

# Needle-free Injection – Eradicating Diseases to Improve Global Health

Needle-free injection technology has evolved significantly over the last 50 years and is now accepted in many routine immunisation settings as a safe and effective vaccine delivery method. Disposable syringe jet injectors are now being used for the delivery of vaccines to eradicate polio, MMR, and influenza, and are showing promising results in vaccine clinical trials for the Zika virus and HPV. The devices are fast, safe, and easy to use, with most providers trained in less than 20 minutes.

Delivering vaccines without a needle addresses a host of issues surrounding needles. For example, there are about 800,000 needle stick injuries annually in the US<sup>1</sup> and this is an even larger issue internationally. Accidental needle sticks have been an ongoing safety issue for providers and patients, accounting for 33,800 new HIV infections, 1.7 million hepatitis B infections and 315,000 hepatitis C infections annually.<sup>2</sup> In addition, as many as 500 million used needles are added to trash dumps and landfills every year, with 75 million of those needles potentially infected with blood-borne illnesses.<sup>2</sup> No needle means no needle-trash, reduction of needle stick injuries and the potential for improved acceptability, coverage and efficiency of vaccine delivery.

### How Needle-free Injectors Work

The spring-powered injectors use a narrow stream of fluid that goes through the skin in about 1/10 of a second. There is no power or electricity needed. Needle-free injectors are precisely designed for

vaccine delivery into certain tissue depths of the body, whether it be intramuscular (into the muscle, see Figure 1), subcutaneous (below the dermis level), or intradermal injection (directly into the dermis level, see Figure 2). Additionally, the needle-free syringe is auto-disabling, eliminating the possibility of reuse, and calibrated for a specific vaccine volume, either 0.5mL or 0.1mL dose. While needle injection is largely dependent upon the provider's technique, which can have a wide variation in terms of accuracy and injection speeds, needle-free injection uses a simple point-and-click approach, resulting in consistent delivery every time.

As shown in Figures 3a-3d and 4a-4e, the needle-free injectors are easy to use, employing a simple four-step process, and most users are self or web-based trained in less than 20 minutes.

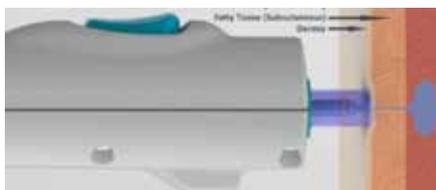


Figure 1: The 0.5mL PharmaJet@ Stratis@ Injector delivers vaccines to the intramuscular (IM) and subcutaneous (SC) depths.

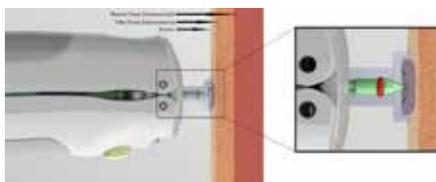


Figure 2: The 0.1mL PharmaJet@ Tropis@ Injector delivers vaccines to the intradermal (ID) depth.

### IM and SC Needle-free Injections (0.5mL Disposable Syringe)

#### 1. Prepare the Injector



Figure 3a

#### 2. Fill Syringe



Figure 3b

#### 3. Load Injector



Figure 3c

#### 4. Give Injection



Figure 3d

The workflow using the PharmaJet intramuscular/subcutaneous needle-free device (Stratis) is comparable to needle-syringe (See YouTube video: <https://www.youtube.com/watch?v=0ag-v7bv960>).



## ID Needle-free Injections (0.1mL Disposable Syringe)

### 1. Prepare the Injector



Figure 4a

### 2. Fill Syringe



Figure 4b

### 3. Load Injector



Figure 4c

### 4. Give Injection



Figure 4d Deltoid Injection



Figure 4e Lateral Thigh Injection

The workflow using the PharmaJet intradermal needle-free device (Tropis) is 25% faster than a needle-syringe (See YouTube video: [https://www.youtube.com/watch?v=prwEHS3KN\\_8](https://www.youtube.com/watch?v=prwEHS3KN_8)).

