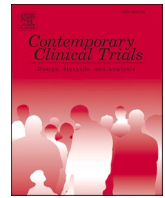




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The WE SENSE study protocol: A controlled, longitudinal clinical trial on the use of wearable sensors for early detection and tracking of viral respiratory tract infections

Amir Hadid^{a,b,*}, Emily G. McDonald^c, Matthew P. Cheng^d, Jesse Papenburg^e, Michael Libman^d, Phillippe C. Dixon^{f,g}, Dennis Jensen^{a,b,h}

^a Clinical Exercise and Respiratory Physiology Laboratory, Department of Kinesiology and Physical Education, Faculty of Education, McGill University, Montréal, Quebec, Canada

^b McGill Sport Science Research Institute, Faculty of Education, McGill University, Montréal, Quebec, Canada

^c Research Institute of the McGill University Health Centre, Division of General Internal Medicine, Department of Medicine, Montreal, Quebec, Canada

^d Research Institute of McGill University Health Center, Department of Medicine, Divisions of Infectious Diseases and Medical Microbiology, Infectious Diseases and Immunity in Global Health Program, Montréal, Quebec, Canada

^e Division of Pediatric Infectious Diseases, Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada

^f School of Kinesiology and Physical Education, Faculty of Medicine, Université de Montréal, Montréal, Quebec, Canada

^g Research Center of the Sainte-Justine University Hospital (CRCHUSJ), Montreal, Quebec, Canada

^h Research Institute of the McGill University Health Centre, Translational Research in Respiratory Diseases Program and Respiratory Epidemiology and Clinical Research Unit, Montréal, Quebec, Canada

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ABSTRACT

Background: Viral respiratory tract infections (VRTI) are extremely common. Considering the profound social and economic impact of COVID-19, it is imperative to identify novel mechanisms for early detection and prevention of VRTIs, to prevent future pandemics. Wearable biosensor technology may facilitate this. Early asymptomatic detection of VRTIs could reduce stress on the healthcare system by reducing transmission and decreasing the overall number of cases. The aim of the current study is to define a sensitive set of physiological and immunological signature patterns of VRTI through machine learning (ML) to analyze physiological data collected continuously using wearable vital signs sensors.

Methods: A controlled, prospective longitudinal study with an induced low grade viral challenge, coupled with 12 days of continuous wearable biosensors monitoring surrounding viral induction. We aim to recruit and simulate a low grade VRTI in 60 healthy adults aged 18–59 years via administration of live attenuated influenza vaccine (LAIV). Continuous monitoring with wearable biosensors will include 7 days pre (baseline) and 5 days post LAIV administration, during which vital signs and activity-monitoring biosensors (embedded in a shirt, wristwatch and ring) will continuously monitor physiological and activity parameters. Novel infection detection techniques will be developed based on inflammatory biomarker mapping, PCR testing, and app-based VRTI symptom tracking. Subtle patterns of change will be assessed via ML algorithms developed to analyze large datasets and generate a predictive algorithm.

Conclusion: This study presents an infrastructure to test wearables for the detection of asymptomatic VRTI using multimodal biosensors, based on immune host response signature.

ClinicalTrials.gov registration: NCT05290792

1. Background and rationale

Viral respiratory tract infection (VRTI) is the most common illness in humans, affecting billions of people worldwide and burdening the

healthcare system and economy. In the United States alone, it is estimated that annual influenza epidemics have resulted in approximately 610,660 life-years lost, and a total economic burden of \$87.1 billion [1]. In Canada, it is estimated that there are, on average, 12,200

* Corresponding author at: Department of Kinesiology and Physical Education, Currie Gymnasium, 475 Pine Avenue West, Montreal, Quebec H2W 1S4, Canada.
E-mail address: Amir.hadid@mcgill.ca (A. Hadid).

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hospitalizations and 3500 deaths attributable to influenza annually [2]. Taking into additional consideration the current SARS-CoV-2 pandemic, which has infected hundreds of millions of people and resulted in millions of deaths worldwide [3], there is a critical unmet need to identify novel ways to prevent the spread of VRTIs.

There are currently no tools available to continuously assess, in real time, objective physiological response markers to viral replication and the impact on the host immune system. An individual's inflammatory response to infection is primarily measured by the presence of symptoms. In response to infection, certain pathophysiologic processes occur in the host that only cause classical signs and symptoms once the level of organ damage reaches, or exceeds, a certain threshold [4]. Prior to that, many people have few to no symptoms, but can be infectious to others [5]. For example, fever, although measurable and objective, lacks sensitivity for detection of SARS-CoV-2 [6]. Furthermore, a variable proportion of VRTI cases remain asymptomatic, despite high transmission potential [7]. From a public health perspective, the ability to reduce the spread of viral transmission by asymptomatic or minimally symptomatic individuals could lower the reproductive number (R_0), which in the case of a pandemic (e.g., influenza, SARS-CoV-2) would help to “flatten the curve” [8]. The current approach involves contact tracing and testing, which requires testing infrastructure, obtaining biological samples, and it can be poorly sensitive in asymptomatic individuals (missing as many as 30% of cases) [9]. An additional and complementary technology to pair with the present contact tracing, test and contain strategy could become a critical public health mitigation strategy for VRTIs.

