REVIEW

Immunogenicity, safety and tolerability of intradermal influenza vaccines

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ABSTRACT

Intradermal influenza vaccination has been studied for more than 80 y. The revived interest in this strategy of vaccination is a result of the innovative technologies in needle design allowing more precise injection and making the device easier to use. Furthermore, clinical trials on these novel devices have demonstrated significant dose sparing effects, improved immunogenicity and very few adverse effects. This review compares intradermal vaccination with various devices with subcutaneous and intramuscular vaccination. We also discussed the role of topical adjuvant before intradermal vaccination.

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Introduction

Influenza infection causes half a million deaths globally every year.¹ Older adults, young children and patients with chronic illness are particularly at risk. Annual influenza vaccination is currently the most effective way of preventing influenza infection. Nevertheless, underlying immunosenescence or immunosuppression of these at-risk individuals minimizes the vaccine efficacy.^{2,3} Influenza vaccine mismatch secondary to antigenic drift further compromises the vaccine effect. Intradermal (ID) influenza vaccination has emerged as an important strategy to overcome such obstacles. The abundant antigen presenting cells, including the dendritic and Langerhans cells presence in the dermis facilitate the vaccine antigens uptake to the regional lymph nodes, thereby stimulating the T and B cells to differentiate.

Various studies have demonstrated the safety and non-inferior if not better clinical efficacy of ID influenza vaccination.^{4–9} Furthermore, reduced dosage ID demonstrated equally good antibody response.⁴ In fact, ID immunization has been practiced for many years. Edward Jenner was the first to use ID cowpox vaccination for the prevention of smallpox in early 19th century.¹⁰ One hundred years later, Calmette and Guérin developed the attenuated Bacille Calmette-Guérin (BCG) vaccine where tuberculin was given intradermally by the Mantoux technique.¹¹ In 1961, Benjamin Rubin further improved the ID inoculation of smallpox vaccine by using the bifurcated needle.¹² Apart from influenza, smallpox¹³ and BCG,¹⁴ other viruses including hepatitis A¹⁵ and B,^{16,17} rabies,¹⁸ tick-borne encephalitis,¹⁹ measles²⁰ and inactivated polio²¹ ID vaccines have been studied. In this article, we review the immunogenicity, safety and tolerability of ID influenza vaccines delivered by various devices.

Conventional needle

Immunogenicity

The early ID influenza vaccination was given via the conventional needle. Francis et al performed the first ID influenza vaccination study in 1936,²² demonstrating similar immunogenicity between the ID and subcutaneous (SC) route. In the 1940s, Van Gelder et al compared a single and reduced dose of 0.1 mL intradermal combined Type A and B influenza vaccination with 2 doses of 0.1 mL ID influenza vaccination given 2 weeks apart, and single dose of 1 mL subcutaneous vaccination in 1953 naval personnel.²³ The single dose intradermal vaccination resulted in the highest mean antibody titer when compared with the 2 doses intradermal or the single higher dose SC vaccination. Further studies by Bruyn et al showed similar results with higher mean titer rise for adults receiving the single 0.1 mL ID and the children receiving the 2 doses 0.1 mL ID vaccination, for both the PR8 and Lee strains, when compared with the full dose 1 mL SC vaccination.^{24,25} Subsequent trials with the Asian (A/Japan/305) strain by Hilleman, Sanger and Sigel showed equivalent immunogenicity with both routes.^{26–28} In addition, Kirkham reported similar clinical effectiveness between the 2 routes during influenza outbreak in Mason City, Iowa in 1957.²⁹ Studies by Philip and Marks using the A2/IACHI/2/68 vaccine showed similar seroconversion rate between the ID and SC route.^{30,31} Nevertheless, the study by Philip showed a significantly higher geometric mean titers (GMT) achieved with the SC route, when compared with the ID or nasal routes. Later study by Halperin with the bivalent “split virus” influenza vaccine containing the influenza A/New Jersey/76 and A/Victoria/75 strains also showed similar efficacy with the 2 routes.³² On the contrary, study by Appleby in 40

nurses and 18 R.A.F. pilots showed significantly higher GMT of 1350 and antibody rise of 23.6 via the SC route, comparing to GMT of 540 and antibody rise of 6.5 via the ID route, using the PR8 vaccine.³³ Vaccination with the PR8 vaccine by either route failed to demonstrate heterologous protection against a non-vaccine strain of the NED virus. Another study by Boger also showed better seroprotection with the SC vaccination with the Asian (Japan/305) strain in the elderly population.³⁴

