Without symptoms (N=283)**		**Total (N=850)**	
		N	%	N	%	N	%
Sex	Female	278	49	125	44·2	403	47·4
	Male	289	51	158	55·8	447	52·6
Age (in years)	0-9	12	2·1	26	9·2	38	4·5
	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
	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
	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
rRT-PCR Cq values		28·9	5·3	30·2	5·1	29·3	5·3

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	12 395	2803	27·8
No mass screening	17 248 (+39·1%†)	3557 (+26·9%)	40·6 (+45·9%)
Full participation	7258 (-41·4%)	1949 (-30·5%)	11·2 (-59·9%)
No sector targeting	13 053 (+5·3%)	2924 (+4·3%)	31·5 (+13·2%)
No regional targeting	12 589 (+1·6%)	2803 (0·0%)	28·5 (+2·4%)

*Total number of cases includes both detected and undetected cases.

†Percentages in the table show the difference to the actual development scenario.

Figures

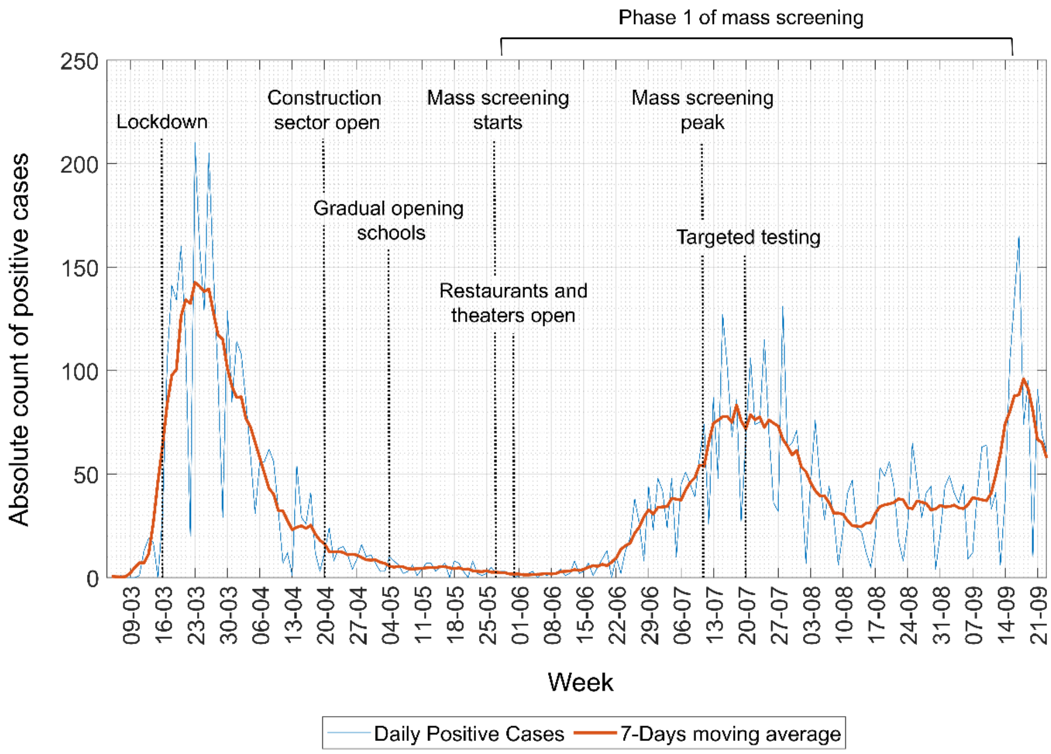

Figure 1: Epidemic curve for COVID-19 in Luxembourg

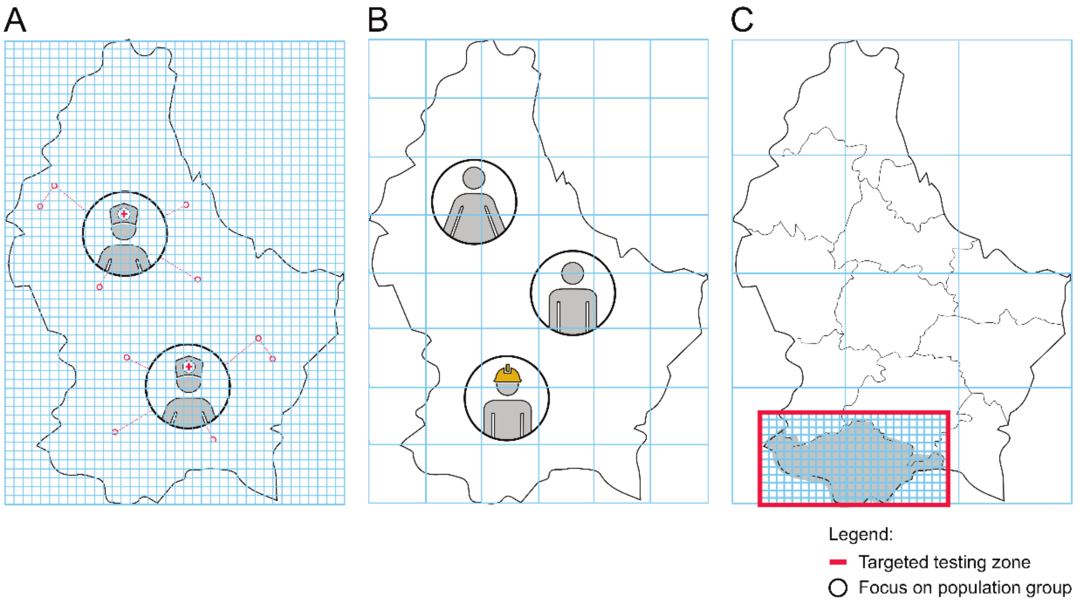

Figure 2: Strategic and tactical mass testing

The frequencies of invitations resulted in (A) small mesh sizes for high-risk sectors and (B) larger mesh sizes for medium-risk sectors. (C) The prevalence in the population was monitored and targeted invitations were sent in the case of regional flare-ups.