Activity and physiological trackers are increasingly used globally to monitor an individual's health through continuous or frequent measurement of body functions (physiology) such as heart rate, heart rate variability (HRV), skin temperature, peripheral capillary oxygen saturation (SpO_2), physical activity, and indices of sleep quality. Evidence suggests that use of wearable biosensor technology may permit detection of VRTIs, and assist in medical diagnosis in the early stages of disease development - even before the onset of clinical symptoms [10–19] - or in state-level real-time surveillance of influenza [20]. Both of these capabilities are vital to enact timely outbreak response measures and to halt or minimize ongoing transmission. Despite promising results, previous studies of wearables for early detection of VRTIs have been mostly based on biometric data from consumer grade wearables, meaning data collection has been mostly limited to heart rate, HRV, and body temperature [10–20]. Prior studies have also relied heavily on patient reported symptoms and could not address asymptomatic or minimally symptomatic infections [10–20]. Failure to identify such infections has important public health implications in as much some SARS-CoV-2 outbreak investigations have reported that asymptomatic individuals were the source of up to 69% of infections [21].

Compared to symptoms, changes in the concentration of circulating inflammatory biomarkers may provide a more objective means of tracking VRTIs. [22] McClain et al. found that only 53% of human subjects inoculated with influenza developed symptoms. Yet they still demonstrated increased circulating levels of inflammatory biomarkers as early as 12–29 h post-inoculation, including interleukin (IL)-6, IL-8, IL-15, monocyte chemoattractant protein (MCP)-1 and interferon gamma-induced protein-10 (IP-10). These results confirmed the presence of significant systemic inflammatory host responses during the pre-symptomatic phase of a VRTI [22]. We hypothesized that inflammatory biomarkers combined with wearable biosensor-derived physiometers could be a viable early detection strategy for VRTI, as inflammatory biomarkers could enrich the data collected from wearable sensors, above and beyond patient reported symptoms.

Although human viral challenge studies can provide a tightly controlled environment for VRTI diagnostics and dynamics, their practical utility is extremely limited due to excessive costs and rigorous safety requirements such as quarantine in a dedicated facility [23–25]. In the current Wearable Sensors for Early Detection and Tracking of

Viral Respiratory Tract Infections (WE SENSE) study, we aim to leverage FluMist®, an intranasal live-attenuated influenza vaccine (LAIV), as a proxy to a viral “challenge” to the immune system. Although the expected viral replication related symptoms are mild following administration of LAIV, the host immune response should resemble that of mild influenza [26]. The LAIV will be used as a test case, representing a scenario of low grade, attenuated viral replication, which can still engender a host immune response (as indicated by temporal changes in circulating levels of inflammatory blood biomarkers) and associated subtle changes in physiology, activity levels, sleep quality, and participant-reported symptoms. Subtle patterns of change might only be detectable by machine learning (ML)-based analyses. Specifically, applying ML to the large amounts of data collected using advanced wearable biosensor technologies alongside temporal changes in circulating inflammatory biomarker concentrations has the potential to allow for future early detection and tracking of VRTI.

The overarching aim of the WE SENSE study is to define a sensitive set of physiological and immunological signature patterns in response to a controlled viral challenge following administration of LAIV in human participants through ML to analyze large amounts of physiological data collected continuously using wearable vital signs monitoring systems. We hypothesize that, using ML, subtle changes in inflammatory status can be detected by continuously monitoring only physiological parameters that are available from wearables.

2. Methods and analysis

2.1. Study design and experimental infection protocol

This is a single center, controlled, longitudinal study. The experimental study design and timeline for assessments is outlined in Table 1. The Research Ethics Board approval for the study was granted by the Research Institute of the McGill University Health Center (RI-MUHC) (WE SENSE/2022-7591). The SPIRIT reporting guidelines were used to construct this protocol [27].

A simulated low grade VRTI will be induced in 60 healthy adults aged 18–59 years via controlled administration of FluMist® Quadrivalent (AstraZeneca).¹ Initial screening will include a visit to the RI-MUHC's Centre for Innovative Medicine (CIM), where eligibility will be assessed, and written informed consent obtained. To rule out asymptomatic VRTI (e.g., influenza, SARS-CoV-2) during the baseline (pre-LAIV) period, a nasopharyngeal 21-multiplex polymerase chain reaction (PCR) test will be performed at screening (Table 1). Eligible participants will have baseline assessments beginning the morning of Day -7 until inoculation (Days -7 to 0) (Table 1). Participants will be seen twice daily (once before 10 h00 and once again before 20 h00) at the CIM on the 5 days after inoculation, including Day 0 (Table 1). Participants will attend scheduled visits only. No overnight stays at the facility will be required.

2.2. Participants

Participants will be recruited through posted announcements and word-of-mouth in the Montreal and surrounding area.

2.2.1. Inclusion criteria

Men or women aged 18–59 years who did not receive the 2021–22 seasonal influenza vaccine and who are not planning to get another

¹ Updated status at the time of review of this manuscript: enrollment took place between December 2021 and February 2022, with 58 participants enrolled. Data retrieval and sample analysis were ongoing at the time of study protocol review. No changes were made to the protocol since it was approved by the institutional review board and registered on [ClinicalTrials.gov](https://www.clinicaltrials.gov) except for shortening of the post inoculation follow-up period from 7 to 5 days.

vaccine during the 14-day observation period. The lower age limit was selected as the study aims to identify VRTI in adults. The upper age limit was selected as this is the approved upper limit for FluMist® administration.

2.2.2. Exclusion criteria

Any PCR-confirmed VRTI at screening; any infectious symptoms (fever, cough, rhinorrhea, sore throat, diarrhea, loss of smell or taste) within the previous 7 days prior to the screening visit; any chronic medical condition; body mass index $>35 \text{ kg/m}^2$; any prescription drug other than oral contraceptives or routinely consumed medications without changes in dosing at least 6 weeks prior to screening date; contraindication to LAIV [28]; self-reported current smoker; self-reported ex-smoker with >20 pack year smoking history; self-reported recreational drug use; self-reported history of substance abuse; pregnant or attempting to become pregnant due, primarily, to FluMist® product warning and, secondarily, to unique and potentially confounding temporal physiological changes (a pregnancy test [stick/strip] will be performed as part of the screening assessment); Guillain-Barré syndrome (GBS) or GBS-like episode occurred within 6 weeks of any prior influenza vaccination; compromised immune function; severe asthma (defined as currently on oral or high-dose inhaled glucocorticosteroids or active wheezing) or medically attended wheezing in the 7 days prior to the proposed date of inoculation, due to increased risk of wheezing following administration of LAIV, which is not contraindicated for people with a history of stable asthma or recurrent wheeze.

