CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Needleless Injectors for the Administration of Vaccines: A Review of Clinical Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	July 17, 2020
Report Length:	33 Pages

CADTH

Authors: Changhua Yu, Melissa Walter

Cite As: Needleless Injectors for the Administration of Vaccines: A Review of Clinical Effectiveness. Ottawa: CADTH; 2020 Jul. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to **Requests@CADTH.ca**

Abbreviations

AE	Adverse events
BCG	Bacille Calmette-Guérin
CI	Confidence interval
DSJI	Disposable-syringe jet injector
DTP	Diphtheria – tetanus – pertussis
fIPV	Fractional dose of inactivated poliovirus vaccine
HB	Hepatitis B
HI	Hemagglutination inhibition
Hib	Hemophilus influenza type B
HPV	Human papillomavirus
ID	Intradermally
IM	intramuscularly
IPV	Inactivated poliovirus vaccine
MMR	Measles-mumps-rubella
NFJI	Needle free jet injector
N-S	Needle and syringe
RCT	Randomized controlled trial
SC	Subcutaneously

Context and Policy Issues

A needleless or needle-free jet injector (NFJI) uses a high-pressure stream jet to puncture the skin surface without using a needle.[1] NFJIs have been used for vaccine or drug administration worldwide for many decades.[2,3] The scope of the use of NFJIs has been continuously widened.[2] NFJIs can be used for intradermal, subcutaneous or intramuscular injection.[1] In the literature, NFJIs are also termed as needleless injector, jet injector (JI), disposable syringe jet injector (DSJI) in different countries by different manufacturers. In this document, the terms of NFJI, needleless injector, JI, DSJI are interchangeable. The NFJI's operating mechanisms, applications, efficacy and safety have been constantly evolving and improving over the years.[2] The commonly used NFJIs are PharmaJet injector (PharmaJet, USA),[4-10] Med-Jet H4 injector (the newest model of Med-Jet injector, MIT Canada),[11] Biojector (Bioject Medical Technologies Inc. USA)[12-16] and LectraJet (LectraJet, D'Antonio Consultants International, Inc., USA).[17] NFJIs have been suggested to be the future of vaccine administration and therapeutic applications.[2]

Comparing traditional (standard, conventional) needle and syringe (N-S) intramuscular injection, one of the advantages of using NFJI by intradermal injection is dose-sparing for vaccination. A typical example of the dose-sparing is that NFJIs for intradermal injection have been used, as dose-sparing strategies for the inactivated polio vaccine (IPV) in developing countries.[10,14-16] In addition, NFJIs are preferred by individuals with an aversion to needles.[1,18] Compared with N-S, other potential benefits by using NFJIs include reduced risks such as needle-stick injury and cross-contamination.[1] However, the NFJIs are also reportedly associated with a higher frequency of local injection site reactions than the use of N-S.[18]

Effective dose-sparing strategies for vaccine delivery may be useful for large scale vaccination programs or in situations of limited vaccine supply. One suggested strategy is to administer vaccines using NFJIs by intradermal route.

The purpose of this report is to review the comparative clinical effectiveness of vaccines administered using a NFJI with that using N-S for individuals of all ages.

Research Question

What is the comparative clinical effectiveness of vaccines administered using a needleless injector versus a needle syringe for individuals of all ages?

Key Findings

Fourteen randomized controlled trials (RCTs) regarding the comparative clinical effectiveness of vaccines administered using a needleless injector versus a needle syringe (N-S) were identified in this review. Five RCTs were for influenza vaccine, four for inactivated polio vaccine (IPV), two for measles, mumps and rubella (MMR) vaccination, one for the diphtheria–tetanus–pertussis, hepatitis B, and hemophilus influenza type B (DTP-HB-Hib) vaccine, one for human papillomavirus vaccination (HPV) and one for Bacille Calmette-Guérin (BCG) vaccination. Four needle-free jet injectors (NFJIs) used in the included trials are PharmaJet Injector, Med-Jet H4 injector, Biojector and LectraJet injector.

For influenza vaccine: the findings observed in five RCTs indicated that influenza vaccine administered by NFJI, intradermally achieved similar immune response (e.g., seroconversion, seroprotection, antibody titer) compared with that administered by traditional N-S, intramuscularly. No evidence of a dose-sparing strategy for influenza vaccine using NFJI was identified.

For IPV vaccine: the findings reported in four RCTs showed that compared with conventional full dose IPV (i.e., 0.5 ml) given by N-S, intramuscularly, a fractional dose of IPV (i.e. 0.1 ml or 1/5 of full dose), given by NFJI, intradermally demonstrated a similar seroconversion rate (both initial and boosting response), but lower antibody titer.

The findings from two RCTs for MMR vaccination indicated that there was no statistically significant difference observed between NFJI, subcutaneously and N-S, subcutaneously in terms of immune response (e.g., seroconversion rate, antibody titer).

For DTP-HB-Hib, HPV and BCG vaccine, the immune response (e.g., seroconversion rate, or seroprotection rate/ antibody titer or T-cell [CD4/CD8] response) introduced by NFJI were also similar to that observed in the N-S group.

Regardless of the type of vaccine, or type of NFJI, numerically more unsolicited and solicited local adverse reactions (e.g., redness, swelling, induration and infiltration) were observed with NFJIs than with traditional N-S injection. However, the frequency of unsolicited and solicited systemic AEs (e.g., fever, headache, muscles aches, tiredness, nausea) were numerically lower in NFJI, intradermal injection group compared with N-S intramuscular injection group.

In conclusion, the vaccines administered by NFJI were reported to be as immunogenic as that by N-S. However, more local injection reaction, but fewer systemic adverse events associated with NFJI were also reported. Despite some limitations of the study designs, the comparative effectiveness and safety profile of vaccines (e.g., influenza, IPV or MMR) administered by NFJI and N-S were consistent regardless the type of vaccine and the type of NFJIs. Future studies assessing NFJI as a dose–sparing strategy comparing with conventional N-S are needed, especially for the influenza vaccine.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were needleless injectors and vaccines. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and June 15, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Individuals of all ages
Intervention	Any vaccine administered using a NFJI (ID, IM or SC)
Comparator	Any vaccine administered using a N-S (ID, IM or SC)
Outcomes	Clinical effectiveness (e.g., vaccine efficacy, mortality, hospitalizations, immunogenicity, patient satisfaction, and safety [e.g., rates of adverse events, solicited local and systemic reactions])
Study Designs	Health technology assessments, Systematic Reviews, Randomized Controlled Trials, Non-Randomized Studies.

ID = intradermally; IM = intramuscularly; NFJI= needle free jet injector; N-S = needle and syringe; SC = subcutaneously.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications or were published prior to 2010. Studies on experimental vaccines (such as HIV vaccine, Ankara vaccine), and mixed interventions that did not present results separately (i.e. subgroup analysis) for comparing NFJI with N-S were excluded.

Critical Appraisal of Individual Studies

The included RCTs were assessed with SIGN 50 Methodology Check list 2.[19] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 230 citations were identified in the literature search. Following screening of titles and abstracts, 208 citations were excluded and 22 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full text review. Of these potentially relevant articles, nine publications were excluded for various reasons, and 14 RCTs met the inclusion criteria and were included in this report.[4-17] No health technology assessments or systematic reviews were identified. Appendix 1 presents the PRISMA [20] flowchart of the study selection.

Summary of Study Characteristics

The details regarding the characteristics of included studies are provided in Table 2 in Appendix 2.

Study Design

Fourteen RCTs were included for this report. Among the 14 RCTs, two were phase 1 RCTs[8,13] and one was a pilot RCT.[9] Three RCTs were non-inferior study design.[6,7,10]

Country of Origin

Of the 14 RCTs, countries indicated for the first authors of the primary studies were Canada for one RCT,[11] USA for three RCTs,[7,13,17] Cuba for two,[15,16] India for two,[4,5] and one RCT each for Australia,[9] Brazil,[6] Hong Kong,[8] Oman,[14] South Africa[12] and The Netherlands.[10]

Patient Population

Among the 14 RCTs, five were conducted for people receiving the influenza vaccine;[7,9,11,13,17] four for people receiving IPV;[10,14-16] two for those vaccinated against measles–mumps–rubella (MMR);[5,6] and one each for people vaccinated against human papillomavirus (HPV);[8] diphtheria–tetanus–pertussis, hepatitis B, and hemophilus influenza type B (DTP-HB-Hib);[4] and (Bacille Calmette-Guérin) BCG[12] respectively. Seven RCTs were conducted in an adult population.[7-11,13,17] Four were in infants (age 6 to 20 months),[4-6,16] two in newborns,[14,15] and one in newborns and adults.[12]

Interventions and Comparators

Among the 14 identified RCTs that evaluated NJFIs, Seven used the PharmaJet injector;[4-10] five used the Biojector;[12-16] one used the LectraJet injector[17] and one used the Met-Jet H4 injector.[11] The NFJIs were used intradermally, intramuscularly or subcutaneously.

All RCTs compared NFJIs to traditional N-S injection intradermally, intramuscularly or subcutaneously.

While in most of RCTs, the vaccine regimens (e.g., duration, dose, route, frequency) in both intervention and comparator groups were the same, several studies compared different dose, or/and different route as well as different injection device.[13,16,10,15,14]

Outcomes

Immunogenicity (such as seroconversion, seroprotection, antibody titer), unsolicited and solicited local and systemic adverse events were reported. For example, for influenza

vaccine. Antibody titer was measured with standard hemagglutination inhibition (HI) assays.[11]

Summary of Critical Appraisal

The overall critical appraisal of the included RCTs is briefly presented below. The detailed information on critical appraisal is available in Table 3, in Appendix 3.

The research objectives were clearly reported in all 14 RCTs. The only difference between groups was the different injection devices (i.e., NJFI vs. N-S) used in the vaccine injection. The outcome measurements in all RCTs were standard and reliable. Conflict of interest information was declared in most of the RCTs.

