Augmentation of immune response to vaccinations through osteopathic manipulative treatment: a study of procedure

Abstract

Context: Anecdotal evidence suggested that osteopathic manipulative treatment (OMT) may have imparted survivability to patients in osteopathic hospitals during the 1918 influenza pandemic. In addition, previous OMT research publications throughout the past century have shown evidence of increased lymphatic movement, resulting in improved immunologic function qualitatively and quantitatively.

Objectives: The following is a description of a proposed protocol to evaluate OMT effects on antibody generation in the peripheral circulation in response to a vaccine and its possible use in the augmentation of various vaccines. This protocol will serve as a template for OMT vaccination studies, and by adhering to the gold standard of randomized controlled trials (RCTs), future studies utilizing this outline may contribute to the much-needed advancement of the scientific literature in this field.

Methods: This manuscript intends to describe a protocol that will demonstrate increased antibody titers to a vaccine through OMT utilized in previous historical studies. Confirmation data will follow this manuscript validating the protocol. Study participants will be divided into groups with and without OMT with lymphatic pumps. Each group will receive the corresponding vaccine and have antibody titers measured against the specific vaccine pathogen drawn at determined intervals.

Results: These results will be statistically evaluated. Our demonstration of a rational scientific OMT vaccine antibody augmentation will serve as the standard for such investigation that will be reported in the future. These vaccines could include COVID-19 mRNA, influenza, shingles, rabies, and various others. The antibody response to vaccines is the resulting conclusion of its administration. Osteopathic manipulative medicine (OMM) lymphatic pumps have, in the past through anecdotal reports and smaller pilot studies, shown effectiveness on peripheral immune augmentation to vaccines.

Conclusions: This described protocol will be the template for more extensive scientific studies supporting osteopathic medicine’s benefit on vaccine response. The initial vaccine studies will include the COVID-19 mRNA, influenza, shingles, and rabies vaccines.

Keywords: COVID-19; immune system; infectious diseases; lymphatics; osteopathic manipulative treatment (OMT); vaccination

The human immune system is a diverse and intertwined defensive barrier that will prevent pathogen invasion of the host [1]. Medical research has investigated the means to augment this protective response in passive or active ways [2]. Active refers to the act of immunization of pathogen whole or pieces with or without haptons, and mRNA.
Despite the success of immunizations in preventing disease, there has been interest in vaccine enhancement of antibody titer formation. Evidence exists from the literature for over a century, from anecdotal and pilot studies, suggesting that osteopathic manipulative treatment (OMT) has improved survivability after infection and that OMT increases certain immunological qualitative and or quantitative responses to vaccination [3].

Osteopathic manipulative medicine (OMM) considers a whole-person approach with patients. This approach involves looking for ways to enhance the body’s self-healing capability. We propose that patients primed with OMT are more likely to mount a more robust and enduring immune response to vaccinations. Specifically useful in this regard are the OMT techniques known as the lymphatic pump techniques (LPT), which increase lymphatic circulation [4]. This increase in lymphatic circulation is advantageous for mounting immune responses because vaccine antigens are carried by antigen-presenting cells (APCs) to lymph nodes and other secondary lymphoid tissues through lymphatic vessels, where the antigens will activate T-lymphocytes, which in turn activate B-lymphocytes to produce protective antibodies [5].

Early in the 20th century, Whiting [6] showed that the lymphatic pump increased the phagocytic index. This study’s conclusions assumed that the specific antibodies were present for opsonization, but the work focused on improving the innate immune system rather than the adaptive system. This study amplifies the importance of lymphatic techniques on preadaptive consequences.

Later in the 20th century, the adaptive immune system responses were challenged by lymphatic techniques. Measal [7] showed that antibody titers to pneumococcus were increased when performing the lymphatic pump after administration of the pneumococcus vaccine to medical students. Although a primarily bacterial response, it demonstrates the pump’s comprehensive effect on the immune response to antigen type.