2.2.3. Subject discontinuation and withdrawal criteria

A participant's decision to withdraw from the study at any time will not affect the quality of care and services that they are entitled to or the relationship with the researcher(s) responsible for the project and the other staff member(s), nor will they be subject to any prejudice to future treatment by the study physician(s). Participants will be withdrawn from the study if: they do not follow study instructions; they have a serious adverse event related to the study; it is not in their best interest to continue with the study; there are administrative reasons to abandon the study (e.g., they cannot arrive to the planned visits after signing ICF). In the event that a participant is withdrawn from the trial, no further data will be collected about them or their health for the purpose of this study. Participants who will be withdrawn from the trial will be informed by a member of the research team, who communicate with the participant in person or via telephone.

2.3. Assessments / procedures

2.3.1. VRTI detection

In the event that a participant develops symptoms compatible with a VRTI during the pre-LAIV baseline period (Table 1), we will perform a repeat nasopharyngeal 21-multiplex PCR test, if possible. While these participants will be removed from the final analysis, their data will be

retained for separate (exploratory) analyses. Following inoculation, nasopharyngeal swabs will be taken daily and kept frozen. These samples will be analyzed using reverse transcription PCR assays targeting influenza A, influenza B, SARS-CoV-2 and respiratory syncytial virus to identify and confirm the presence of influenza RNA in nasopharyngeal swab samples, and to rule out incident co-infection(s) of potentially common pathogens. Some degree of myalgias and a low-grade fever may be observed for 24 h following administration of the LAIV, which do not prompt additional testing unless persistent or bothersome for >24 –48 h.

2.3.2. Symptom assessment and reporting

The following symptoms will be assessed using a validated questionnaire, the Wisconsin Upper Respiratory Symptom Survey (WURSS), [29] through a web-based survey twice daily (once before 12 h00 and once again before 22 h00) during the 12-day observation period (Table 1): nasal discharge; nasal obstruction; sneezing; headache; sore throat; malaise; muscle ache; cough; chilliness; decreased appetite; stomachache; vomiting; diarrhea; shortness of breath; and wheeze. Symptom severities will be graded as 0 (absent) to 7 (severe). In addition, participants will be asked to report any workouts/structured exercise, and consumption of caffeine, medication(s) and/or alcohol via the Hexoskin app.

2.3.3. Wearable vital signs monitoring systems

Three platforms will be used for continuous monitoring of physiological and activity parameters using wearable biosensors: Oura ring (Oura Oy, Finland); Biobeat watch (Biobeat technologies LTD, Israel); and Astroskin/Hexoskin shirt (Hexoskin, Canada) (Fig. 1). These devices were selected to complement each other in terms of the physiological parameters (physiomarkers) measured, the type of state monitored (sleep vs rest vs physical activity) and the expected user compliance in order to maximize wear time. Astroskin/Hexoskin shirts were selected due to their unique ability to record high resolution ECG and respiration signals. Importantly, they are the only devices of the 3 platforms selected, capable of generating reliable physiological measurements during physical activity. Specifically, they were evaluated and validated during various tasks for accurately detecting breathing patterns [30], measuring tidal volume [31], respiratory rate, and heart rate [32,33]. Data acquisition frequency for Astroskin/Hexoskin shirt is 250 Hz for the ECG, 125 Hz for the respiration signal, 50 Hz for the accelerometry data, and 1 Hz for all other parameters. Biobeat is a medical device, FDA approved, designed for remote patient monitoring during rest, and uniquely capable of reliable continuous blood pressure measurement [34,35]. The selected sampling rate for biobeat is 5 min intervals. Oura ring (gen 2) is a consumer grade wearable, designed for long term continuous wear, i.e., the highest wear time to charge time ratio compared to the other wearables, validated for sleep duration monitoring [36], and provided reliable nocturnal measurements of heart rate and heart rate variability (RMSSD) when compared to electrocardiogram based measurements; Pearson correlation coefficient was found to

Table 1

Study design and timeline for assessments.

	Screening Days – 11 to – 7	Pre-LAIV Days – 7 to 0		Administration of LAIV Day 0		Post-LAIV Days 1–3 Day 4		
		AM	PM	AM	PM	AM	PM	PM
Medical screening	✓	–	–	–	–	–	–	–
Informed consent	✓	–	–	–	–	–	–	–
VRTI screening (nasal swab)	✓ [#]	✓(Day-7)	–	–	–	✓	–	–
Symptom survey	–	✓	✓	✓ (Pre-LAIV)	✓	✓	✓	✓
Blood sampling	–	✓(Day-7)	–	✓ (Pre-LAIV)	✓	✓	✓	✓
Physiological response assessment	–	✓(Day-7)	–	✓ (Pre-LAIV)	–	✓	–	–
Wearable vital signs monitoring	–	Continuous						

[#]At least 72 h will be allowed to ensure that baseline VRTI screening via nasopharyngeal 21-multiplex test results are returned and negative. Only after a screening negative at baseline for a VRTI will participants be entered into the 12-day observation period. **Abbreviations:** VRTI, viral respiratory tract infection; LAIV, Live Attenuated Influenza Vaccine (FluMist® Quadrivalent); AM, morning; PM, afternoon/evening



