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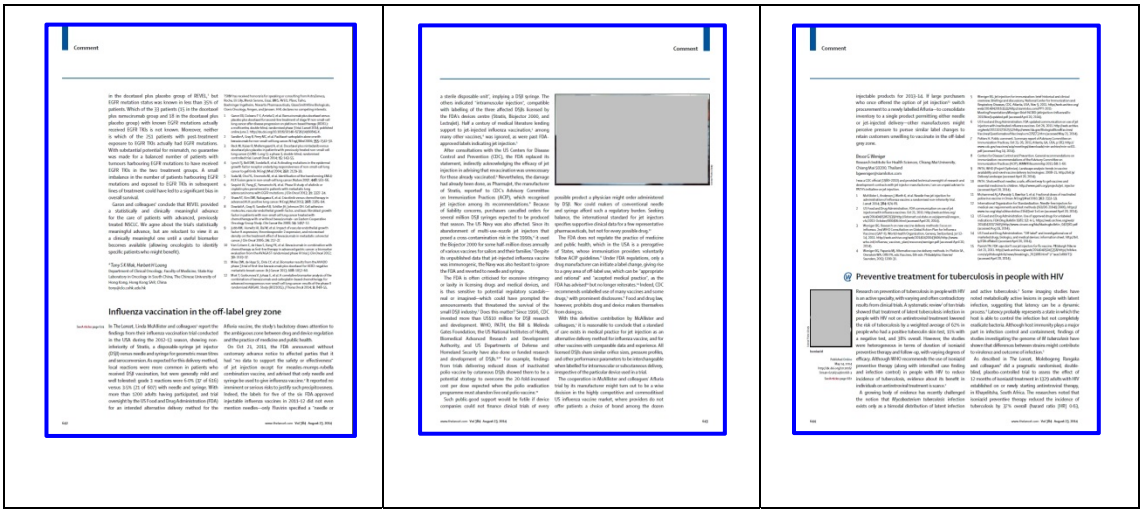

Influenza vaccination in the off-label grey zone

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In *The Lancet*, Linda McAllister and colleagues[1] report the findings from their influenza vaccination trial conducted in the USA during the 2012–13 season, showing non-inferiority of Stratis, a disposable-syringe jet injector (DSJI) versus needle and syringe for geometric mean titres and seroconversion. As expected for this delivery method, local reactions were more common in patients who received DSJI vaccination, but were generally mild and well tolerated: grade 3 reactions were 6·0% (37 of 616) versus 3·5% (21 of 607) with needle and syringe. With more than 1200 adults having participated, and trial oversight by the US Food and Drug Administration (FDA) for an intended alternative delivery method for the Afluria vaccine, the study's backstory draws attention to the ambiguous zone between drug and device regulation and the practice of medicine and public health.

On Oct 21, 2011, the FDA announced without customary advance notice to affected parties that it had "no data to support the safety or effectiveness" of jet injection except for measles-mumps-rubella combination vaccine, and advised that only needle and syringe be used to give influenza vaccine.[2] It reported no imminent or serious risks to justify such precipitousness. Indeed, the labels for five of the six FDA-approved injectable influenza vaccines in 2011–12 did not even mention needles—only Fluvirin specified a "needle or

a sterile disposable unit", implying a DSJI syringe. The others indicated "intramuscular injection", compatible with labelling of the three affected DSJIs licensed by the FDA's devices centre (Stratis, Biojector 2000, and LectraJet). Half a century of medical literature lending support to jet-injected influenza vaccination,[3] among many other vaccines,[4] was ignored, as were past FDA-approved labels indicating jet injection.[5]

After consultations with the US Centers for Disease Control and Prevention (CDC), the FDA replaced its statement, indirectly acknowledging the efficacy of jet injection in advising that revaccination was unnecessary for those already vaccinated.[6] Nevertheless, the damage had already been done, as PharmaJet, the manufacturer of Stratis, reported[7] to CDC's Advisory Committee on Immunization Practices (ACIP), which recognised jet injection among its recommendations.[8] Because of liability concerns, purchasers cancelled orders for several million DSJI syringes expected to be produced that season. The US Navy was also affected. Since its abandonment of multi-use-nozzle jet injectors that posed a cross-contamination risk in the 1990s,[4] it used the Biojector 2000 for some half-million doses annually of various vaccines for sailors and their families.[5] Despite its unpublished data that jet-injected influenza vaccine was immunogenic, the Navy was also hesitant to ignore the FDA and reverted to needle and syringe.

The FDA is often criticised for excessive stringency or laxity in licensing drugs and medical devices, and is thus sensitive to potential regulatory scandals— real or imagined—which could have prompted the announcements that threatened the survival of the small DSJI industry.[7] Does this matter? Since 1996, CDC invested more than US$10 million for DSJI research and development. WHO, PATH, the Bill & Melinda Gates Foundation, the US National Institutes of Health, Biomedical Advanced Research and Development Authority, and US Departments of Defense and Homeland Security have also done or funded research and development of DSJIs.[9,10] For example, findings from trials delivering reduced doses of inactivated polio vaccine by cutaneous DSJIs showed them to be a potential strategy to overcome the 20-fold-increased cost per dose expected when the polio eradication programme must abandon live oral polio vaccine.[11]