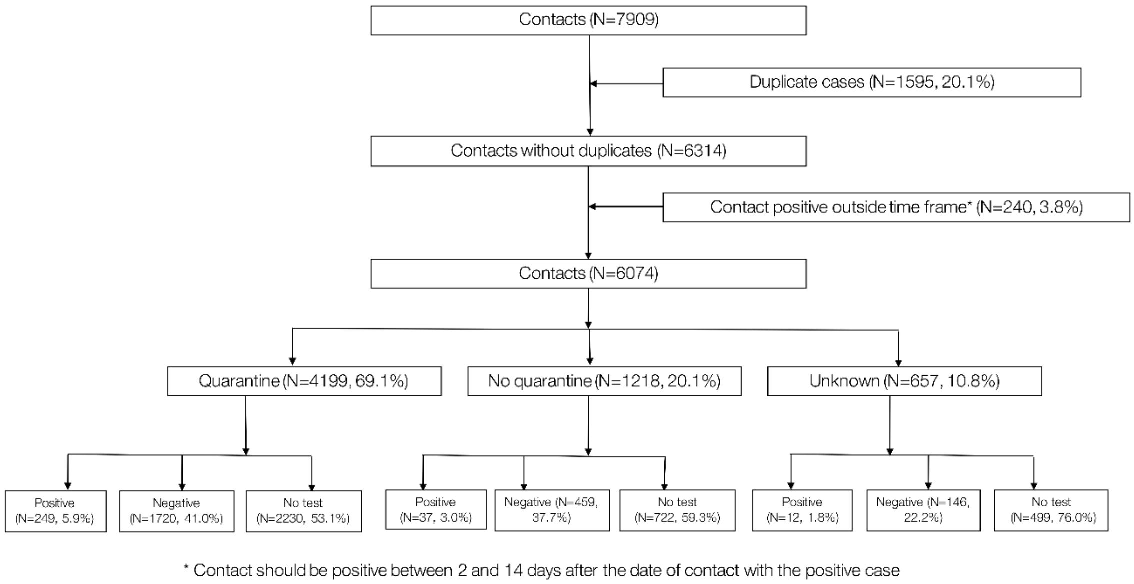

Figure 3: Flowchart detailing numbers of contacts resulting from the 850 identified index cases