## Protecting Every Last Child: Fractional Dose Delivery and Polio Eradication

Polio is a crippling and potentially fatal infectious disease, mainly affecting children under five years old, and there is no cure. The move from oral polio vaccine (OPV) to injectable polio vaccine (IPV) to eliminate “wild” types of polio has created a worldwide shortage. It is estimated that less than half the amount of polio vaccine is available to

support the global demand, and this shortage is anticipated to continue for years to come.<sup>3,4</sup> As part of its Global Polio Eradication Initiative (GPEI), the World Health Organization has been working closely with PATH and the Gates Foundation to clinically evaluate alternate delivery options and technologies, including fractional dose needle-free delivery, to address increases in demand and vaccine supply shortages.<sup>5</sup>

Multiple clinical studies evaluated the effectiveness of one full dose of polio vaccine (0.5mL) administered intramuscularly vs. two fractional doses (0.1mL) administered intradermally, with either a needle and syringe or a needle-free injection device (PharmaJet® Tropis®). As summarised in Figure 5, the studies found that two fractional doses of intradermal IPV (fIPV) (2 doses x 0.1mL) were superior to one full dose (0.5mL) administered intramuscularly<sup>6</sup>, thus using 60% less vaccine.<sup>7</sup> This means 2–3x more children can be vaccinated with the same amount of vaccine.

Two fIPV doses are more immunogenic than one full dose

Author	Year Published	Country	Schedule	% Immunogenicity	
				One Full-Dose IPV	Two Fractional Doses IPV
Resik	2013	Cuba	IPV	63% (4 mos)	88% (4+8mos)
Anand A.	2015	Bangladesh	IPV	39% (6wks)	81% (6+14 wks)

Figure 5. IPV Fractional dose immunogenicity<sup>8</sup>

Fractional dose polio vaccine delivery has been endorsed by the WHO and the Indian Ministry of Health, as it also provides a more cost-effective option. Specifically, the WHO Strategic Advisory Group of Experts (SAGE) recommends that countries adopt a two fractional dose IPV schedule in the routine immunisation and outbreak response.<sup>9</sup> The Technical Advisory Group on Vaccine-preventable Diseases (TAG) and Pan American Health Organization (PAHO) endorsement states that “countries that administer more than 100,000 doses of IPV each year and have the capability to adequately train health care workers and supervise implementation should immediately begin to prepare to implement a fractional dose IPV

schedule. These countries include Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Ecuador, El Salvador, Honduras, Nicaragua, Paraguay, Peru, Uruguay and Venezuela.”<sup>10</sup>

While the clinical studies provided a workable solution for the supply shortage, they also recognised the ongoing difficulty of administering vaccines intradermally with the Mantoux technique using a needle and syringe. Administration can be slow, technically difficult, inconsistent, and painful (see Figures 6a and 6b). Additionally, many healthcare workers are not familiar with the intradermal technique, making it unsuitable for house-to-house campaigns, and the inconsistent delivery is less than ideal for mass immunisations. Conversely, the PharmaJet Needle-free Injector is easy-to-use and requires minimal training (see Figures 6c and 6d). Healthcare workers that have used the device found that they quickly became proficient in providing consistent and rapid injections.<sup>11</sup>

## Comparing Needles to Needle-free for Intradermal Injections

### Mantoux Technique (Needle)



Figure 6a



Figure 6b

### Needle-free Technique



Figure 6c



Figure 6d

Figure 6: Comparison of Mantoux technique with needle (a and b) to Needle-free technique (c and d)

The needle-free injector’s simple point-and-click design ensures consistent and accurate intradermal injection. Additionally, the preparation and administration time is 50–70% less than needle and syringe, making it an ideal choice for vaccination campaigns.<sup>12</sup> And, because there is no needle, healthcare workers can work fast and not have to worry about needle sticks. The PharmaJet needle-free device is currently being used as part of the polio eradication effort in Bangladesh, Cuba, Gambia and Pakistan.

## MMR Vaccine Delivered without a Needle

Measles is a leading cause of childhood deaths globally, with 3 million cases diagnosed and nearly 1 million deaths each year. The WHO estimates that global immunisation coverage for measles containing vaccine in 2013 was 84%, with many countries still well below the recommended 95% level required to interrupt endemic measles transmission. For example, in India, the coverage averages only 66%, with rates below 50% in many parts of the country.<sup>13</sup>

A recently completed Phase IV clinical study, supported by the Gates Foundation and PATH, included 300+ children aged 15-18 months over a 12-month period. The objective of the study was to demonstrate the non-inferiority of seropositivity of MMR vaccine administered using the needle-free injector to MMR vaccine administered by needle and syringe for all three components of the vaccine. Secondly, there was an objective to assess and compare the safety of MMR vaccine administered by needle-free jet injector vs. needle and syringe. The results showed comparable non-inferiority performance and safety to that of the traditional needle and syringe.<sup>14</sup> Needle-free injection is being used to administer the MMR vaccine TRESIVAC NF (needle-free) in Cambodia and India.