Several key limitations of the RCTs include: the randomization method and/or allocation concealment were not described in seven RCTs,[6,7,11,13-16] and most of the studies were not blinded or had a partially blinded design, therefore, there was a potential risk for selection bias or treatment bias. However, as the efficacy outcome measurement of vaccination was immune response (e.g., seroconversion, antibody titer) which was objectively measured using standard and valid laboratory methods, the results of the immune response assessment was unlikely affected by the quality of the study design, although adverse events collection might be affected. The study by Bavdekar (2019)[4] was terminated early due to a high frequency of local injection-site reactions in the NFJI group, resulting in a reduced sample size not powered to compare the two groups for the immunogenicity outcomes. Two were phase 1 RCTs[8,13] and one was a pilot RCT,[9] and in each of these three studies, the sample sizes were not powered to compare the two groups for the immunogenicity outcomes. Two RCTs[4,16] had a drop-out rate greater than 20%. No intention to treat analysis (ITT) was used in 10 RCTs. Five RCTs were conducted on one research site. Finally, seven RCTs were conducted in countries where the clinical standard practice may differ from Canadian clinical settings (i.e., India, Cuba, Oman, Brazil or South Africa).

Summary of Findings

Findings are briefly summarized below. The details are available in Appendix 4: Table 4.

Efficacy outcomes

For influenza vaccination

Five RCTs were conducted for the influenza vaccine.[7,9,11,13,17]

The RCT by Shapiro et al. (2019),[11] was conducted in Canada. Eighty healthy adults were included. The objective of the study was to assess patient attitudes, safety and immunogenicity of the seasonal influenza vaccine delivered by NFJI (Med-Jet H4), ID compared to the traditional N-S, IM. The study found that, overall, the participants readily accepted NFJI, ID vaccination. Fifty six percent of participants in the NFJI group indicated they would prefer to receive vaccinations by NFJI, ID in the future. Immune response (such as seroconversion, seroprotection, antibody geometric mean titers [GMT]) in the NFJI, ID and N-S, IM groups were similar for all influenza strains in the vaccine. It also reported no statistically significant differences between the NFJI and N-S groups in terms of the frequency of functional CD4+T cells.

The RCT by McAllister et al. (2014)[7] was conducted in USA. A total of 1250 healthy adults participated in the study. The aim of the study was to compare the safety and assess the

non-inferior immunogenicity of a trivalent inactivated influenza vaccine administered by NSJI (Stratis; PharmaJet) versus by N-S. The non-inferiority margin was defined as the upper bound of the 95% CI of each ratio for the A/H1N1, A/H3N2, and B strains at less than 1.5. The authors reported that the immune response (i.e., seroconversion and antibody GMT) in the NFJI, ID group was non-inferior to the N-S, IM group for all influenza strains in the vaccine.

The RCT by Petrovsky et al. (2013)[9] was a small size (N= 46 healthy adults) pilot RCT conducted in Australia. The purpose of the study was to effectiveness of the NFJI (Stratis; PharmaJet) for trivalent influenza vaccine as compared to N–S injection. Similar immune response (i.e., seroconversion, or seroprotection, GMT) was observed for all influenza strains between NFJI, IM and N-S, IM groups. The authors indicated that NFJI was an alternative strategy for the administration of influenza vaccines especially for individuals with needle phobia.

In the RCT by Ledgerwood et al. (2012),[13] the authors reported two phase 1 studies (VRC 305 and VRC 304). Study VRC 304 did not meet the inclusion criteria for this report because there was no N-S injection comparator in the trial. Therefore, only Study VRC 305 is reported in this current review. In the study VRC 305 (N = 44 healthy adults), it was indicated that NFJI (Biojector) induced a higher frequency of immune response (antibody responses or T-cell responses) than that induced by N-S.

The RCT by Simon et al. (2011)[17] was conducted in USA with 60 healthy adults participating. The objective of the study was comparing the safety and immunogenicity of an IM dose of the 2009–2010 seasonal, trivalent, inactivated influenza vaccine delivered by NFJI (LectraJet), IM with that by N–S, IM. No statistically significant differences between NFJI and N-S were noted in terms of immune response (i.e. seroconversion, seroprotection or antibody GMT). The authors indicated that relatively small sample sizes precluded non-inferiority evaluation.

For inactivated poliovirus vaccine

Four RCTs were carried out using IPV.[10,14-16]

The RCT by Resik et al. (2015)[16] was carried out in Cuba. A total of 729 children (12 to 20 months of age) who had previously received two doses of oral poliovirus vaccine (OPV) were included. The purpose of the study was to compare the immune response of fractional dose of IPV (fIPV, i.e., 0.1 ml) administered by NFJIs (newly designed Biojector and PharmaJet), ID, with that of full-dose IPV (0.5 ml) by N-S, IM or fIPV dose by BCG N-S. it was found that the immune response (combination of boosting and seroconversion) induced with fIPV administered by NJFI, ID was similar to fIPV administered by BCG N-S injection. But, fIPV (delivered by all three NFJIs or BCG N-S injection) induced significantly lower boosting response compared to full-dose IPV by N-S.

The RCT by Soonawala et al. (2013)[10] was conducted in The Netherlands. A total of 125 healthy adults (mean age: 21.5 years) with a well-documented DTP-IPV vaccination history were included in the study. The aim of the study was to compare the immunogenicity and tolerability of fIPV booster vaccination administered by NFJI (PharmaJet), ID to full-dose and fIPV by N-S, IM. After 28 days, antibody GMT were slightly lower in the fIPV by NFJI, ID group (i.e., ID-JI-0.1 group) than full dose of IPV by N-S injection, IM (i.e., the reference group, IM-NS-0.5). The RCT was designed as non-inferiority trial. The non-inferiority margin was defined as the lower limit of the 95% confidence interval (95% CI) for the group difference at less than –1, which corresponds to a difference of 1 serum dilution in the

microneutralization assay. Only if the margin was not crossed for any of the three poliovirus strains (PV1, PV2, PV3), was the overall verdict 'non-inferior'. The author indicated that the non-inferiority margin was based upon a combination of statistical reasoning and clinical judgment. The author indicated that the between treatment group differences were not statistically significant, but the non-inferiority criterion was not met. The authors also suggested that fIPV by NFJI ID may be sufficient for routine poliovirus vaccination.

The RCT by Resik et al. (2010)[15] was conducted in Cuba as part of an evaluation of strategies to make IPV affordable for developing countries. The aim of the study was to compare the immunogenicity and safety of fIPV (0.1 mL, i.e., 1/5 of a full dose) ID administered by NFJI with that of full doses IM administered by N-S injection. A total of 471 healthy newborns were included. It was reported that 30 days after completing the 3-dose schedule of IPV, the seroconversion rates in the fIVP NFJI, ID group were 52.9%, 85.0%, and 69.0% for poliovirus types 1, 2, and 3, respectively. The seroconversion rates in the full dose IPV, N-S, IM group were 89.3%, 95.5%, and 98.9% of newborns for poliovirus types 1, 2, and 3, respectively. The seroconversion rates were statistically significantly lower with NFJI than N-S for all three types of vaccines. The median antibody titers were statistically significantly lower in the fIVP, NFJI, ID arm than in the full dose of IPV, N-S, IM arm ($P < 0.001$). The authors indicated that the findings demonstrated the feasibility of fIVP, NFJI, ID as a dose-sparing strategy but also showed that fIPV NFJI, ID resulted in a lower immune response compared with full dose IVP, N-S, IM.

The RCT by Mohammed et al. (2010)[14] was conducted in Oman as part of an evaluation of strategies for making the IPV affordable for developing countries. The purpose of the study was to compare the immunogenicity and safety of fIPV (0.1 mL, i.e., 1/5 of a full dose) administered by NFJI (Biojector, 2000), ID with that of full dose by N-S, IM injection. A total of 400 healthy newborns were included. It was reported that 30 days after completing the 3-dose schedule of IPV (i.e., at 7 months), the seroconversion rates in the fIVP, NFJI, ID group were 97.3%, 95.7%, and 97.9%, for poliovirus types 1, 2, and 3, respectively. The seroconversion rates in the full dose IPV, N-S IM group were 100% in the full-dose IPV, N-S, IM group for all 3 types of poliovirus vaccine. For type 2 vaccine, the seroconversion rate was statistically significant lower with NFJI than N-S. No statistically significant differences were reported for type 1 and type 3 vaccine. The median antibody titers were statistically significantly lower in the fIVP, NFJI, ID group than in the full dose of IPV, N-S, IM arm ($P < 0.001$). The author indicated that the findings demonstrated the similar seroconversion rate but lower antibody titer of fIVP, NFJI, ID compared with full dose IVP, N-S, IM.

For MMR vaccination

Two RCTs were conducted for the measles – mumps – rubella (MMR) vaccination.[5,6]

The RCT by Bavdekar et al. (2018)[5] was conducted in India. The aim of the study was to compare immunogenicity and safety of the MMR vaccine administered by NFJI (PharmaJet), SC, with that by N-S injection, SC. A total of 341 healthy children (15 to 18 months of age) who had received a measles vaccine at 9 months of age were included. On day 35, seropositivity rates for measles were 97.5% (95% CI , 93.8% to 99.3%) in the NFJI arm and 98.7% (95% CI 95.5% to 99.8%) in the N-S group; for mumps, the seropositivity rates were 98.8% (95% CI, 95.6% to 99.8%) in the NFJI group and 98.7% (95% CI, 95.5% to 99.8%) in the N-S group; and for rubella, the seropositivity rates were 98.8% (95% CI, 95.6% to 99.8%) in the NFJI arm and 100% (95% CI, 97.7% to 100.0%) in the N-S arm. The difference of the seroconversion rates between NFJI and N-S groups were not

statistically significant for all three vaccines (MMR). The difference of the antibody level between NFJI and N-S groups were not statistically significant either for three vaccines (MMR). The author concluded that MMR vaccination by NFJI was as immunogenic as that by N-S.