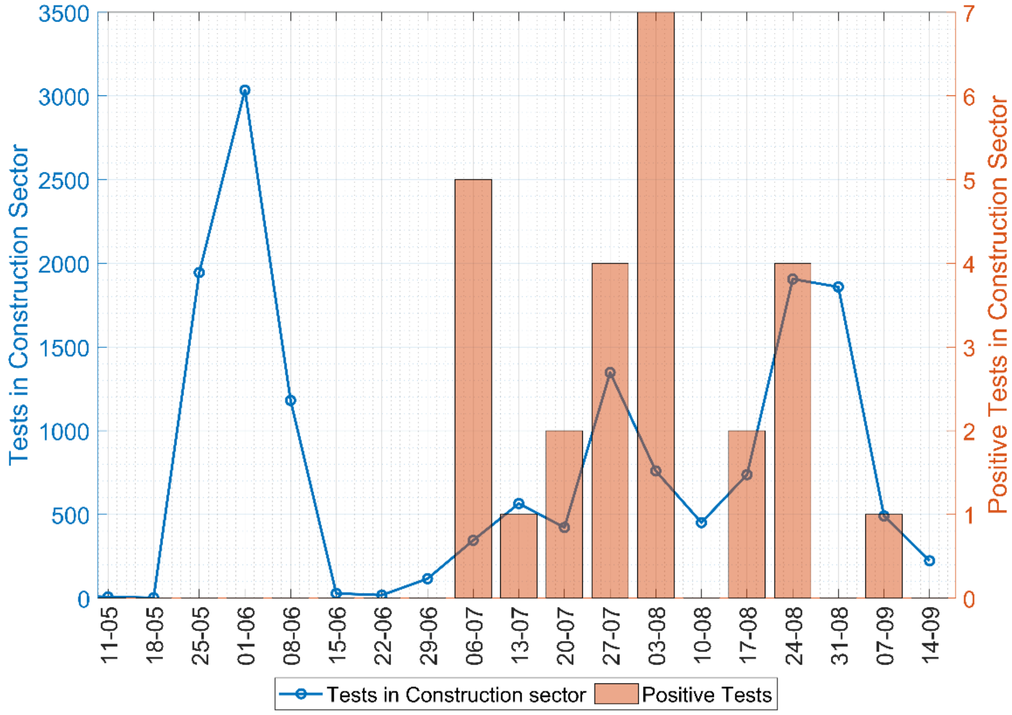

Figure 4: Testing in the construction sector since its reopening

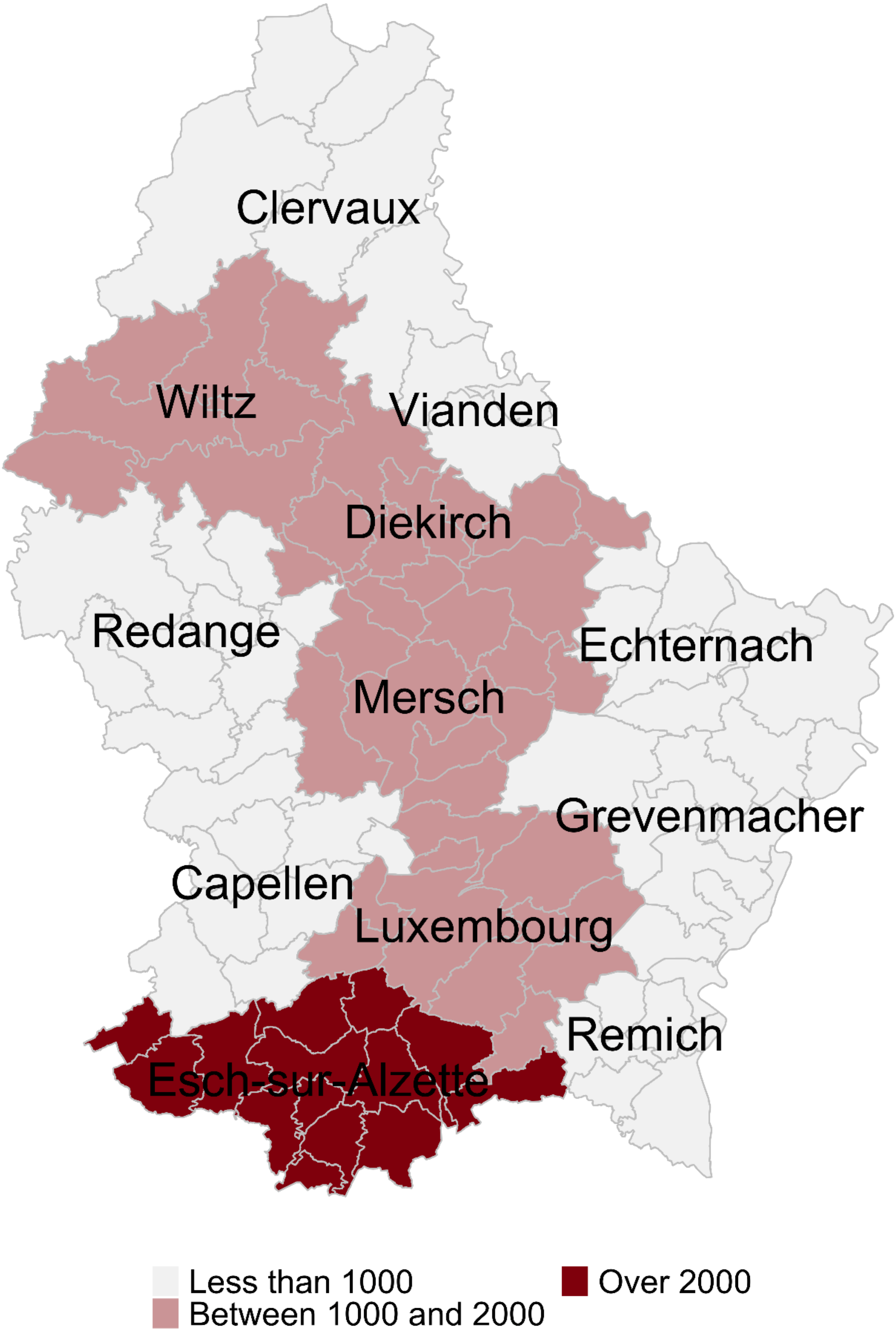

Figure 5: Cumulative numbers of cases per 100 000 population, by canton

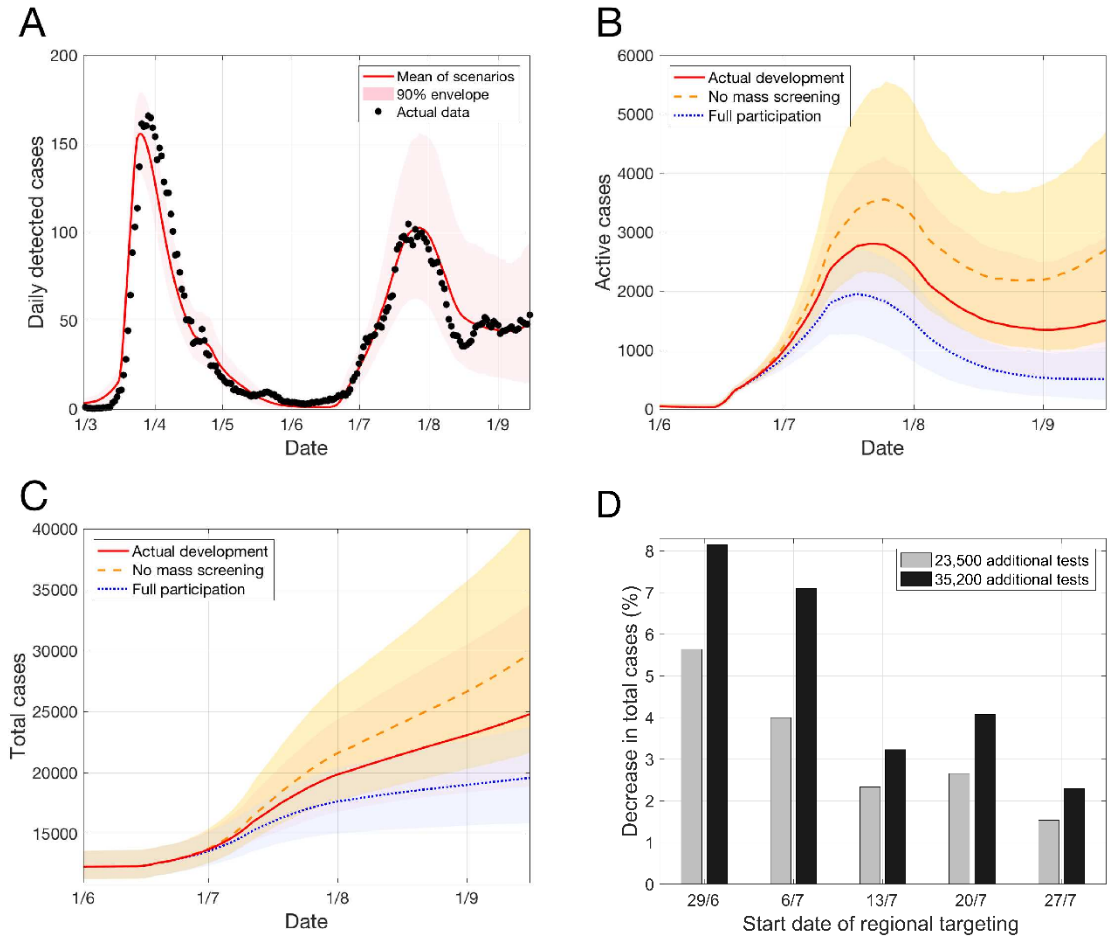

Figure 6: Impact analysis by agent-based modeling

(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.

