Challenges and Innovations in Vaccine Delivery

10th Annual African Vaccinology Course (AAVC):

Developing Vaccinology Expertise for Africa-

10–14 November 2014 Cape Town, South Africa

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13 November 2014

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Photo: PATH

Age groups targeted to receive vaccines

Infants

Young children (e.g., measles 2nd dose)

Pre-adolescents (human papillomavirus)

Women of child-bearing age (tetanus toxoid)

Expanded age groups during campaigns

(*e.g., polio, measles, meningitis A*)

Age groups

Courtesy Robert Steinglass—John Snow, Inc. (JSI)

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Current challenges to vaccine delivery

- Training and availability for health care workers.
- Routine, supplementary immunization activity, and outbreak response.
- Appropriate vaccine management.
- Supply access (e.g., needles and syringes, safety boxes).
- Needlestick injuries to health care workers.
- Disposal of sharps waste—community needlestick injuries.

Photo: World Health Organization

Photo: World Health Organization

Unsafe injections and disposal

Infections resulting from unsafe injections:*

- Hepatitis B: 15 million.
  - 25% of all new infections.
- Hepatitis C: 1 million.
  - 8% of all new infections.
- Human immunodeficiency virus: 340,000.
  - 14% of all new infections.
- Bacterial: 3 million.
  - 7% of all new infections.

Photo: PATH\Mark Clifford

Photo: PATH

*Report of the 2010 Safe Injection Global Network Meeting. Available at: http://www.who.int/injection_safety/toolbox/sign2010_meeting.pdf.

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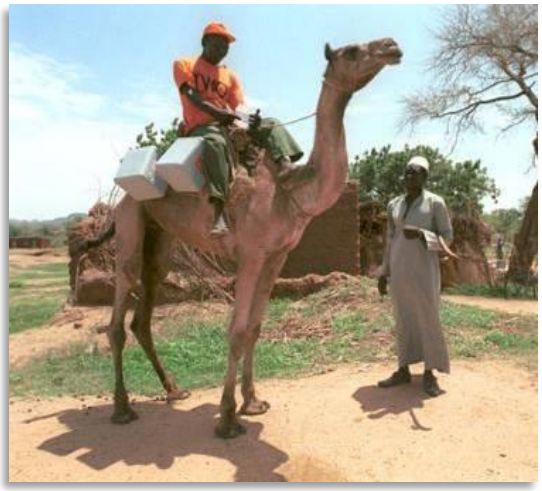
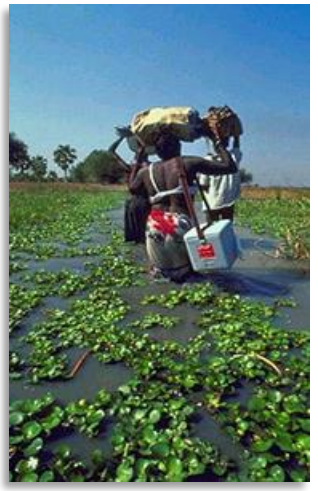
Last-mile logistics involve unreliable cold chain





All photos: PATH except where noted

Photo: UNICEF

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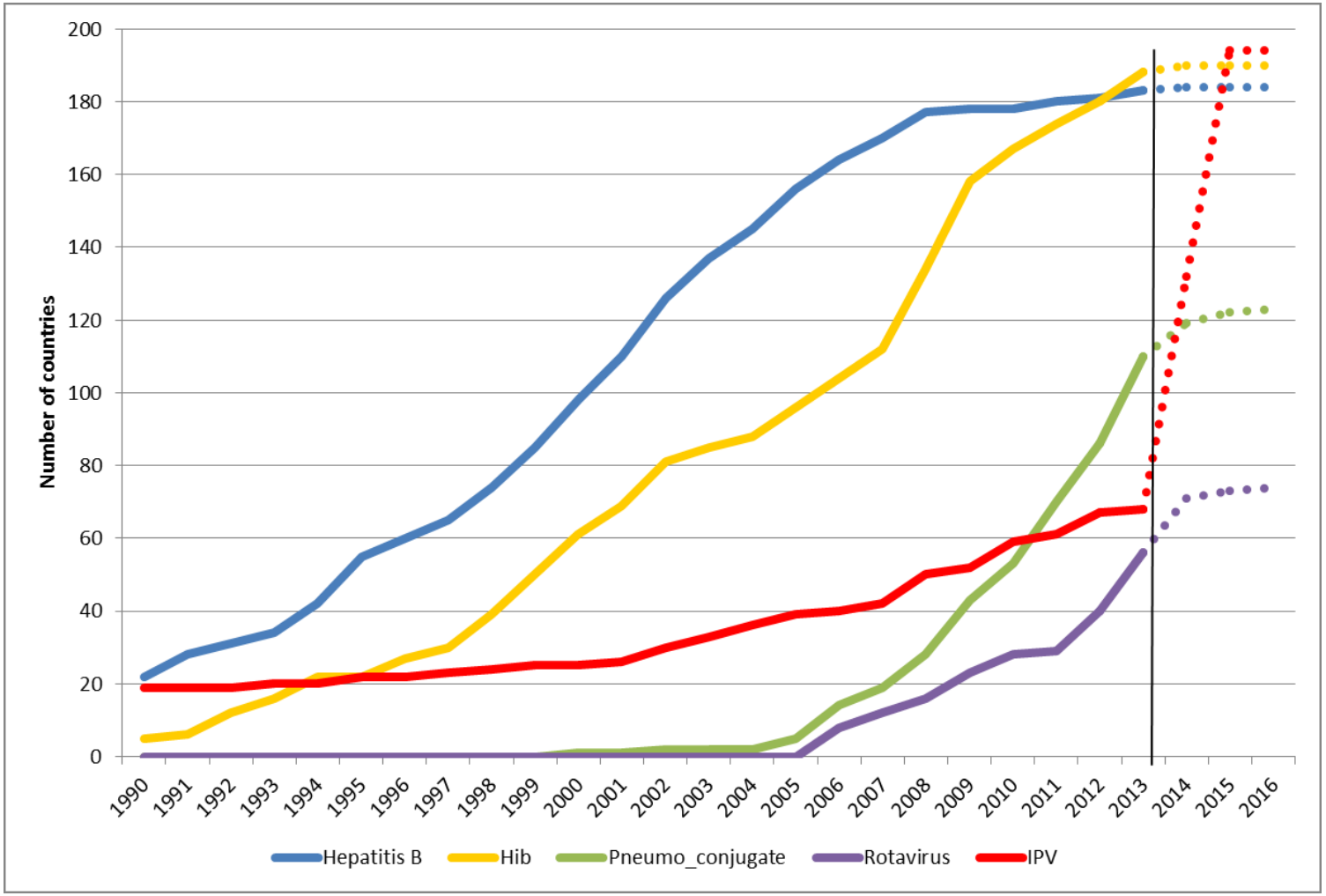
New vaccine introductions



