Changes in behavior and biomarkers during the diagnostic decision period for COVID-19, influenza, and group A streptococcus (GAS): a two-year prospective cohort study in Israel

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Summary

Background Limited knowledge exists regarding behavioral and biomarker shifts during the period from respiratory infection exposure to testing decisions (the diagnostic decision period), a key phase affecting transmission dynamics and public health strategy development. This study aims to examine the changes in behavior and biomarkers during the diagnostic decision period for COVID-19, influenza, and group A streptococcus (GAS).

Methods We analyzed data from a two-year prospective cohort study involving 4795 participants in Israel, incorporating smartwatch data, self-reported symptoms, and medical records. Our analysis focused on three critical phases: the digital incubation period (from exposure to physiological anomalies detected by smartwatches), the symptomatic incubation period (from exposure to onset of symptoms), and the diagnostic decision period for influenza, COVID-19, and GAS.

Findings The delay between initial symptom reporting and testing was 39 [95% confidence interval (CI): 34–45] hours for influenza, 53 [95% CI: 49–58] hours for COVID-19, and 38 [95% CI: 32–46] hours for GAS, with 73 [95% CI: 67–78] hours from anomalies in heart measures to symptom onset for influenza, 23 [95% CI: 18–27] hours for COVID-19, and 62 [95% CI: 54–68] hours for GAS. Analyzing the entire course of infection of each individual, the greatest changes in heart rates were detected 67.6 [95% CI: 62.8–72.5] hours prior to testing for influenza, 64.1 [95% CI: 61.4–66.7] hours prior for COVID-19, and 58.2 [95% CI: 52.1–64.2] hours prior for GAS. In contrast, the greatest reduction in physical activities and social contacts occurred after testing.

Interpretation These findings highlight the delayed response of patients in seeking medical attention and reducing social contacts and demonstrate the transformative potential of smartwatches for identifying infection and enabling timely public health interventions.

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Keywords: Wearables; Incubation period; Heart rate; Infectious disease

Introduction

Infectious diseases pose a significant threat to human health.[1] Similar to controlling the spread of wildfires, early detection of infectious diseases is instrumental in containing outbreaks. However, nearly all infections start silently and gradually progress until clinical symptoms appear. In this silent period, known as the incubation period, pathogens inhibit the immune system's major pathways, allowing an extended period of unhindered replication.[2,3] The replication rate, type, and

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Research in context

Evidence before this study

Nearly all infectious diseases begin silently and progressively worsen until clinical symptoms appear, leading to personal decisions such as modifying social activities and seeking diagnostic tests and treatment. Limited knowledge exists regarding the changes in behavior and biomarkers during the period from respiratory infection exposure to the decision to undergo testing (the diagnostic decision period), a crucial phase affecting transmission dynamics and public health strategy development. To the best of our knowledge, no comprehensive study has been conducted to examine these changes during the diagnostic decision period for COVID-19, influenza, and group A streptococcus (GAS). We searched Google Scholar, PubMed, and preprint services (including medRxiv, bioRxiv, and SSRN) for relevant studies between November 1, 2023, and February 1, 2024. We imposed no language restrictions and utilized search terms ("human behavior" OR "social behavior" OR "behavioral" OR "physiological" OR "biomarkers") AND "reactions during" AND ("incubation period" OR "time from exposure to symptoms" OR "time from exposure to testing") AND ("of" OR "for") AND ("influenza" OR "influenza-like illness" OR "COVID-19" OR "SARS-CoV-2" OR "Group A streptococcus" OR "GAS"). We identified relevant studies for influenza and COVID-19 only.

For influenza, we found a clinical trial involving participants deliberately exposed to influenza while equipped with wearable devices. The primary objective was to assess the impact of pharmaceutical intervention. Within the placebo group, comprising 45 participants, a discernible increase in heart rate and blood pressure was observed, peaking on the third day post-exposure compared to the 24 h preceding exposure. However, the study did not investigate behavioral alterations or physiological responses throughout the diagnostic decision period.

For COVID-19, we found several studies. A retrospective study of 2745 individuals who owned wearable devices and were diagnosed with COVID-19 between February 16 and September 9, 2020 identified variations in heart rate and respiratory rate manifesting as early as 10 days before symptom onset. A separate observational study focusing on 297 health workers equipped with smartwatches identified significant changes in heart rate variability metrics occurring seven days before a positive COVID-19 diagnosis. In another observational prospective study involving 32 subjects who tested positive for COVID-19, changes in heart rate, steps taken, and time asleep were observed during the pre-symptomatic period. We did not find related papers discussing GAS.

Added value of this study

Our study bridges a crucial knowledge gap regarding the early stages of infectious diseases. Through a novel two-year prospective cohort study of 4795 participants in Israel, integrating smartwatch data, self-reported symptoms, and medical records, we analyze three key phases—the digital incubation period (from exposure to anomalies in physiological measures), the incubation period (from exposure to symptom onset), and the diagnostic decision period (from exposure to testing)—for influenza, COVID-19, and GAS. Our data included 490 episodes of influenza, 2206 episodes of COVID-19, and 320 episodes of GAS during the study period. We found a significant reduction in physical activities and contact encounters post-testing, but the greatest changes in heart rates were detected 67.6 [95% confidence interval (CI): 62.8–72.5] hours prior to testing for influenza, 64.1 [95% CI: 61.4–66.7] hours prior for COVID-19, and 58.2 [95% CI: 52.1–64.2] hours prior for GAS. The delay between initial symptom reporting and testing was 39 [95% CI: 34–45] hours for influenza, 53 [95% CI: 49–58] hours for COVID-19, and 38 [95% CI: 32–46] hours for GAS, with 73 [95% CI: 67–78] hours from anomalies in heart measures to symptom onset for influenza, 23 [95% CI: 18–27] hours for COVID-19, and 62 [95% CI: 54–68] hours for GAS.

Implications of all the available evidence

Our findings underscore a critical delay in testing and behavior change: individuals tend to seek testing and alter their behaviors only after their condition begins to improve, specifically after the peak of the illness, as evidenced by self-reported symptoms and heart rate measures. This delay from symptom onset to testing, with behavioral adjustments occurring predominantly on or after the test day, highlights a significant gap in timely disease management. Additionally, we found that changes in heart rate and heart rate variability precede symptom reporting, indicating the need to reassess the conventional incubation period to include digital markers. These insights are vital for improving understanding of transmission dynamics and advancing public health response strategies.

length of suppressed symptoms vary considerably between pathogens. Once detected by the immune system, variations in heart measures including resting heart rate, heart rate, and heart rate variability (HRV) can serve as biomarkers for the inflammatory response.[4,5] While behavioral adaptations such as self-isolation play a significant role in influencing disease transmission,[6–8] a crucial gap persists in our understanding of the relationship between the early stages of infection and subsequent changes in individual behavior.