More recent studies replaced the SC by intramuscular (IM) vaccination. An open-label study by Belshe published in 2004, randomized 119 healthy adult subjects to receive an ID injection of reduced dose of trivalent inactivated influenza vaccine, containing 6 μg of hemagglutinin for each antigen, and equal number to receive IM injection of 15 μg of hemagglutinin for each antigen.³⁵ The needle used for ID vaccination was a conventional beveled needle, protruded by 1.5 mm from a plastic disk to limit skin penetration. Once again, the immunogenicity was similar between the ID and IM groups, achieving 100% seroprotection rate in both groups and equivalent GMT and seroconversion rate. Similar study performed by Kenney with an even lower dose ID vaccination of 3 μg of hemagglutinin for each antigen, in young healthy adults 18–40 y of age, demonstrated similar to or better than that of IM vaccination.³⁶

Safety and adverse reactions

Overall, these earlier studies showed that both ID and SC vaccination routes were safe. Earlier study showed greater incidence of mild local reactions with the intradermal route, while the subcutaneous route had more severe local and systemic reactions.²³ Later studies however, showed similar systemic side effects.³² The most recent studies showed similar systemic side effects between the ID or IM routes but conflicting results on the local side effects,^{33,34} with more studies suggesting more local side effects with the ID routes. Nevertheless, all local reactions were mild and transient.

The soluvia needle

Immunogenicity

Intanza® (Sanofi Pasteur) is a prefilled, single-dose, seasonal influenza vaccine for ID injection.³⁷ The vaccine was delivered by the Becton Dickinson Soluvia microinjection system with a single 1.5 mm needle penetrating perpendicular to the skin into the ID region. The prefilled syringe consisted of 2 dosages, a reduced dose of 9 μg or full dose of 15 μg concentrated in 0.1 mL. Various studies have compared the immunogenicity of Intanza® 9 μg or 15 μg ID vaccination with IM vaccination. ID vaccination with both doses showed non-inferior or even higher immunogenicity in both young and older adults.^{38–46} In addition, 3 studies demonstrated cross-protection of the Intanza® 15 μg against heterologous non-vaccine containing A/H3N2 strains in older adults.^{39,41,44}

Safety and adverse reactions

Local adverse effects were more frequent with ID vaccination with the Soluvia needle when compared with the IM

vaccination but were mild and resolved within 72 hours.^{38–46} There were no differences in the occurrence of systemic side effects. Various surveys among general practitioners, the general public and health care workers showed preference toward using ID vaccination with the Soluvia needle than IM vaccination.^{47–51}

The micronjet needle

Immunogenicity

The MicronJet is a microneedle device designed by the Nanopass™.⁵² The device can be attached to any standard luer-lock syringe. There are 2 versions of the MicronJet™ needle device. The original device has 4 microneedles that were 450 μm length, requiring insertion at 60° and lowering the syringe while in skin to 30°. The improved version of the MicronJet600 has only 3 pyramid-shaped microneedles of 600 μm length, requiring insertion at 45° with no subsequent adjustment of position.⁴⁰

The initial phase I/II trial with the original MicronJet device was tested in healthy adults, using the commercially available Fluarix 2006/2007 influenza vaccine (GSK).⁵³ ID vaccination with the 3 μg HA/strain and 6 μg HA/strain was compared with the 15 μg HA/strain, delivered IM with a standard 26G needle. Similar immunogenicity was demonstrated between the low dose ID and the IM group with 5-fold dose sparing. A second study during the 2009 swine flu pandemic used the A/2009/H1N1 monovalent vaccine also demonstrated similar efficacy and dose sparing effect.⁵⁴ Further study performed in the immunosenescence elderly subjects using both the unadjuvanted influenza vaccine (Fluvirin™, Novartis) and the MF-59-adjuvanted vaccinations.⁵⁵ ID vaccination with the unadjuvanted formulation showed higher immunogenicity in the A/H1N1 strain and non-inferior GMT in the A/H3N2 and B strains, when compared with the unadjuvanted IM vaccination given at 5 times the dosage. Although the adjuvanted IM vaccination showed higher GMT than the unadjuvanted ID vaccination in the A/H1N1 and B strains, the dosage was 2.5 times higher in the adjuvanted formulation. A phase II study conducted in 2010 in Hong Kong compared the MicronJet600 device against the Intanza device head to head. The study compared the 3 μg HA/strain or 9 μg HA/strain delivered intradermally via the MicronJet600, with the ID Intanza9 (9 μg HA/strain) and the conventional IM Fluzone (15 μg HA/strain). The study demonstrated that both ID vaccinations generated better immunogenicity than the IM vaccination, with no significant difference in immune response between the 2 ID vaccine devices.⁴⁰ The latest study using the virosomal influenza vaccines (Inflexal V™) also showed better immunogenicity when the vaccine was administered via the ID route with the MicronJet600 device in the elderly.⁵⁶

Safety and adverse reactions

ID vaccination with the MicronJet device was generally safe. Local adverse effects including erythema and swelling were more frequent with the ID device when compared with the IM vaccination but were self-limiting.^{53–56} Questionnaire showed that vaccinees felt less painful and more acceptable to use the

MicronJet device when compared with the conventional IM needle.⁵⁷ Systemic adverse events were similar between both the ID and IM routes.