The RCT by de Menezes Martins et al. (2015)[6] was conducted in Brazil. A total of 582 healthy infants (12 to18 months of age) who had not received their first dose of MMR vaccine and who were up to date on all other routine vaccines were included. The objective of the study was to determine whether the immunogenicity to MMR vaccine delivered to infants by a NFJI (the first generation PharmaJet), SC was non-inferior to that administered by N-S, SC. The authors noted that the first generation of PharmaJet had been discontinued. Non-inferiority was defined as a difference of less than 10% on the upper limit of the 95% confidence interval (CI) for the difference in seroconversion rates between the two treatment groups (NFJI and N-S). The seroconversion responses in NFJI (the first generation PharmaJet) group to rubella virus were non-inferior to those of N-S group. However, the seroconversion rates for measles and mumps viruses in NFJI (the first generation PharmaJet), SC did not meet non-inferiority criteria when compared with the N-S, SC group.

For DTP-HB-Hib vaccination

Bavdekar et al.[4] conducted a RCT in India for comparing the immune response and safety for DTP-HB-Hib vaccination administered by NFJI (PharmaJet), IM with N-S IM injection. Three hundred forty infants were planned for this study, but the study was terminated early because of a higher frequency of injection site reactions, especially moderate and severe local AEs in the NFJI group. A total of 212 subjects were randomized at the time of study discontinuation. Therefore, the study was not sufficiently powered to compare immunogenicity between NFJI and N-S injections treatment groups. It was reported that seropositivity rate in the NFJI group was similar to that of N-S injection for all five antigens.

For human papillomavirus vaccination

Nelson et al.,[8] conducted a small size (N=42), phase 1 RCT that compared the immune response and safety of the human papillomavirus (HPV) vaccine, administered by NFJI (PharmaJet) with that by N-S injection. The purpose of the study was to determine whether a larger study might be feasible by comparing immunogenicity, safety of HPV administered by NJFI, ID with by N-S, IM or ID. A total of 42 healthy females (18 to 26 years of age) were included. It was reported that on Day 35 after the 1st vaccination, 77.5% of subjects showed seroconversion for HPV16 and 57.5% for HPV18. However, all participants in the study demonstrated a seroconversion on 35 days after 2nd vaccination. The author indicated that a larger clinical study to determine the immunogenicity, safety of HPV administered by NFJI, ID with by N-S, IM would be feasible.

For BCG vaccination

Geldenhuys et al.[12] conducted a RCT in South Africa to compare the safety and immunogenicity of BCG administration by the NFJI (Biojector), ID with that by N-S injection, ID. Healthy adults (N= 30) and healthy newborn infants (N=66) were included. The author reported that antigen-specific T-cell immune responses, that is the frequencies of BCG-specific clusters of differentiation 4 (CD4) and clusters of differentiation 8 (CD8) T-cells co-expressing IFN-gamma, TNF-alpha, IL-2, and/or IL-17, were not statistically significant different between the NFJI, ID and N-S, ID groups.

Adverse events

Adverse events were reported in all included studies and included unsolicited AEs (local and systemic AEs) and solicited AEs (local and systemic AEs). Overall, regardless of the type of NFJIs (i.e., PharmaJet, Met-Jet H4, Biojector, LectraJet) or type of vaccines (i.e., influenza, IPV, MMR, DTP-HB-Hib, HPV or BCG), it was generally reported that NFJIs, ID were associated with numerically higher frequencies of unsolicited and solicited local reaction AEs (e.g., redness, swelling induration and infiltration) than traditional N-S injection. However, the frequencies of unsolicited and solicited systemic AEs (e.g., fever, headache, muscles aches, tiredness, nausea) were similar or numerically lower in NFJI, ID compared with N-S injection, IM.

In one study,[10] it was reported that vaccination with a NFJI (PharmaJet) was less painful compared with a N-S injection.

It was noted that the RCT by Bavdekar[4] was terminated prematurely because of a high frequency of local injection-site reactions in the NFJI group. The author indicated that Pentavalent vaccine (DTP-HB-Hib) includes whole-cell pertussis vaccine and an aluminum adjuvant, which may have contributed to more local AEs associated with the NFJI. However, it was reported that the first generation of PharmaJet was discontinued from the market.[4,6]

Limitations

There are various limitations associated with the body of evidence in this report on the comparative clinical effectiveness of vaccines administered using a NFJI with that using N-S.

Three out of 14 studies were designed as phase 1 or small size pilot studies. The sample size was not powered to detect the between group difference (NFJI vs. N-S). In this case, similar response observed between groups should not be interpreted as “no difference” or “non-inferior.”

In addition, the NFJI’s operating mechanisms, applications, efficacy and safety have been constantly evolving and improving over the years. For example, the first generation of PhamaJet used in one included study[6] was discontinued from the market. Therefore, the application value of the findings from this study may be limited.

Furthermore, except for IPV, there was no evidence identified using NFJI, ID for fractional dose (or reduced dose) of vaccine as a dose-sparing strategy for influenza and other vaccines.

Finally, some RCTs were conducted in countries (e.g., India, Cuba, Oman, Brazil or South African) where the clinical standard practice may differ from Canadian clinical settings, therefore, whether the findings can be generalized to the Canadian setting is uncertain.

Conclusions and Implications for Decision or Policy Making

Fourteen RCTs[4-17] regarding the comparative clinical effectiveness of NFJIs versus N-S for vaccine administration were identified in this review. Five RCTs[7,9,11,13,17] were for influenza vaccine, four for IPV,[10,14-16] two for MMR,[5,6] one for DTP-HB-Hib,[4] one for HPV[8] and one for BCG.[12] Four NFJIs used in the included trials are PharmaJet Injector (PharmaJet, USA),

Med-Jet H4 injector (Med-Jet, MIT Canada,), Biojector (Bioject Medical Technologies Inc. USA) and LectraJet (D'Antonio Consultants International, Inc., USA).

For the influenza vaccine, the findings observed in five RCTs indicated that influenza vaccine administered by NFJI, ID achieved similar immune response (e.g., seroconversion, seroprotection, antibody titer) compared with that administered by traditional N-S, IM. No evidence of a dose-sparing strategy for influenza vaccine using NFJI was identified.

For the IPV vaccine, the findings reported in four RCTs showed that compared with conventional full dose IPV (i.e., 0.5 ml) given by N-S, IM, a fractional dose of IPV (i.e. 0.1 ml or 1/5 of full dose), given by NFJI, ID demonstrated a similar seroconversion rate (both initial immunization or boosting) but lower antibody titer.

The findings from two RCTs for MMR indicated that there was no statistically significant difference observed between NFJI, SC and N-S, SC in terms of immune response (e.g., seroconversion rate, antibody titer) for the MMR vaccine.

For DTP-HB-Hib, HPV and BCG vaccines, the immune response (e.g., seroprotection and seropositivity rate) introduced by NFJIs was also similar to that observed in the N-S group.

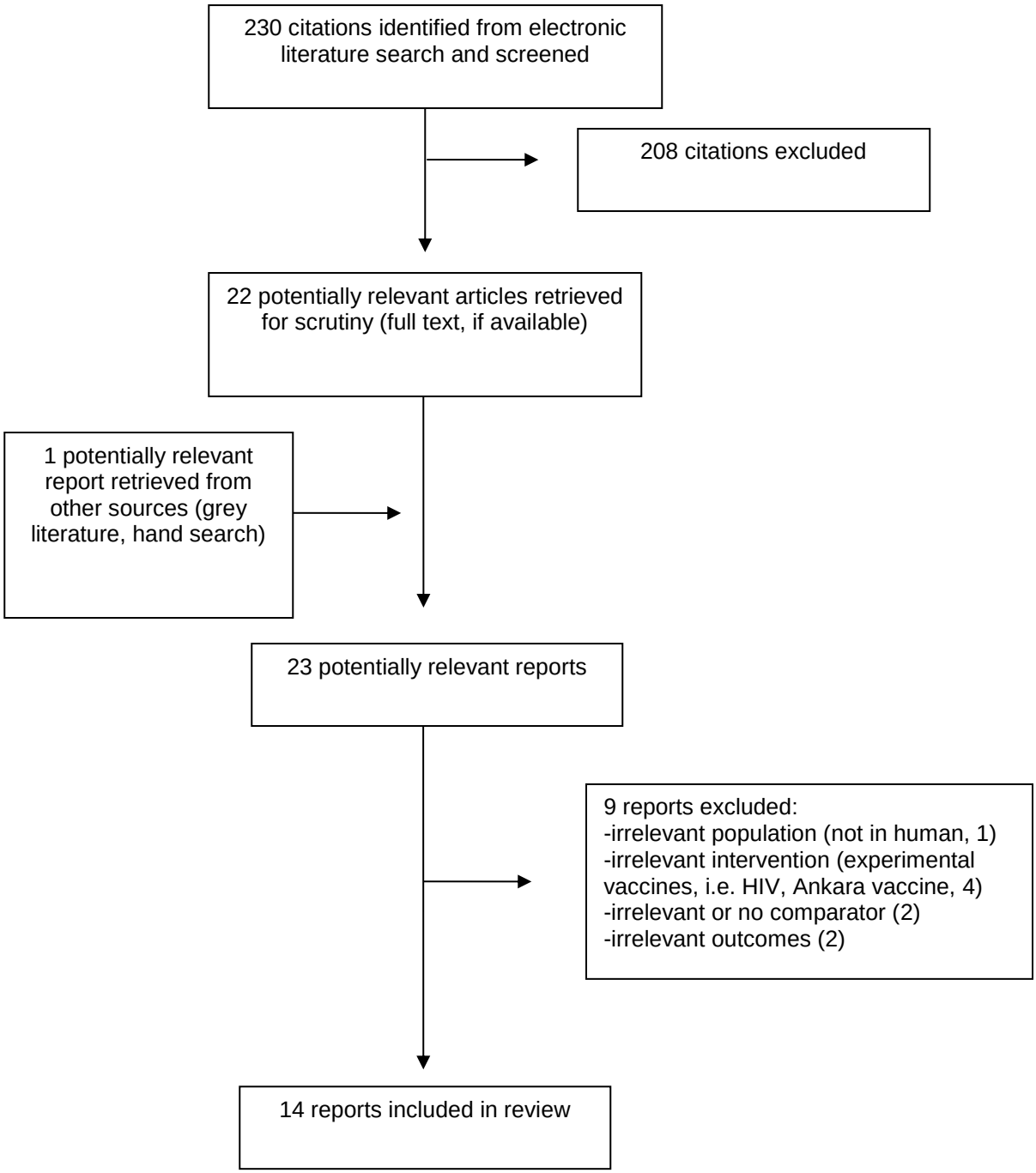
Regardless of the type of vaccine, or type of NFJI, more unsolicited and solicited local adverse reactions (e.g., redness, swelling, induration and infiltration) were observed with NFJIs than with traditional N-S injection. However, the frequencies of unsolicited and solicited systemic AEs (e.g., fever, headache, muscles aches, tiredness, nausea) were similar or numerically lower in NFJI, ID compared with N-S injection, IM.