Understanding behavioral dynamics is crucial for devising effective public health strategies to combat infectious diseases. Various models investigating infectious disease responses have underscored the critical

impact of behavioral adaptation during disease progression.[9–12] Behavioral adaptations include reducing physical contact, accelerating diagnostic testing, and initiating early treatment. However, a notable limitation of these models is their theoretical nature, often devoid of empirical data to substantiate their assumptions.[13]

Wearable technology, such as smartwatches, offers an innovative approach to continuous monitoring of physiological responses throughout the course of an individual's infection.[14–17] These devices can detect physiological anomalies signaling disease presence more promptly and accurately than self-reported symptoms. Several empirical studies have demonstrated the ability of wearable sensors to detect communicable diseases such as COVID-19, influenza, and rhinovirus with significant accuracy, often identifying infections before the appearance of symptoms.[15,18–24]

Limited knowledge exists at the individual level regarding changes in behavior and biomarkers during the diagnostic decision period—the interval from exposure to an infectious disease to the decision to undergo testing. This phase is critical as it significantly influences transmission dynamics and the development of effective public health interventions. A clinical trial involving wearable devices and deliberate exposure to the influenza virus revealed increased heart rate and blood pressure among participants.[25] An analysis of cell-phone call records during the 2009 H1N1v pandemic found reduced mobility among individuals diagnosed with influenza-like illness.[26] For COVID-19, studies have identified variations in heart rate, HRV, steps, and respiratory rate preceding symptom onset,[18,27,28] emphasizing the importance of recognizing early markers for timely interventions. Yet, a holistic understanding of behavioral and physiological shifts during the diagnostic period remains incomplete.

We combined daily symptom questionnaires with data from wearable sensors, aiming to examine the changes in behavior and biomarkers during the diagnostic decision period (from exposure to the decision to undergo testing) for COVID-19, influenza, and group A streptococcus (GAS). We examined three critical periods: the digital incubation period (from exposure to anomalies in physiological measures), the symptomatic incubation period (from exposure to symptom onset), and the diagnostic period. Using a comprehensive dataset that combines data from electronic medical records (EMRs) and smartwatch sensor data along with daily participant questionnaires from 4795 participants in an ongoing clinical trial, we identified events related to positive diagnoses of influenza, COVID-19, and GAS, including symptom onset and diagnosis. We correlated these findings with measures that may influence disease transmission: physical activity as measured by the smartwatches (daily steps, distance walked, active time, active calories) and number of daily contacts and sports duration as reported by the participants. Our study illuminates the lag between infection and testing and underscores the revolutionary role of smartwatches and patient self-reporting in paving the way for better understanding disease progression and quicker public health responses.

Methods

Participants and study design

The ongoing PerMed prospective observational study included 4795 participants aged 18 and older, recruited between Nov 16, 2020 and May 11, 2023 from various locations across Israel (SI Appendix B). Participant recruitment was carried out through social media advertisements and word-of-mouth. Each participant signed an informed consent form after receiving a detailed explanation of the study from a professional survey company.

Eligibility for the PerMed study required participants to be 18 years or older, members of Maccabi Healthcare Services (Maccabi) at the time of enrollment and for at least the preceding two years, smartphone users, and capable of providing written informed consent independently. Maccabi, the second-largest healthcare provider in Israel,[29] serves approximately 25% of the population, totaling around 2.5 million members.

We analyzed the data of individuals who tested positive for influenza, COVID-19, or GAS, as recorded by health professionals in their EMRs or self-reported in the application, from the day of enrollment until the end of October 2023 (Fig. 1).

All participants received both oral and written advice about the study and provided written informed consent for participation. The study was approved by the Helsinki institutional review board of Maccabi Healthcare Services (protocol number 0122-20-MHS).

Procedures

Participants completed a one-time enrollment questionnaire. All participants received Garmin Vivosmart 4 smartwatches and installed two applications on their mobile phones: (1) the PerMed application (SI Appendix B), which collects daily self-reported questionnaires, and (2) an application that passively records smartwatch data. All participants downloaded the same application on their cell phones, regardless of the operating system.

Participants were encouraged to wear their smartwatches as much as possible. A survey company used a dedicated dashboard to monitor compliance, ensuring that participants completed their questionnaires at least twice per week, kept their smartwatches charged and properly worn, and resolved any technical issues with the mobile applications or smartwatches (SI Appendix D).

The questionnaire allowed participants to report observed signs and symptoms during influenza,

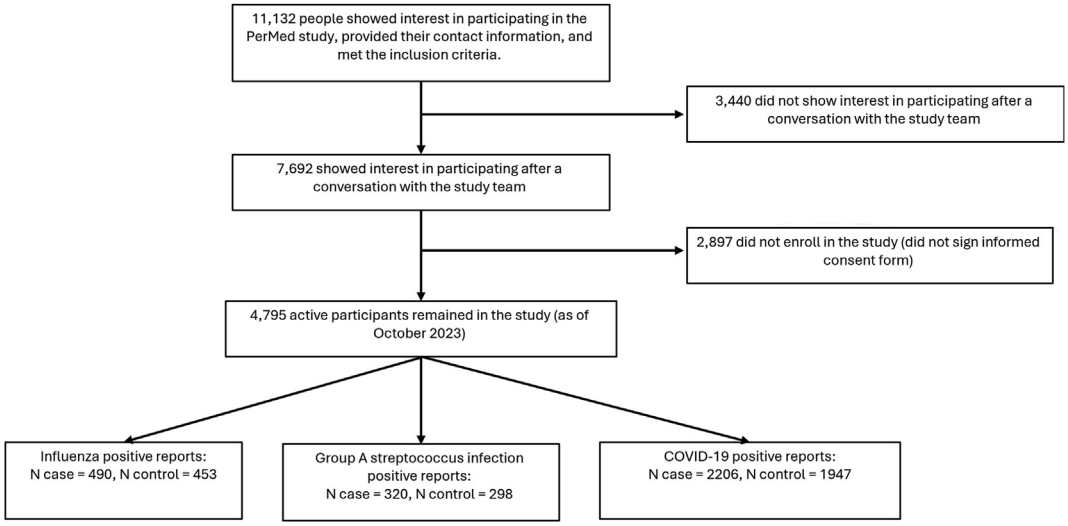

Fig. 1: **Trial profile for the study cohort.**

COVID-19, or GAS infections, with an option to add other symptoms as free text (SI Appendix B). Among other features, the smartwatch collects data on heart rate, HRV-based stress, and daily resting heart rate. We focused on these measures because they provide continuous information on two major human body systems: the cardiovascular and the nervous systems.[14] Additionally, heart rate is a vital sign that is often used to detect inflammation in general and heart inflammation specifically, and is recorded by a wide variety of smartwatches and sampled in high frequency in our database (every 15 s as opposed to resting heart rate, which was calculated daily).