Intradermal vaccination with topical imiquimod pretreatment

Imiquimod is a synthetic Toll-like receptor 7 (TLR7) agonist used for the treatment of DNA virus infection, especially in the treatment of dermatological human papillomavirus infection.⁵⁸ Study from our center has demonstrated imiquimod improve vaccine immunogenicity against influenza virus in mouse model.⁵⁹ Lately, a double blind randomized controlled trial with topical 5% imiquimod ointment pretreatment before ID influenza vaccination with the Intanza® 15 µg was performed by our team.⁶⁰ The topical imiquimod ointment was applied to a marked 16cm² square on the deltoid 5 minutes before vaccination. The intradermal vaccine was injected in the center of the marked area after the ointment was fully absorbed. Participants were instructed to keep the ointment for at least 6 hours after vaccination. Results from this study demonstrated significantly better immunogenicity in seroconversion, seroprotection and geometric mean titer (GMT)-fold at day 7, 21 and 1 y when compared with ID Intanza® 15 µg alone or IM vaccination with the same dosage. The improved immunogenicity was most remarkable on the day 7 seroconversion rate and GMT-fold increase in all 3 influenza strains (influenza A/California/07/2009 (H1N1)-like virus, influenza A/Perth/16/2009-like virus and influenza B/Brisbane/60/2008-like virus). The superior immunogenicity was maintained up to 1 y in all 3 virus strains in the seroconversion rate and GMT-fold increase. The improved immunogenicity also translated into better clinical protection with fewer hospitalizations for influenza or pneumonia. Local side effects including grade 2 redness and grade 1 swelling and pain were significantly higher in the imiquimod and intradermal vaccination group. There were no differences in systemic side effects. All adverse events were self-limiting.

Subsequently, we performed a second double blind randomized controlled trial with similar strategy on young healthy adults.⁶¹ The results demonstrated significantly better immunogenicity on day 7 and 21 with topical imiquimod before ID Intanza® 15 µg against the 3 vaccine strains (influenza A/California/07/2009 (H1N1)-like virus, influenza A/Victoria/361/2011 (H3N2)-like virus and influenza B/Massachusetts/2/2012-like virus). Furthermore, it demonstrated significantly better immunogenicity in all 3 parameters of seroprotection, seroconversion and GMT fold increase on day 7 and 21 after vaccination, against 4 heterologous non-vaccine influenza strains, including the antigenically drifted A/HK/485197/14 (H3N2 Switzerland-like lineage), prototype A/WSN/1933 (H1N1), A/HK/408027/09 (prepandemic seasonal H1N1) and B/HK/418078/11 (Victoria lineage). Fewer young subjects experienced local or systemic adverse events when compared with the elderly cohorts, with no differences between the imiquimod/ID vaccination group and the IM group. This could be related to the relatively fragile and thinner ID skin layer in the elderly patients.

Therefore, pretreatment with topical imiquimod significantly expedited, augmented and prolonged the efficacy of

influenza vaccination. Most important of all, it translated into better clinical protection and offered protection against heterologous non-vaccine influenza viruses.

Meta-analysis of intradermal influenza vaccine

Four recent meta-analysis investigated the immunogenicity and adverse events of ID influenza vaccination. The first study by Young et al. analyzed 13 randomized, controlled, open-label trials.⁵ Seven out of 8 studies for 18–60-year old and 4 out of 6 studies showed comparable efficacy between ID and IM vaccination, while 2 out of 6 studies in the over 60-year old showed superior efficacy for ID vaccination. Local adverse events including erythema, swelling, induration and pruritus in the first 7 d were more frequent in ID vaccination. Another meta-analysis by Marra et al. investigated the immunogenicity of ID vaccination against specific influenza vaccine strains. The pooled immunogenicity outcomes of 13 trials showed no difference in seroconversion, seroprotection and GMT rise against the A/H1N1 and B strains between ID and IM vaccination.⁶ A lower pooled seroconversion and seroprotection rate against A/H3N2 strain was found in ID vaccination, with comparable GMT rise. A higher dose of ID vaccine in the older population improved the immunogenicity. Once again, ID vaccination was associated with higher incidence of local events within 7 d post-vaccination. The last 2 meta-analysis by Pleggi et al. showed similar seroprotection rate for all 3-vaccine strains in both immunocompromised and elderly patients.^{8,9} There was no difference in systemic side effects but significantly more local injection site reactions in the ID vaccination group.