Source: WHO/IVB Database as of 18 October 2013
Date of slide: 18 October 2013

Courtesy Robert Steinglass—JSI

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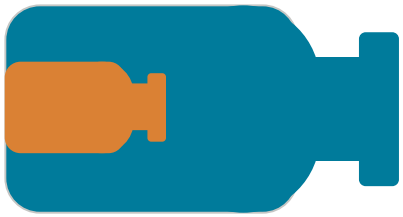
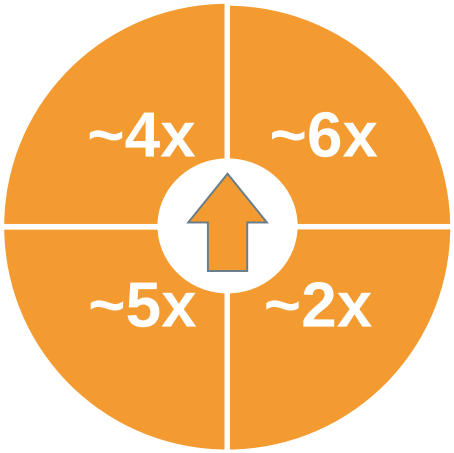
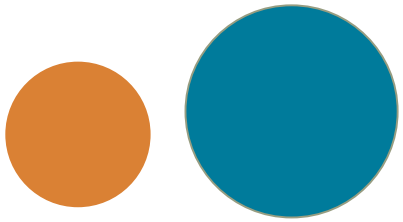
Challenges to the immunization supply chain

Growing volume (cm^3) to vaccinate per child

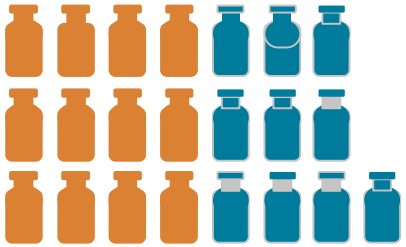






Introduction of more expensive vaccines

Increasing number of doses



Increase in stock keeping units

2010 **2020**

Note: All figures relate to Gavi-vaccines
1. UNICEF Supply 2012 Financial report, WHO data for Pneumo and Rota vaccines, and HPV (only for girls);
2. 2010: Gavi Shipment Data; 2020; Gavi SDF Forecast; Including volume for GAVI future graduated countries;
3. Comparison based on 2013 Price; 2020 Vaccines include: Rota, Pneumo; HPV; 2010' vaccines include:YF, Measles, DPT, OPV (UNICEF SD);
4. Gavi Background SDF Information; 2010": estimates based on 2009 data; 2020: estimates based on 2013 forecast

Courtesy Robert Steinglass—JSI

New vaccines—new challenges

- Increase in number of vaccines (from 6 to 12–15).
- Age restrictions (rotavirus vaccine upper age limit).
- New target age groups (HPV: adolescents) requiring new service delivery channels.
- New messages (syndromes, partial protection).
- Integrated approaches to disease control.
- Cost of new vaccines.
- Cold chain/logistics challenges (bulk and waste disposal).

Most new vaccines require a well-functioning routine immunization program.

Courtesy Robert Steinglass—JSI

Vaccine wastage

	Cambodia (95% MCV1 coverage)	Nigeria (57% MCV1 coverage)
Average measles vaccine wastage rate in health centers	58%	19%
Average number of children before opening measles vaccine vial	2.2	6.2
Proportion of parents saying they were turned away for vaccination	4%	30%
Proportion of turned away who never received vaccine	12%	53%
Vaccines missed among turned away	MCV: 63%	BCG: 33% MCV: 26%

Source: unpublished data, 2011 Nigeria CDC/WHO/NPHCDA study, 2013 Cambodia WHO/CDC/MOH study in nationally representative samples of health facilities

Courtesy Robert Steinglass—JSI

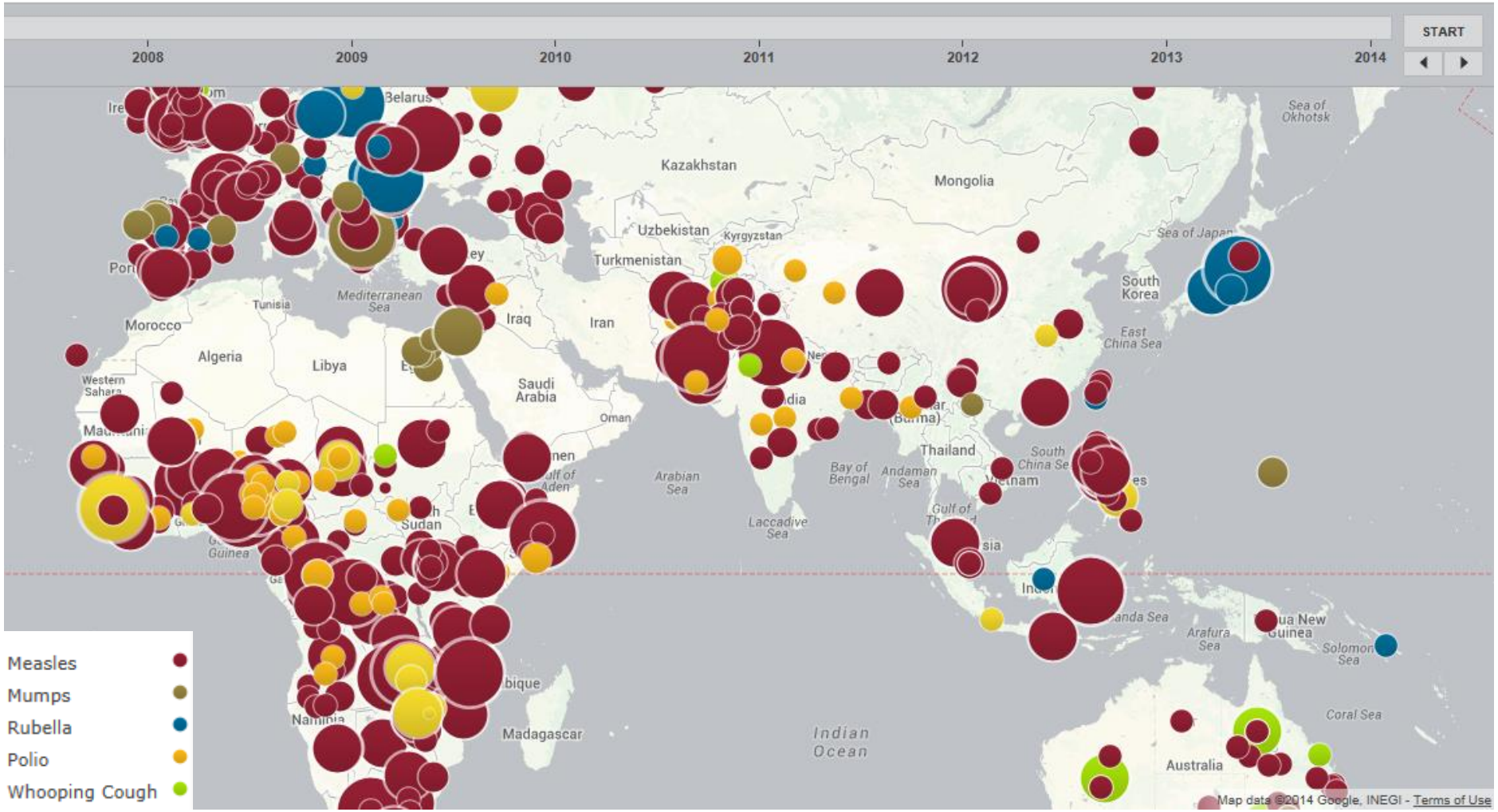
Single versus multidose vial tradeoffs

Comparison of the Major Programmatic and Economic Advantages of Single- Versus Multidose Vaccine Containers[a]		
	Single-dose	Multidose
Production	Eliminates use of thiomersal	Faster filling rate
Packaging		Cheaper packaging costs
Distribution	Simplified logistics	Smaller and lighter for transport
Cold chain		Smaller cold chain volume
Safety	Less risk of contamination Ensures more accurate dose delivery	
Syringe usage (for injectable vaccines)		Requires fewer reconstitution syringes (for lyophilized vaccines)
Vaccine wastage	Significantly less vaccine wastage	
Coverage rates	Facilitates innovative outreach strategies Prevents missed opportunities due to reluctance to open a multidose container for small sessions	
Medical waste		Smaller medical waste volume[b]

[a] Adapted from Drain PK, Nelson CM, Lloyd JS. Single-dose versus multidose vaccine vials for immunization programmes in developing countries. Bull World Health Org 2003; 81 (10): 726-31.
[b] Compact prefilled autodisable syringes (Uniject) have less waste volume than multidose vials with syringes.