To minimize data inconsistencies across different smartwatch brands, all participants were equipped with Garmin Vivosmart 4 smart fitness trackers. These devices feature an optical wrist heart rate monitor that continuously tracks the user's heart rate. The frequency of heart rate measurement varies and sometimes depends on the user's activity level: it increases when the user starts an activity. As HRV data was not easily accessible through Garmin's application programming interface, we utilized Garmin's stress level measurement, which is based on HRV.[30–33] Specifically, the device uses heart rate data to determine the interval between heartbeats, with decreased variability between beats correlating with higher stress levels, and vice versa. In our study, we identified heart rate samples approximately every 15 s and an HRV sample every 180 s.

Several preventive measures were implemented to minimize participant attrition and discomfort, thus improving the quality, continuity, and reliability of the collected data. Firstly, participants who did not complete their daily questionnaire by 1900 h received a reminder through the PerMed application. Secondly, a dedicated dashboard enabled the survey company to identify participants who repeatedly neglected to complete the daily questionnaire or to wear their smartwatch. These participants were contacted (via text or phone call) and encouraged to adhere to the study protocol. Thirdly, to engage participants, a weekly summary report was generated in the PerMed application, and a monthly newsletter with recent findings and smartwatch tips was sent out. At the end of the two-year study, participants received all their insights and were gifted with the smartwatch.

A dedicated data collection platform was developed to collect, for each participant, data from the smartphone sensors and daily questionnaires via the Permed application, and from the smartwatch sensors via the Garmin server (SI Appendix C, Supplementary Fig. S4). This data is securely stored at Tel Aviv University facilities. The exact date of testing for each positive diagnosis was recorded in the individual's medical record if they sought care. If participants conducted a rapid test, they were instructed to report the testing time in the PerMed app. For participants with more than one positive record, only the earliest recorded testing time was used for each disease (SI Appendix E).

Statistical analysis

Our statistical analyses proceeded by identifying the earliest testing date for each case of influenza, COVID-19, and GAS; identifying the time at which the first symptom was reported; estimating the time when the individual was exposed to the disease; and identifying the first time at which an anomaly in heart rate measure was detected by the smartwatch (Supplementary Fig. S1).

Establishing case definitions for influenza, COVID-19, and GAS

Positive diagnoses were either recorded in the individual's medical record following clinical care or self-reported in the application for those using home rapid test kits. Participants were instructed to report the test time and result in the app. In cases where participants had multiple positive reports, we used only the earliest reported time for each disease (SI Appendix D, Supplementary Table S1).

An influenza case was defined as testing positive on an antigen influenza or PCR test, with no positive COVID-19 test within a ±14-day range.

We defined a COVID-19 case as one where an individual tested positive through either a PCR test administered by Maccabi or via an antigen test at home.

A GAS case was defined as positive either via a throat culture test or a rapid antigen test. Additionally, a diagnosis was considered a GAS case if 1) the individual reported being diagnosed with a throat infection, 2) received antibiotics, and 3) was not diagnosed with COVID-19 or influenza within a 14-day window before and after the report. This inclusion is based on the use of clinical criteria, such as the US centers for Disease Control and Prevention (CDC) criteria, for diagnosing GAS.

For each disease-specific cohort, we established control groups consisting of individuals not diagnosed with the disease, and who had no illness reports for three weeks before and one week following the test date. We also excluded individuals reporting a fever over 37.5 °C or experiencing sensations of warmth. We matched control participants to the infected participants based on sex (female, male) and age brackets: 20–29, 30–39, 40–49, 50–59, 60–69, and 70+ years. For each control participant, we analyzed their heart rate data on the same dates as their matched counterpart.

Estimation of early phase periods of infections

Digital incubation period: We introduce this term to describe the period from exposure to the pathogen until a physiological anomaly is detectable through digital means. The digital incubation period might also be regarded as the "true incubation period" since physiological changes, such as heart rate variations, are in fact clinical symptoms, irrespective of whether they are perceptible to the patient.

Incubation period: This refers to the time from pathogen exposure to the initial appearance of symptoms and signs that are perceivable by the individual.

Diagnostic decision period: This is the interval between exposure to the pathogen and the point of testing.

To estimate these periods, we first identified episodes where participants were diagnosed with COVID-19, influenza, or GAS, based on our case definitions. The date of testing was established as the point when the individual underwent a first diagnostic test within a horizon of 14 days. Next, we identified the first new symptom by reviewing self-reported symptoms from the week leading up to the testing date, including the day of testing itself. We chose to consider one week before because a symptom is likely sufficiently "new" if it was reported in the week just before testing (from –6 days to the day of testing) and not in the preceding week (–13 to –7 days from testing). For instance, if a participant reported a headache one day before testing and also nine days prior, we did not consider the headache as a first symptom. We then associated specific symptoms with each disease according to US CDC guidelines:

- For influenza: Feeling hot, having a temperature over 37.5 °C, chills, sore throat, cough, muscle pain, weakness, feeling cold, and headache.
- For COVID-19: Feeling hot, temperature over 37.5 °C, chills, cough, loss of taste or smell, muscle pain, sore throat, dyspnea, weakness, vomiting, headache, and diarrhea.
- For GAS: Feeling hot, temperature over 37 .5 °C, sore throat, and vomiting.

To ensure that the individuals were not infected in the baseline, we excluded participants who reported fever symptoms during the baseline period.

The exact time of exposure is unknown. However, drawing on existing literature, the incubation period for influenza is typically 1–4 days,[34] for COVID-19 is 2–5 days,[2] and for GAS is 2–5 days.[35] To estimate the time of exposure conservatively, we assume the exposure occurred at a point that allows for the maximum plausible duration between exposure and the average onset of the first symptom. We excluded participants who did not have at least one questionnaire filled out during the week before exposure and one week after exposure. Estimates for these three points (exposure, first symptom, and testing date) allowed us to identify the incubation period and the diagnostic decision period.

To estimate the digital incubation period, we sought to identify anomalies in individuals based on heart rates and HRV-based stress. We first filtered out all data points captured during periods of physical activity. This exclusion applies to sessions that participants actively logged via the Garmin Connect application during sports activities as well as those autonomously detected by the smartwatch. The device's algorithm, which primarily utilizes motion data, is designed to identify and exclude periods of physical exercise, postural changes, and recovery phases at intervals of every 3 min,[30] thereby efficiently recognizing various types of exercises, including walking and running. Additionally, we conservatively removed segments lasting 3 min where insufficient data points made it challenging to ascertain the existence of physical activity.

We then determined the average values of each participant's heart rate and HRV-based stress over 6-h

periods (SI Appendix E). This calculation began two weeks prior to the estimated exposure time and continued until two weeks after. Following this, for each participant and every 6-h window, we computed the difference between the average of the measured values and the average from the corresponding 6-h period in the previous week that occurred before estimated exposure, while maintaining consistency in the day and time.