Lessons learned from the meta-analysis

Overall, these meta-analysis suggested a non-inferior immunogenicity and efficacy with the reduced dose 3 µg or 9 µg ID vaccination, when compared with the full-dose 15 µg IM influenza vaccination regardless of age. However, when the ID vaccine dose is increased to 15 µg, which is the same dosage as the conventional IM vaccination, ID vaccination showed significantly better immunogenicity, suggesting that the immunological response is dose-related. Immediate local (i.e. erythema, induration and ecchymosis) and systemic (i.e., fever, malaise and lethargy) adverse reactions were similar between the 2 strategies. Late local adverse events including beyond 1 week were consistently higher in the ID vaccination group, which was self-limiting. The ID vaccination strategy should be adopted in both elderly and immunocompromised patients.

Discussions

The strategy of ID influenza vaccination has been used for more than 80 y. Multiple studies and meta-analysis have demonstrated its non-inferior to superior immunogenicity and clinical efficacy, with excellent safety profile and tolerability among the vaccinees. Nevertheless, this route of vaccination is still underused in the clinic. This is likely to be related to the following reasons. Firstly, ID administration of vaccine requires special training and experience, especially when using the

Mantoux technique. Secondly, the vaccine has to be prepared and drawn into another syringe before vaccination.

In spite of these hurdles, there are several major reasons why ID influenza vaccination should replace the conventional IM vaccination. Firstly, full dose ID vaccination, especially with the topical imiquimod pretreatment, has been demonstrated to significantly expedite, improve and prolong the influenza vaccine immunogenicity, in both the young and the elderly subjects. Secondly, such strategy has been proven to offer heterologous protection against non-vaccine contained or antigenically drifted influenza virus. Thirdly, ID influenza vaccines have similar immunogenicity and safety at reduced doses compared with full dose IM vaccination. Therefore, ID influenza vaccination may be a strategy to increase availability of the vaccine to more people, especially during influenza pandemics, when there is a shortage of vaccine supply. Fourthly ID vaccination can be administered to patients on anticoagulants when IM vaccination is contraindicated. Fifthly, other new injection systems with various types of microneedles and prefilled-dosage syringe, and other needle-free vaccine patch are under trials. Personally, I found that intradermal injection techniques with both the Soluvia and MicronJet needles were easy to master. These new systems should attract both medical practitioners and patients to opt for intradermal influenza vaccination. Finally, and most important of all, such superior immunogenicity with ID vaccination and topical imiquimod pretreatment has been shown to translate into better clinical protection with fewer hospitalization for influenza and pneumonia.

Conclusions

ID influenza vaccination with topical imiquimod pretreatment should be promoted and encouraged. This strategy of annual influenza vaccination is of utmost importance for elderly subjects with immunosenescence and immunocompromised patients for various reasons. Further studies with topical imiquimod pretreatment and improved microneedle with prefilled full-dose quadrivalent influenza vaccine might attract more clinical practitioners,⁶² the general public and health care workers to adopt the ID vaccination.

Disclosure of potential conflicts of interest

Author IFNH acts as advisory board member and received travel grant/speaker honorarium from the following organizations: Pfizer, AstraZeneca, GSK, MSD, Sanofi Pasteur and Gilead.