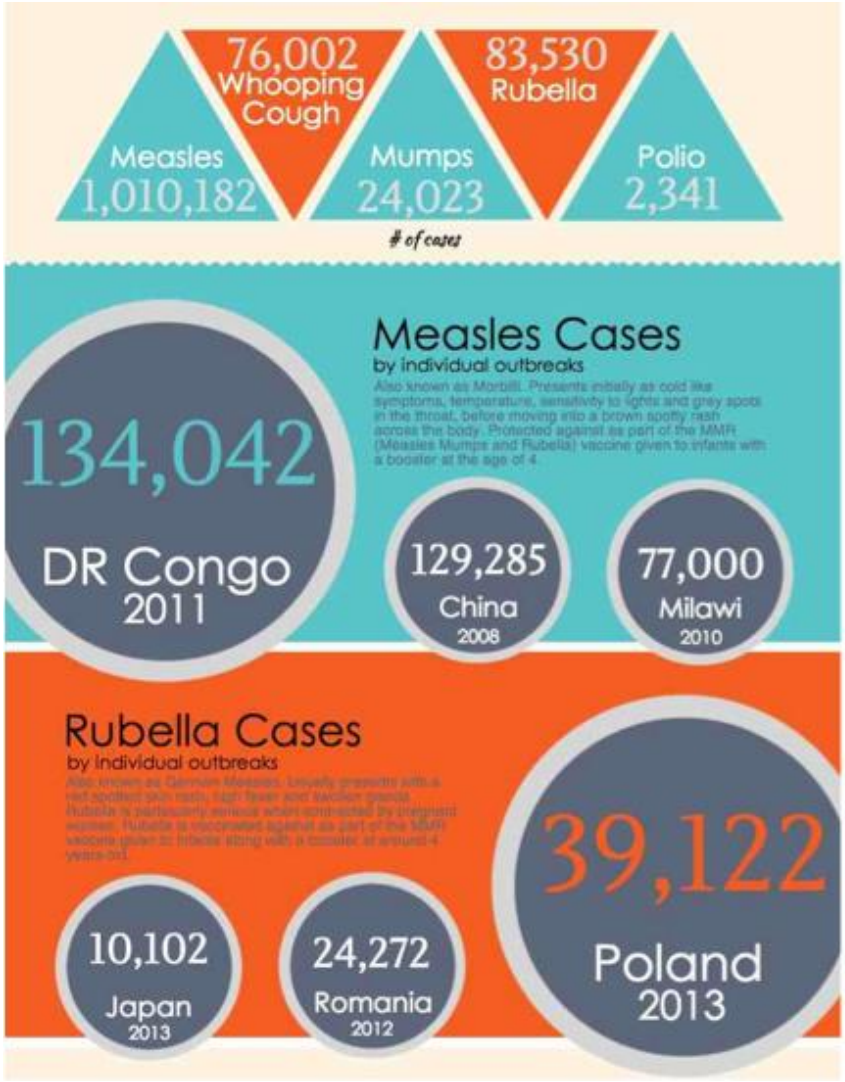
Courtesy Robert Steinglass—JSI

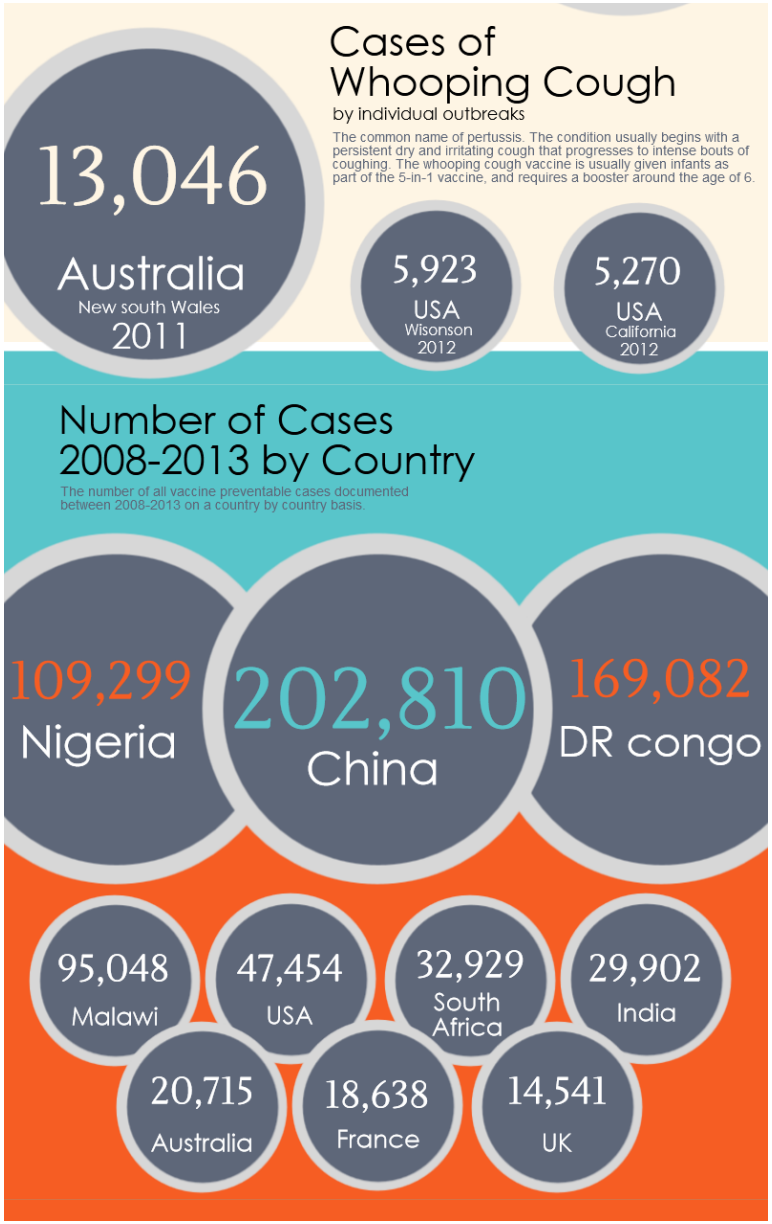
Vaccine-preventable disease outbreaks 2008–2014 (all)



http://www.cfr.org/interactives/GH_Vaccine_Map

Vaccine preventable outbreaks 2008–2013





http://www.vaccinenation.org/2014/01/28/infographic-the-largest-preventable-outbreaks