Participants lacking recorded data for these intervals (e.g., if they did not consistently wear their smartwatch before and after the exposure period) were excluded from this analysis. The differences in these averages were found to have similar means and variances and were very weakly correlated.[14] Subsequently, we applied X-bar control charts,[36,37] using the data from exposure until testing (SI Appendix E, Supplementary Figs. S5 and S6). An anomaly was identified conservatively as the first instance where the 6-h differences in average heart rate and average HRV-based stress exceeded the control limits.[14] For validation, we extended our search to a broader range that encompasses the baseline period—spanning a week before the estimated incubation period through to the testing phase—to ensure that the initially identified anomaly does not occur during the baseline period. To confirm that the anomalies detected in the X-bar charts are not merely single-point outliers, we conducted a segmented regression analysis in which we fit the data to two linear segments and calculated the total sum of squared errors for any potential segment combination (SI, Supplementary Figs. S7 and S8).

To assess whether the most significant changes in heart rate occurred before or after testing, our procedure entailed two steps. First, for each individual, we pinpointed the maximum average difference in heart rates over a 6-h span during the diagnostic decision period. We then identified the maximal 6-h difference in heart rates following the diagnostic decision period, ensuring an equal number of data points both before and after the diagnostic decision period. This approach allowed for a balanced comparison of similar intervals. Subsequently, we applied a paired sample t-test to statistically analyze these differences.

Employing the same procedure, we aimed to identify whether significant changes in behavioral metrics occurred before the testing day or started on the testing day and continued thereafter. We assessed the daily number of contacts and the duration of sports activities as reported by participants, and daily step counts, active calories, active time, and total daily distance computed by the smartwatch.

Role of the funding source

The funders of this study had no role in data collection, analysis, interpretation, writing of the manuscript, or the decision to submit the manuscript.

Results

Details of the cohort are provided in Table 1. Among the 4795 participants, our data included 490 episodes of influenza, 2206 episodes of COVID-19, and 320 episodes of GAS during the study period. We were able to match 453 participants for influenza, 1947 for COVID-19 and 329 for GAS based on age and sex for control groups. Among those infected with influenza, 279 (56.9%) participants were women and 211 (43.1%) were men. Their age ranged from 22 to 90 years, with a median age of 50 years. Among those infected with COVID-19, 1137 (51.5%) participants were women and 1069 (48.5%) were men. Their age ranged from 20 to 89 years, with a median age of 43 years. Among those infected with GAS, 182 (57.9%) participants were women and 137 (42.8%) were men. Their age ranged from 20 to 76 years, with a median age of 38 years. The control cohort for each disease was similarly matched by sex, age, BMI, and presence of comorbidities (Table 1).

For each disease—influenza, COVID-19, and GAS—we calculated the average time from exposure to detection of heart rate anomalies in participants (heart rate and HRV-based stress), symptom onset, and testing. Using existing literature to estimate the benchmark exposure times, we defined three distinct periods relative to exposure: the digital incubation period, the incubation period, and the diagnostic decision period (Fig. 2). We found a considerable lag between testing time and symptom onset: 39 [95% confidence interval (CI): 34–45] hours for influenza, 53 [95% CI: 49–58] hours for COVID-19, and 38 [95% CI: 32–46] hours for GAS. The delay in testing was also demonstrated in physiological measures. When we ran the same method on the control participants' heart rate measures, no anomaly was found.

The maximal changes in heart rate before testing were significantly higher on average than those observed at or after the time of testing (paired t-tests, p-values < 0.001 for all three diseases), with heart rates averaged over a duration of 6 h. Specifically, the change was 4.6 beats per minute (BPM) [95% CI: 3.2–5.9] for influenza, 3.6 [95% CI: 2.8–4.3] BPM for COVID-19, and 5.5 [95% CI: 3.4–7.6] BPM for GAS.

The maximum difference occurred 67.6 [95% CI: 62.8–72.5] hours prior to the test for influenza, 64.1 [95% CI: 61.4–66.7] hours prior to the test for COVID-19, and 58.2 [95% CI: 52.1–64.2] hours prior to the test for GAS, indicating that by the time participants tested themselves, their general health condition had already improved. We found a similar pattern for HRV-based stress. No significant difference in heart rate or HRV was observed for the control groups (p values < 0.001).

We identified a considerable lag between the detection of heart rate anomalies by the smartwatches and the onset of symptoms as reported by the participants: 73 [95% CI: 68–78] hours from anomalies in heart measures to symptom onset for influenza, 23 [95% CI:

	Case cohort			Control cohort		
	Influenza (n = 490)	COVID-19 (n = 2206)	Group A strepto-coccus (n = 320)	Influenza (n = 453)	COVID-19 (n = 1947)	Group A strepto-coccus (n = 298)
Sex						
Female	279 (56.9%)	1137 (51.5%)	182 (56.9%)	261 (57.6%)	987 (50.7%)	172 (57.7%)
Male	211 (43.1%)	1069 (48.5%)	138 (43.1%)	192 (42.4%)	960 (49.3%)	126 (42.3%)
Age (years)						
20–29	61 (12.4%)	388 (17.6%)	56 (17.5%)	57 (12.6%)	341 (17.5%)	53 (17.8%)
30–39	83 (16.9%)	521 (23.6%)	118 (36.9%)	72 (15.9%)	449 (23.1%)	110 (36.9%)
40–49	96 (19.6%)	441 (20.0%)	74 (23.1%)	88 (19.4%)	398 (20.4%)	67 (22.5%)
50–59	115 (23.5%)	426 (19.3%)	36 (11.2%)	109 (24.0%)	394 (20.2%)	34 (11.4%)
60–69	93 (19.0%)	295 (13.4%)	23 (7.2%)	85 (18.8%)	245 (12.6%)	23 (7.7%)
70+	42 (8.6%)	135 (6.1%)	13 (4.1%)	42 (9.3%)	120 (6.2%)	11 (3.7%)
Median (IQR)	50 (38–61)	43 (33–56)	38 (32–47)	53 (37–61)	44 (33–57)	38 (31–48)
BMI[a]						
<30	375 (76.5%)	1722 (78.0%)	249 (77.8%)	358 (79.0%)	1522 (78.2%)	240 (80.5%)
≥30	113 (23.1%)	476 (21.6%)	71 (22.2%)	95 (21.0%)	421 (21.6%)	58 (19.5%)
Unspecified	2 (0.4%)	8 (0.4%)	0	0	4 (0.2%)	0
Median (IQR)	26 (23–29)	25 (22–29)	26 (23–29)	25 (22–29)	25 (23–29)	24 (22–28)
Comorbidities[b]						
No	417 (85.1%)	1943 (88.1%)	283 (88.4%)	387 (85.4%)	1711 (87.9%)	268 (89.9%)
Yes	73 (14.9%)	263 (11.9%)	37 (11.6%)	66 (14.6%)	236 (12.1%)	30 (10.1%)
Population sector						
General Jewish	414 (84.5%)	2072 (93.9%)	270 (84.4%)	430 (94.9%)	1832 (94.0%)	275 (92.3%)
Ultra-orthodox Jewish	6 (1.2%)	46 (2.1%)	10 (3.1%)	10 (2.2%)	46 (2.4%)	9 (3.0%)
Arab	5 (1.0%)	14 (0.6%)	4 (1.3%)	2 (0.5%)	19 (1.0%)	3 (1.0%)
Unknown	65 (13.3%)	74 (3.4%)	36 (11.2%)	11 (2.4%)	50 (2.6%)	11 (3.7%)

[a]BMI is defined as weight in kilograms divided by the square of the height in meters. [b]Comorbidities were at least one of the following: diabetes, heart disease, chronic lung disease, immune suppression, cancer, or renal failure.