References

- [1] World Health Organization. Media centre. Influenza (Seasonal). Fact sheet, November, 2016. Available at: <http://www.who.int/media-centre/factsheets/fs211/en/> (accessed June 17, 2017)
- [2] Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. *N Engl J Med* 2007; 357:1373-81; PMID:17914038; <https://doi.org/10.1056/NEJMoa070844>
- [3] Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. *Ann Intern Med* 1995; 123:518-27; PMID:7661497; <https://doi.org/10.7326/0003-4819-123-7-199510010-00008>
- [4] Ansaldi F, Durando P, Icardi G. Intradermal influenza vaccine and new devices: a promising chance for vaccine improvement. *Expert Opin Bio Ther* 2011; 11:415-27; <https://doi.org/10.1517/14712598.2011.557658>
- [5] Young F, Marra F. A systematic review of intradermal influenza vaccines. *Vaccine* 2011; 29:8788-801; PMID:21968444; <https://doi.org/10.1016/j.vaccine.2011.09.077>
- [6] Marra F, Young F, Richardson K, Marra CA. A meta-analysis of intradermal versus intramuscular influenza vaccines: immunogenicity and adverse events. *Influenza Other Respir Viruses* 2013; 7:584-603; PMID:22974174; <https://doi.org/10.1111/irv.12000>
- [7] Camilloni B, Basileo M, Valentini S, Nunzi E, Iorio AM. Immunogenicity of intramuscular MF59-adjuvanted and intradermal administered influenza enhanced vaccines in subjects aged over 60: A literature review. *Hum Vaccin Immunother* 2015; 11:553-63; PMID:25714138; <https://doi.org/10.1080/21645515.2015.1011562>
- [8] Pileggi C, Mascaro V, Bianco A, Nobile CG, Pavia M. Immunogenicity and Safety of Intradermal Influenza Vaccine in the Elderly: A Meta-analysis of randomized controlled trials. *Drugs Aging* 2015; 32:857-69; PMID:26442860; <https://doi.org/10.1007/s40266-015-0303-8>
- [9] Pileggi C, Lotito F, Bianco A, Nobile CG, Pavia M. Immunogenicity and safety of intradermal influenza vaccine in immunocompromised patients: a meta-analysis of randomized controlled trials. *BMC Infect Dis* 2015; 15:427; PMID:26466898; <https://doi.org/10.1186/s12879-015-1161-z>
- [10] Gross CP, Sepkowitz KA. The myth of the medical breakthrough: smallpox, vaccination, and Jenner reconsidered. *IJID* 1998; 3:54-60; PMID:9831677
- [11] Calmette A. Preventive vaccination against tuberculosis with BCG. *Proc R Soc Med* 1931; 24:1481; PMID:19988326
- [12] Rubin BA. A note on the development of the bifurcated needle for smallpox vaccination. *WHO Chron* 1980; 34:180-1; PMID:7376638
- [13] Baxby D. Smallpox vaccination techniques; from knives and forks to needles and pins. *Vaccine* 2002; 20:2140-9; PMID:11972983; [https://doi.org/10.1016/S0264-410X\(02\)00028-2](https://doi.org/10.1016/S0264-410X(02)00028-2)
- [14] Salisbury DM, Begg NT. Tuberculosis: BCG immunization. In: *Immunization against infectious disease*. London: HMSO, 1996:219-41. Available at: http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_113539.pdf (accessed June 17, 2017)
- [15] Frösner G, Steffen R, Herzog C. Viroosomal hepatitis A vaccine: comparing intradermal and subcutaneous with intramuscular administration. *J Travel Med* 2009; 16:413-9; PMID:19930383; <https://doi.org/10.1111/j.1708-8305.2009.00351.x>
- [16] Sangare L, Manhart L, Zehrung D, Wang CC. Intradermal hepatitis B vaccination: a systematic review and meta-analysis. *Vaccine* 2009; 27:1777-86; PMID:19200451; <https://doi.org/10.1016/j.vaccine.2009.01.043>
- [17] Braddick MR. Intradermal hepatitis B vaccine. *Lancet* 1989; 1:957-8; [https://doi.org/10.1016/S0140-6736\(89\)92533-6](https://doi.org/10.1016/S0140-6736(89)92533-6)
- [18] Fishbein DB, Pacer RE, Holmes DF, Ley AB, Yager P, Tong TC. Rabies pre exposure prophylaxis with human diploid cell rabies vaccine: a dose-response study. *J Infect Dis* 1987; 156:50-5; PMID:3598225; <https://doi.org/10.1093/infdis/156.1.50>
- [19] Zoulek G, Roggendorf M, Deinhardt F, Kunz C. Different immune responses after intradermal and intramuscular administration of vaccine against tick borne encephalitis virus. *J Medical Virol* 1986; 19:55-61; PMID:3701303; <https://doi.org/10.1002/jmv.1890190109>
- [20] Whittle HC, Rowland MG, Mann GF, Lamb WH, Lewis RA. Immunisation of 4-6 month old Gambian infants with Edmonston-Zagreb measles vaccine. *Lancet* 1984; 2:834-7; [https://doi.org/10.1016/S0140-6736\(84\)90873-0](https://doi.org/10.1016/S0140-6736(84)90873-0)
- [21] Mohammed AJ, AlAwaidey S, Bawikar S, Kurup PJ, Elamir E, Shaban MM, Sharif SM, van der Avoort HG, Pallansch MA, Malankar P,