## Needle-free Flu Shots

Influenza is one of the most common preventable infectious diseases. In the US alone, approximately 10-20% of the population contracts influenza each year, which accounts for about 226,000 hospitalisations and 36,000 deaths annually.<sup>15</sup> While morbidity and mortality affect mostly the young and old, all age groups are affected. The US Department of Health and Human Services (HHS) has established a Healthy People 2020 campaign that includes the goal of 70 per cent flu vaccination compliance by the year 2020, versus 43 per cent in 2016.<sup>16,17</sup>

In 2014, *The Lancet* published a study that demonstrated that the delivery of an influenza vaccine with the PharmaJet needle-free jet injector compared favourably

to a traditional needle and syringe delivery. This was the first definitive non-inferiority study to measure the immune responses to all three influenza viruses induced after administration of a seasonal flu vaccine by a jet injection device as compared to a needle and syringe. The study also found that 89 per cent of the people receiving the needle-free injection reported they would choose a needle-free injection over needle and syringe for their next injection.<sup>18</sup>

## Patient and Provider Feedback – using Needle-free to Increase Compliance and Productivity

The Centers for Disease Control and Prevention (CDC) recommends annual flu shots for all adults, yet only around 43% of them receive the yearly vaccination; many citing a fear of needles as a reason for non-compliance. Needle-free devices provide an option for the one in four adults who have a fear of needles.<sup>17,19</sup>

More than half of adults aged 20-64 years who are employed are affected by the flu, resulting in about 111 million lost working days every year. Workplace health influenza immunisation programmes are an important factor to consider for addressing decreased productivity, when a simple flu shot could decrease work absenteeism and significantly reduce the spread of influenza to others. According to the US National Institute for Occupational Safety and Health (NIOSH), the cost associated with sick days and lost productivity is approximately \$7 billion in the US annually. Despite the potential benefits of vaccination,

one study showed that only about 20% of healthy working-age adults aged 18-49 years receive an annual flu shot.<sup>20,21,22</sup>

During the 2016-17 influenza season the PharmaJet Stratis® needle-free injection system was used in multiple workplace health influenza clinics. There were 35 vaccination events, which included employees from BP Oil, Cargill, Denver International Airport, Ernst & Young, Morgan Stanley, Terumo BCT, TriNet, and Xerox, among others. Surveys were completed by patients and caregivers to collect feedback regarding the acceptability and usability of the device, whether it should be an option for next year, and the potential to increase influenza immunisation coverage at a particular site.<sup>23</sup>

## Patient Surveys

Overall, 1018 surveys were completed by working individuals, 18-64 years of age, who received a needle-free flu shot at one of the influenza vaccination events. Figure 7 shows results for each of the three key questions regarding satisfaction, likelihood of choosing a needle-free injection next year, and likelihood of recommending a needle-free injection. In summary (see Figure 7a-c):

- The majority of patients (97%) were satisfied with the needle-free shot
- 95% of patients responded that they would choose needle-free again next year
- 95% said they were likely to recommend the needle-free option to friends and family

How satisfied were you with today's needle-free flu shot?



Figure 7a: Satisfaction with needle-free injection

For next year's flu vaccination, will you choose to receive your flu shot with a needle-free injection?

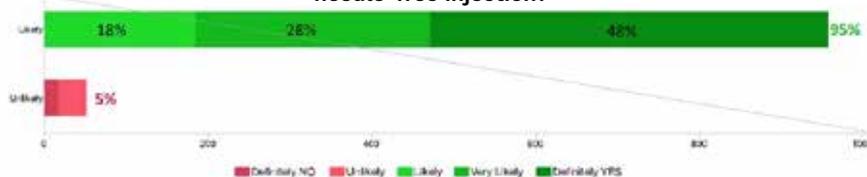


Figure 7b: Likelihood of choosing a needle-free injection next year

How likely are you to recommend a needle-free flu shot to your family and friends?