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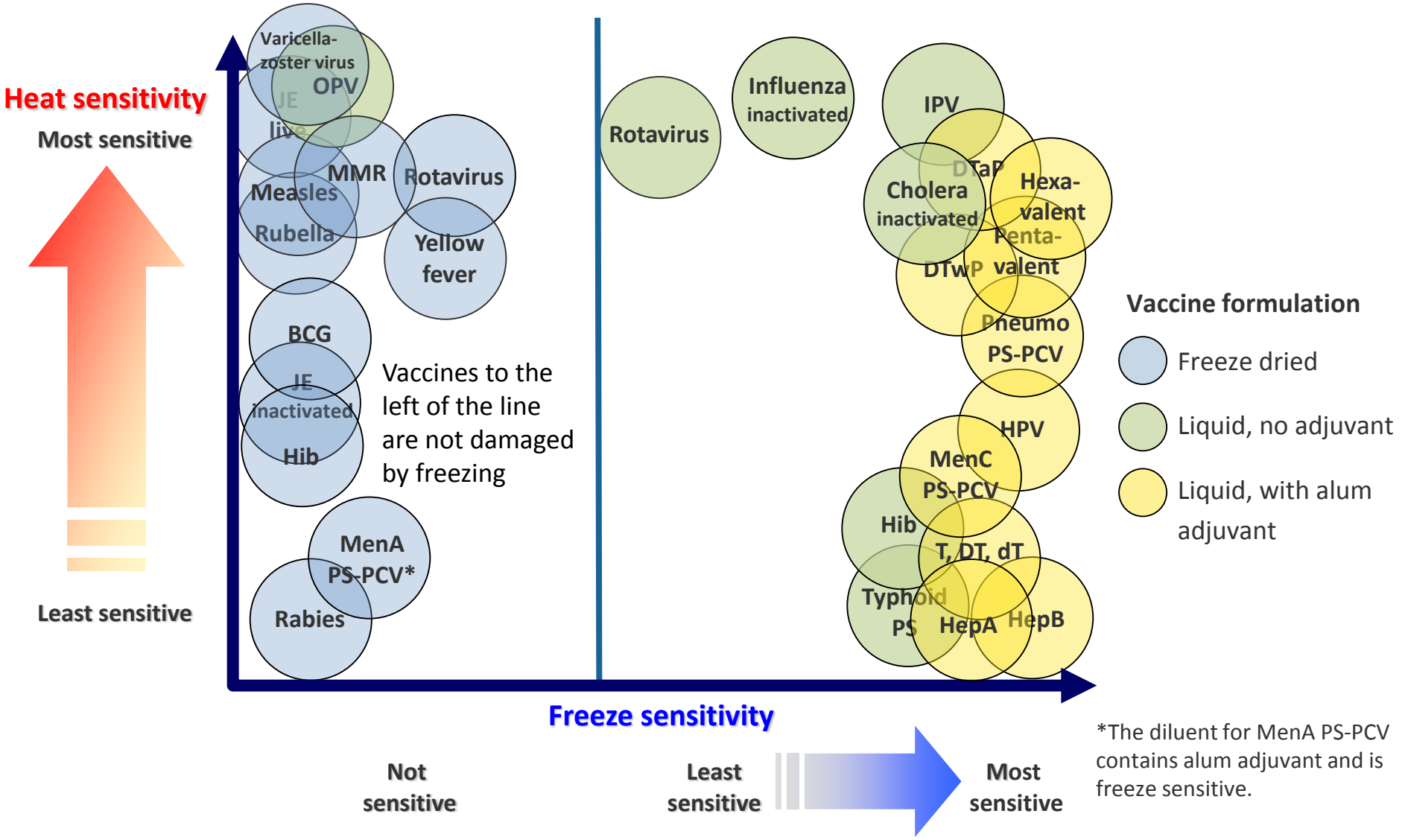
Temperature sensitivity of vaccines



*The diluent for MenA PS-PCV contains alum adjuvant and is freeze sensitive.

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Value-added product attributes

- **Enhanced thermostability** (heat and freeze protection) enables supply logistics and distribution at or beyond the cold chain.
- **Compact, low-weight packaging** minimizes product volume and reduces space requirements.
- Increased **potential for fractional dosing** reduces supply and delivery costs.
- **Ease of use** is improved within different delivery scenarios (routine immunization or mass campaign).

Source: World Health Organization (WHO). *Vaccine Presentation and Packaging Advisory Group Generic Preferred Product Profile for Vaccines*. Geneva: WHO; 2009. Available at: http://www.who.int/immunization_delivery/systems_policy/VPPAG_Generic_PPP_and_Workplan.pdf.

Value-added product attributes (continued)

- **Simplified product preparation** reduces the number of steps and requirements, helping to ensure effective delivery.
- **Autodisable features** prevent reuse and potential disease transmission.
- Innovative materials (including primary container, secondary, and tertiary packaging) **minimize environmental impact, the risk of needlestick injury, and unsafe medical waste**.
- **Improved patient/parent acceptance** increases willingness for vaccination.

Source: World Health Organization (WHO). *Vaccine Presentation and Packaging Advisory Group Generic Preferred Product Profile for Vaccines*. Geneva: WHO; 2009. Available at: http://www.who.int/immunization_delivery/systems_policy/VPPAG_Generic_PPP_and_Workplan.pdf.

New vaccine delivery technologies

Delivery devices

- Disposable-syringe jet injectors*
- Intradermal delivery devices*
- Microneedles*
- Intranasal delivery
- Aerosol/dry powder inhalation
- Electroporation

Packaging

- Prefilled syringes/ compact prefilled autodisable devices*
- Blow-fill seal/multi-mono dose*
- Integrated reconstitution*

Formulation

- Fast-dissolving tablets and gels
- Solid-dose implants

∗ discussed in presentation

All photos: PATH

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Autodisable and reuse-prevention syringe pricing—baseline technologies

Autodisable (AD)syringes	Type	Total awarded quantity (units)	Weighted average price per unit (USD)
0.5 mL AD syringe	 For immunization injections of all 0.5ml dose vaccines	1,158,000,000	**$0.0396**
0.1 mL AD syringe	 For immunization injections of BCG vaccine	440,000	**$0.0410**
0.05 mL AD syringe	 **For immunization injections of BCG vaccine**	**84,000,000**	**$0.0463**

Syringe, re-use prevention (RUP), 2 mL			Long-term arrangement fixed-unit prices based on incoterm FCA port/ airport of origin
Supplier name	Product	Product type	**June 2013-May 2015**
Helm Medical GmbH		**Syringe, RUP, 2 ml, with fixed needle/BOX—100**	**$4.25**

Sources: (1) United Nations Children's Fund (UNICEF). *2014-2015 AD Syringes Projections: Quantities and Pricing*. New York: UNICEF; 2014. Available at: http://www.unicef.org/supply/files/2014-2015_AD_Syringes_Projections.pdf. (2) UNICEF. *Re-Use Prevention Syringes Current LTA's Price Data*. New York: UNICEF; 2011. Available at: http://www.unicef.org/supply/files/Re-Use_Prevention_(RUP)_syringes_current_LTAs_price_data.pdf.