- et al. Fractional doses of inactivated poliovirus vaccine in Oman. *N Engl J Med* 2010; 362:2351-9; PMID:20573923; <https://doi.org/10.1056/NEJMoa0909383>
- [22] Francis T, Magill T. The antibody response of human subjects vaccinated with the virus of human influenza. *J Exp Med* 1937; 65:251; PMID:19870599; <https://doi.org/10.1084/jem.65.2.251>
- [23] Van Gelder D, Greenspan F, Dufresne N. Influenza vaccination: comparison of intracutaneous and subcutaneous methods. *Naval Med Bulletin* 1947; 47:197
- [24] Bruyn H, Meikeljohn G, Brainerd H. Influenza vaccination: A comparison of antibody response obtained by various methods of administration. *J Immunol* 1949; 62:1; PMID:18131592
- [25] Bruyn H, Meikeljohn G, Brainerd H. Influenza vaccine. *Amer J Dis Child* 1949; 77:149; <https://doi.org/10.1001/archpedi.1949.02030040158001>
- [26] Hilleman M, Flatley F, Anderson S, Luecking ML, Levinson DJ. Antibody response in volunteers to Asian influenza vaccine. *JAMA* 1958; 166:1134; <https://doi.org/10.1001/jama.1958.02990100022005>
- [27] Sanger M. Immunization after intradermal and subcutaneous injection of Asian influenza vaccine. *Ann Allergy* 1959; 17:173; PMID:13650417
- [28] Beasley AR, Sigel MM, Schlaepfer GG, Edwards HK, Mangels M Jr, Wellings FM. Antibody responses of children to Asian influenza vaccine. *J Fla Med Assoc* 1960; 46:1367-71
- [29] Kirkham L. Asiatic influenza in a midwestern town. *J Iowa Med Soc* 1958; 45:593
- [30] Philips C, Forsyth B, Christmas W, Gump DW, Whorton EB, Rogers I, Rudin A. Purified influenza vaccine: clinical and serologic responses to varying doses and different routes of immunization. *J Infect Dis* 1970; 122:26; PMID:5433710; <https://doi.org/10.1093/infdis/122.1-2.26>
- [31] Marks M, Eller J. Intradermal influenza immunization. *Am Rev Respir Dis* 1971; 103:579; PMID:5550353
- [32] Halperin W, Weiss WI, Altman R, Diamond MA, Black KJ, Iaci AW, Black HC, Goldfield M. A comparison of the intradermal and subcutaneous routes of influenza vaccination with A/New Jersey/76 (swine flu) and A/Victoria/75: report of a study and review of the literature. *Am J Public Health* 1979; 1247-50; PMID:507256; <https://doi.org/10.2105/AJPH.69.12.1247>
- [33] Appleby JC, Himmelweit F, Stuart-Harris CH. Immunization with influenza virus A vaccines. Comparison of intradermal and subcutaneous routes. *Lancet* 1951; 1:1384-7; PMID:14842090; [https://doi.org/10.1016/S0140-6736\(51\)92840-1](https://doi.org/10.1016/S0140-6736(51)92840-1)
- [34] Boger W, Liu O. Subcutaneous and intradermal vaccination with Asian vaccine. *JAMA* 1975; 165:1687; <https://doi.org/10.1001/jama.1957.72980310001010>
- [35] Belshe RB, Newman FK, Cannon J, Duane C, Treanor J, Van Hoecke C, Howe BJ, Dubin G. Serum antibody responses after intradermal vaccination against influenza. *N Engl J Med* 2004; 351:2286-94; PMID:15525713; <https://doi.org/10.1056/NEJMoa043555>
- [36] Kenney RT, Frech SA, Muenz LR, Villar CP, Glenn GM. Dose sparing with intradermal injection of influenza vaccine. *N Engl J Med* 2004; 351:2295-301; PMID:15525714; <https://doi.org/10.1056/NEJMoa043540>
- [37] Altmar RL, Patel SM, Keitel WA. Intanza®: a new intradermal vaccine for seasonal influenza. *Expert Rev Vaccines* 2010; 9:1399-40; PMID:21105776; <https://doi.org/10.1586/erv.10.134>
- [38] Ansaldi F, Durando P, Icardi G. Intradermal influenza vaccine and new devices: a promising chance for vaccine improvement. *Expert Opin Bio Ther* 2011; 11:415-27; <https://doi.org/10.1517/14712598.2011.557658>
- [39] Ansaldi F, Canepa P, Ceravolo A, Valle L, de Florentiis D, Oomen R, Vogel FR, Denis M, Samson SI, Icardi G. Intanza® 15 mg intradermal influenza vaccine elicits cross-reactive antibody responses against heterologous A(H3N2) influenza viruses. *Vaccine* 2012; 30:2908-13; PMID:22342501; <https://doi.org/10.1016/j.vaccine.2012.02.003>
- [40] Hung IF, Levin Y, To KK, Chan KH, Zhang AJ, Li P, Li C, Xu T, Wong TY, Yuen KY. Dose sparing intradermal trivalent influenza (2010/2011) vaccination overcomes reduced immunogenicity of the 2009 H1N1 strain. *Vaccine* 2012; 30:6427-35; PMID:22910287; <https://doi.org/10.1016/j.vaccine.2012.08.014>