In conclusion, the vaccinations administered by NFJI, ID were reported to be as immunogenic as that by N-S, intramuscularly. However, more local injection reactions, but fewer systemic AEs associated with NFJI were reported. Despite some limitations of the study designs, the comparative effectiveness and safety profile of vaccines (e.g., influenza, IPV or MMR) administered by NFJI and N-S were consistent regardless the type of vaccine and the type of NFJIs. Future studies assessing NFJI as a dose–sparing strategy for comparing with conventional N-S are needed, especially for the influenza vaccine.

References

1. Needle-free Injection Systems for Administering Medications. *(ECRI Custom Rapid Response)*. Plymouth Meeting (PA): ECRI Institute; 2015: www.ecri.org. Accessed 2020 Jul 7.
2. Mohizin A, Kim JK. Current engineering and clinical aspects of needle-free injectors: A review. *Journal of Mechanical Science and Technology.* 2018;32:5737-5747.
3. Ab Rahman B, Thye SL. INJEX (Needle Free Drug Delivery System). Putrajaya (MY): Health Technology Assessment Section (MaHTAS), Ministry of Health Malaysia; 2013: https://www.moh.gov.my/index.php/database_stores/store_view_page/30/208. Accessed 2020 Jul 7.
4. Bavdekar A, Malshe N, Ravichandran L, et al. Clinical study of safety and immunogenicity of pentavalent DTP-HB-Hib vaccine administered by disposable-syringe jet injector in India. *Contemp Clin Trials Commun.* 2019;14:100321.
5. Bavdekar A, Oswal J, Ramanan PV, et al. Immunogenicity and safety of measles-mumps-rubella vaccine delivered by disposable-syringe jet injector in India: A randomized, parallel group, non-inferiority trial. *Vaccine.* 2018;36(9):1220-1226.
6. de Menezes Martins R, Curran B, Sousa Maia MdL, et al. Immunogenicity and safety of measles-mumps-rubella vaccine delivered by disposable-syringe jet injector in healthy Brazilian infants: a randomized non-inferiority study. *Contemp Clin Trials.* 2015;41:1-8.
7. McAllister L, Anderson J, Werth K, et al. Needle-free jet injection for administration of influenza vaccine: a randomised non-inferiority trial. *Lancet.* 2014;384(9944):674-681.
8. Nelson EA, Lam HS, Choi KC, et al. A pilot randomized study to assess immunogenicity, reactogenicity, safety and tolerability of two human papillomavirus vaccines administered intramuscularly and intradermally to females aged 18-26 years. *Vaccine.* 2013;31(34):3452-3460.
9. Petrovsky N, Honda-Okubo Y, Royals M, Bragg K, Sajkov D. A randomized controlled study to assess the immunogenicity and tolerability of a 2012 trivalent seasonal inactivated influenza vaccine administered via a disposable syringe jet injector device versus a traditional pre-filled syringe and needle. *Trials Vaccinol.* 2013;2:39-44.
10. Soonawala D, Verdijk P, Wijmenga-Monsuur AJ, et al. Intradermal fractional booster dose of inactivated poliomyelitis vaccine with a jet injector in healthy adults. *Vaccine.* 2013;31(36):3688-3694.
11. Shapiro JR, Hodgins B, Hendin HE, et al. Needle-free delivery of influenza vaccine using the Med-Jet R H4 is efficient and elicits the same humoral and cellular responses as standard IM injection: A randomized trial. *Vaccine.* 2019;37(10):1332-1339.
12. Geldenhuys. A randomized clinical trial in adults and newborns in South Africa to compare the safety and immunogenicity of bacille Calmette-Guerin (BCG) vaccine administration via a disposable-syringe jet injector to conventional technique with needle and syringe. *Vaccine.* 2015;33(37):4719-4726.
13. Ledgerwood JE, Hu Z, Gordon IJ, et al. Influenza virus h5 DNA vaccination is immunogenic by intramuscular and intradermal routes in humans. *Clinical & Vaccine Immunology: CVI.* 2012;19(11):1792-1797.
14. Mohammed AJ, AlAwaidy S, Bawikar S, et al. Fractional doses of inactivated poliovirus vaccine in Oman. *N Engl J Med.* 2010;362(25):2351-2359.
15. Resik S, Tejeda A, Lago PM, et al. Randomized controlled clinical trial of fractional doses of inactivated poliovirus vaccine administered intradermally by needle-free device in Cuba. *J Infect Dis.* 2010;201(9):1344-1352.
16. Resik S, Tejeda A, Mach O, et al. Immune responses after fractional doses of inactivated poliovirus vaccine using newly developed intradermal jet injectors: a randomized controlled trial in Cuba. *Vaccine.* 2015;33(2):307-313.
17. Simon JK, Carter M, Pasetti MF, et al. Safety, tolerability, and immunogenicity of inactivated trivalent seasonal influenza vaccine administered with a needle-free disposable-syringe jet injector. *Vaccine.* 2011;29(51):9544-9550.
18. Hibberd PL. Seasonal influenza vaccination in adults. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2020: www.uptodate.com. Accessed 2020 Jun 12.
19. A guideline developer's handbook. *(SIGN publication no. 50)*. Edinburgh (GB): Scottish Intercollegiate Guidelines Network; 2015: https://www.sign.ac.uk/assets/sign50_2015.pdf. Accessed 2020 Mar 24.
20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Studies for influenza vaccination				
Shapiro JR, 2019, Canada[11]	RCT Objective: to assess patient attitudes, safety and immunogenicity of the seasonal influenza vaccine delivered by Med-Jet injection), ID compared to the traditional N-S, IM	Healthy adult Age: 18 - 49 years N = 80 adults	Intervention: NFJI (MedJet H4, CANADA), ID N = 40 Comparator: N-S: IM N= 40 (In N-S group: Single dose vaccine; N= 19; multiple dose vial vaccine: N =21) (Note: Med-Jet H4 -The newest model of Med-Jet, MIT Canada)	Patient attitudes Seroconversion rates, Seroprotection rates; GMT AEs Length of follow-up: 21 days after vaccination
McAllister L, 2014, USA[7]	RCT Objective: to compare the safety and show the non-inferior immunogenicity of a trivalent inactivated influenza vaccine given by Jet injector versus N-S	Healthy adults Age: 18 - 64 years N = 1250	Intervention: NFJI (Stratis, PharmaJet, USA), IM N = 623 Comparator: N-S, IM N= 627	Seroconversion rates, GMT AEs Length of follow-up: 28 days after vaccination.
Petrovsky N, 2013, Australia[9]	RCT (Pilot study) Objective: to test the utility of the DSJI for delivery of trivalent vaccine as compared to N–S	Healthy adult Age: 18 - 78 years N = 46	Intervention: NFJI (Stratis, PharmaJet USA), IM N = 22 Comparator: N-S: SC/IM N= 24	Seroconversion rates, Seroprotection rates; GMT AEs Length of follow-up: 28 days after vaccination.

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Ledgerwood JE, 2012 USA[13]	RCT (Phase 1, Only Study VRC 305 reported for this review, Study VRC 304 was a single arm trial, no N-S comparator) Objective: (Study VRC 305) to compare NFJI, ID injections Avian influenza vaccine with N-S injection	Healthy adult Age: 22 – 60 years N = 44	Intervention: NFJI (Biojector, USA), ID Total N = 33 Note: Group 1: 0.5mg, ID, N = 11; Group 2: 0.5mg × 2, ID (at same arm), N=11 Group 3: 0.5mg × 2, ID, (0.5 mg at each arm), N=11 Comparator: N-S: 0.5 mg, ID N= 11	Antibody concentration T Cell Response AEs Length of follow-up: 12 weeks (4 weeks after 3rd injection)
Simon JK, 2011, USA[17]	RCT Objective: To Compare safety and immunogenicity of IM dose of the 2009–2010 seasonal, trivalent, inactivated influenza vaccine by DFJI with by N–S.	Healthy adult Age: 18 - 49 years N = 60	Intervention: DFJI (LectraJet, USA) N = 30 Comparator: N-S, IM N= 30	Seroconversion rates, Seroprotection rates; GMT AEs Length of follow-up: 28 days after vaccination. For AEs: Up to 90 days
Studies for IPV				
Resik S, 2015, Cuba[16]	RCT Objective: to compare the immune response of fIPV administered by NFJI with that of full-dose IPV by N-S.	Children previously received two doses of OPV, Age: 12 - 20 months N= 729	Intervention: NFJI - fIPV dose (0.1ml), ID ●Jet injector X (Conventional Biojector 2000 [Bioject], ID): N=145 ●Jet injector Y (newly designed Pen injector [Bioject]) ID, N= 153 ●Jet injector Z (Newly designed PharmaJet), ID N= 145	Combination of boosting and seroconversion, AEs Length of follow-up: 21 days after vaccine