	Oura ring	BioBeat watch	Astroskin/Hexoskin shirt
Heart rate	✓	✓	✓
Heart rate variability	✓	✓	✓
ECG	-	-	✓
Stroke volume, cardiac output, pulse pressure, systemic vascular resistance, mean arterial pressure	-	✓	-
Systolic blood pressure	-	✓	✓*
Peripheral capillary oxygen saturation	-	✓	✓*
Respiratory rate	✓	✓	✓
Tidal volume, minute ventilation	-	-	✓
Skin temperature	✓	✓	✓*
Activity levels (e.g., steps, calories, cadence)	✓	-	✓
Sleep (NREM, REM, timing, quality)	✓	-	✓

Fig. 1. Physiological and activity parameters that will be assessed by wearable vital signs monitoring systems in the WE SENSE study. * denotes Astroskin only. ECG- electrocardiogram, NREM- non rapid eye movement, REM- rapid eye movement.

be 0.99 and 0.92, and mean bias was -0.44 bpm and -14.97 ms, for the heart rate and RMSSD parameters, respectively [37]. Oura ring provide physiological heart rate and heart rate variability every 5 min during sleep, and activity data in 5 min intervals during daytime.

With the exception of bathing, showering, and charging the device (s), participants will be instructed to wear the three devices continuously for 12 consecutive days: 7-days prior to and 5-days after inoculation with LAIV (Table 1). Specifically, they will be instructed to wear the devices as much as tolerated during a 24-h period, during any formal or informal physical activity/exercise (e.g., grocery shopping, housework), and continuously overnight while sleeping. Physiological and activity parameters will be collected automatically and stored on a secure and encrypted cloud-based server that protects the anonymity of all study volunteers. Participants will not be exposed to the continuous monitoring results, except for short periods of signal quality checks that will be performed during the visits at the CIM. The following quality checkpoints were established following an internal pilot that demonstrated that a continuous communication between the research team members and the participants is required in order to minimize data loss due to user errors, device malfunction, and transmission errors: signal quality will be assured on the days of onsite visit at the CIM, by comparing the signal acquired from the wearable sensors to the vital signs measured using a medical device cart (Carescape V100 Vital Signs Monitor, GE) . A research assistant will monitor the data acquisition process online in real-time and provide participants with remote technical assistance to maximize wear time and quality of the biosensor signals acquired, if/when necessary. Finally, on days that participants will not have an on-site visit scheduled, a member of the research team will call the participants to check if there are any issues of signal/wear, and to assure maximal wear time. All wearable devices will be returned by study participants, and after ensuring that the data is downloaded, all participant data will be erased from the devices. The participants will be offered to keep the Oura ring and will be asked if they wanted their data to be erased or not.

All devices will be synchronized to allow for accurate partitioning

and extraction of relevant data segments. The Astroskin/Hexoskin device will be considered the gold-standard device for sleep, ECG, and respiration data monitoring. Thus, the Astroskin/Hexoskin device will be used to segment biosensor data of all devices into periods of interest, including sleep (rapid and non-rapid eye movement), rest, and wakefulness/activity based on the algorithm of Pion-Massicotte et al. [38] Astroskin/Hexoskin quality flags will be used to ensure that ECG and respiratory data have sufficient integrity (e.g., uninterrupted lead-skin contact) for analysis. In the case of missing or corrupted Astroskin/Hexoskin data, the Biobeat watch (first choice) or Oura ring (second choice) outputs will be used. Raw data obtained using Biobeat and Oura ring will be denoised using a sliding-window moving average.

2.3.4. Inflammatory cytokines and biomarkers

A venous blood sample for measurement of inflammatory cytokines and biomarkers (see below) will be obtained by a healthcare professional once in the morning of Day -7 (baseline sample #1) and then twice daily starting Day 0, with baseline sample #2 collected prior to inoculation on Day 0 (Table 1). Venous blood samples will be fractionated into serum and plasma, and stored at -80 °C for later analysis.

Anticipating subtle or no change in symptoms following inoculation with LAIV, measuring changes in circulating levels of inflammatory cytokines are critically important to quantifying the magnitude of each participants' LAIV-related immune response and the temporal association of this immune response with contemporaneous changes in physiological and activity parameters assessed with the three wearable biosensors. Admittedly, it is challenging to predict a priori with certainty which inflammatory biomarkers will be most sensitive to the detection of LAIV-induced immune responses, as such prior data from humans is not available. For this reason, an exploratory panel of inflammatory cytokines will be analyzed in duplicate by Eve Technologies (Calgary, AB) using a 48-multiplex panel focused on inflammatory biomarkers, with an emphasis placed on IL-6, IL-8, IL-10, IL-15, MCP-1 and IFN- γ that are expected to rise following induced influenza challenge [22]. Following an initial exploratory analysis of the major

inflammatory biomarkers that change in response to the inoculation (pre vs post inoculation levels), a composite score that represents the average ratio between pre and post inoculation levels of these selected VRTI specific inflammatory biomarkers will be created, reducing the risk of introducing type I error due to a single biomarker artifact. In addition, a host immune response signature (MeMed, Israel) will be determined for each participant based on a score combining three proteins: tumor necrosis factor-related apoptosis-inducing ligand (TRAIL); interferon gamma induced protein-10 (IP-10); and C-reactive protein (CRP). This host response signature differentiates between bacterial and viral respiratory infection [39], with differential expression of TRAIL and IP-10 observed during viral infection [40] and perhaps also as part of our participants' LAIV-related immune response.

2.3.5. Exercise physiological response assessment

This assessment is used to increase the physiological demand beyond that of sedentary activity, thus, increasing the likelihood of uncovering any hidden physiological pattern(s) related to the LAIV-induced immune response.