- [41] Ansaldi F, Orsi A, de Florentiis D, Parodi V, Rappazzo E, Coppelli M, Durando P, Icardi G. Head-to-head comparison of an intradermal and a virosome influenza vaccine in patients over the age of 60: evaluation of immunogenicity, cross-protection, safety and tolerability. *Hum Vaccin Immunother* 2013; 9:591-8; <https://doi.org/10.4161/hv.23240>
- [42] Leroux-Roels I, Weber F. Intanza® 9 µg intradermal seasonal influenza vaccine for adults 18 to 59 years of age. *Hum Vaccin Immunother* 2013; 9:115-21; PMID:23442585; <https://doi.org/10.4161/hv.22342>
- [43] Hoon Han S, Hee Woo J, Weber F, Joo Kim W, Ran Peck K, Il Kim S, Hwa Choi Y, Myung Kim J. Immunogenicity and safety of Intanza®/IDflu® intradermal influenza vaccine in South Korean adults: a multicenter, randomized trial. *Hum Vaccin Immunother* 2013; 9:1971-7; PMID:23778938; <https://doi.org/10.4161/hv.25295>
- [44] Camilloni B, Basileo M, Di Martino A, Donatelli I, Iorio AM. Antibody responses to intradermal or intramuscular MF59-adjuvanted influenza vaccines as evaluated in elderly institutionalized volunteers during a season of partial mismatching between vaccine and circulating A(H3N2) strains. *Immun Ageing* 2014; 11:10; PMID:24860610; <https://doi.org/10.1186/1742-4933-11-10>
- [45] Chan TC, Hung IF, Chan KH, Li CP, Li PT, Luk JK, Chu LW, Chan FH. Immunogenicity and safety of intradermal trivalent influenza vaccination in nursing home older adults: a randomized controlled trial. *J Am Med Dir Assoc* 2014; 15:60; <https://doi.org/10.1016/j.jamda.2014.07.014>
- [46] Camilloni B, Basileo M, Valente S, Nunzi E, Iorio AM. Immunogenicity of intramuscular MF59-adjuvanted and intradermal administered influenza enhanced vaccines in subjects aged over 60: A literature review. *Hum Vaccin Immunother* 2015; 11:553-63; PMID:25714138; <https://doi.org/10.1080/21645515.2015.1011562>
- [47] Arnou R, Frank M, Hagel T, Prébet A. Willingness to vaccinate or get vaccinated with an intradermal seasonal influenza vaccine: a survey of general practitioners and the general public in France and Germany. *Adv Ther* 2011; 28:555-65; PMID:21626269; <https://doi.org/10.1007/s12325-011-0035-z>
- [48] Eizenberg P, Booy R, Naser N, Mason G, Stamboulia D, Weber F. Acceptance of Intanza® 9 µg intradermal influenza vaccine in routine clinical practice in Australia and Argentina. *Adv Ther* 2011; 28:640-9; PMID:21751080; <https://doi.org/10.1007/s12325-011-0042-0>
- [49] Prymula R, Usluer G, Altinel S, Sichova R, Weber F. Acceptance and opinions of Intanza/IDflu intradermal influenza vaccine in the Czech Republic and Turkey. *Adv Ther* 2012; 29:41-52
- [50] Dhont PA, Albert A, Brenders P, Podwipinska A, Pollet A, Scheveneels D, Tihon F, Verheyden I, Victor J, Samson SI. Acceptability of Intanza® 15 µg intradermal influenza vaccine in Belgium during the 2010-2011 influenza season. *Adv Ther* 2012; 29:562-77; PMID:22678831; <https://doi.org/10.1007/s12325-012-0025-9>
- [51] Coleman BL, McNeil SA, Langley JM, Halperin SA, McGeer AJ. Differences in efficiency, satisfaction and adverse events between self-administered intradermal and nurse-administered intramuscular influenza vaccines in hospital workers. *Vaccine* 2015; 33:6635-40; PMID:26529074; <https://doi.org/10.1016/j.vaccine.2015.10.095>
- [52] Gardeniers HJ, Luttge R, Berenschot EJ, de Boer MJ, Yeshurun SY, Hefetz M, van't Oever R, van den Berg A. Silicon micromachined hollow microneedles for transdermal liquid transport. *J Microelectromech Syst* 2003; 12:855-62; <https://doi.org/10.1109/JMEMS.2003.820293>
- [53] Van Damme P, Oosterhuis-Kafeja F, Van der Wielen M, Almagor Y, Sharon O, Levin Y. Safety and efficacy of a novel microneedle device for dose sparing intra-dermal influenza vaccination in healthy adults. *Vaccine* 2009; 27:454-9; PMID:19022318; <https://doi.org/10.1016/j.vaccine.2008.10.077>
- [54] Hung IF, Levin Y, To KK. Quantitative and qualitative analysis of antibody response after dose sparing intradermal 2009 H1N1 vaccination. *Vaccine* 2012; 30:2707-8; <https://doi.org/10.1016/j.vaccine.2011.12.069>