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			Comparator: N-S ●N-S group: full dose IPV (0.5ml), IM N= 146 ●BCG N-S group, fIPV dose, IM N=143	
Soonawala D, 2013, The Netherlands[10]	RCT Objective: to compare the immunogenicity and tolerability of fIPV booster vaccination administered with a jet injector (PharmaJet) by ID to full-dose and fIPV with N-S by IM	●Healthy adult ●received exactly 6 combined DTP-IPV vaccinations according to the National Immunization Program (i.e. at age 3 months, 4 months, 5 months, 11 months, 4 years and 9 years) were eligible. Age: mean: 21.5 years N= 125	Intervention: NFJI (PharmaJet) ●NFJI, ID 0.1 ml IPV N=32 ●NFJI, IM, 0.5 ml IPV N= 30 Comparator: N-S, ●N-S, IM, 0.1ml IPV N= 31 ●N-S, IM, 0.5 ml IPV N= 32	GMC AEs Length of follow-up: 28 days after vaccination
Resik S, 2010, Cuba[15]	RCT Objective: To compare the immunogenicity and safety of fIPV given by NFJI, ID with full doses given by N-S, IM.	Healthy infants Age: newborn N= 471	Intervention: NFJI (Biojector, 2000) , ID fIPV (0.1ml) N= 235 Comparator: N-S N-S IM, 0.5ml full dose IPV N= 236	Seroconversion rates, Antibody titer AEs Length of follow-up: 18 weeks
Mohammed AJ, 2010, Oman[14]	RCT Objective:	Healthy infants Age: newborn N= 400	Intervention: NFJI (Biojector, 2000), ID fIPV (0.1ml)	Seroconversion rates, Antibody titer

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	To compare the immunogenicity and safety of fIPV given by NFJI, ID, with full doses given by N-S, IM.		N= 200 Comparator: N-S IM, 0.5ml full dose IPV N= 200	AEs Length of follow-up 7 months
Studies for MMR				
Bavdekar A, 2018, India[5]	RCT Objective: to compare immunogenicity and safety of the MMR vaccine administered by NFJI, SC, with by N-S, SC.	Healthy children who had received measles vaccine at 9 months of age Age: 15 – 18 months N= 341	Intervention: NFJI (Stratis, PharmaJet), SC N = 170 Comparator: N-S, SC N= 170	Seropositive Antibody titer (GMT) AEs Length of follow-up: 35 days after vaccination
de Menezes Martins R, 2015, Brazil[6]	RCT Objective: to determine if immunogenicity to MMR vaccine delivered to infants via a NFJI was non-inferior to that administered by N-S	Healthy infants who have not received their first dose of MMR vaccine and up to date on all other routine vaccines. Age: 12 – 18 months N= 582	Intervention: NFJI (First-generation PharmaJet) Comparator: N-S, SC For Measles vaccine NJFI: N = 365 N-S: N= 182 For Mumps vaccine NFJI: N =364 N-S: N= 183 For rubella vaccine NFJI: N = 368 N-S: N= 184 Note: NFJI, the first generation of PharmaJet was discontinued)[6]	Seropositive Antibody titer (GMC) AEs Length of follow-up: 35 to 56 days after vaccination.
Study for DTP-HB-Hib vaccination				
Bavdekar A 2019, India[4]	RCT Objective: to determine	Healthy children Age: 6- 8 weeks	Intervention: NFJI (Stratis, PharmaJet), IM	Combination of Seroprotection and seropositivity

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	whether the seropositivity rate after vaccination via NFJI was non-inferior to that via N-S, and to compare the safety of vaccination by NFJI versus N-S	N= 210	N = 105 Comparator: N-S, IM N= 105	AEs Length of follow-up: 4–6 weeks after the third dose
Study for HPV vaccination				
Nelson EA, 2013, Hong Kong[8]	RCT (Phase 1) Objective: to determine whether a larger study might be feasible by comparing immunogenicity, safety of HPV administered by NFJI, ID with by N-S, IM	Healthy female Age: 18 – 26 years N = 42	Intervention: NFJI (PharmaJet), 20% dose of vaccine, ID N = 10 Comparator: N-S ●N-S IM, full dose; N= 11 ●N-S IM, 20% dose; N= 10 ● N-S ID, full dose: N = 9	Seroconversion AEs Length of follow-up: 6 months
Study for BCG vaccination				
Geldenhuys A, 2015, South Africa[12]	RCT Objective: to compare the safety and immunogenicity of BCG vaccination via NFJI with via N-S	●Healthy adult: Age: 18 - 50 years N= 30 ●Healthy newborn: Age: ≤ 48 hours N= 66	Intervention: DFJI (Biojector), ID N = 15 adult; N= 33 newborn; Comparator: N-S , ID N = 15 adult; N= 33 newborn;	T cell response AEs Length of follow-up: Adults: 12 weeks Newborn: 14 weeks

AE = adverse events; DSJI = disposable-syringe jet injector; DTP = diphtheria – tetanus - pertussis vaccination ; fIPV = Fractional dose of inactivated poliovirus vaccine; HB = hepatitis B; Hib = Hemophilus influenzae type b conjugate (pentavalent) vaccination; ID = intradermal; IM = intramuscular; IPV = Inactivated poliovirus vaccine; ISR = immune status ratio; MD = multiple dose; MMR = measles-mumps-rubella vaccine; NFJI = Needle free jet injector; N-S = needle and syringe; RCT = Randomized controlled trial; SC = subcutaneously; SD = single dose.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using SIGN 50 Check list [19]

Strengths	Limitations
Bavdekar A, 2019[4]	
• Research question clearly defined • Randomization method clearly described • Randomization allocation described • Blinded design except for staff administering the vaccine was described • The characteristics were distributed similarly across treatment groups. • Only difference between groups was treatment under investigation • Outcome was standard, valid and reliable • Conducted in multiple sites • Declared conflict of interest	• Early termination due to high frequency of injection site reactions in the DSJI group, resulting in a sample size that did not allow use of statistical analyses to compare the two groups for the immunogenicity outcomes • High dropout (NFJI: 42%; N-S: 36%) • No conclusion was drawn
Bavdekar A, 2018[5]	
• Research question clearly defined • Randomization method clearly described • Randomization allocation described • Blinded design except for staff administering the vaccine was described • The characteristics were distributed similarly across treatment groups. • Only difference between groups was treatment under investigation • Outcome was standard, valid and reliable • Low dropout (5.5%) • Conducted in multiple sites • Declared conflict of interest	• Participant gender was not well-balanced • Efficacy outcome not analyzed in ITT population
Shapiro JR, 2019[11]	
• Research question was clearly defined • Randomization method was clearly described • All immunologic assays were performed by operators blinded to group assignment. • The characteristics were distributed similarly across treatment groups. • Only difference between groups is treatment under investigation • The characteristics were distributed similarly across treatment groups. • Outcome was standard, valid and reliable • No dropout • Intention to treat analysis applied • Declared conflict of interest	• Allocation concealment not described • Not blinded design. • Conducted at one center
McAllister L, 2014[7]	
• Research question was clearly defined • Randomization method was clearly described	• Allocation concealment not described • No true ITT analysis applied

Strengths	Limitations
• Blind design except participants • The characteristics were distributed similarly across treatment groups. • Only difference between groups is treatment under investigation • Outcome was standard, valid and reliable • No dropout reported • Conducted in multiple sites • Declared conflict of interest	
Petrovsky N, 2013[9]	
• Research question was clearly defined • Randomization method clearly described • Randomization allocation concealment described • The between grope comparison of characteristics were Not reported. • Only difference between groups is treatment under investigation • Outcome was standard, valid and reliable • No dropout • ITT analysis • Declared no conflict of interest	• Not a blinded study design • A pilot study, small sample size, not powered for between group comparison • Study conducted in single site
Ledgerwood JE, 2012[13]	
(Study VRC 305) • Research question was clearly defined • Only difference between groups is treatment under investigation • Outcome was standard, valid and reliable • Low dropout (< 15%) • Declared no conflict of interest	• Randomization method not clearly described • Allocation concealment not described • Open label design • The between grope comparison of characteristics were Not reported. • A phase 1 RCT, small sample size, not powered for between group comparison • No true ITT analysis applied
Simon JK, 2011[17]	
• Research question was clearly defined • Randomization method was clearly described • Randomization allocation concealment described • Blind design was clearly described • Only difference between groups is treatment under investigation • Outcome was standard, valid and reliable • No dropout reported • ITT analysis • Declared conflict of interest	• The demographic characteristics not well balanced across treatment groups • Conducted in single site
Geldenhuys A 2015[12]	
• Research question clearly defined • Randomization method clearly described • Randomized allocation concealment described. • Study team were partially blinded.	• Adult participants and nurses were not blinded • Conducted in single center

Strengths	Limitations
• The characteristics were distributed similarly across treatment groups. • Only difference between groups was treatment under investigation • Outcome was standard, valid and reliable • No dropout • Intention to treat analysis applied • Declared no conflicts of Interest	
de Menezes Martins R, 2015[6]	
• Research question clearly defined • Physician collecting the AEs was blinded to the injection method (Study team were partially blinded) • The characteristics were distributed similarly across treatment groups. • Only difference between groups was treatment under investigation • Outcome was standard, valid and reliable • Low dropout (<2%) • Conducted in multiple sites • Declared conflict of interest	• Randomization method was not clearly described; • Allocation concealment was not described • Not true ITT analysis
Resik S, 2015[16]	
• Research question clearly defined • The characteristics were distributed similarly across treatment groups. • Only difference between groups was treatment under investigation • Outcome was standard, valid and reliable • Declared no conflicts of Interest	• Randomization method not clearly described • Allocation concealment not described. • Blind design not reported • High drop out (26%) • Not ITT analysis • Conducted in single center
Soonawala D, 2013[10]	
• Research question clearly defined • Randomization method clearly described • Randomized allocation concealment described. • The characteristics were distributed similarly across treatment groups. • Only difference between groups was treatment under investigation • Outcome was standard, valid and reliable • Low drop out (<5%)	• Not blind design • Not ITT analysis for immunogenicity • Conducted in single center • Conflicts of interest not declared
Resik S, 2010[15]	
• Research question clearly defined • Partially blinded design (laboratory investigators) • The characteristics were distributed similarly across treatment groups. • Only difference between groups was treatment under investigation • Outcome was standard, valid and reliable • Conducted in multiple sites	• Randomization method not clearly described • Allocation concealment not described • High drop out (> 15%) • Not ITT analysis for immunogenicity • Conflicts of interest not declared