Participants will complete a 3-min constant-rate stair stepping test (3-min CRSST) on Days -7, 0, 1, 2 and 3 (Table 1). The 3-min CRSST requires participants to step up and down a 20 cm step to the pace of a constant external audio beep. All participants will complete all 3-min CRSSTs at 30 steps/min. Cardiac and respiratory parameters will be collected at rest and during each 3-min CRSST using the wearable devices. Using Borg's 0–10 category ratio (CR10) scale [41], ratings of perceived breathlessness intensity, breathlessness unpleasantness and leg discomfort will be assessed at rest, within the last 15-s of each minute of exercise, and at the end of the 3-min CRSST.

2.4. Data analysis

2.4.1. Primary exposure

Inoculation with FluMist® LAIV.

2.4.2. Primary outcome

Intra-individual changes of physiological and activity parameters before and after inoculation with LAIV (explored through ML algorithms).

2.4.3. Secondary outcomes

An ML binary classifier algorithm capable of predicting intra-participant infection state. Algorithm inputs will be time series signals captured from the wearable devices during the pre-inoculation stages (non-infected) and time surrounding infected state (infected), as confirmed by the RT-PCR test post inoculation. As a limited, unpredictable percentage of positive samples by RT-PCR is anticipated post inoculation [26], we will also quantify the early-detection ability of the model by assessing performance at time segments other than that of positive RT-PCR result, based on changes in circulating inflammatory cytokine levels and MeMed's host immune response signature score. An inflammatory composite score will be calculated for each participant based on these main pro-inflammatory biomarkers and will represent the ratio between post to pre inoculation levels. Then, this score will be used to train the physiological features to detect changes in inflammatory biomarker levels as the predicted clinical outcome, i.e., we intend to develop the predictive model to detect post inoculation changes in inflammatory biomarker levels using the physiological parameters acquired using the wearables.

The use of an intranasal LAIV generally leads to a measurable immune response mimicking natural infection. However, LAIV must replicate in the upper respiratory tract to elicit an immune response; therefore, the presence of pre-existing antibodies or cross-reactive T cells could inhibit viral infection and replication [42]. We estimated that at least 80% of the participants will demonstrate a measurable immune response following inoculation, as Basha et al. found that 87% of healthy

adults developed H3N2 HA-specific T-cell responses from administration of LAIV [43]. To conclude, to prevent false negative and false positive cases in the analysis, the models will be trained to predict intra-individual changes in a pro-inflammatory biomarker composite score compared to baseline values.

We will follow standard pre-processing steps such as data standardization, artifact detection, filtering, and handling of missing values, using the FLIRT framework and toolkit [44]. Following this step, only participants who have high quality physiological data covering >50% of both the pre and post inoculation periods will be used for the model training. Then data integration, feature engineering, new features creation (with physiological relevance), and external factors acquisition such as weather, population, etc. will be performed.

Traditional ML methods will be explored (e.g., Random Forest and gradient boosting). In addition, given the complexity and time-varying nature of the multi-device data, deep learning methods will be developed. Deep-learning differs from traditional ML by automatically extracting features from the underlying input signal instead of depending on discrete features developed by a human operator (feature engineering) [45]. As in recent research aiming to predict the early-onset of septic shock [46], long short-term memory (LSTM) architectures will be preferred. Convolutional neural network models will also be explored, given their relatively simple architecture. ML algorithms will be trained and tested using a standard 80/20 split. Fivefold cross-validation will be used to provide the most accurate estimate and avoid over-fitting by reducing biasness. Trained model performance will be evaluated on the test data set. Models will be developed in Python using the Keras [47] framework and trained on a secured multi-core GPU server. Performance will be assessed using the F1-score, accuracy, sensitivity, and specificity. Unique to the proposed research is that each participant will serve as their own control, relying on the baseline measurements obtained over the 7-day period prior to inoculation with LAIV.

Generally, sample size is difficult to assess in studies relying on ML analyses. Therefore, we based our sample size estimation on recent literature. Specifically, two studies demonstrated successful ML-based detection tools developed based on vital signs collected from participants that tested positive for COVID-19, one analysis included 32 participants [16] and the other included 54 participants [18]. To further estimate the required sample size via traditional statistical analyses methods, a power analysis was performed. For this analysis, we selected resting heart rate (RHR) as one of the most basic parameters that is expected to change following inoculation. Based on data from Altini et al., mean resting heart rate is 57 ± 8 bpm, and is increased by 6% during illness days [48]. Using two-tailed Z-test with $\alpha = 0.05$, we estimate that 56 participants will provide 80% power to detect 6% (3 bpm) increase in RHR following inoculation. Taking into consideration the relatively homogenous population (age 18–59 years old, healthy, with no background illness or morbidity), we anticipate even less variability in the RHR results, that translates to even smaller necessary sample size. In addition, the multi sensor, high sensitivity devices used in this study, and the fact that contemporary ML-based analyses (versus classical statistical analyses) utilizing complex neural networks will be employed to detect subtle changes/patterns in physiological markers pre and post controlled inoculation, we believe 56 participants will be more than sufficient for an effective model training and validation. Therefore, a sample size of 60 participants will be selected to address the objectives of this study.

The data architecture, analysis and ML algorithms will be developed by a team overseen by a Biomedical Engineer expert in AI/ML techniques for vital signs signals acquired from wearable sensors, a Biomedical Engineer experienced with prediction model development and design, and supported by an ML expert.

2.5. Safety

In the event that a participant experiences an adverse event during this study, details of the event will be recorded as a Note to File, and if serious, in the MUHC Reportable Serious Event Logs. All serious adverse event/reaction reports will be submitted to the MUHC REB (see [Section 2.5.1 'Adverse Events: Recording and Reporting'](#) for further detail).