Supplementary Material

Mass Screening for SARS-CoV-2 uncovers significant transmission risk from asymptomatic carriers

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Supplementary Table 1: Regression analysis

The baseline category is:

- Man
- Age 30-39
- Living in Luxembourg (country and city)
- In the general population
- With annual earnings lower than 30k
- Without any medical flag

For positivity:

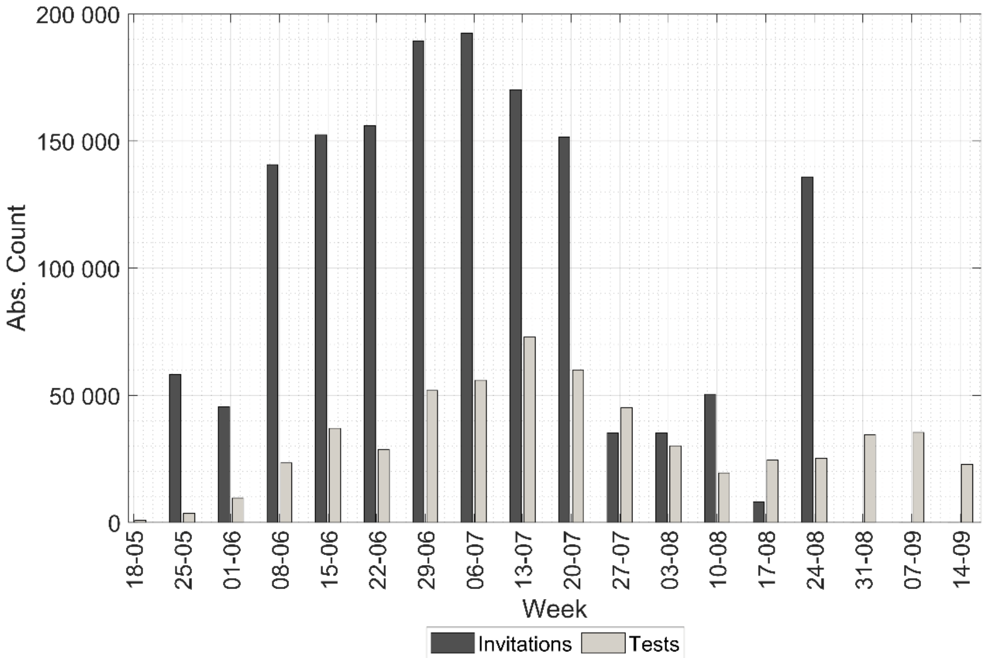
term	estimate	std.error	statistic	p.value
(Intercept)	0.001119	0.187	-36.34	3.663e-289
i_genderWomen	0.9126	0.0919	-0.9949	0.3198
i_ageGroup1020 to 29	1.931	0.167	3.939	8.166e-05
i_ageGroup1040 to 49	1.766	0.1697	3.35	0.0008076
i_ageGroup1050 to 59	1.464	0.1788	2.134	0.03284
i_ageGroup1060 to 69	0.8645	0.2379	-0.6121	0.5405
i_ageGroup1070 to 79	0.5295	0.3407	-1.867	0.06196
i_ageGroup10Less than 9	0.3524	0.2828	-3.688	0.0002264
i_ageGroup10More than 80	0.3746	0.454	-2.163	0.03056
geo1_Germany	0.101	0.6735	-3.404	0.0006632
geo2_Belgium	0.3639	0.5189	-1.948	0.05143
geo3_France	0.6494	0.4715	-0.9157	0.3598
geo4_Other	2.175e-06	165.8	-0.07866	0.9373
geoest	0.3277	0.2391	-4.667	3.056e-06
geonord	0.4567	0.1764	-4.442	8.926e-06
geoOther	0.9225	1.097	-0.07357	0.9414
geosud	1.043	0.1084	0.3868	0.6989
risk_cathigh_risk	2.242	0.122	6.62	3.594e-11
risk_catmedium_risk	1.411	0.1181	2.915	0.003559
wage_category30 to 60k	0.5357	0.102	-6.119	9.425e-10
wage_category60 to 90k	0.206	0.2543	-6.214	5.167e-10
wage_category90k+	0.4407	0.2899	-2.826	0.004713
wage_categorywage_missing	0.3379	0.4548	-2.386	0.01704
medication_use	1.075	0.07132	1.008	0.3134

For participation:

term	estimate	std.error	statistic	p.value
(Intercept)	0.8673	0.01205	-11.82	3.217e-32
i_genderWomen	1.174	0.005218	30.67	1.262e-206
i_ageGroup1020 to 29	0.6915	0.01108	-33.3	4.275e-243
i_ageGroup1040 to 49	1.07	0.01095	6.161	7.247e-10
i_ageGroup1050 to 59	1.024	0.01108	2.12	0.03398
i_ageGroup1060 to 69	0.8923	0.01259	-9.051	1.42e-19
i_ageGroup1070 to 79	0.7137	0.01476	-22.85	1.549e-115
i_ageGroup10Less than 9	0.6536	0.01263	-33.67	1.363e-248
i_ageGroup10More than 80	0.3375	0.01792	-60.6	0
geo1_Germany	0.4433	0.02256	-36.06	8.454e-285
geo2_Belgium	0.4897	0.02231	-32.01	8.534e-225
geo3_France	0.4014	0.02157	-42.32	0
geo4_Other	0.1041	0.1239	-18.26	1.582e-74
geoest	0.9341	0.01002	-6.811	9.69e-12
geonord	0.758	0.009118	-30.38	1.003e-202
geoOther	0.2226	0.1243	-12.08	1.274e-33
geosud	0.9211	0.007219	-11.38	5.436e-30
risk_cathigh_risk	1.89	0.009146	69.62	0
risk_catmedium_risk	1.416	0.007079	49.17	0
wage_category30 to 60k	1.376	0.006954	45.93	0
wage_category60 to 90k	1.872	0.01065	58.9	0
wage_category90k+	1.533	0.0163	26.2	2.777e-151
wage_categorywage_missing	0.8756	0.0207	-6.417	1.391e-10
medication_use	1.048	0.00398	11.84	2.438e-32