Table 1: **Description of case and control cohorts.**

18–27] hours for COVID-19, and 62 [95% CI: 54–68] hours for GAS.

Behavioral changes

We evaluated daily behavior throughout the early stage of infection, focusing on measures that may be associated with transmission. These include daily steps, daily distance walked, active time, and active calories collected by the smartwatches, as well as the number of daily contacts and sports duration reported by the participants. Overall, we found that the greatest reduction in these measures was observed on the day of testing or after the day of testing (Supplementary Table S2). For example, compared to baseline, on the day of testing we observed a reduction of 2372 [95% CI: 1783, 2962] in daily steps for patients with influenza, 1884 [95% CI: 1597–2173] for COVID-19, and 2042 [95% CI: 1267–2817] for GAS, and a reduction of 2.84 [95% CI: 1.52–4.16] in daily physical contacts for patients with influenza, 1.26 [95% CI: 0.31–2.20] for COVID-19, and 3.65 [95% CI: 1.46–5.83] for GAS (Fig. 3, Supplementary Table S2). In contrast, we observed smaller or no reductions in the same measures on the day of symptom onset compared to a matching day (daily steps: influenza 1428 [95% CI: 865–1991], COVID-19 700 [95% CI: 395–1005], GAS 1802 [95% CI: 1129–1474]; daily contacts: influenza 0.13 [95% CI: −2.00 to 2.25], COVID-19 0.55 [95% CI: −0.53 to 1.63], GAS 0.77 [95% CI: −2.81 to 4.36]), and no reduction at the time when the smartwatches detected anomalies in the heart measures. We found a similar pattern for daily distance walked, active time, active calories, and sports duration (Supplementary Fig. S2 and Table S2).

Self-reported reactions

Next, we evaluated the association between the decision to undergo testing and the specific symptoms reported by individuals. We calculated the daily proportion of individuals reporting each symptom each day (Fig. 4). For influenza, the most common self-reported symptoms were sore throat, cough, and general weakness. For COVID-19, individuals frequently reported experiencing a cough, weakness, sore throat, and headaches. For GAS, the predominant symptoms included a sore throat, fever exceeding 37 .5 °C, and feeling hot.

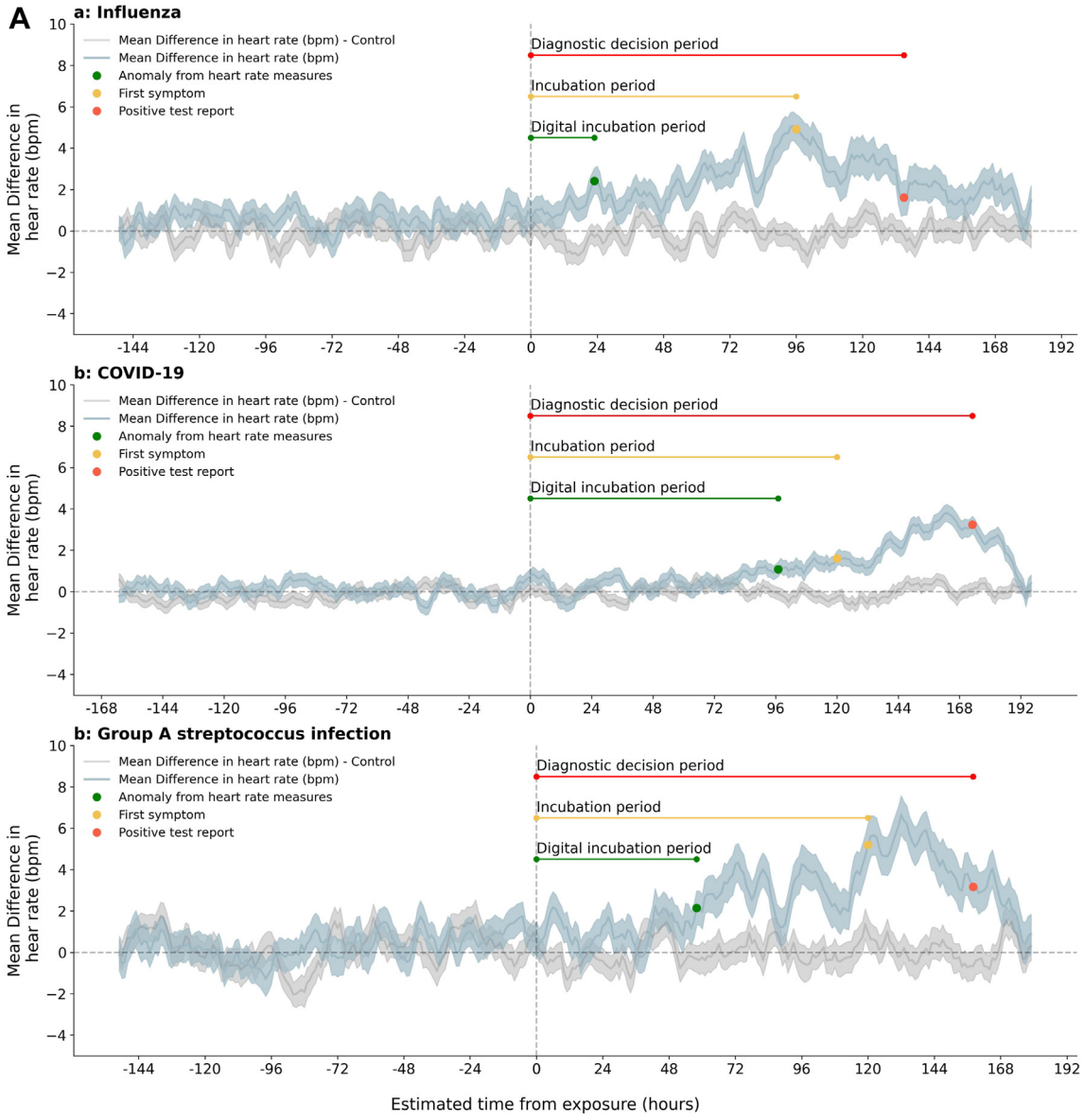

Fig. 2: **Changes in heart rate and heart rate variability (HRV) following infection with influenza, COVID-19, and group A streptococcus (GAS), throughout the early phase of infection for case groups (blue) and control groups (gray).** For each group, the difference is compared to the matching time of the week that occurred before exposure, as recorded by the smartwatches. The panels show the mean difference between the baseline period and the period after baseline for case groups (in blue) and control groups (in gray). Mean values are depicted as solid lines and standard error ranges are shown as shaded regions. The green point indicates the average time of detection of heart rate measure anomalies; this is the end point of the digital incubation period. The yellow point indicates the average time of the first reported symptom; this is the endpoint of the symptomatic incubation period. The red point indicates the average time of testing. **A**) Changes in heart rate following infection with influenza, COVID-19, and group A streptococcus (GAS). (Case groups: n influenza = 311; n COVID-19 = 1114; n GAS = 193. Control groups: n influenza = 383; n COVID-19 = 1617; n GAS = 239). **B**) Changes in heart rate variability (HRV)-based stress. (Case groups: n influenza = 313; n COVID-19 = 1118; n GAS = 193. Control groups: n influenza = 387; n COVID-19 = 1625; n GAS = 242).