Strengths	Limitations
Mohammed AJ, 2010[14]	
• Research question clearly defined • The characteristics were distributed similarly across treatment groups. • Only difference between groups was treatment under investigation • Outcome was standard, valid and reliable • Low drop out (< 7.5%) • Declared conflicts of interest • Conducted in multiple sites	• Randomization method not clearly described • Allocation concealment not described • Not blinded design • Not ITT analysis for immunogenicity
Nelson EA, 2013[8]	
• Research question was clearly defined • Randomization method clearly described • Randomization allocation concealment described • Partial blinded design • Only difference between groups is treatment under investigation • Outcome was standard, valid and reliable • Low dropout (<5%) • Declared no conflict of interest	• The between grope comparison of characteristics were Not reported. • It is phase 1 RCT, small sample size, not powered for between group comparison • No true ITT analysis applied

ITT = intention to treat; RCT = randomized controlled trial.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Influenza vaccination	
Shapiro JR, 2019[11]	
Immunogenicity: (NFJI vs. N-S, 21 days post vaccination) Seroconversion rates: No statistically significant different between two groups (data presented in a figure) Seroprotection rates: No statistically significant different between two groups (data presented in a figure) GMTs: No statistically significant different between two groups (data presented in a figure) Note: Seroconversion was defined as subject with a ≥ 4-fold increase in hemagglutination Inhibition (HI) titers from day 0 to day 21; Seroprotection was defined as achieving hemagglutination Inhibition (HI) titers greater or equal to 40. No statistically significant differences between the NFJI and N-S groups in terms of the frequency of functional CD4+T cells **Patient attitudes** At day 21 postimmunization, 56% of those in the NFJI group indicated they would prefer to receive vaccinations by NFJI in the future. **AEs** **On Day 0 to Day 4:** <u>Local reaction AEs (i.e., redness, swelling, pain, itching):</u> Participants in the NFJI group experienced greater swelling and redness but not pain within 30 min of vaccination. By the evening of day 0, similar rates of local and systemic reactions were reported by all participants, and local reactions were generally resolved by day 4 post-immunization in all groups. <u>Systemic symptoms on Day 4 (headache, muscles aches, tiredness, nausea) n (%):</u> NFJI vs. N-S: 4 (10%) vs. 0 (0%) **After Day 4,** n (%) <u>Local reaction AEs (i.e., redness, swelling, pain, itching):</u> NFJI vs. N-S: 7 (17.5%) vs. 5 (12.5%) <u>Systemic symptom AEs:</u> NFJI vs. N-S: 3 (7.5%) vs. 3 (7.5%)	On page 1332: These data suggest that the Med-Jet is an acceptable means of delivering seasonal influenza vaccine. The system was attractive to subjects, rapidly learned by skilled vaccine nurses and elicited both humoral and cellular responses that were indistinguishable from those elicited with needle injection…" On page 1337: " this study demonstrates that the Med-Jet delivery system performs well in terms of patient attitudes, safety and the immune response elicited by a commercial influenza vaccine. …"

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">McAllister L, 2014[7]</td></tr>
<tr><td>

Immunogenicity for different type of influenza vaccine and AEs (28 days post vaccination)

Seroconversion rate, %	NFJI	N-S	Rate difference (95%CI)
H1N1	37.5	38.4	0.8 (-4.8, 6.5)
H3N2	43.8	45.1	1.3 (-4.5, 7.1)
B	34.9	35.2	0.3 (-5.5, 5.9)
GMT	**NFJI**	**N-S**	**Rate ratio (95%CI)**
H1N1	282.9	280.6	0·99 (0·8–1·12)
H3N2	247.3	265.9	1·08 (0·96–1·21)
B	42.5	39.7	0·94 (0·83–1·06)
AEs	**NFJI**	**N-S**	**Rate difference (95%CI)**
Local AEs on day 0, %	47.3	17.2	Not reported
Solicited AEs, day 0-6, %	95.1	85.0	Not reported
Systemic AEs	Not reported	Not reported	No significant difference

Note: Seroconversion was defined as 4-time increase in titer after immunization when the baseline titer was ≥10; or in titer ≥ 40 after immunization when the baseline titer was ≤ 10.

</td><td>

On p 680: "In conclusion, the results from this study support the use of the jet injection device as an acceptable method for administration of Afluria. Moreover, jet injection needle free administration addresses needle fear and the safety risks for patients and health-care providers associated with traditional administration of vaccines by needle and syringe. These qualities might contribute to the reduction of barriers to immunization in the US adult population to help reach CDC goals for annual influenza vaccine coverage."

</td></tr>
<tr><td colspan="2">Petrovsky, 2013, Australia[9]</td></tr>
<tr><td>

Immunogenicity for different type of influenza vaccine (28 days post vaccination)

	DFJI	N–S
H1N1		
GMT, pre/post	34.2/80.0	29.1/75.5
GMT fold increase, % (95% CI)	2.3 (1.3–3.4)	2.6 (1.4–3.8)
Seroconversion, % (95% CI)	31.8 (12.3–51.3)	33.3 (14.4–52.2)
Seroprotection, % (95% CI)	86.4 (72.1–100)	79.2(63.0–95.4)
H3N2		
GM, pre/post	23.4/49.9	23.8/42.4
GMT fold increase	2.1 (1.1–3.2)	1.8 (1.0–2.6)
Seroconversion, % (95% CI)	31.8 (12.3–51.3)	12.5 (0.7–25.7)
Seroprotection, % (95% CI)	72.7 (54.1–91.3)	66.7 (47.8–85.6)
B/Brisbane/60/2008		
GMT, pre/post	15.5/22.0	11.2/16.8
GMT fold increase, % (95% CI)	1.4 (0.7–2.2)	1.5 (0.9–2.1)
Seroconversion, % (95% CI)	4.5% (4.2–13.2)	4.1% (3.8–12.0)
Seroprotection, % (95% CI)	18.2% (2.1–34.3)	16.7% (1.8–31.6)

Note: seroconversion defined as 4-fold increase in titer over baseline; seroprotection defined as postimmunization titer of 1:40 or greater.

AEs:

Local reaction AEs: (i.e., redness, swelling, pain, itching)
NFJI: 43 AEs in 22 subjects
N-S: 19 AEs in 24 subjects

Systemic AEs: (fever/chills, headache, muscle ache, fatigue, nausea, diarrhea)
NFJI: 2 subjects (9.1%)
N-S: 10 subjects (41%)

</td><td>

No conclusion drawn by the author.
However, on page 1 the author indicated that "… the Stratis DSJI is a viable alternative strategy for the administration of seasonal influenza vaccines with particular appeal for individuals with needle phobia."

</td></tr>
</table>

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Ledgerwood JE, 2012[13]</td></tr>
<tr><td>

(Study VRC 305 only)

Immunogenicity (4 weeks after 3rd vaccination)

Antibody titer

<table>
<tr><th></th><th colspan="3">Magnitude of H5 specific antibody responses</th><th rowspan="2">T cell response</th></tr>
<tr><th></th><th>HAI titer (Log10)</th><th>ELISA titer (Log10)</th><th>ID8 titer (neutralization assay)</th></tr>
<tr><td>0.5mg ID, NFJI</td><td>0%</td><td>55%</td><td>0%</td><td rowspan="4">Not extractable (data was presented in figure)</td></tr>
<tr><td>0.5 mg X2, ID, one arm, NFJI</td><td>10%</td><td>80%</td><td>0%</td></tr>
<tr><td>0.5 mg X2, ID, two arms (i.e., 0.5 mg ID each arm), NFJI</td><td>22%</td><td>67%</td><td>40%</td></tr>
<tr><td>0.5mg ID, N-S</td><td>0%</td><td>60%</td><td>33%</td></tr>
</table>

ELISA = enzyme-linked immunosorbent assay; HAI = hemagglutination inhibition; ID80 = The 80% inhibition serum titer.

T-cell responses: ICS-CD4 (intracellular cytokine staining for interleukin-2 and gamma interferon-CD4)

ID injection by NFJI induced a higher frequency of response than ID injection by N-S (Data presented in figure, not extractable)

Unsolicited AEs: Not reported

Solicited AEs:

Local AEs:

At least with one AEs, n (%)
NFJI, 0.5mg, ID: 7 (64)
NFJI, 1mg ID, same arm: 9 (82)
NFJI, 1mg ID, different arms 10 (91)
N-S, 0.5 mg, ID: 7 (70%)

Systemic AEs:
At least with one AEs
NFJI, 0.5 mg, ID: 6 (54%)
NFJI, 1mg, ID, same arm: 8 (73%)
NFJI, 1mg different arms: 8 (73%)
N-S-ID: 6 (60%)

</td><td>

No conclusion drawn by the author.

However, on page 1. it was indicated that "These studies demonstrated that the DNA vaccine encoding H5 is safe and immunogenic and served to define the proper dose and route for further studies. The i.d. injection route did not offer a significant advantage over the i.m. route, and no difference was detected by delivery to one site versus splitting the dose between two sites for i.d. vaccine administration. The 4-mg dose (i.m) was further investigated in prime-boost regimens."