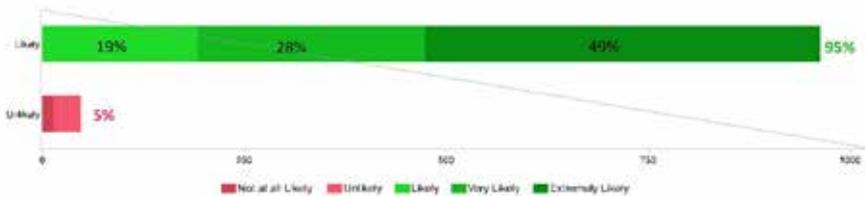


Figure 7c: Likelihood of recommending a needle-free injection to family or friends.

Figure 7: Patient survey results regarding: a) satisfaction with the needle-free injection they just received; b) likelihood of choosing a needle-free injection next year; and c) likelihood of recommending a needle-free injection to family or friends.

## Future Vaccines

### NIH Clinical Trial for Needle-free Zika Vaccine Shows Promise

There are now more than 30,000 diagnosed Zika cases in every state but Alaska, with most of those in the US territory of Puerto Rico. Because it is now known that Zika can be transmitted through mosquitoes, blood and sex, that number is expected to rise. The National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health (NIH) is using the Stratis 0.5mL needle-free device in a DNA vaccine clinical trial for a Zika vaccine, and the results are promising. DNA vaccines are a rapidly developing field. Unlike traditional vaccines, like for flu or measles, that contain whole viruses, DNA vaccines contain just a tiny piece of a virus's genetic code, making them safe and easy to work with. For these vaccines to work, the DNA vaccine must get directly into the cells. For that purpose, a new delivery method was needed.<sup>25</sup> Various pre-clinical and clinical preliminary studies have shown that the performance of nucleic acid-based vaccines (DNA and RNA) when injected with needle-free injectors have been superior to needle-syringe delivery and at least equivalent to other delivery methods.<sup>26</sup>

The NIH announced the start of the Phase II Zika vaccine trial in March 2017, which consists of two studies in the US, Central and South America. Part A will further evaluate the vaccine's safety and ability to stimulate an immune response in participants, and assess the optimal dose for administration. Part B will attempt to determine if the vaccine can effectively prevent disease caused by Zika infection. "A safe and effective vaccine is urgently needed to prevent the often-devastating birth defects that can result from Zika virus infection during pregnancy," says NIAID Director, Dr Anthony S. Fauci. "Evidence also is accumulating that Zika can cause a variety of health problems in adults as well."<sup>27</sup>

### Needle-free Providing a More Comfortable Experience – HPV Vaccine

Human papillomavirus or HPV is the main cause of cervical cancer affecting 530,000 women annually and an additional 10 million women are impacted by a long pre-invasive

## Healthcare Provider Surveys

Combining surveys from providers at these flu clinics and those from previous seasons, there were a total of 67 healthcare providers that completed the survey, including contract nurses, pharmacists and occupational health nurses. (24) In summary (see Figure 8a-d):

- 91% said they were satisfied with ease of use
- 87% would like the option of needle-free next year
- 82% said they would be likely to recommend needle-free flu shots to their colleagues
- 45% thought that offering a needle-free option could increase flu vaccinations by more than 10% at their facility.

How satisfied were you with the ease of use?

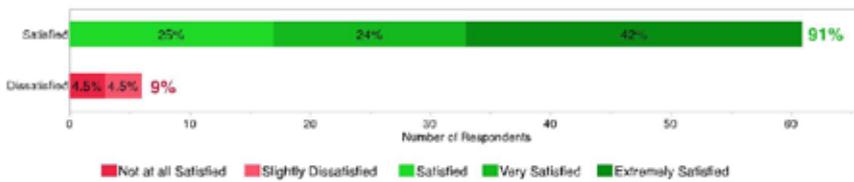


Figure 8a: Satisfaction with ease of use

For next year's flu vaccinations, would you like the option of needle-free shots at your facility?



Figure 8b: Wanting the option of needle-free shots in their facility

How likely are you to recommend needle-free flu shot to your colleagues?



Figure 8c: Likelihood of recommending to colleagues

How much could your flu vaccinations increase next year by offering the option of a needle-free flu shot?