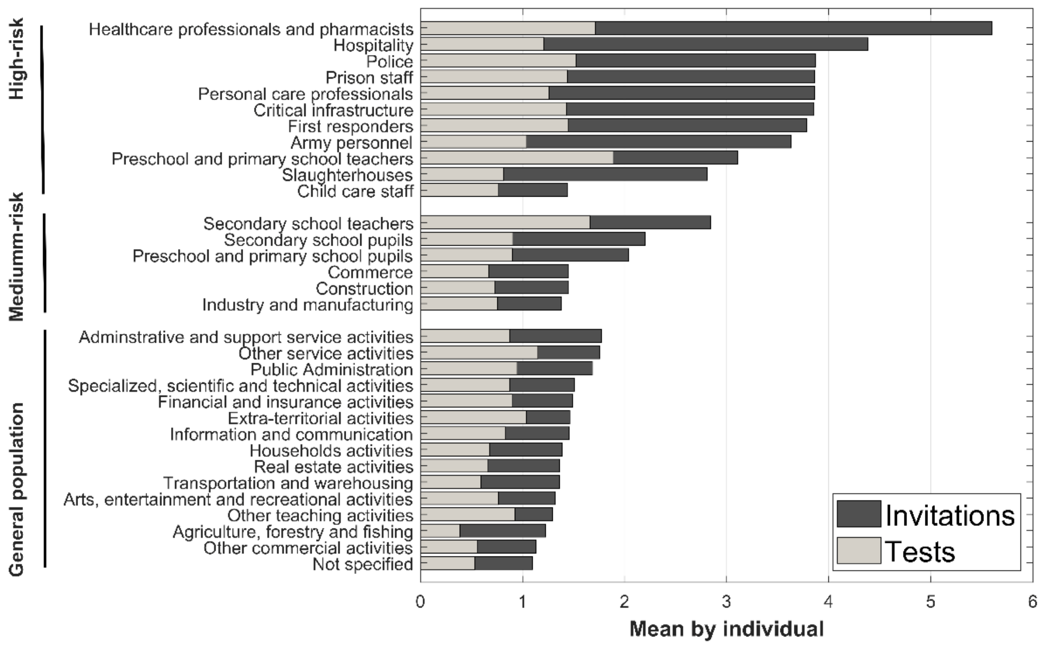
Supplementary Table 2: Sectors and numbers of individuals per risk categories

Category	Sector	Number of Individuals
High-risk	Healthcare professionals	27 123
	Army personnel	1064
	Preschool and primary school teachers	7649
	Child care staff	3415
	Personal care professionals	4352
	Police	2494
	Hospitality staff	11 646
	Staff in critical sectors	2398
	Prison staff	445
	Slaugtherhouses	622
	First responders	4346
Medium-risk	Construction workers	25 956
	Commerce	13 681
	Pupils in primary schools	51 764
	Pupils in secondary schools	45 013
	Secondary school teachers	5530
	Industry	10 653
General population	Rest of the individuals not part of the above categories.	357 913



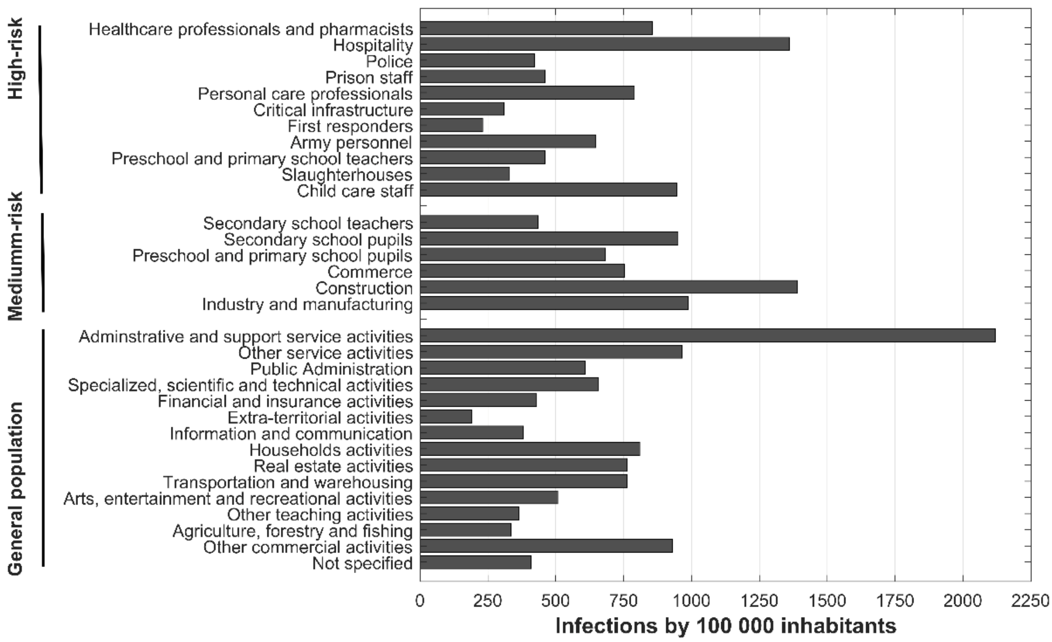
Supplementary Figure 1: Numbers of postal invitations sent, and tests performed per week

The number of invitations constantly increased from late May to reach its peak at around 200,000 in the week starting on 6th July. There was a clear decrease in the number of invitations from the end of July until the week of 24th August, coinciding with the end of the collective holiday period in the construction sector. Regarding the number of tests performed, it was lower than the number of invitations per week until the week starting on 27th July. The peak of tests was reached with around 75,000 tests performed during the week starting on 13th July which coincided with the start of the school summer vacation period.