2.5.1. Adverse events: Recording and reporting

Participants will be advised to report changes in symptoms or health status to a member of the research team, which may or may not be related to their underlying condition (e.g., breathlessness, cough, sputum, fatigue) or the 3-min CRSST.

2.5.1.1. Recording of non-serious adverse events/reactions. All non-serious adverse events will be recorded by the researcher as a Note to File, detailing the issue, resolution and corrective action. Non-serious events are those that are expected (i.e., known side-effect/complication of supervised exercise training or study measurements) and are not life threatening, do not require hospitalization or do not result in disability. Participants will be followed up via telephone call(s) until the adverse event is resolved. Follow up communication will be recorded as a Note to File.

2.5.1.2. Recording and reporting of serious adverse events. Participants who report serious adverse events/reactions will be advised by the researcher to present to the nearest emergency department or call 911. If the adverse event occurs during a study visit, the researcher will follow the MUHC emergency procedures. All serious adverse events/reactions are to be recorded in the MUHC Reportable Serious Events Log in accordance with the MUHC's Standard Operating Procedure and requirements established by Health Canada.

2.5.2. Management of participant data

The investigator(s)/institution(s) permit trial-related monitoring, audits, REB review, and regulatory inspection(s), providing direct access to source data/documents. All participant data collected as part of the WE SENSE study will be maintained and stored for a minimum of 25 years after the study ends for the exclusive objectives of this study and then destroyed.

Participant information collected as part of this study will be stored at the CIM until the study is complete, and then transferred to the Clinical Exercise & Respiratory Physiology Laboratory at McGill University. Participant data will be stored in a de-identified format by assigning participants a unique identifying number. Records that link the participant's unique identifying number to their identifying information will be stored in a separate secure location to study data. Only researchers listed as investigators on this protocol will have access to study data. Computerized files will be securely stored on a password-protected computer and servers. Paper records containing names and addresses will be filed securely in a locked cabinet in a locked room. All the information collected during the study will remain strictly confidential to the extent provided by law.

2.5.3. Incidental findings

We expect a low percentage of positive nasal swab results at screening and post inoculation visits due to pathogens that are not influenza. Any positive COVID-19 result will be communicated to the participant and a health professional of their choice (family doctor or treating physician). If the participant has no family doctor, a MD from the study team would be made available for telephone consultation/advice.

2.6. Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3. Ethics and dissemination

The RI-MUHC's Research Ethics Board (WE SENSE / 2022-7591) approved the WE SENSE protocol. Participants will receive both verbal and written information explaining the purpose of the study and they will provide written informed consent. Participants will receive a compensation for their time and travel associated with the study procedures.

Results will be published in international peer-reviewed journals and summaries will be provided to the funders of the study as well as participants upon request.

4. Conclusion

The WE SENSE study presents an infrastructure to test wearable technologies for the detection of asymptomatic or minimally symptomatic VRTI using an extensive multimodal set of physiological biosensors and based on changes in circulating levels of objective immune host response biomarkers. This may facilitate future capacity to identify public health strategies to intervene rapidly for infection control purposes and where they exist, to institute treatments. In addition, the establishment of extensive benchmarking physiological data for the use of wearable technologies in infection detection would serve the medical and scientific community in focusing the development of sensitive and efficient wearable devices and physiometers for VRTI detection.

Author statement

The study concept and design were conceived by AH, EM and DJ. ML, JP, MC, and PD assisted in refining the study design. AH is responsible for data collection. Analyses will be conducted by AH, PD, and DJ. AH prepared the first draft of the manuscript. All authors critically revised the manuscript and approved the submitted version.

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Data access statement

Data is accessible to all the researchers listed on this manuscript.

Declaration of Competing Interest

None.

Data availability

No data was used for the research described in the article.