Such public-good support would be futile if device companies could not finance clinical trials of every possible product a physician might order administered by DSJI. Nor could makers of conventional needle and syringe afford such a regulatory burden. Seeking balance, the international standard for jet injectors specifies supportive clinical data for a few representative pharmaceuticals, but not for every possible drug.[12]

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The FDA does not regulate the practice of medicine and public health, which in the USA is a prerogative of States, whose immunisation providers voluntarily follow ACIP guidelines.[8] Under FDA regulations, only a drug manufacturer can initiate a label change, giving rise to a grey area of off-label use, which can be "appropriate and rational" and "accepted medical practice", as the FDA has advised[13] but no longer reiterates.[14] Indeed, CDC recommends unlabelled use of many vaccines and some drugs,[5] with prominent disclosures.[8] Food and drug law, however, prohibits drug and device makers themselves from doing so.

With this definitive contribution by McAllister and colleagues,[1] it is reasonable to conclude that a standard of care exists in medical practice for jet injection as an alternative delivery method for influenza vaccine, and for other vaccines with comparable data and experience. All licensed DSJIs share similar orifice sizes, pressure profiles, and other performance parameters to be interchangeable when labelled for intramuscular or subcutaneous delivery, irrespective of the particular device used in a trial.

The cooperation in McAllister and colleagues' Afluria trial by its manufacturer might turn out to be a wise decision in the highly competitive and commoditised US influenza vaccine market, where providers do not offer patients a choice of brand among the dozen

injectable products for 2013–14. If large purchasers who once offered the option of jet injection[15] switch procurement to a newly labelled Afluria—to consolidate inventory to a single product permitting either needle or jet-injected delivery—other manufacturers might perceive pressure to pursue similar label changes to retain customers unwilling to vaccinate in the off-label grey zone.

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1 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:** 674–81.

2 US Food and Drug Administration. FDA communication on use of jet injectors with influenza vaccines. Oct 21, 2011. http://web.archive.org/web/20140405062939/http://listsmart.osl.state.or.us/pipermail/oregon_vfc/2011-October/000406.html (accessed April 20, 2014).

3 Weniger BG. Research on new vaccine delivery methods: Focus on influenza. 2nd WHO Consultation on Global Action Plan for Influenza Vaccines (GAP-II). World Health Organization, Geneva, Switzerland, Jul 12– 14, 2011. http://web.archive.org/web/20140420043606/http://www.who.int/influenza_vaccines_plan/resources/weniger.pdf (accessed April 20, 2014).

4 Weniger BG, Papania MJ. Alternative vaccine delivery methods. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines, 6th edn. Philadelphia: Elsevier/ Saunders, 2013; 1200–31.

5 Weniger BG. Jet injection for immunization: brief historical and clinical overview. Briefings and discussions, National Center for Immunization and Respiratory Diseases, CDC, Atlanta, USA, Nov 9, 2011. http://web.archive.org/web/20140420163533/http://siamlotus.com/PPT-2011-MeetingPresentations/Weniger-Brief-NCIRD-JetInjection+InfluenzaEtc-2011Nov9updated.pdf (accessed April 20, 2104).

6 US Food and Drug Administration. FDA updated communication on use of jet injectors with inactivated influenza vaccines. Oct 26, 2011. http://web.archive.org/web/20111027162552/http://www.fda.gov/BiologicsBloodVaccines/Vaccines/QuestionsaboutVaccines/ucm276773.htm (accessed May 21, 2014).

7 Potters H. Public comment. Summary report of Advisory Committee on Immunization Practices, Oct 25–26, 2011, Atlanta, GA, USA, p 183. http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-oct11.pdf (accessed Aug 14, 2014).

8 Centers for Disease Control and Prevention. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011; **60:** 1–60.

9 PATH, WHO (Project Optimize). Landscape analysis: trends in vaccine availability and novel vaccine delivery technologies: 2008–25. http://bit.ly/DeliveryLandscape (accessed April 20, 2014).

10 PATH. Shots without needles: a safe, efficient way to get vaccines and essential medicines to children. http://www.path.org/projects/jet_injector (accessed April 20, 2014).

11 Mohammed AJ, AlAwaidy S, Bawikar S, et al. Fractional doses of inactivated poliovirus vaccine in Oman. *N Engl J Med* 2010; **362:** 2351–59.

12 International Organization for Standardization. Needle-free injectors for medical use: requirements and test methods (ISO/DIS 21649:2006). https://www.iso.org/obp/ui/#iso:std:iso:21649:ed-1:v1:en (accessed April 20, 2014).

13 US Food and Drug Administration. Use of approved drugs for unlabeled indications. *FDA Drug Bulletin* 1982; **12:** 4–5. https://web.archive.org/web/20140420172605/http://www.circare.org/fda/fdadrugbulletin_041982.pdf (accessed Aug 19, 2014).

14 US Food and Drug Administration. "Off-label" and investigational use of marketed drugs, biologics, and medical devices: information sheet. http://bit.ly/FDAofflabel2 (accessed April 20, 2014).

15 Parrish TN. FDA says don't use jet injectors for flu vaccine. *Pittsburgh Tribune* Oct 21, 2011. http://web.archive.org/web/20140405045358/http://triblive.com/x/pittsburghtrib/news/breaking/s_763188.html (accessed April 20, 2014).