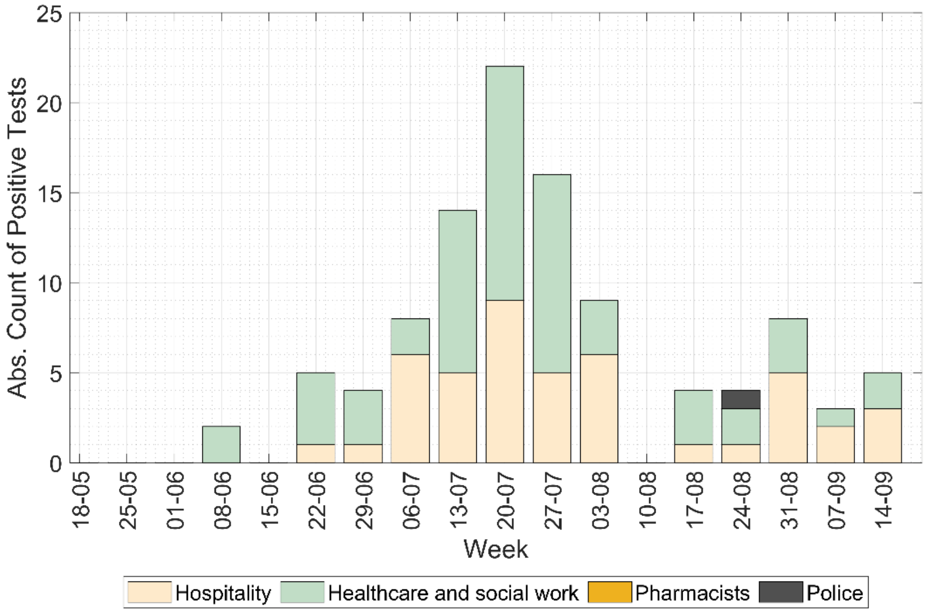


Supplementary Figure 2: Numbers of individual invitations in the different work sectors

Bar intensity represents absolute value, not cumulative. Refer to Suppl. Note 4 for details.