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New and alternative delivery technologies

- Many new technologies are needle free.
- Some are compatible with existing vaccine formats (e.g., vials or ampoules).
- Others are integrated with formulation (e.g., combination products).
- Improved ease of vaccine delivery, efficacy, cost-effectiveness, and safety are areas of focus.
- Developers include industry, academic, and nonprofit research groups.

Photo: Georgia Tech

Photo: The Hindu

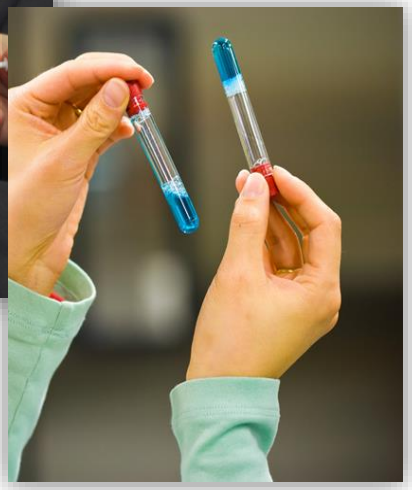
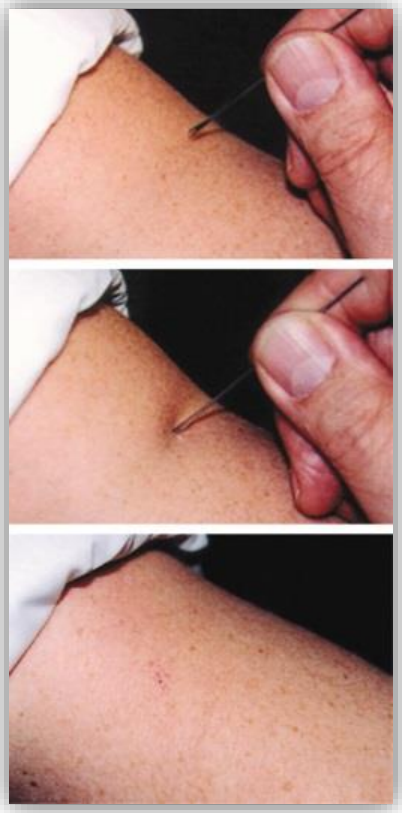


Photo: PATH

Innovative delivery technologies of the past—smallpox

- The first half of the smallpox eradication program used high-speed jet injectors with intradermal nozzles, delivering tens of millions of doses.
- Bifurcated needles replaced jet injectors for the later half of eradication.
- Alternative delivery technologies were critical in the success of smallpox eradication.



Photos: Bruce Weniger

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Potential public health benefits

- Increase vaccine access and coverage—enable community health workers to deliver vaccines.
- Improve immunogenicity.
- Reduce the need for and the number of injections.
- Reduce risk of infections/cross-contamination.
- Reduce potentially dangerous sharps waste.

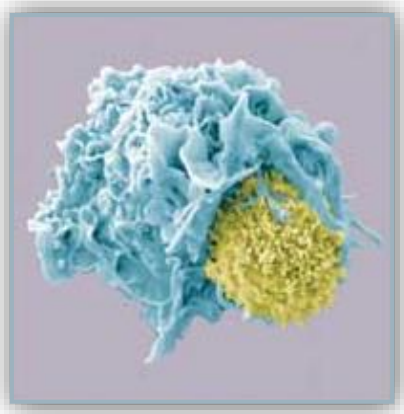

Photo: World Health Organization

Image: PATH

Potential public health benefits

- Relieve tensions and fears surrounding immunization.
- Reduce dropout by optimizing schedules.
- Reduce health worker workload—simplified administration and reconstitution (free up time for other tasks).
- Reduce cold chain dependency through improved thermostability (heat and freeze stability)—incorporation of enhanced formulation in presentation.


Photo: Ümit Kartoglu

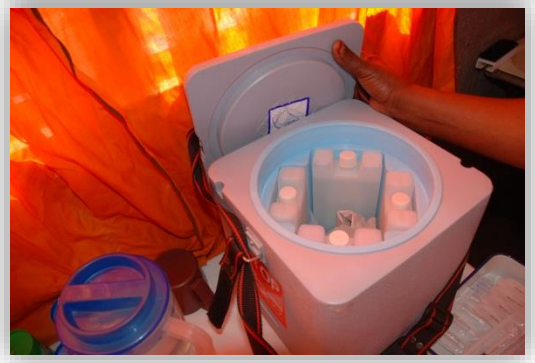
Photo: PATH/Debra Kristensen


Photo: PATH/Debra Kristensen

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Disposable-syringe jet injectors

Photo: PharmaJet

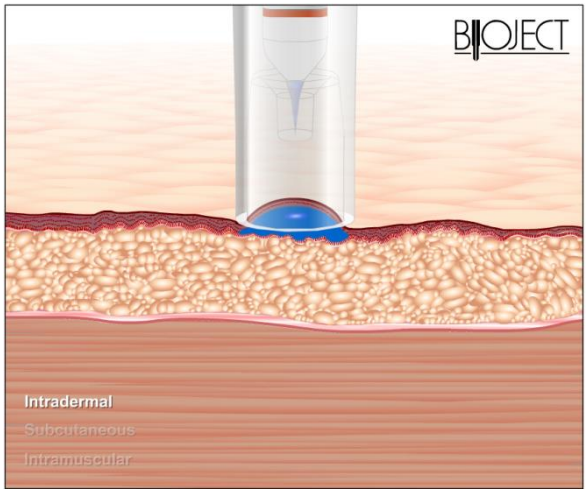
Photo: PATH

Photo: PATH

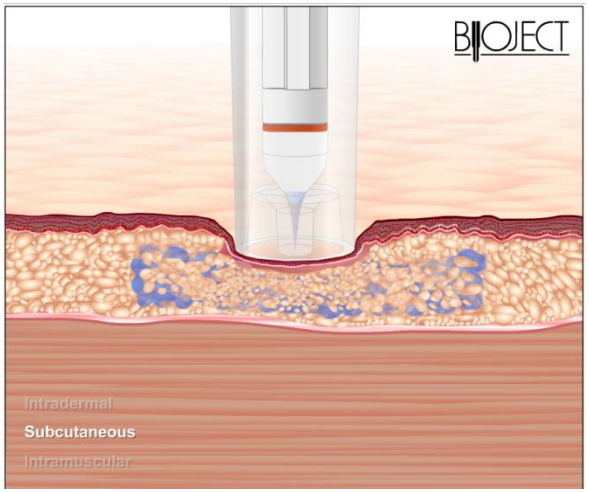
Delivery using jet injectors

Jet injectors deliver vaccines and medicines without using needles; instead, jet injectors generate a pressurized liquid stream that pushes through the skin, penetrating it to deliver injections into the tissue.

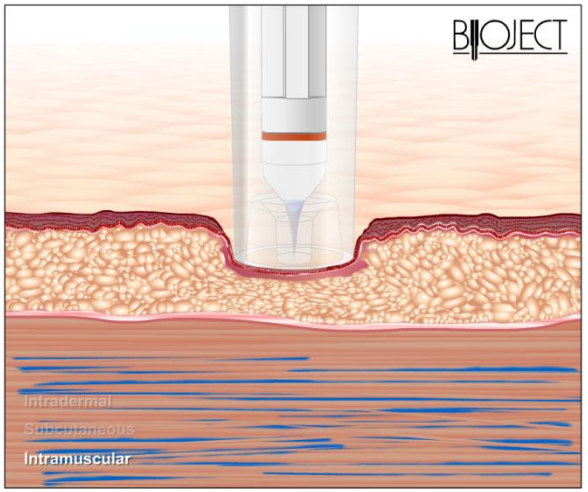
A PharmaJet DSJI injection in action.