On the testing day, patients typically reported multiple symptoms: an average of 4.73 symptoms for influenza, 2.96 for COVID-19, and 1.59 for GAS (Fig. 4). We identified a substantial variation between specific symptoms and the decision to seek testing. For example, for patients reporting a body temperature exceeding 37.5 °C, testing occurred within 24–48 h for all three diseases: for influenza, 63% of participants were tested within the first 24 h and 69.7% within 48 h; for COVID-19, the respective figures were 60.3% and 83.8%; and for GAS, the

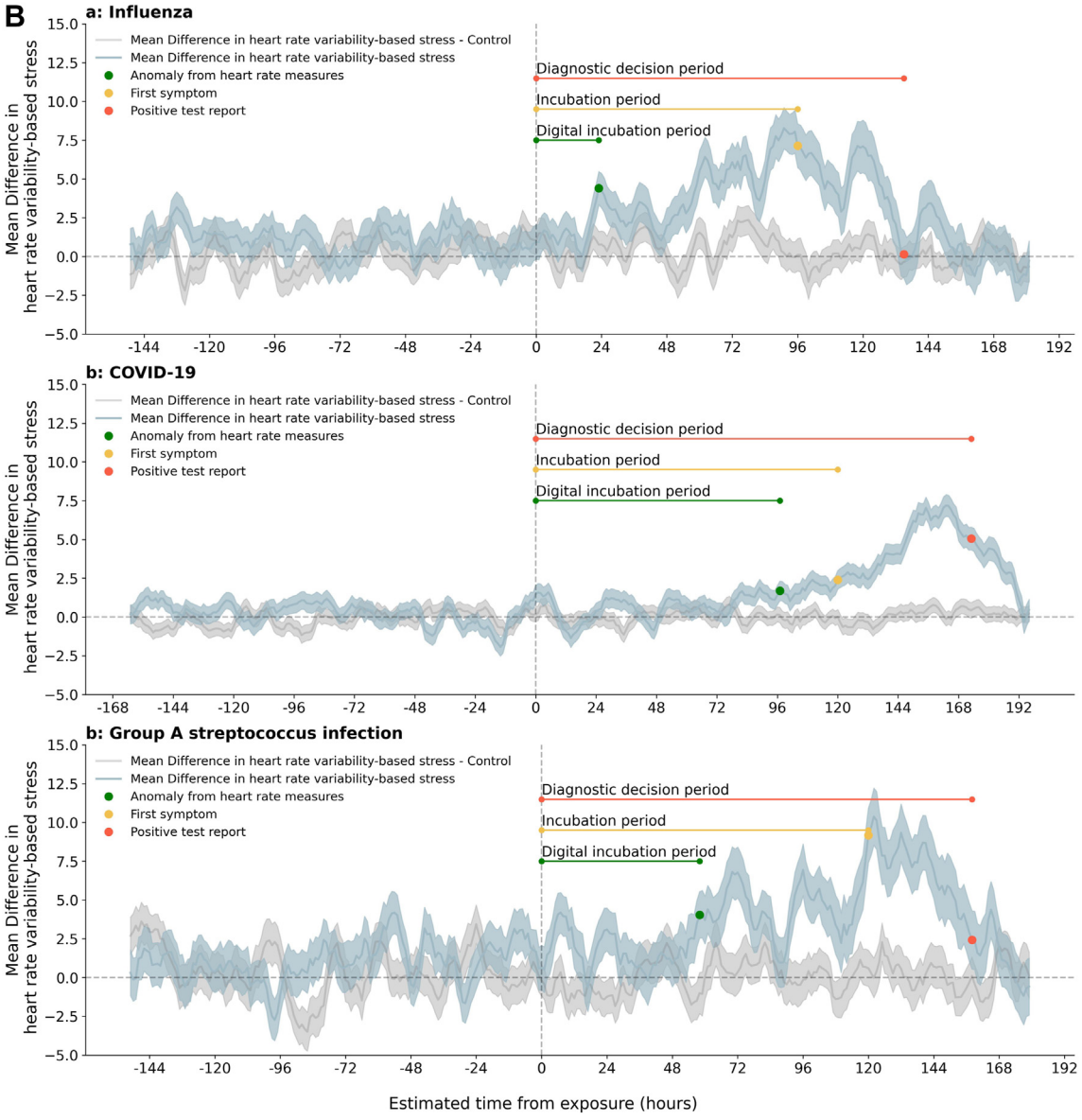

Fig. 2: (continued)

respective figures were 53.4% and 67.1%. The presence of a sore throat was associated with a more moderate testing response: within 48 h of symptom onset, only 51.9% of influenza patients, 66.1% of COVID-19 patients, and 53.4% of GAS patients sought testing (Supplementary Fig. S3).

Discussion

Our study highlights two aspects of infectious disease management: the behavioral response of patients after symptom onset and the transformative role of smartwatch data in early detection. We observed a notable delay in patients reducing physical activities after the onset of symptoms which, considering the peak transmissibility phases of COVID-19, influenza, and GAS, suggests that early testing and self-isolation are crucial to curb transmission. Our research supports the utilization of smartwatch data in detecting the changes in heart rate and heart rate variability that precede the reporting of symptoms. These findings advocate for a reevaluation of the traditional incubation period, incorporating digital markers to enable timely testing and self-isolation.