The immune system is a complicated and diverse protective response mode of the human body. Based on previously published data, we have chosen historically utilized LPTs for our proposed procedural development to augment the vaccine response [3]. We hypothesize that the incorporation of OMT into vaccine protocols will increase antibody (immunoglobulin G (IgG)) responses and prolong the duration of antibody titers to vaccine pathogens when compared to patients solely receiving vaccinations without OMT intervention. We propose that future studies utilizing this protocol will demonstrate that enhanced antibody formation is not exclusive to specific vaccines but extends to a spectrum of vaccines such as COVID-19 mRNA, rabies, influenza, and shingle vaccines.

### Methods

The following method description will demonstrate a step-by-step process of evaluating antibody titer improvement to vaccines utilizing OMT protocols. All studies must be conducted as randomized controlled trials (RCTs) that are prospective in nature and will measure the effectiveness of adding OMT to vaccination protocols. Institutional Review Board (IRB) approval must be obtained. Approval for this protocol was provided by the Western University of Health Sciences IRB, Reference #: FB21/IRB026. An initial study utilizing this protocol was registered at ClinicalTrials.gov with Registration #: NCT04928456.

There is a need for key individuals and academic institutions to be gathered into a working group. This working group should meet weekly to monthly, depending on the study’s progress. The group should include:

- A college(s) of osteopathic medicine,
- A department of skilled osteopathic practitioners with the potential to train others to participate in the procedure in case of expansion of the testing population,
- An accessible testing population of adults,
- Interested funding source representatives,
- Phlebotomists,
- PhDs and laboratory staff for scientific verification and storage of samples,
- Association with a commercial laboratory for specific antibody testing
- Statisticians (needed at the inception of the study for power analysis to determine population size and at the conclusion of the study for statistical significance), and
- Administrative staff for meeting schedule development, and minutes recording

### Inclusion criteria

The inclusion criteria are current or matriculating students in a health or education program, university staff or faculty, and the general public who will receive a vaccine. Enrollment in the study with informed consent and baseline labs should be completed before receipt of the first vaccination.

### Exclusion criteria

The exclusion criteria should be created to disqualify any participant who may have any immune modulating response, such as the presence of any primary or secondary immune deficiency, any immune-mediated disorders, and the use of any immune-altering medications. Utilizing OMT for any other purpose outside the study would skew the sought response. Therefore, the use of OMT or other physical manipulation such as acupuncture, physical therapy, chiropractic, or massage therapy in the previous 4 weeks before study enrollment, and the inability to receive OMT with LPTs for any reason, would be considered as part of the exclusion criteria. Participants will be excluded if they have other conditions that would prevent the use of OMT and put the patient at risk such as pregnancy, previous study-specific virus infections depending on the study, or contraindications to the vaccine, or if they are on anticoagulation therapy.
Study protocol

The statistician should determine a study population size utilizing a power analysis. Participants from a university campus community who will receive the vaccine should be gathered. The participants should be randomly separated into a control population that will not receive OMT with lymphatic techniques and one that will receive OMT. Both populations will be de-identified for data collection, and information will be stored in a password-encrypted thumb drive. The participants should receive a nominal gift for participation in the study, which would be distributed at significant milestones. Each participant should be consented to participate by the study investigators. A full description of participant flow in the study can be found in Figure 1. There should be no form of coercion of the participants in each study. Appropriate protocols to remain Occupational Safety and Health Administration (OSHA)-compliant can be utilized.

OMT with LPT should be performed by qualified faculty, postdoctoral fellows, and trained osteopathic medical students coordinated through the OMM and Osteopathic Principles and Practice (OPP) departments. The OMT protocol proposed here was developed by two separate departments of Neuromusculoskeletal Medicine and Osteopathic Manipulative Medicine (NMM/OMM). There was an initial review of the literature, educational instruction manuals, and shared clinical experience utilized in a consensus process. With the variability in the way that the physicians performed techniques, meetings were held to review commonalities and generate protocols based on those consensus approaches. The techniques were written up and distributed among the group, with the opportunity for editing and commenting until a consensus was reached. One of the common variabilities during the discussions was concerning the endpoints of direct and indirect techniques. Because of the variability, the decision was made to utilize a time limit of 1 min for each technique. It is possible, given physician experience, to perform some of these treatments adequately in less than 1 min. The following are the techniques that treatment providers should employ based on these discussions, which include myofascial release (MFR) of the thoracic inlet, pectoral traction, diaphragm release with MFR, splenic pump, and thoracic pump. Explanations of the treatments