ID injection with a DSJI.



SC injection with a DSJI.



IM injection with a DSJI.

All images: Bioject

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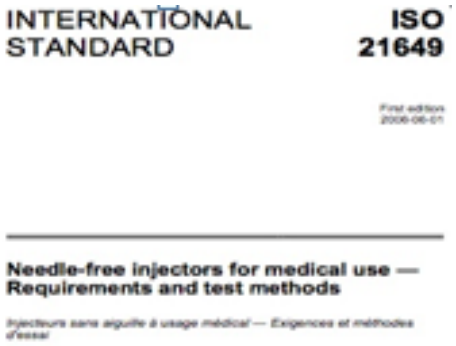
Acronyms: DSJI, disposable-syringe jet injector; ID, intradermal; IM, intramuscular; SC, subcutaneous.

DSJI WHO prequalification

- Prequalification requirements are based upon the International Organization for Standardization standard for jet injectors (ISO+).
- Requires device clearance through globally recognized national regulatory authority.
- PharmaJet Stratis® technology was the first DSJI to complete this process (January 2013).



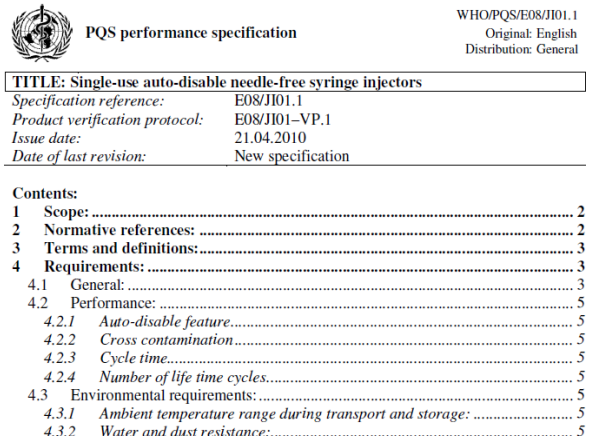
INTERNATIONAL STANDARD

ISO 21649

First edition
2006-06-01

Needle-free injectors for medical use — Requirements and test methods

Injecteurs sans aiguille à usage médical — Exigences et méthodes d'essai



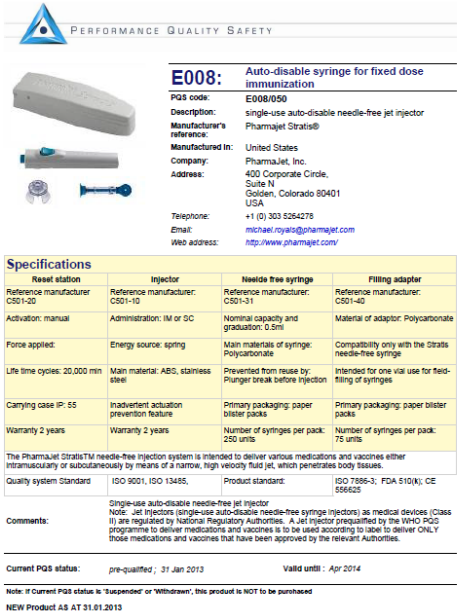
PQS performance specification

WHO/PQS/E08/JI01.1
Original: English
Distribution: General

TITLE: Single-use auto-disable needle-free syringe injectors

Specification reference:	E08/JI01.1
Product verification protocol:	E08/JI01–VP.1
Issue date:	21.04.2010
Date of last revision:	New specification

Contents:



PERFORMANCE QUALITY SAFETY

E008: Auto-disable syringe for fixed dose immunization

PQS code:	E008/050
Description:	single-use auto-disable needle-free jet injector
Manufacturer's reference:	Pharmajet Stratis®
Manufactured in:	United States
Company:	PharmaJet, Inc.
Address:	400 Corporate Circle, Suite N Golden, Colorado 80401 USA
Telephone:	+1 (0) 303 5254276
Email:	michael.royals@pharmajet.com
Web address:	http://www.pharmajet.com/

Specifications

Reset station	Injector	Needle free syringe	Filling adapter
Reference manufacturer: C501-20	Reference manufacturer: C501-10	Reference manufacturer: C501-31	Reference manufacturer: C501-40
Activation: manual	Administration: IM or SC	Nominal capacity and graduation: 0.5ml	Material of adaptor: Polycarbonate
Force applied:	Energy source: spring	Main materials of syringe: Polycarbonate	Compatibility only with the Stratis needle-free syringe
Life time cycles: 20,000 min	Main material: ABS, stainless steel	Prevented from reuse by: Plunger break before injection	Intended for one vial use for field-filling of syringes
Carrying case IP: 55	Inadvertent actuation prevention feature	Primary packaging: paper blister packs	Primary packaging: paper blister packs
Warranty 2 years	Warranty 2 years	Number of syringes per pack: 250 units	Number of syringes per pack: 75 units

The PharmaJet StratisTM needle-free injection system is intended to deliver various medications and vaccines either intramuscularly or subcutaneously by means of a narrow, high velocity fluid jet, which penetrates body tissues.

Quality system Standard	ISO 9001, ISO 13485,	Product standard:	ISO 7886-3; FDA 510(k); CE 556625

Comments: Single-use auto-disable needle-free jet injector
Note: Jet Injectors (single-use auto-disable needle-free syringe injectors) as medical devices (Class II) are regulated by National Regulatory Authorities. A Jet injector prequalified by the WHO PQS programme to deliver medications and vaccines is to be used according to label to deliver ONLY those medications and vaccines that have been approved by the relevant Authorities.

Current PQS status: *pre-qualified ; 31 Jan 2013* **Valid until :** *Apr 2014*

Note: if Current PQS status is 'Suspended' or 'Withdrawn', this product is NOT to be purchased

NEW Product AS AT 31.01.2013

Acronyms: DSJI, disposable-syringe jet injector; World Health Organization, WHO.

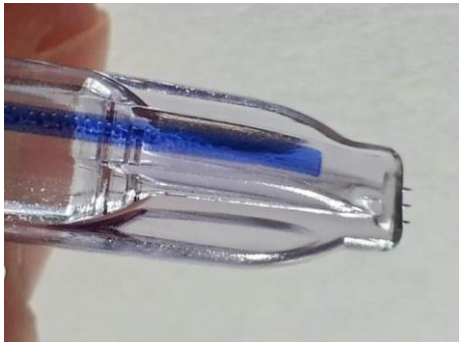
ID delivery device categories

Needle-based devices (standard needle and syringe, hollow microneedles, mini-needles, ID adapters)

Disposable-syringe jet injectors

Microneedle patches (solid coated or dissolvable)

Field filled or prefilled with liquid vaccine



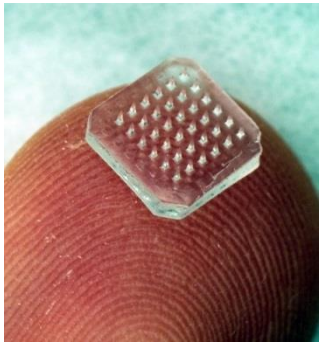


Photo: Georgia Institute of Technology

All photos: PATH except where noted

Acronym: ID, intradermal.