- [55] Della Cioppa G, Nicolay U, Lindert K, Leroux-Roels G, Clement F, Castellino F, Galli C, Groth N, Levin Y, Del Giudice G. A dose-range study in older adults to compare the safety and immunogenicity profiles of MF59[®]-adjuvanted and non-adjuvanted seasonal influenza vaccines following intradermal and intramuscular administration. *Hum Vaccines Immunotherapeutics* 2014; 10(6):1701-10; <https://doi.org/10.4161/hv.28618>
- [56] Levin Y, Kochba E, Shukarev G, Rusch S, Herrera-Taracena G, van Damme P. A phase 1, open-label, randomized study to compare the immunogenicity and safety of different administration routes and doses of virosomal influenza vaccine in elderly. *Vaccine* 2016; 34:5262-72; PMID:27667332; <https://doi.org/10.1016/j.vaccine.2016.09.008>
- [57] Levin Y, Kochba E, Hung I, Kenney R. Intradermal vaccination using the novel microneedle device MicronJet600: Past, present, and future. *Hum Vaccin Immunother* 2015; 11:991-7; PMID:25745830; <https://doi.org/10.1080/21645515.2015.1010871>
- [58] Chen XZ, Mao XH, Zhu KJ, Jin N, Ye J, Cen JP, Zhou Q, Cheng H. Toll like receptor agonists augment HPV 11 E7-specific T cell responses by modulating monocyte-derived dendritic cells. *Arch Dermatol Res* 2010; 302:57-65; PMID:19578865; <https://doi.org/10.1007/s00403-009-0976-0>
- [59] Zhang AJ, Li C, To KK, Zhu HS, Lee AC, Li CG, Chan JF, Hung IF, Yuen KY. TLR7 agonist imiquimod in combination with influenza vaccine expedite and augment humoral immune responses against influenza A(H1N1)pdm09 infection in BALB/c mice. *Clin Vaccine Immunol* 2014; 21:570-9; PMID:24521786; <https://doi.org/10.1128/CVI.00816-13>
- [60] Hung IF, Zhang AJ, To KK, Chan JF, Li C, Zhu HS, Li P, Li C, Chan TC, Cheng VC, et al. Immunogenicity of intradermal trivalent influenza vaccine with topical imiquimod: a double blind randomized controlled trial. *Clin Infect Dis* 2014; 59:1246-55; PMID:25048848; <https://doi.org/10.1093/cid/ciu582>
- [61] Hung IF, Zhang AJ, To KK, Chan JF, Li P, Wong TL, Zhang R, Chan TC, Chan BC, Wai HH, et al. Topical imiquimod before intradermal trivalent influenza vaccine for protection against heterologous non-vaccine and antigenically drifted viruses: a single-centre, double-blind, randomised, controlled phase 2b/3 trial. *Lancet Infect Dis* 2016; 16:209-18; PMID:26559482; [https://doi.org/10.1016/S1473-3099\(15\)00354-0](https://doi.org/10.1016/S1473-3099(15)00354-0)
- [62] Bragazzi NL, Orsi A, Ansaldi F, Gasparini R, Icardi G. Fluzone[®] intra-dermal (Intanza[®]/Istivac[®] Intra-dermal): An updated overview. *Hum Vaccin Immunother* 2016; 12:2616-27; PMID:27246556; <https://doi.org/10.1080/21645515.2016.1187343>