Figure 1: Projected flow of participants throughout the course of each proposed study.
Table 1: Proposed OMT procedures, rationales, and methods to be utilized in the anticipated augmentation of vaccine protocol.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Rationale</th>
<th>Method</th>
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<tr>
<td>Myofascial release (MFR) of the thoracic inlet</td>
<td>The thoracic inlet can be considered a potential myofascial diaphragm or choke point for terminal lymph drainage because the right lymphatic duct and the thoracic duct empty into the right and left subclavian veins, respectively. Treating this region may help relieve any myofascial restrictions impeding the flow and drainage of the low-pressure lymphatic system</td>
<td>The operator’s hands encircle the thoracic inlet, fingers anteriorly, and thumbs posteriorly. A slight compressive force is added inward on the thoracic inlet to engage Sibson’s fascia. The tissues are followed in their resistance to side-bending, rotation, and flexion or extension, and they are held in that position as the patient breathes in and out. The operator follows the tissue release (unwind) until the direct barrier has been released. If the tissues do not respond to direct treatment within 30 s, then the treatment will be changed to indirect MFR. The operator would then follow tissue preferences into the directions of ease rather than into the resistance to side-bending, rotation, and flexion or extension. The entire MFR treatment to the thoracic inlet will take 1 min</td>
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<td>Pectoral traction</td>
<td>Pectoral traction may influence lymph flow by means of influencing the pectoralis major and minor muscles. By exerting superior traction on the anterior axillary fold and, specifically, the pectoralis minor, the range of motion of the first six ribs is augmented during inhalation, thereby increasing the negative pressure in the thorax, as well as the intrathoracic volume of the chest. This treatment also releases fascia in the axilla, with the potential to improve lymphatic drainage from the site of vaccine injection in the deltoid muscle</td>
<td>The operator stands at the head of the bed with the patient supine. The finger pads of both hands are placed into the anterior axillary fold and wrapped around the pectoralis major muscle. The operator leans backward, causing the hands and fingers to move the cephalad into the patient’s axilla. The patient takes several deep breaths, at which time the operator increases the cephalad movement of the hands during inhalation and resists caudal movement during exhalation. This process is repeated for 1 min</td>
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<td>Diaphragm release with MFR</td>
<td>Normalization of motion of the thoracic diaphragm may increase negative pressure in the thorax, improving the return of lymphatic fluid to the vascular system</td>
<td>The operator stands at the side of the supine patient, facing cephalad. The hands are placed along the anterolateral costal cage with the thumbs just under the anterior costal margin. The operator then induces motion through the inferior costal cage in rotation, side-bending, and lateral translation. The operator will engage the direct restrictive barriers and augment the release with normal respiration. The operator follows the tissue release (unwind) until the direct barrier has been released. If the tissues do not respond to direct treatment within 30 s, then the treatment will be changed to indirect MFR. The operator would then follow tissue preferences in the direction of ease rather than into the restrictive barriers. The treatment will occur over 1 min</td>
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<tr>
<td>Splenic pump</td>
<td>Rhythmic pumping of the spleen may improve circulation and relieve passive congestion. The spleen plays a role in the lymphatic system and is a site of antibody production</td>
<td>The operator stands on the left side of the supine patient. The hands are placed anteriorly and posteriorly in the left upper quadrant of the abdomen. The right hand is introduced posteriorly on the lower costal cage and the left hand is on the abdominal wall immediately below the costal margin. An initial compressive force is applied to engage the spleen and then a percussive or vibratory force is introduced through the left costal cage into the spleen. This treatment will last for 1 min</td>
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<tr>
<td>Thoracic pump</td>
<td>The creation of negative pressure in the thoracic cage during inspiration is a key driver of lymphatic fluid return to the vascular system. By adding compression during exhalation to increase positive pressure and utilizing the elastic qualities of the rib cage during inhalation, this technique increases the ability of the thoracic cage to expand rapidly and thus increases negative pressure during respiration</td>
<td>The operator stands at the head of the patient and places their hands on the anterior upper chest wall and introduces rhythmic pumping action during the exhalation phase of respiration at a rate of 100–120 cycles per minute. During inhalation, the operator will resist the upward motion of the rib cage, and during exhalation, the operator will increase the compression of the rib cage. At the end of several cycles, the operator will suddenly release the compression, facilitating a rapid, deep inhalation. The entire thoracic pump treatment will last for 1 min</td>
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OMT, osteopathic manipulative treatment.
and the rationale for their use are described further in Table 1. The procedures need to be standardized among the administrators of OMT. A detailed in-person or video instructional session describing the mechanics of each technique should be performed for each administrator of OMT before the beginning of the study.