ID delivery devices: Needle based

Manufacturer	Device	Development Status	Image
West Pharmaceutical Services, Inc. (West)	ID Adapter	Commercialized	A
BD	Soluvia™	Commercialized (influenza vaccine)	B
Star Syringe, Ltd.	Star ID	Preclinical	C
NanoPass	MicronJet 600	Commercialized	D

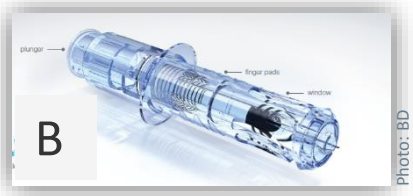
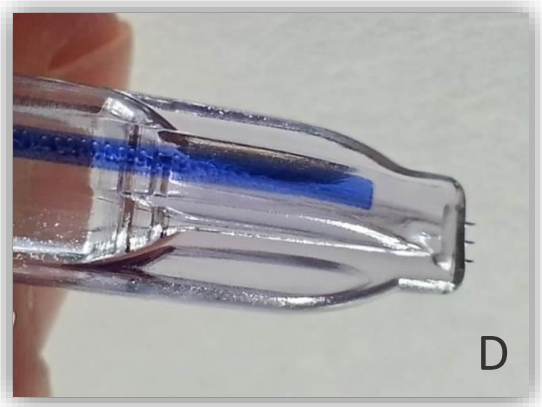


Photo: BD

Photo: Star Syringe



All photos: PATH except where noted

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Acronym: ID, intradermal.

ID delivery devices: Disposable-syringe jet injectors

Manufacturer	Device	Development Status (for ID delivery)	Image
PharmaJet®	Tropis	Clinical	A
Bioject	ID Pen	Clinical	B
	Zetajet®	Clinical	—
	Biojector® 2000	Device clearance	D
Medical International Technologies	Dart	Preclinical	C
	H4	Preclinical	—

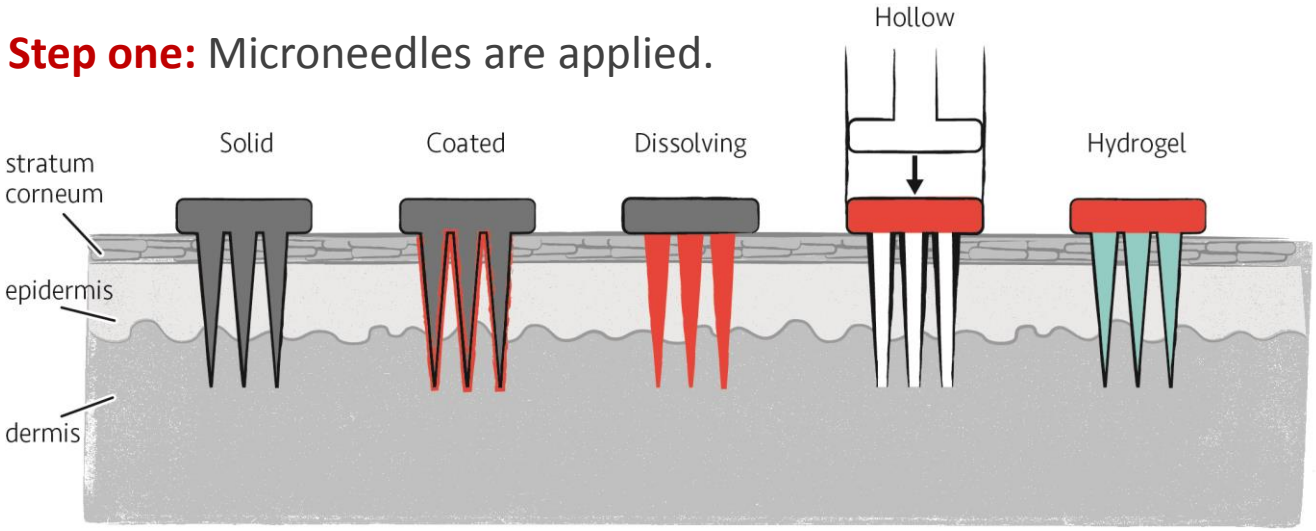
All photos: PATH

Acronym: ID, intradermal.

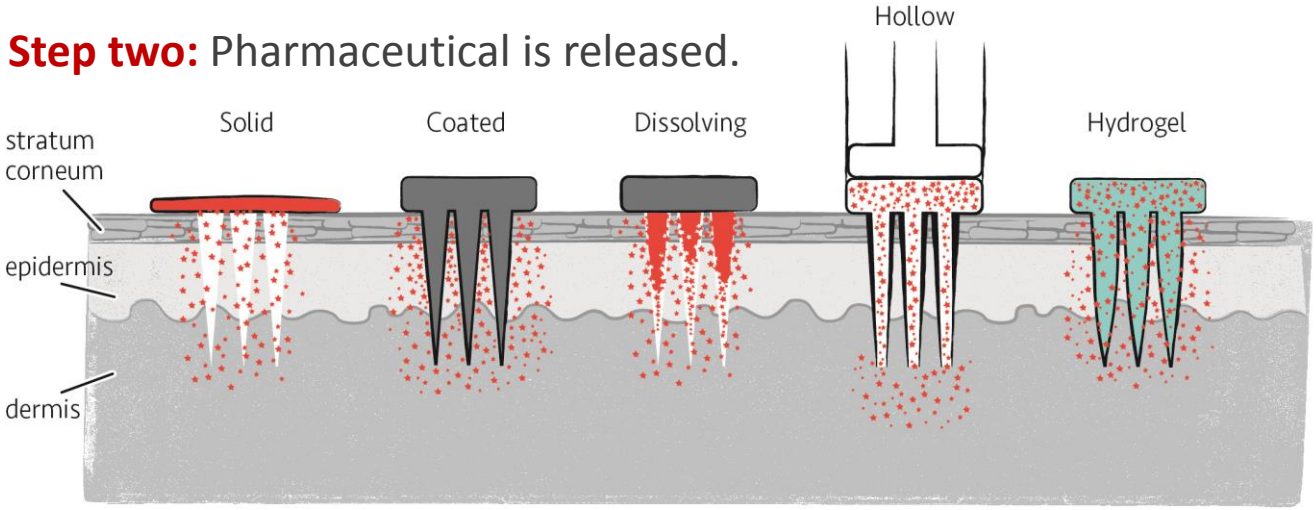
Comparison of microneedle types

Solid, coated, dissolving, hollow, and hydrogel.

Step one: Microneedles are applied.



Step two: Pharmaceutical is released.