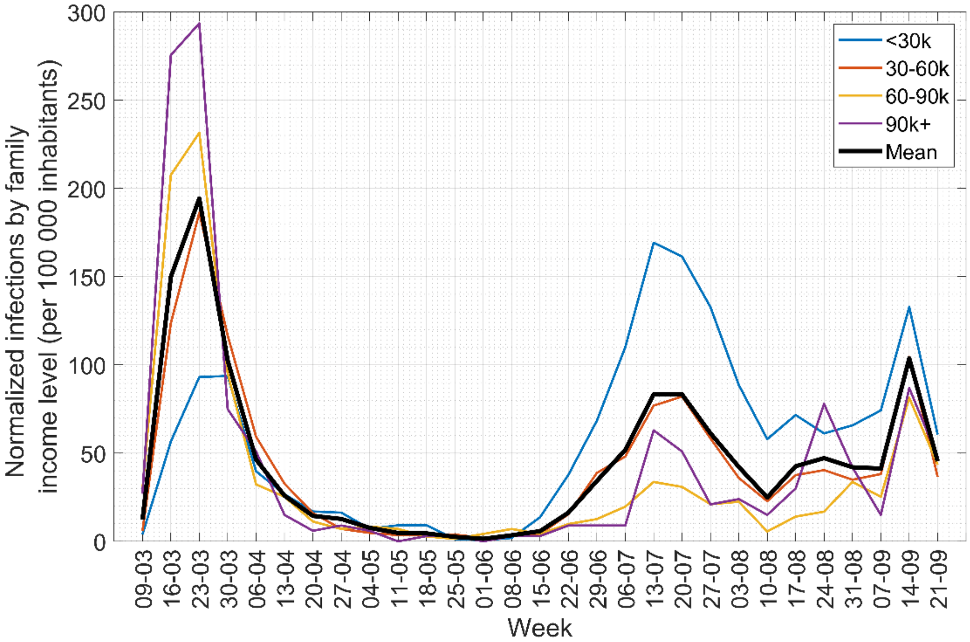


Supplementary Figure 3: Prevalence per work sector

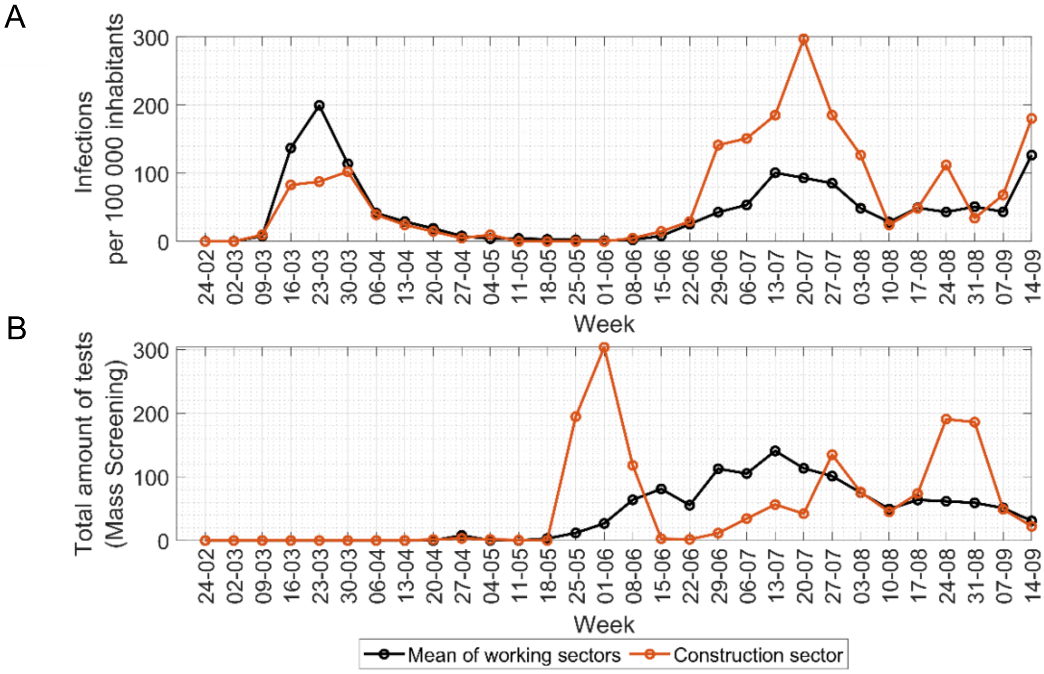


Supplementary Figure 4: Dynamics of positive tests for four high-risk work sectors

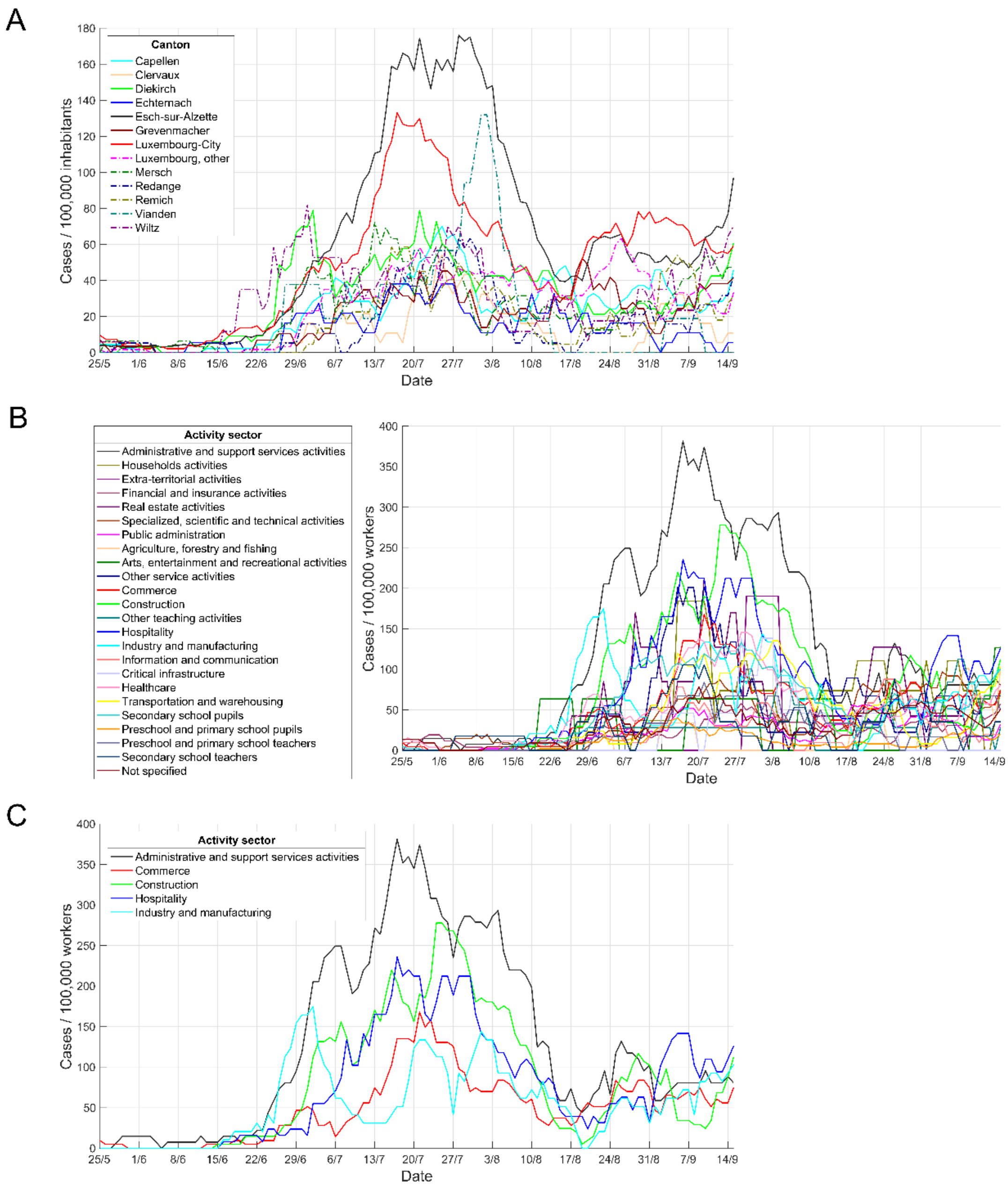
While during the early weeks of testing, there were more positive tests in the healthcare and social work sector, the hospitality sector exhibited increased numbers of positive tests from early July onwards. In contrast, no positive test result was identified amongst pharmacists and only one positive test was reported for the police.



Supplementary Figure 5: Prevalence per income category



Supplementary Figure 6: Prevalence and testing in the construction sector (A) Prevalence in the construction sector compared to other work sectors. (B) Number of tests performed in the construction sector in relation to other work sectors.



Supplementary Figure 7: Number of cases in the preceding week in different groups

(A) Cases in different cantons. A threshold of 150 cases per week per 100,000 inhabitants would have triggered a targeted testing of the canton of Esch-sur-Alzette on 16th July. (B) Cases in different economic sectors. (C) Sectors with more than 5,000 workers that cross the threshold of 150 cases per 100,000 workers. A targeted strategy would have been triggered in industry and manufacturing on 29th June, in administrative and support sector on 1st July, in construction on 7th July, in hospitality on 13th July, and in commerce on 21st July.