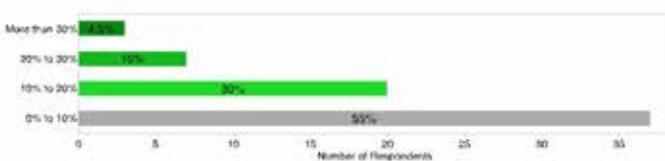


Figure 8d: How much vaccination could be increased by offering needle-free

Figure 8: Healthcare provider survey results regarding: a) satisfaction with ease of use; b) needle-free option for next year c) likelihood to recommend to colleagues; and d) how much vaccination could be increased by offering needle-free

disease called cervical intraepithelial neoplasia (CIN). Current standard therapy for CIN 2/3 varies between countries and regions and often involves surgical removal of the affected tissue. These invasive procedures are associated with bleeding, infection, cervical stenosis, scarring and, most importantly, pre-term deliveries in subsequent pregnancies. As a result, there is a significant need for an effective therapeutic vaccine to treat existing HPV infection and associated pre-malignancies and malignancies of the cervix and thereby prevent the development of cervical cancer caused by human papillomavirus.<sup>28,29</sup>

In late 2016, Vaccibody AS announced the results of the Phase I clinical trial of their VB10.16 HPV vaccine delivered with the Stratis needle-free jet injector. Martin Bonde, the CEO of Vaccibody AS noted, "While other DNA vaccines developed for this indication require delivery with *in vivo* electroporation, which is quite painful for the patients, VB10.16 is delivered by needle-free injection, which we believe improves patient compliance tremendously and will be a significant asset in further development of this product."<sup>29</sup> Given that multiple vaccine doses are required for the HPV vaccine, improved compliance with needle-free is an important advantage over traditional methods.

In March 2017, Vaccibody AS announced the start of their Phase IIa clinical study: an exploratory, open-label, multi-centre study with VB10.16 immunotherapy for the treatment of high-grade cervical intraepithelial neoplasia (CIN 2/3) caused by human papillomavirus 16 (HPV 16). The vaccine is also being delivered with the Stratis needle-free injection system.<sup>29</sup>

1. United States. Centers for Disease Control and Prevention. National Institute for Occupational Safety and Health. Preventing Needlestick Injuries in Health Care Settings. N.p.n.d. Web. <http://www.cdc.gov/niosh/docs/2000-108/pdfs/2000-108.pdf>
2. Health-care waste, World Health Organization Fact sheet No 253, November 2015; <http://www.who.int/mediacentre/factsheets/fs253/en/>
3. IPV introduction and RI strengthening, WHO; [http://www.who.int/immunization/diseases/poliomyelitis/endgame\\_objective2/inactivated\\_polio\\_vaccine/en/](http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/inactivated_polio_vaccine/en/)
4. Inactivated Polio Vaccine Supply and

- Demand Update, September 2016, Unicef Supply Division; [https://www.unicef.org/supply/files/Inactivated\\_Polio\\_Vaccine\\_IPV\\_-\\_september\\_2016.pdf](https://www.unicef.org/supply/files/Inactivated_Polio_Vaccine_IPV_-_september_2016.pdf)
5. To help end polio, intradermal delivery takes center stage, Vaccine and Pharmaceutical Technologies News and Updates – PATH, May 2016, <http://www.path.org/newsletters/vaccine-technologies-newsletter.php>
  6. Immunogenicity to poliovirus type 2 following two doses of fractional intradermal inactivated poliovirus vaccine: A novel dose sparing immunization schedule. Anand A., et al. *Vaccine*, 2017 May 19;35(22):2993-2998; <https://www.ncbi.nlm.nih.gov/pubmed/28434691>
  7. Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial, Anand A., et al., *Vaccine*. 2017 May 19;35(22):2993-2998. doi: 10.1016/j.vaccine.2017.03.008. Epub 2017 Apr 20.
  8. Use of fractional dose IPV in routine immunization programmes: Considerations for decision-making, WHO Polio Global Eradication Initiative, March 2017; [http://www.who.int/immunization/diseases/poliomyelitis/endgame\\_objective2/inactivated\\_polio\\_vaccine/fIPV\\_considerations\\_for\\_decision-making\\_March2017.pdf?ua=1](http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/inactivated_polio_vaccine/fIPV_considerations_for_decision-making_March2017.pdf?ua=1)
  9. Weekly epidemiological record, World Health Organization, June 2, 2017, page 309, <http://apps.who.int/iris/bitstream/10665/255611/1/WER9222.pdf?ua=1>
  10. Ad hoc Virtual TAG Meeting 20176, 10, March 2017, Washington D.C., USA, p. 7; [http://www.who.int/immunization/sage/meetings/2017/april/6\\_2017\\_TAG\\_Ad-hoc\\_Meeting\\_Report\\_EN.pdf](http://www.who.int/immunization/sage/meetings/2017/april/6_2017_TAG_Ad-hoc_Meeting_Report_EN.pdf)
  11. PharmaJet Inc., Doc. #60-10214-001A Cambodia Healthcare Worker Interview Video
  12. Intradermal Administration of Fractional Dose of Inactivated Poliovirus Vaccine (fIPV) Using Tropis® Intradermal Needle Free Injection System, Karachi Pakistan, Community Based Polio Vaccination Campaign, December 2016; Ali Faisal Saleem, Mach Ondrej, Muhammad Tahir Yousafzai, Attaullah Baig, Roland Sutter, Anita KM Zaidi, Aga Khan University, Karachi Pakistan, WHO, Geneva, Switzerland
  13. Serum Institute of India website, Health FAQ – Measles, [http://www.seruminstitute.com/content/faq\\_measles.htm](http://www.seruminstitute.com/content/faq_measles.htm)
  14. Effect of jet injection on infectivity of measles, mumps, and rubella vaccine in a bench model, Coughlin, MM, et al., *Vaccine* (2015), <http://dx.doi.org/10.1016/j.vaccine.2015.07.013>
  15. Norwalk MP, et al, Improving Influenza Vaccination Rates in the Workplace. *Am J Preventive Med*, 2010, Vol 38 pp 237-246
  16. Healthy People 2020, Office of Disease Prevention and Health promotion (ODPHP), HealthyPeople.gov. Immunization and Infectious Diseases IID-12.12. <https://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives> Updated March 23, 2016v
  17. Flu Vaccination Coverage, United States 2316-2017 Influenza Season, CDC, <https://www.cdc.gov/flu/fluview/coverage-1617estimates.htm>
  18. Needle-free jet injection for administration of influenza vaccine: a randomized