Images: PATH

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ID delivery devices: Microneedle patches

Developer	Device	Development Status	Patch type	Components	Image
Georgia Institute of Technology	—	Preclinical	Dissolvable	Patch (potentially no applicator needed)	A
Corium	MicroCor®	Preclinical	Dissolvable	Patch and integrated applicator	B
Vaxxas / University of Queensland	Nanopatch™	Preclinical	Solid coated	Patch and applicator	C

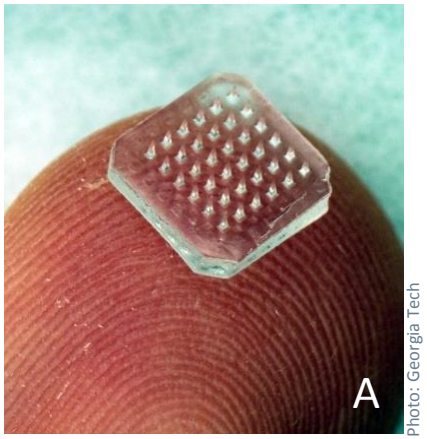


Photo: Georgia Tech

Photo: Corium

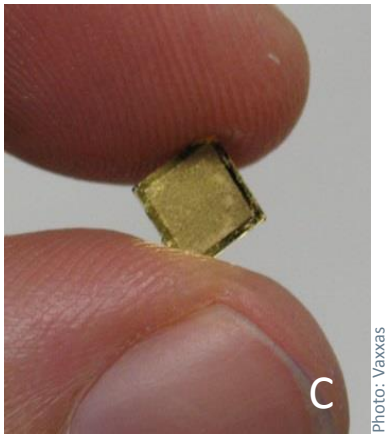


Photo: Vaxxas

Acronym: ID, intradermal.

Oral Prefill Technologies

Manufacturer	Device	Development Status	Image
BD®	Uniject DP	Market available	A
Rommelag	BFS	Market available	B
	BFS MMD	In development	C
Lameplast	Tube	Market available	D

Photos: PATH/Patrick McKern

Photo: PATH/Greg Kachmarik

PATH 3D-printed prototype.

Acronyms: BFS, blow-fill seal; MMD, multi-mono dose.

Technology example: Multi-mono dose

Multi-mono dose:

- A conjoined strip of single-dose containers with a single label and vaccine vial monitor.
- Separating a single container from the strip opens the container.
- Formed using BFS or other plastic container technologies.

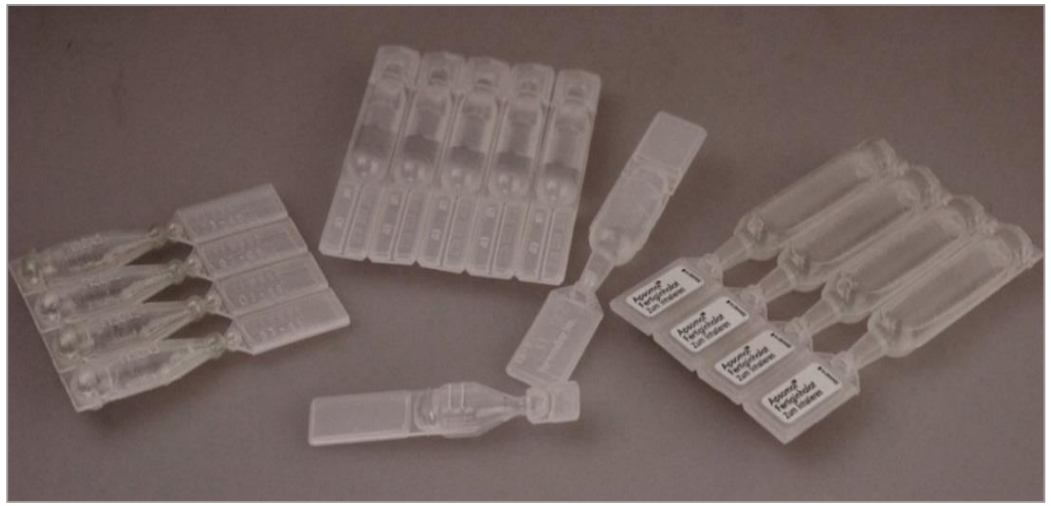
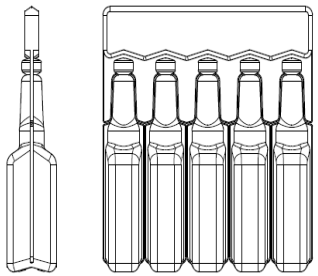


Photo: PATH

Conjoined BFS packaging.



Images: PATH

CAD models of multi-mono-dose design.

Photo: PATH/Greg Kachmarik

PATH 3D-printed prototype.

Acronyms: BFS, blow-fill seal; CAD, computer-aided design.

Parenteral prefill technologies

Manufacturer	Device	Development Status	Image
BD®	Uniject	Market available	A
BD®	Hypak	Market available	B
Gerresheimer	Gx RTF®	Market available	C
Taisei Kako Co., Ltd	ClearJect™ (COC polymer)	Market available	D
Rommelag	BFS for injection	In development	E
Angela Brevetti	Secureject®	Market available	F

Acronyms: BFS, blow-fill seal; RTF, ready to fill.

Reconstitution Technologies

Manufacturer	Device	Development Status	Image
Vetter	Lyo-Ject	Market available	A
Eulysis	SVS	In development	B
LyoGo	LyoGo	In development	C
LyoTip	LyoTip	In development	D

A

Photo: Vetter

B

Photo: Eulysis

C

Photo: Lyogo

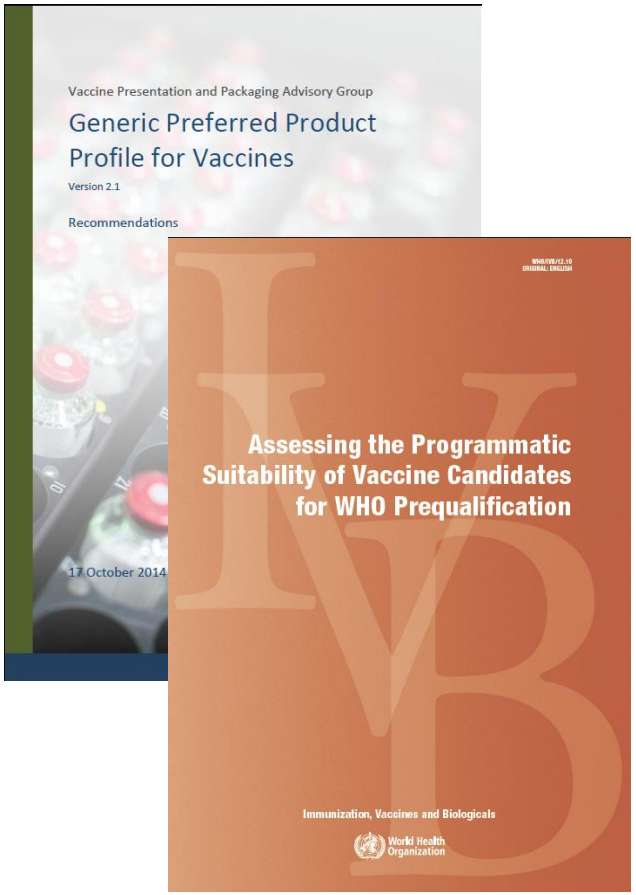
D

Photo: LyoTip

Acronym: SVS, single-vial system.

Key considerations—vaccine delivery technologies

- Integrate new technology early in vaccine development process.
- Ensure alignment with generic preferred product profile for vaccines—pursue consultation with VPPAG.
- Confirm programmatic suitability for WHO prequalification.
- Estimate device costs (cost of goods, cost per delivered dose).
- Assess potential cold chain impact.
- Confirm human factors/health care worker usability.



Thank you

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Photo: PATH/Mike Wang