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References

- N.A. Molinari, I.R. Ortega-Sanchez, M.L. Messonnier, et al., The annual impact of seasonal influenza in the US: measuring disease burden and costs, *Vaccine* 25 (27) (2007) 5086–5096, <https://doi.org/10.1016/j.vaccine.2007.03.046> [published Online First: 2007/06/05].
- D.L. Schanzer, A. McGeer, K. Morris, Statistical estimates of respiratory admissions attributable to seasonal and pandemic influenza for Canada, *Influenza Other Respir. Viruses* 7 (5) (2013) 799–808, <https://doi.org/10.1111/irv.12011> [published Online First: 2012/11/06].
- Johns Hopkins University. Coronavirus Resource Center [Available from: <https://coronavirus.jhu.edu/map.html>].
- A. Casadevall, L.-a. Pirofski, What is a host? Attributes of individual susceptibility, *Infect. Immun.* 86 (2) (2018) e00636–17.
- X. Qiu, A.I. Nergiz, A.E. Maraolo, et al., The role of asymptomatic and pre-symptomatic infection in SARS-CoV-2 transmission—a living systematic review, *Clin. Microbiol. Infect.* 27 (4) (2021) 511–519.
- C. Menni, A.M. Valdes, M.B. Freidin, et al., Real-time tracking of self-reported symptoms to predict potential COVID-19, *Nat. Med.* (2020) 1–4.
- M. Yanes-Lane, N. Winters, F. Fregonese, et al., Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: a systematic review and meta-analysis, *PLoS One* 15 (11) (2020), e0241536, <https://doi.org/10.1371/journal.pone.0241536> [published Online First: 2020/11/04].
- A. Catching, S. Capponi, M.T. Yeh, et al., Examining the interplay between face mask usage, asymptomatic transmission, and social distancing on the spread of COVID-19, *Sci. Rep.* 11 (1) (2021) 1–11.
- J. Watson, P.F. Whiting, J.E. Brush, Interpreting a covid-19 test result, *Bmj* 369 (2020), m1808, <https://doi.org/10.1136/bmj.m1808> [published Online First: 2020/05/14].
- A. Alavi, G.K. Bogu, M. Wang, et al., Real-time alerting system for COVID-19 and other stress events using wearable data, *Nat. Med.* 28 (1) (2022) 175–184, <https://doi.org/10.1038/s41591-021-01593-2> [published Online First: 2021/12/01].
- N. Goldstein, A. Eisenkraft, C.J. Arguello, et al., Exploring early pre-symptomatic detection of influenza using continuous monitoring of advanced physiological parameters during a randomized controlled trial, *J. Clin. Med.* 10 (21) (2021), <https://doi.org/10.3390/jcm10215202> [published Online First: 2021/11/14].
- E. Grzesiak, B. Bent, M.T. McClain, et al., Assessment of the feasibility of using noninvasive wearable biometric monitoring sensors to detect influenza and the common cold before symptom onset, *JAMA Netw. Open* 4 (9) (2021), e2128534, <https://doi.org/10.1001/jamanetworkopen.2021.28534> [published Online First: 2021/09/30].
- R.P. Hirten, M. Danieletto, L. Tomalin, et al., Physiological data from a wearable device identifies SARS-CoV-2 infection and symptoms and predicts COVID-19 diagnosis: observational study, *J. Med. Internet Res.* (2021), <https://doi.org/10.2196/26107> [published Online First: 2021/02/03].
- X. Li, J. Dunn, D. Salins, et al., Digital health: tracking physiomes and activity using wearable biosensors reveals useful health-related information, *PLoS Biol.* 15 (1) (2017), e2001402, <https://doi.org/10.1371/journal.pbio.2001402> [published Online First: 2017/01/13].
- A.E. Mason, F.M. Hecht, S.K. Davis, et al., Detection of COVID-19 using multimodal data from a wearable device: results from the first TempPredict study, *Sci. Rep.* 12 (1) (2022) 3463, <https://doi.org/10.1038/s41598-022-07314-0> [published Online First: 2022/03/04].
- T. Mishra, M. Wang, A.A. Metwally, et al., Pre-symptomatic detection of COVID-19 from smartwatch data, *Nat. Biomed. Eng.* 4 (12) (2020) 1208–1220, <https://doi.org/10.1038/s41551-020-00640-6> [published Online First: 2020/11/20].
- A. Natarajan, H.W. Su, C. Heneghan, Assessment of physiological signs associated with COVID-19 measured using wearable devices, *NPJ Digit. Med.* 3 (1) (2020) 156, <https://doi.org/10.1038/s41746-020-00363-7> [published Online First: 2020/12/11].
- G. Quer, J.M. Radin, M. Gadaleta, et al., Wearable sensor data and self-reported symptoms for COVID-19 detection, *Nat. Med.* (2020), <https://doi.org/10.1038/s41591-020-1123-x>.
- A. Shapiro, N. Marinsek, I. Clay, et al., Characterizing COVID-19 and influenza illnesses in the real world via person-generated health data, *Patterns (N Y)* 2 (1) (2021), 100188, <https://doi.org/10.1016/j.patter.2020.100188> [published Online First: 2021/01/29].
- J.M. Radin, N.E. Wineinger, E.J. Topol, et al., Harnessing wearable device data to improve state-level real-time surveillance of influenza-like illness in the USA: a population-based study, *Lancet Digital Health* 2 (2) (2020) e85–e93, [https://doi.org/10.1016/s2589-7500\(19\)30222-5](https://doi.org/10.1016/s2589-7500(19)30222-5).
- J.C. Emery, T.W. Russell, Y. Liu, et al., The contribution of asymptomatic SARS-CoV-2 infections to transmission on the Diamond Princess cruise ship, *Elife* 9 (2020), <https://doi.org/10.7554/eLife.58699> [published Online First: 2020/08/25].
- M.T. McClain, R. Henao, J. Williams, et al., Differential evolution of peripheral cytokine levels in symptomatic and asymptomatic responses to experimental influenza virus challenge, *Clin. Exp. Immunol.* 183 (3) (2016) 441–451, <https://doi.org/10.1111/cei.12736> [published Online First: 2015/10/29].
- B.L. Innis, F. Berlanda Scorza, J.S. Blum, et al., Meeting report: convening on the influenza human viral challenge model for universal influenza vaccines, part 1: value; challenge virus selection; regulatory, industry and ethical considerations; increasing standardization, access and capacity, *Vaccine* 37 (35) (2019) 4823–4829, <https://doi.org/10.1016/j.vaccine.2019.06.080> [published Online First: 2019/08/01].
- B.L. Innis, F.B. Scorza, J.S. Blum, et al., Convening on the influenza human viral challenge model for universal influenza vaccines, part 2: methodologic considerations, *Vaccine* 37 (35) (2019) 4830–4834, <https://doi.org/10.1016/j.vaccine.2019.06.053> [published Online First: 2019/08/01].
- R. Lambkin-Williams, N. Noulin, A. Mann, et al., The human viral challenge model: accelerating the evaluation of respiratory antivirals, vaccines and novel diagnostics, *Respir. Res.* 19 (1) (2018), <https://doi.org/10.1186/s12931-018-0784-1>.
- N.J. Carter, M.P. Curran, Live attenuated influenza vaccine (FluMist®; FluenzTM), *Drugs* 71 (12) (2011) 1591–1622.
- A.-W. Chan, J.M. Tetzlaff, P.C. Götzsche, et al., SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials, *Bmj* (2013) 346.
- AstraZeneca Canada, FLUMIST® QUADRIVALENT Influenza Vaccine (live, attenuated), Product Monograph, 2020.
- B. Barrett, R.L. Brown, M.P. Mundt, et al., Validation of a short form Wisconsin upper respiratory symptom survey (WURSS-21), *Health Qual. Life Outcomes* 7 (1) (2009) 1–20.
- E. Harbour, M. Lasshofer, M. Genitrini, et al., Enhanced breathing pattern detection during running using wearable sensors, *Sensors (Basel)* 21 (16) (2021), <https://doi.org/10.3390/s21165606> [published Online First: 2021/08/29].
- D. Manneke, F. de Jongh, H. van Helvoort, The accuracy of tidal volume measured with a smart shirt during tasks of daily living in healthy subjects: cross-sectional study, *JMIR Form. Res.* 5 (10) (2021), e30916, <https://doi.org/10.2196/30916> [published Online First: 2021/10/19].
- J. Montes, J.C. Young, R. Tandy, et al., Reliability and validation of the hexoskin wearable bio-collection device during walking conditions, *Int. J. Exercise Sci.* 11 (7) (2018) 806.
- C.M. Smith, S.N. Chillrud, D.W. Jack, et al., Laboratory validation of hexoskin biometric shirt at rest, submaximal exercise, and maximal exercise while riding a stationary bicycle, *J. Occup. Environ. Med.* 61 (4) (2019), <https://doi.org/10.1097/JOM.0000000000001537> e104–e11. [published Online First: 2019/04/05].
- D. Nachman, A. Eisenkraft, N. Goldstein, et al., Influence of sex, BMI, and skin color on the accuracy of non-invasive cuffless photoplethysmography-based blood pressure measurements, *Front. Physiol.* 13 (2022), 911544, <https://doi.org/10.3389/fphys.2022.911544> [published Online First: 2022/07/19].
- D. Nachman, Y. Gepner, N. Goldstein, et al., Comparing blood pressure measurements between a photoplethysmography-based and a standard cuff-based manometry device, *Sci. Rep.* 10 (1) (2020) 16116, <https://doi.org/10.1038/s41598-020-73172-3> [published Online First: 2020/10/02].
- S. Ghorbani, H.A. Golkashani, N. Chee, et al., Multi-night at-home evaluation of improved sleep detection and classification with a memory-enhanced consumer sleep tracker, *Nat. Sci. Sleep.* 14 (2022) 645–660, <https://doi.org/10.2147/NSS.S359789> [published Online First: 2022/04/22].
- R. Cao, I. Azimi, F. Sarhaddi, et al., Accuracy assessment of our ring nocturnal heart rate and heart rate variability in comparison with electrocardiography in time and frequency domains: comprehensive analysis, *J. Med. Internet Res.* 24 (1) (2022), e27487, <https://doi.org/10.2196/27487> [published Online First: 2022/01/19].
- J. Pion-Massicotte, R. Godbout, P. Savard, et al., Development and validation of an algorithm for the study of sleep using a biometric shirt in young healthy adults, *J. Sleep Res.* 28 (2) (2019), e12667, <https://doi.org/10.1111/jsr.12667> [published Online First: 2018/02/24].
- L. Ashkenazi-Hoffnung, K. Oved, R. Navon, et al., A host-protein signature is superior to other biomarkers for differentiating between bacterial and viral disease in patients with respiratory infection and fever without source: a prospective observational study, *Eur. J. Clin. Microbiol. Infect. Dis.* 37 (7) (2018) 1361–1371, <https://doi.org/10.1007/s10096-018-3261-3> [published Online First: 2018/04/28].