</td></tr>
<tr><td colspan="2">Simon JK, 2011[17]</td></tr>
<tr><td>

Immunogenicity for different type of influenza vaccine (28 days post vaccination)

<table>
<tr><td>Seroprotection: %, (95% CI)</td><td>77 (61–92)</td><td>87 (74–99)</td><td>0.5</td></tr>
<tr><td></td><td>NFJI</td><td>N–S</td><td>P value</td></tr>
<tr><td>H1N1</td><td></td><td></td><td></td></tr>
</table>

</td><td>

On page 9544: "DSJI delivery of TIV is well-tolerated and immunogenic"

</td></tr>
</table>

Main Study Findings				Authors' Conclusion
GMT (95% CI)	213 (127–357)	199 (131–301)	0.8	
Seroconversion: % (95%CI)	80 (65–95)	63(45–81)	0.3	
Seroprotection: %, (95% CI)	83 (69–97)	90 (79–100)	0.5	
H3N2				
GMT (95% CI)	426 (253–717)	301 (177–511)	0.3	
Seroconversion: %, 95%CI	80 (65–95)	67 (49–84)	0.4	
Seroprotection: %, (95% CI)	100 (NA)	93 (84–100)	0.5	
B				
GMT Day 28 (95% CI)	111 (71–175)	131 (83–206)	0.6	
Seroconversion: %, 95%CI	73 (57–90)	57 (38–75)	0.3	

Note: Seroconversion was defined as achieving a ≥4-fold rise in HI titer with a post-vaccination titer or ≥40 if a pre-vaccination titer was ≤10.
Seroprotection was defined as an HI titer ≥40 (dilution ≥1:40)

Hemagglutination inhibition (HI) were calculated as the inverse of the highest dilution that inhibited hemagglutination

AEs

Unsolicited AEs

NFJI: 19 events in 17 subjects

N-S: 20 AEs in 17 subjects

Local AEs:
The most common local AE during the 3 days post-vaccination

NFJI vs: N-S

Erythema, 97% of NFJI vs. 73% of the N–S;
Induration, 93% of the NFJI vs. 27% of the N–S;

Systemic AEs

NFJI vs: N-S

Fatigue, 33% in NFJI vs. 47% in the N–S
Myalgia: 23% in NFJI vs. 37% in N–S

Solicited AEs: all mild or moderate. Except one subject in N-S experienced severe headache and fatigue on day 2 post-vaccination after exposed to contacts with illness.

IPV vaccination					
Resik S, 2015[16]					
Immune response (combination of boosting and seroconversion, 21 days post vaccination)					No conclusion was drawn by the author Interpretations: on page 1 " One of the two new injectors demonstrated its ability to streamline intradermal fIPV administration, however, further investigations are needed to assess the potential contribution
	NFJIs			N-S	
	Injector X, (fIPV, ID)	**Injector Y (fIPV, ID)**	**Injector Z (fIPV, ID)**	**N-S (full dose IPV, IM)**	**BCG N-S (fIPV, ID)**
Type 1					
n/N	32/54	23/57	28/52	51/57	21/43

Main Study Findings	Authors' Conclusion

%, (95%CI)	59.3 (46.0, 71.3)	40.4 (28.6, 53.3)	53.8 (40.5, 6.7)	89.5 (78.9, 5.1)	48.8 (34.6, 3.2)
Type 2					
n/N	45/87	24/106	55/101	80/91	40/81
%, (95%CI)	51.7 (41.4, 61.9)	22.6 (15.7, 31.5)	54.5 (44.8, 3.8)	87.9 (79.6, 93.1)	49.4 (38.8, 0.0)
Type 3					
n/N	103/125	54/121	98/132	120/124	93/118
%, (95%CI)	82.4 (74.8, 88.1)	44.6 (36.1, 535.5)	74.2 (66.2, 0.9)	96.8 (92.0, 8.7)	78.8 (70.6, 5.2)

Injector X: conventional NFJI - Biojector 2000, (Bioject);

Injector Y: one new NFJI- prototype intradermal pen injector (Bioject);

Injector Z: one new NFJI - prototype Tropis (PharmaJet);

Note: seroconversion defined as from seronegative (<8) to seropositive (≥8); seropositive defined as reciprocal titres of poliovirus neutralizing antibody ≥8; boosting defined as ≥ 4-time increase in titres; Immune response indicated the combination of boosting and seroconversion

AEs:

Local reactions, such as redness, induration and infiltration, were more frequent in NFJI than in N-S.

	NFJIs			N-S	
	Injector X, (fIPV, ID)	**Injector Y (fIPV, ID)**	**Injector Z (fIPV, ID)**	**N-S (full dose IPV, IM)**	**BCG N-S (fIPV, ID)**
Local AEs:					
Redness, n (%)	8(5.5)	0(0)	1(0.7)	2 (1.4)	0(0)
Induration, n (%)	10(6.9)	3(2)	2(1.3)	0(0)	0(0)
Infiltration, n (%)	9(6.2)	4(2.6)	1(0.7)	0(0)	0(0)

Injector X: conventional NFJI - Biojector 2000, (Bioject);

Injector Y: one new NFJI- prototype intradermal pen injector (Bioject);

Injector Z: one new NFJI - prototype Tropis (PharmaJet);

of fIPV in the polio endgame plan."

Soonawala D, 2013[10]

Immunogenicity (28 days post vaccination)

Antibody level after IPV booster vaccination

At day 28	NFJIs		N-S	
	ID-JI-0.1ml	**IM-JI-0.5 ml**	**IM-N&S-0.1ml**	**IM-N&S-0.5 ml**
	n = 30	**n = 30**	**n = 30**	**n = 30**
IPV type 1	6.94 (6.02–7.87)	6.35 (5.83–6.86)b	6.06 (5.39–6.74)	7.14 (6.45–7.83)
IPV type 2	7.71 (6.88–8.55)	7.55 (6.89–8.21)	6.54 (5.70–7.38)	8.13 (7.27–9.00)
IPV type 3	6.19 (5.43–6.95)b	6.44 (5.60–7.28)	5.61 (4.52–6.71)	7.26 (6.32–8.21)

On page 3694: "Fractional-dose intradermal IPV booster vaccination using a PharmaJet injection system was well tolerated and immunogenic. Antibody titers in the fractional-dose intradermal group were slightly lower than after standard full-dose intramuscular vaccination…"

Main Study Findings	Authors' Conclusion

Note: Data presented with Mean log2 GMC with 95% confidence interval (IU/mL)

AEs

	ID-JI-0.1ml (n = 32)	IM-JI-0.5 ml (n = 30)	IM-NS-0.1 ml (n = 31)	IM-N&S-0.5 ml (n = 32)
Local AEs				
Erythema – n (%)	28 (88)	25 (83)	6 (19)	9 (28)
Swelling – n (%)	19 (59)	12 (40)	3 (10)	0
Induration – n (%)	11 (34)	11 (37)	3 (10)	3 (9)
Soreness vaccination site – n (%)	5 (16)c	17 (57)	15 (48)	16 (50)
Arm stiffness – n (%)	5 (16)d	9 (30)	11 (35)	13 (41)
Systemic adverse events				
Fever – n (%)	0	0	1 (3)	0
Myalgia – n (%)	3 (9)	3 (10)	4 (13)	2 (6)
Fatigue – n (%)	10 (31)	6 (20)	10 (32)	8 (25)
Headache – n (%)	8 (25)	6 (20)	9 (29)	6 (19)

Resik S, 2010[15]

Immunogenicity (30 days post 3rd dose vaccination)

Type of IPV	NFJI, ID, fIPV (N= 187)	N-S. IM full dose of IPV (N= 177)	P
Seroconversion rate (%)			
Type 1	52.9	89.3	<0.001
Type 2	85.0	95.5	0.001
Type 3	69.0	98.9	<0.001
Titer — median (95% CI)			
Type 1	19 (19-22)	85 (54-99)	<0.001
Type 2	45 (45-54)	214 (178-295)	<0.001
Type 3	32 (24-45)	295 (214-355)	<0.001

Note: Seroconversion was defined as a 4-fold increase in titer over expected decline in maternally derived antibody

AEs

local adverse effects (e.g., induration, pain, and redness at the inoculation site.

Local AEs after each dose

	Biojector, ID fIPV N= 187	NS. IM full dose of IPV N= 177
1st dose, n (%)	63 (33.5)	46 (25.7)
2nd dose, n(%)	36 (19)	36 (20)
3rd dose, n(%)	29(15.4)	17(9.5)

No systemic AEs were reported. No solicited AEs reported

On page 2: "This large-scale evaluation demonstrates the feasibility of fractional doses dermally as an antigen-sparing strategy but also shows that IPV given to infants at 6, 10, results in suboptimal immunogenicity (especially for the fractional doses arm."

Mohammed AJ, 2010[14]

Immunogenicity (at 7 months)

Type of IPV	NFJI, ID, fIPV (N= 187)	N- S, IM full dose of IPV (N= 186)	P

On page 2351: "These data show that fractional doses of inactivated poliovirus vaccine administered intradermally at 2, 4, and 6 months, as compared

Main Study Findings	Authors' Conclusion

Seroconversion rate (%) at 7 months			
Type 1	97.3	100.0	0.07
Type 2	95.7	100.0	0.01
Type 3	97.9	100	<0.13
Reciprocal titer — median (95% CI)			
Type 1	228 (144 – 287)	724 (575 – 912)	<0.001
Type 2	287 (228 – 456)	1149 (912 – 1149)	<0.001
Type 3	362 (287 – 456)	≥1448 (≥1448 – ≥1448)	<0.001

Note: Seroconversion was defined as a 4-fold increase in the antibody titer over the expected decline in the titer of maternally derived antibodies in a successive specimen.

AEs:

SAE

	NFJI, ID, fIPV (N= 187)	N- S, IM full dose of IPV (N= 186)	P
N of subjects with SAE	18	24	0.40
n of SAE			
Infection	39		No significant difference
Anemia	1		Not reported
Falls	2		

Note: SAE - all requiring hospitalisation; No additional AEs reported

with full doses of inactivated poliovirus vaccine given intramuscularly on the same schedule, induce similar levels of seroconversion but significantly lower titers."

MMR vaccination

Bavdekar A 2018[5]

Immunogenicity results (35 days post vaccination)

	Day 35		
	NFJI (n = 161)	N-S (n = 157)	Difference in percentage
Measles			
Seropositive subjects, N	157	155	-
Seropositive rate, %, 95% CI	97.5 (93.8, 9.3)	98.7 (95.5, 99.8)	1.2 (4.0, 6.4)
Mumps			
Seropositive subjects, N	159	155	-
Seropositive rate, %, 95% CI	98.8 (95.6, 9.8)	98.7 (95.5, 99.8)	- 0.1 (-5.0, 4.9)
Rubella			
Seropositive subjects, N	159	157	-
Seropositive rate, %, 95% CI	98.8 (95.6, 9.8)	100 (97.7,100.0)	1.2 (-3.7, 6.2)

percentage of seropositivity for all vaccine components was less than 10%; thus, the seropositivity of the MMR DFJI was non-inferior to that of the MMR, N-S .