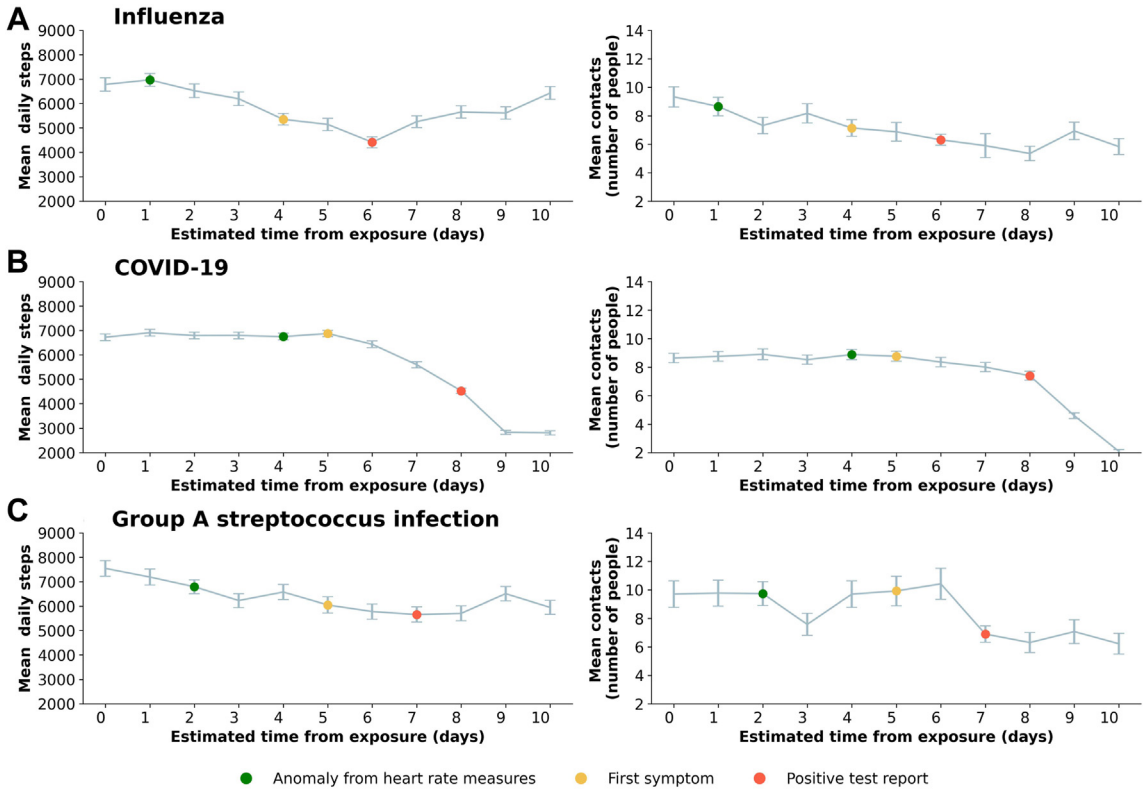

Fig. 3: **Behavioral measures compared to baseline over time for influenza (panel A), COVID-19 (panel B), and group A streptococcus (panel C), as recorded by the smartwatches (steps) or reported in the questionnaires (number of contacts with other people) (Steps: n influenza = 312; n COVID-19 = 1079; n GAS = 200; Daily contacts: n influenza = 155; n COVID-19 = 540; n GAS = 87).** Mean values are depicted as solid lines and standard errors are shown as error bars. The 0 point represents the estimated mean time of exposure based on the first symptom and the literature incubation period upper bound. The green point indicates the average day of detection of heart rate measure anomalies; this is the endpoint of the digital incubation period. The yellow point indicates the average day of the first reported symptom; this is the endpoint of the symptomatic incubation period. The red point indicates the average day of a positive test or self-report.

We found a delay between heart rate anomalies and the initial reporting of symptoms, as well as a substantial behavioral change that occurs only on the test day or after. The clinical symptoms detected as anomalies in the heart measures were unseen or ignored by patients. At symptom onset, patients had modest behavior change but the greatest behavior change occurred after testing—by which time the impact on disease transmission may be minimal. Prior research has estimated that the transmissibility peaks on or around the day of symptom onset for influenza,[38,39] approximately one day before symptom onset for COVID-19,[40–42] and during the incubation period for GAS.[43] Our results also reveal that physical activity reduction typically occurred after heart rate patterns began reverting to baseline levels. These findings of the behavioral patterns of infected individuals highlight the value of distributing rapid test kits to facilitate early self-isolation and reduce further transmission.

Our study provides substantial evidence supporting the use of smartwatch data for the early detection of infectious diseases, which suggests a paradigm shift in the examination of the incubation period for infectious diseases. Our anomaly detection algorithm identified changes in both heart rate and heart rate variability from smartwatch data at least one day before infected individuals reported symptoms for all three diseases under study. Examining these variations in heart rate patterns will increase clinical understanding of the incubation period for infectious diseases. Future research on disease transmission should include related symptoms detectable by smartwatches or other wearable devices when measuring the incubation period, or alternatively, present data on the digital incubation period alongside traditional metrics.

Our study has several limitations. First, participants were recruited via advertisements on social media and word-of-mouth, making our cohort a convenience sample. The demanding study requirements—wearing the smartwatch and filling out daily questionnaires for two years—made participation less appealing to certain