Supplementary Notes

1. Quality of the rRT-PCR assay and of the pooling strategy

The Fast Track Diagnostics™ (FTD) assay had previously been compared with the generic test N gene (CDC) rRT-PCR and with the commercially available Allplex™ 2019 n-CoV Assay from Seegene Inc. (Seoul, South Korea). The FTD assay was found to have a better analytical sensitivity (limit of detection of the generic N gene assay: 2 RNA copies/reaction, versus below 4 RNA copies/reaction for the Seegene Inc. assay, using the EDX SARS-CoV-2 standard (Exact Diagnostics, Fort Worth, Texas, USA).
The sensitivity and specificity of the pooling strategy, by comparing pools and unique samples tested with the FTD assay reached 100% (30/30) and 100% (20/20), respectively. Excellent correlation (R^2=0·994) and only a slight shift of Cq values were observed with an average ΔCq of 0·6±0·6 between single sample (Cq range: 17.6-36.5) and pooled samples (Cq range: 18.3-37.8).

2. Parameters of the Model

The model was parametrized based on the different lockdown measures in place and fitted to the identified cases as well as to hospital data. In particular, the baseline scenario describing the actual epidemic development including interventions by mass testing, closing economic sectors, and restrictions on private gatherings. The mass testing and contact tracing parameters were based on the number of performed tests and tuned to the numbers of cases identified by mass screening and subsequent contact tracing. To quantify the overall effect of mass testing, the baseline scenario was simulated with and without mass testing as well as for diverse strategy adaptations, where average values and 90% confidence intervals were obtained from 120 individual stochastic simulations for each scenario.

3. Demographic factors linked to participation

Based on the multi-variable logistic regression model for participation in mass screening, women had a 17% greater likelihood to participate in mass screening than men (odds ratio [95% confidence interval], OR 1·16 [1·15-1·17]). When compared to the age category 30-39 years, all the other age groups tended to participate less, with extreme age categories having the lowest ORs: ≤9 years OR 0·68 [0·67-0·70], 70-79 years OR 0·78 [0·76-0·80], and 80 years or more OR 0·37 [0·35-0·38]. Individuals with a disposable household income of less than 30k€/year participated less in mass testing (OR 0·71 [0·70-0·72], when compared to those with 30k€-60k€/year). Finally, we observed that each additional invitation sent to the population resulted in a 20% greater likelihood of participation in the mass screening programme OR 1·20 [1·19-1·20].

4. Invitations and participation per sectors

As per our design, workers in high-risk sectors such as healthcare and social work, hospitality, pharmacists and the police were invited more frequently than the other work sectors. In addition, water production and distribution sector, electricity production and distribution sector, public administration, and other services, received more than two invitations per individual. The other sectors exhibited an average of one invitation per individual (Suppl. Figure 2). The numbers of invitations sent out did translate into higher numbers of individuals being tested (Suppl. Figure 2). Healthcare and social workers had a high mean number of tests performed per individual (on average 1·7 tests performed per individual versus 0·9 for all work sectors). However, preschool and primary school teachers had the highest number of tests per individual (1·9 tests on average), despite not having been invited the most. Secondary school teachers rank after healthcare and social workers with 1·7 tests on average per individual. Workers from the hospitality sector exhibited fewer tests per individual than the other high-risk sectors (1·2 tests performed per individual versus 1·3 for the other high-risk sectors). Overall, participation of individuals related to teaching activities were among the highest, together with extra-territorial and other services activities. Participation for preschool and primary school teachers, secondary school teachers and other teaching activities was on average 61%, 58% and 72% per individual (ranked 4th, 5th and 1st), respectively. The extra-territorial and other services activities sectors exhibited an average of 71% and 65% of participation per individual (ranked 2nd and 3rd, respectively).

5. Prevalence per income categories

Individuals with a higher income had an overall higher prevalence during the first epidemic wave in March and April (Suppl. Figure 5). This contrasts with the second wave, for which the highest prevalence was seen in individuals from the lowest income category while the higher income category ranks below the prevalence of the general population (Suppl. Figure 5). Nevertheless, there was a small peak for the highest income category during the week starting on 24th August, most likely due to the return from summer holidays, as the prevalence within this category was then above that of the general population.

6. Tactical interventions

On 25th May, the services sector received 0·4 invitations per individual. Sustained waves of invitations were sent over the course of June and July following the increase in prevalence, reaching a total of 1·8 invitations per individual (Suppl. Figure 2). Between May 25 and September 15, the prevalence in the service activities sectors was significantly higher than in other sectors with 964·8 cases per 100,000 inhabitants (IRR 1·38, 95% CI [1·37,1·40], P < 0·00001), and reached a daily peak of 67 infected individuals per 100,000 inhabitants. It should be noted, however, that the service sector in Luxembourg represents 0·6% of the working population (2,000 inhabitants), and hence likely subject to stochastic fluctuations in positive cases. Participation in this sector was significantly above average (65·7%), as compared to the average participation across all other sectors (47·2%; Suppl. Figure 2).

On 2nd June, the hospitality sector received 0·8 invitations per individual. Sustained waves of invitations were sent over the course of June and July following the increase of prevalence, reaching a total of 4·4 invitations per individual (Suppl. Figure 2). Between May 25 and September 15, prevalence in the hospitality sector was significantly higher than in other sectors with 1,361 cases per 100,000 inhabitants (IRR 1·94 [1·93,1·97], P < 0·00001), and reached a daily peak of 70·7 infected individuals per 100,000 inhabitants in this activity sector. Participation, however, remained low (27·5%) as compared to the average sector participation (47·3%; Suppl. Figure 2).