Laboratory studies to measure vaccination antibody responses should be performed according to state-of-the-art techniques to determine antibody responses at no charge to the participant per the study schedule. Appropriate tube collection at every blood draw through venipuncture of the accessible arm/hand vein will be necessary. The serum of these samples should be aliquoted and biobanked. Ideally, all serum analyses should be performed simultaneously.

We propose examining serum antibody responses, namely IgG antibody responses. Our choice is substantiated given that IgG titers are recognized as immune correlates for influenza protection, as evidenced by work by Trombetta et al. [8]. Furthermore, for COVID-19 mRNA vaccines, there is encouraging data that suggests that IgG antibodies correlate very strongly with neutralizing antibody titers. Notably, IgG antibodies may serve as a surrogate for neutralizing antibody levels, which themselves exhibit a very high correlation with immunity [9]. Studies have also shown a strong level of correlation between anti-spike IgG in COVID-19 and an overall decreased risk of infection [10, 11].

To illustrate the creation of a vaccine-specific schedule for this OMT-vaccine protocol, we have selected the recent mRNA COVID-19 vaccine as an example in Figure 2. Baseline titers should be measured as a starting point for all comparisons. Vaccine administration would follow CDC and FDA guidelines [12, 13]. For other vaccines, the OMT would be adjusted to the respective vaccination schedule [14]. OMT should be performed two times within 24 h of each vaccine administration. This window aligns with the period in which the mRNA injected into the deltoid myocytes creates copies of the spike protein before degrading [15]. Given reports from the Infectious Disease Society of America (IDSA), which generated spike protein that only lasts a few weeks until the immune system destroys it [16], we propose that blood draws should also be done the week after each injection. Peak levels of immunoglobulin titers have been seen within a few weeks after the second injection [17, 18], justifying blood draws for the few weeks following the second injection. Research on the vaccine response has indicated that antibody titer levels have waned drastically by months 3 and 6 [19–22], suggesting that these would be pertinent antibody levels to measure in the patient populations. Finally, a year would be included to measure the long-term effects of treatment and if there is persistent waning that is notably different in one group vs. another.

Data on age, gender, race, weight, height, body mass index (BMI), and antibody titers will be collected on each de-identified participant. The data will be collected in an encrypted thumb drive. A statistician will evaluate the data and develop demonstrative tables and graphs. In general, the titer of the antibodies at each point of each volunteer will be expressed as a percentage of the baseline prevaccination titer. The active group (receiving OMT) percentages will be compared to the control group (not receiving OMT). The data may be broken up between the given vaccine to determine whether significant differences exist.

Additionally, the investigators should document all use of medication and the duration of its use for participants after each injection of the vaccine. Side effects associated with the vaccination should be thoroughly documented, with type and duration being recorded. Any adverse events of OMT for the intervention group should be documented if any should arise. Any clinically relevant information related to the infection and/or vaccination process should be thoroughly documented, and collection should be designed to be study-specific.

We propose initially studying the adjunctive use of OMT with vaccines that are easily amenable to a proof-of-concept design. Vaccines like the COVID-19 mRNA vaccine, rabies vaccine, influenza vaccine, and shingles vaccine are examples of suitable vaccines due to their alignment with age-appropriate requirements for informed consent by the IRB, their short-course vaccination schedules, and their intramuscular delivery method. A short-term course geared to adults will allow the investigators to ensure the ethical and timeliness requirements of most funding agencies and IRBs.