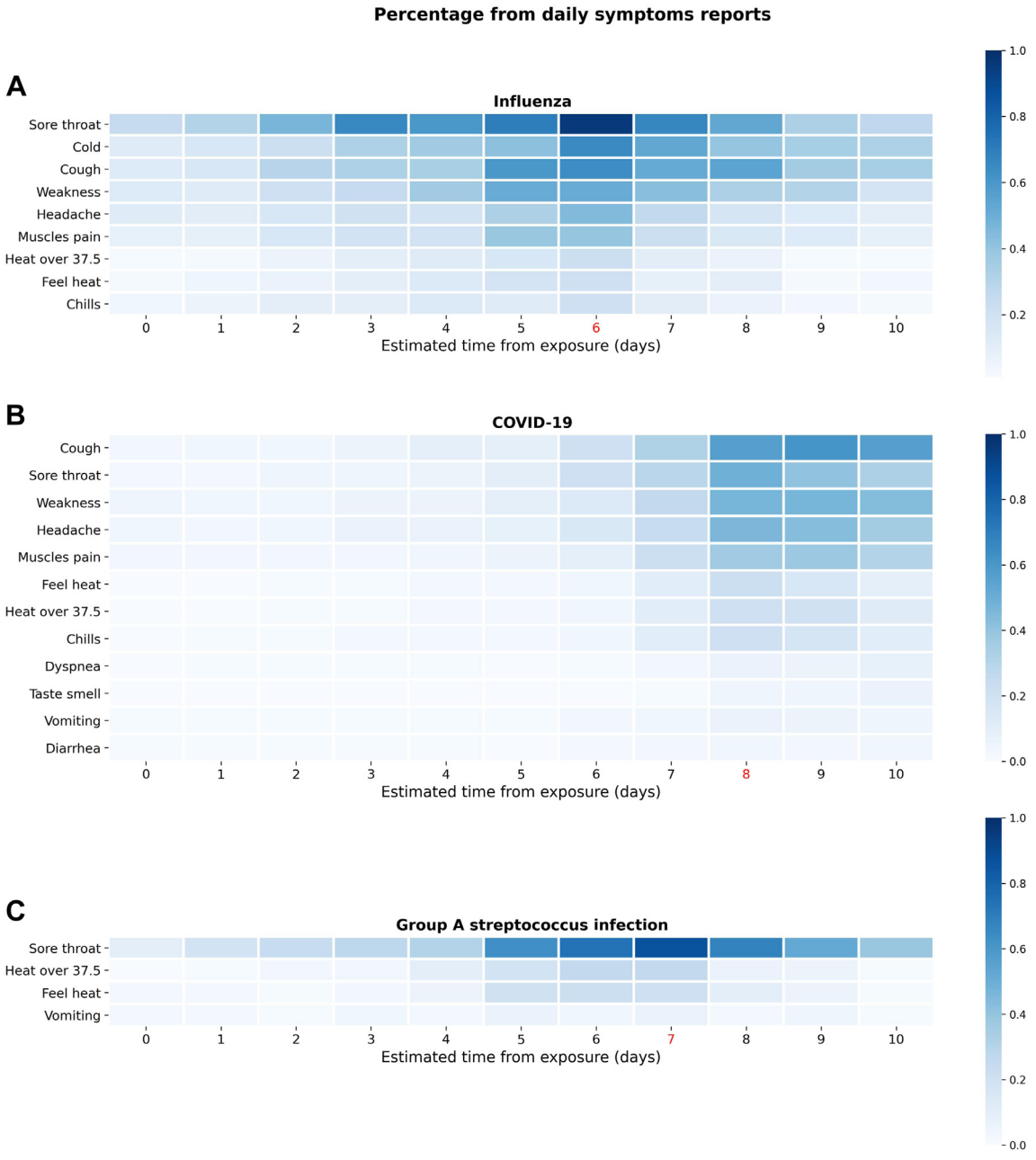

Fig. 4: **Percentage of each symptom self-reported during the days before and after a positive test report for influenza (panel A), COVID-19 (panel B), and Group A streptococcus (panel C) (n influenza = 405; n COVID-19 = 1,304, n GAS = 219).** The darker the color, the higher the percentage of the reported symptoms out of the total reports on a specific day. The positive test report day is marked in red on the x-axis. Day 0 represents the day of estimated exposure. The symptom list for every disease is based on the CDC definitions for known symptoms. For each known symptom defined by the CDC we calculated the percentage of the total reports on the same day where the symptom was reported by positive participants.

populations. We relied on participants' reports to determine the onset of the first symptom and, in some cases, to ascertain the time of positive test confirmation. Although participants were instructed to report daily, potential delays may exist between the actual occurrence of symptoms or test results and their reporting. Additionally, the participants were slightly older than the general Israeli population, so our analyses might not be fully generalizable to the entire Israeli or global population.

Similarly, gaps in smartwatch data collection posed challenges in accurately identifying key time points in disease progression. Additionally, while a significant proportion of positive tests for COVID-19 and GAS were corroborated by PCR tests as recorded by EMRs from Maccabi (92.7% and 48.1%, respectively), influenza diagnosis predominantly relied on self-reports using antigen kits.

Second, the lack of precise information regarding the time and date of exposure introduces uncertainties. Consequently, setting the baseline endpoint as six days before a positive test may be an oversimplification. Third, the clinical importance of continuous monitoring of cardiac metrics, including heart rate and heart rate variability, remains to be fully established in the context of infectious disease surveillance.

Finally, the Garmin smartwatches used in our study are not medical-grade devices, nor are they representative of all wearable technologies. Despite our efforts to rule out other reasons for heart rate anomalies, the lack of fully established baseline data on individuals and information on their activity could limit our ability to attribute physiological changes to infections. However, we note that no anomalies were detected when the same analytical procedures were applied to the matching controls, thereby lending support to our conclusion that there is a link between infections and physiological changes.

It is noteworthy that our anomaly analysis differs from previous studies,[15,18,21–24] offering distinct advantages. Our study has a larger sample size and avoids potential noise and missing values associated with individual-level data by using mean values for anomaly detection. Moreover, while previous studies primarily focused on COVID-19, we considered three different diseases and examined patient behavior in self-isolating and seeking testing.

Future endeavors should focus on the enhancement of smartwatch technology, algorithmic developments, and data collection methodologies. This study has demonstrated the potential of smartwatch-based detection despite being limited by the size and span of the data. The potential of comprehensive and long-term data collection for detecting infectious diseases warrants further investigation. Meanwhile, it is important for smartwatches to incorporate more accurate heart rate and activity monitoring and integrate additional sensors for continuous measurements of other physiological markers such as body temperature and blood oxygen saturation—parameters known to be associated with various infectious diseases. The study has also initiated the comparison of data patterns across different infectious diseases. Future investigations should aim to identify distinct digital signatures associated with various diseases within more diverse populations.

We have introduced a novel concept to the field of infectious diseases: the digital incubation period, defined as the time from exposure to a pathogen until a physiological anomaly becomes detectable through digital means. This period could also be considered the 'true incubation period' since physiological changes, such as heart rate variations, constitute clinical symptoms regardless of the patient's perception. The exploration of the digital incubation period has the potential to significantly contribute to various medical fields, including epidemiology, microbiology, pharmacology, and immunology. Crucially, the early identification of infections before the emergence of symptoms is vital for mitigating the impact of epidemics and preventing pandemics.[44] At the individual level, rapid diagnosis and earlier treatment can halt the progression to more severe disease, enhancing the effectiveness of interventions such as case isolation and treatment.[45] In the realms of immunology and microbiology, research could investigate the relationship between the timing and patterns of the digital and traditional incubation periods. This time may affect expected disease severity and could even be helpful to improve diagnosis. For instance, although RSV and influenza may produce similar symptoms, the known incubation period for influenza is typically 1–2 days, whereas the incubation period for RSV is typically greater than 4 days.[2] This significant time difference suggests that by identifying the gap between the digital and traditional incubation periods could be instrumental in improving the diagnosis—and therefore the control—of infectious diseases.

Through the integration of behavioral data with physiological patterns, our study elucidates the potential of smartwatch-based detection and patient self-testing in the early containment of infectious diseases. This approach could enable more prompt public health interventions, including self-isolation and the initiation of treatment. Despite limitations, the findings suggest a promising avenue for further research and the development of innovative strategies for infectious disease control.

Contributors

Conception and design: DY and MLB. Collection and assembly of data: DY, MY, SS, TP, and ES had access to the raw data and were responsible for verifying the data. Analysis and interpretation of the data: SS, YC, DY, and MLB. Statistical analysis: SS and DY. Drafting the article: SS, DY, and MLB. Critical revision of the article for important intellectual content: all authors. Final approval of the article: All authors. Obtaining funding: DY, ES, and MLB.

Data sharing statement

According to this study's MHS's Helsinki and data utilization committees' guidelines, no patient-level data is to be shared outside the permitted researchers. The Statistical analysis code along with an aggregated version of the data sufficient to reproduce the results reported in this paper will be available upon publication.

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.100934.

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