- [40] I. Srugo, A. Klein, M. Stein, et al., Validation of a novel assay to distinguish bacterial and viral infections, *Pediatrics* 140 (4) (2017).
- [41] G.A. Borg, Psychophysical bases of perceived exertion, *Med. Sci. Sports Exer* 14 (5) (1982) 377–381.
- [42] S. Sridhar, K.A. Brokstad, R.J. Cox, Influenza vaccination strategies: comparing inactivated and live attenuated influenza vaccines, *Vaccines (Basel)* 3 (2) (2015) 373–389, <https://doi.org/10.3390/vaccines3020373> [published Online First: 2015/09/08].
- [43] S. Basha, S. Hazenfeld, R.C. Brady, et al., Comparison of antibody and T-cell responses elicited by licensed inactivated- and live-attenuated influenza vaccines against H3N2 hemagglutinin, *Hum. Immunol.* 72 (6) (2011) 463–469, <https://doi.org/10.1016/j.humimm.2011.03.001> [published Online First: 2011/03/19].
- [44] S. Foll, M. Maritsch, F. Spinola, et al., FLIRT: a feature generation toolkit for wearable data, *Comput. Methods Prog. Biomed.* 212 (2021), 106461, <https://doi.org/10.1016/j.cmpb.2021.106461> [published Online First: 2021/11/05].
- [45] Y. LeCun, Y. Bengio, G. Hinton, Deep learning, *Nature* 521 (7553) (2015) 436–444, <https://doi.org/10.1038/nature14539> [published Online First: 2015/05/29].
- [46] J. Fagerström, M. Bång, D. Wilhelms, et al., LiSep LSTM: a machine learning algorithm for early detection of septic shock, *Sci. Rep.* 9 (1) (2019) 1–8.
- [47] Chollet, et al., Keras. GitHub [Available from: <https://github.com/fchollet/keras>, 2015.
- [48] M. Altini, D. Plews, What is behind changes in resting heart rate and heart rate variability? A large-scale analysis of longitudinal measurements acquired in free-living, *Sensors (Basel)* 21 (23) (2021), <https://doi.org/10.3390/s21237932> [published Online First: 2021/12/11].