Intramuscular delivery is one of the most widely utilized administration routes for vaccines and helps avoid the complexities and variables introduced by oral and mist immunizations. Additionally, intramuscular administration is particularly influenced by the rapid diffusion of vaccine antigens to lymph nodes [23], which we anticipate will be significantly enhanced through the incorporation of OMT with lymphatic techniques. While all these vaccines are antiviral and delivered by intramuscular injections, this protocol should theoretically be conducive to any vaccine, contingent upon proper modifications to accommodate various delivery methods, whether the vaccine is antiviral or antibacterial, and so on.

Discussion

The necessity for OMT vaccination studies is borne out of various studies showing OMT either enhancing the movement
of lymph, and immunocytes, or evidence of OMT directly affecting immune function and outcomes. In various animal studies, OMT has been shown to enhance the movement of lymph and, in turn, the immune system. Increasing lymph flow through lymphatic channels allows for an increased rate of leukocyte movement to the site of infection or foreign invaders. In a study conducted utilizing LPT in canines, OMT showed an increase in lymphatic flow in the thoracic duct, through which 75% of the entire body’s lymph fluid passes [24, 25].

Other animal studies implementing LPT show increased levels of inflammatory cytokines and increased leukocyte count of all leukocyte populations, including neutrophils, monocytes, CD4+ T-cells, CD8+ T-cells, IgG, and IgA in the thoracic duct lymph that can be repeated multiple times with similar results [26–28]. LPTs have also been shown to recruit leukocytes from the gut-associated lymphoid tissue (GALT), which produces 60% of immunoglobulins and where 70–80% of plasma cells in the human body are typically located [29]. LPT has enhanced antibiotic delivery in rats infected with Streptococcus pneumoniae by diminishing bacterial load [30].

Human studies have also given us evidence for the use of OMT to impact immune functioning. Walkowski and colleagues [31] performed OMT in healthy human subjects and saw an increase of CD16+ dendritic cells (DCs) in the peripheral blood circulation in addition to lymphatic circulation and induction of rapid changes in certain cytokine profiles. The T-cell – dependent pathway is the more critical aspect of antibody formation and response. This pathway responds to protein antigens like those found with viral antigens. Jackson et al. [32] showed that utilization of LPT with the hepatitis B vaccine achieved protective titers sooner, with 50% of OMM-treated patients achieving protective titers at 3 months vs. only 16% of patients without OMM achieving protection at that time. This observation supports the idea that the lymphatic pump may create heightened peripheral venous and arterial antibody responses to vaccine antigens.

An increased immune response has been seen in human studies in reference to clinical infections as well. Noll and colleagues [33, 34] found that elderly patients treated with LPT for pneumonia had much shorter hospital stays, shorter durations of medication, lessened mortality, and less respiratory failure compared to conventional care alone.

Given the current literature documenting OMT’s influence on the immune system and previous records indicating improved antibody titer production [32], we believe that large-scale RCTs are needed to provide more gold-standard levels of evidence for the utility of OMT. We acknowledge that, as with any proposal, there are limitations to this design. When developing the protocol for these studies, there were a total of five treatments included with only 1 min allotted for each treatment. The reasons for choosing these treatments are detailed in Table 1, but in addition, this protocol was chosen for its ease of use in a clinical setting so that the results could be replicated in other clinical studies and in the clinic by physicians in practice. Standardization of times and the OMT were of utmost importance in this process. Additionally, this protocol is easily taught to students. We feel it is easily replicable and standardized, which is immensely important for the scientific rigor of clinical trial studies.

Conclusions

Antibody response to vaccines is critical for population protection. Enhancement of this process will create heightened protection for vaccine-naïve populations. We hypothesize that the adjunctive use of OMT, including lymphatic techniques, will increase antibody (IgG) responses and the duration of antibody titers to pathogens after pathogen vaccination. Future studies utilizing this protocol will evaluate the ability of OMT to enhance antibody formation in conjunction with the COVID-19 mRNA, rabies, influenza, and shingle vaccines.

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Research ethics: This proposed study was reviewed by the Western University of Health Sciences Institutional Review Board and was granted approval after a full committee review (IRB reference #FB21/IRB026). The first of these studies was registered at ClinicalTrials.gov (Clinical Trials registration #NCT04928456)

Informed consent: Not applicable.
Author contributions: All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; all authors drafted the article or revised it critically for important intellectual content; all authors gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests: None declared.

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Data availability: The raw data can be obtained on request from the corresponding author.

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