Note: Seropositivity was defined as IgG antibody titers ≥1.10 immune status ratio (ISR), according to the levels given in the Trinity Biotech kit. For measles and rubella, antibody titers were converted from ISR to IU/ml per instructions in the Trinity Biotech kits. For mumps, the ISR values were used.

GMT

	Day 35		
	NFJI (n = 161)	N-S (n = 157)	p-Value
Measles (IU/ml)			
GMT, 95%CI	5.48 (3.71, 8.11)	5.94 (3.92, 9.01)	0.78
Mumps (ISR)			
GMT (95%CI)	3.83 (3.53, 4.14)	3.66(3.39, 3.95)	0.43

On Page 1220: "MMR vaccination via DSJI is as immunogenic as vaccination by N-S. Safety profile of DSJI method is similar to N-S except for injection site reactions which are more with DSJI and are well tolerated."

Main Study Findings	Authors' Conclusion

Rubella (IU/ml)			
GMT (95%CI)	95.27 (70.39, 128.95)	107.06(79.02, 145.06)	0.59

AEs: NFJI vs. NS

n of patients with at least one local AEs: 97 vs. 75
n of patients with at least with one systemic AEs: 51 vs. 46
n of solicited systemic AEs: 86 vs. 70

de Menezes Martins R, 2015[6]

Immunogenicity

Seroconversion rates and GMC for antibodies against measles, mumps, and rubella viruses (35 to 56 days post vaccination)

Antibody	Treatment (N of subjects)	Sero-conversion n (%)	GMC
Measles neutralizing titer (NT)	NS (182)	182 (100.0)	4996.75 mIU/mL
	DSJI (365)	331 (90.7)	3563.20 mIU/mL
	NS vs. NFJI	*(NS-NFJI) difference (95%CI)* 9.3 (5.9, 12.7)	*NS/NFJI ratio (95% CI)* 1.40 (1.19, 1.64)
Mumps IgG	NS (183)	140 (76.5)	661.20 U/mL
	NFJI (364)	226 (62.1)	422.27 U/mL
	NS vs. NFJI	*(NS-NFJI) difference (95%CI)* 14.4 (6.1, 22.7)	*NS/NFJI ratio (95% CI)* 1.57 (1.27, 1.92)
Rubella IgG	NS (184)	183 (99.5)	43.05 IU/mL
	NFJI (368)	365 (99.2)	42.47 IU/mL
	NS vs. NFJI	*(NS-NFJI) difference (95%CI)* 0.3 (−1.5, 2.1)	*NS/NFJI ratio (95% CI)* 1.01 (0.87, 1.18)

Note: Seroconversion was calculated separately for each vaccine antigen as the percentage of baseline-negative vaccines having a post-vaccination antibody level greater than or equal to the following cut-off levels:
• Anti-measles neutralizing titer (NT):≥200milli-international units per mL (mIU/mL) by PRNT;
• Anti-mumps Immunoglobulin G (IgG): ≥231 units/mL by ELISA, or if <231 units/mL by ELISA (Enzygnost® antiparotitis-virus/IgG, Siemens-Behring) and retested by PRNT, then a positive test at a dilution ≥1:10;
• Anti-rubella IgG: ≥4 IU/mL by ELISA (Enzygnost® antirubella-virus/IgG, Siemens-Behring).

Note: Non-inferiority was defined a priori as a difference of less than 10% on the upper limit of the 95% confidence interval (CI) for the difference in Seroconversion rates between the two treatment Groups (NS–NFJI).

AEs
Subjects with AEs (local and systemic AEs) in days 1 to day 10, n (%)
NFJI vs. N-S: 264 (78.8%) vs. 137 (80.6%)

(Local AEs including pain, erythema and swelling; Systemic AEs including fever, loss of appetite, sleepiness, rash, irritability)

On Page 7: "The DSJI is a promising technology with potential for use in mass immunization campaigns and for routine immunization programs in low- and middle-income countries. The use of a sterile, single-dose, disposable, non-reusable syringe in these devices eliminates the risk of blood-borne infections that can be associated with the use of a needle and syringe, and the use of a spring to power the injection makes the DSJI attractive for settings that lack access to other power sources. Parents found the G1 highly acceptable and vaccinators considered it easy to use. While the specific DSJI used in this study cannot be endorsed for use in immunization programs, and has been discontinued, our experiences and recommendations may inform future evaluations of newer DSJIs for routine infant immunizations."

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">DTP-HB-Hib vaccination</td></tr>
<tr><td colspan="2">Bavdekar A 2019[4]</td></tr>
<tr><td>

Immunogenicity

Combination of Seroprotection and seropositivity (4–6 weeks after the third dose vaccination)

Vaccine component	NFJI (N=61)	N -S (N=67)
Diphtheria, n (%)	61 (100.0)	64 (95.5)
Tetanus, n (%)	61 (100.0)	66 (98.5)
Pertussis, n (%)	36 (59.0)	41 (61.2)
Hepatitis B, n (%)	60 (98.4)	66 (98.5)
Hib, n (%)		
≥1.0 µg/mL (long-term protection)	56 (91.8)	62 (92.5)
≥0.15 µg/mL (short-term protection)	61 (100.0)	65 (97.0)

Note: Seroprotection was defined as IgG antibody concentration ≥0.1 IU/mL(diphtheria and tetanus), ≥10 mIU/mL (hepatitis B), and ≥0.15 mcg/mL for short-term protection and ≥1.0 mcg/mL for long-term protection (Hib). As there is no correlate of protection for pertussis, seropositivity was defined as>50 IU/mL as per the kit instructions.

AEs:
Subjects with at least one local reaction: NFJI: n = 102 (with 868 events); N-S: n = 103 (with 612 events)

Subjects with at least one systemic reaction: NFJI: N = 95 (with 595 events); N-S N = 97 (with 555 events)

Solicited systemic AEs:
NFJI: 95 subjects with 595 solicited AEs
N-S: 97 subjects with 555 solicited AEs

</td><td>

No conclusion was drawn by the authors.
On page 1: The author indicated that "Descriptive statistics indicate that seropositivity induced by vaccination with the DSJI was similar to that of N-S for all five antigens, Pentavalent vaccine includes whole-cell pertussis vaccine and an aluminum adjuvant, which may have contributed to the higher number of local reactions with the DSJI…"

Note: The study was terminated prematurely because of high frequency of local injection-site reactions in the NFJI group.

</td></tr>
<tr><td colspan="2">HPV vaccination</td></tr>
<tr><td colspan="2">Nelson EA, 2013[8]</td></tr>
<tr><td>

Immunogenicity

Subjects with seroconversion (35 days post 1st dose vaccination)

HPV vaccines - Cervarix				
Device/route	**NFJI, ID (N=4)**	**NS-ID (N=5)**	**NS-IM (N=5)**	**NS-IM (N=5)**
Dose	20%	20%	20%	Full
Seroconversion to HPV16, n	4	5	4	4
Seroconversion to HPV18, n	3	4	5	4
HPV vaccines - Gardasil				
Device/route	**NFJI, ID (N=6)**	**NS-ID (N=4)**	**NS-IM (N=5)**	**NS-IM (N=6)**
Dose	20%	20%	20%	Full
Seroconversion to HPV16, n	6	3	1	4
Seroconversion to HPV18, n	3	1	1	2

Note: seroconversion was defined as antibody titre ≥ 1:320 for both HPV16 and HPV18 by Day 95 i.e. 35 days after the 2nd vaccine dose.

</td><td>

On page 3458: "This pilot study suggests that a reduced-dose intradermal strategy for HPV vaccines may be feasible. Assuming that a larger study can demonstrate non-inferiority of at least one of the HPV vaccines, the main factor potentially limiting its wider use will be tolerability given the greater reactogenicity of intradermal administration. Intradermal HPV vaccination administered with needle-free jet injection devices warrants further evaluation."

</td></tr>
</table>

Main Study Findings	Authors' Conclusion
AEs: ***Local AEs*** (pain, tender-ness, peeling, swelling, firmness and itch) NFJI, ID vs. N-S, IM: No differences. (No data reported) ***Systemic AEs:*** NFJI, ID vs. N-S, IM: not reported	
BCG vaccination	
Geldenhuys. A 2015[12]	
Immunogenicity **Antigen-specific CD4 and CD8 T-cells** expressing IFN-γ, TNF-α, IL-2, and/or IL-17 NFJI, ID versus N-S, ID: In both adult and infants, no statistically significant differences were observed in either at 10 or at 14 weeks (Data presented in figure, not extractable). **AEs:** **<u>In adult:</u>** ***# of local AEs:*** NFJI: 126 in 15 subjects N-S: 146 in 15 subjects ***# of systemic AEs:*** NFJI: 18 in 15 subjects N-S: 27 in 15 subjects **<u>In infant:</u>** ***# of local AEs:*** NFJI: 138 in 33 subjects N-S: 141 in 33 subjects ***# of systemic AEs:*** NFJI: 20 in 33 subjects N-S: 20 in 33 subjects	On page 2: "BCG vaccination of newborn infants… safety, reactogenicity, and antigen-specific T-cell immune responses did not differ between DSJI and NS techniques."

AE = adverse events; DSJI = disposable-syringe jet injector; DTP = diphtheria – tetanus - pertussis vaccination; fIPV = Fractional dose of inactivated poliovirus vaccine; GMT = geometric mean titer; GMC = geometric mean concentration; HB = hepatitis B; HI= hemagglutination inhibition; Hib = Hemophilus influenzae type b conjugate (pentavalent) vaccination; ID = intradermal; IM = intramuscular; IPV = Inactivated poliovirus vaccine; ISR = immune status ratio; ITT = intention-to-treat; JI = jet injector; MD = multiple dose; MMR = measles-mumps-rubella vaccine; NFJI = Needle free jet injector; N-S = needle and syringe; RCT = Randomized controlled trial; SC = subcutaneously; SD = single dose.