- non-inferiority trial, McAllister, L et al, *Lancet* 2014: 384:674-81
19. Survey of the prevalence of immunization non-compliance due to needle fears in children and adults. Taddio A, Ipp M, Thivakaran S, et al. *Vaccine* 2012; 30: 4807-4812 Web.
  20. Centers for Disease Control and Prevention Website, Frequently Asked Flu Questions 2016-2017 Influenza Season. Accessed October 2016 (<http://www.cdc.gov/flu/about/season/flu-season-2016-2017.htm>)
  21. Lee BY, et al, Economics of Employer-sponsored workplace vaccination to prevent pandemic and seasonal influenza. *Vaccine*, 2010, Vol. 28 (37), pp 5952-5959
  22. US Centers for Disease Control and Prevention Website, National Institute of Occupational Safety and Health Activities: Surveillance Tracking Influenza Cases and Preventive Measures. Accessed 2017. <https://www.cdc.gov/niosh/topics/flu/surveillance.html>
  23. Needle-free jet injection in workplace influenza clinics, Miller, T, et al., ONdrugDELIVERY, May 2017, Issue No. 75, pp. 18-21, <http://www.ondrugdelivery.com/publications/75/PharmaJet.pdf>
  24. Doc. #61-10194, Third Party Review – Stratis PMS Health Care Provider. Internal PharmaJet Document, 2015.
  25. The Zika Virus, Nov. 6, 2016, CBS 60 Minutes, (<http://www.cbsnews.com/news/60-minutes-zika-in-the-united-states-mosquito-disease/>)
  26. Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. Alberer M et al. *Lancet*. 2017 Jul 25. pii: S0140-6736(17)31665-3.
  27. Zika vaccine trial site in Peru led by Fogarty trainee, *Global Health Matters*, May/June 2017, Volume 16, Issue 3
  28. Vaccibody announces positive results from the phase 1 part of the clinical trial, press release, August 25, 2016, [www.vaccibody.com/news](http://www.vaccibody.com/news)
  29. Vaccibody announces positive results from the 12-month analysis of the Phase 1 part of the clinical trial VB C-01 in patients with high-grade cervical dysplasia, press release, June 21, 2017



**Erin Spiegel**

Dr Erin Spiegel is the Regulatory Affairs Manager at PharmaJet, Inc., a medical device company developing needle-free injection technologies. Erin specialises in regulatory strategy for medical devices, drugs, and biologics. She spent the first half of her career developing vaccines and biologics and has expertise in genetic engineering, virology and molecular biology. Erin received her PhD in biophysics and genetics from the University of Colorado and her BS in animal science from the University of Nebraska-Lincoln.

Email: [erin.spiegel@pharmajet.com](mailto:erin.spiegel@pharmajet.com)