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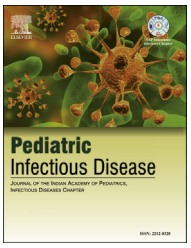

Immunization Update

Prefilled syringes versus vials: Impact on vaccination efficiency and patient safety in Indian private market

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ARTICLE INFO

Article history:
Received 12 August 2013
Accepted 30 November 2013
Available online 19 December 2013

Keywords:
Prefilled syringe
Time and motion study
Vaccination
Vial

ABSTRACT

Background and aim: Considering the proportion of unsafe injection practices in India, an evaluation of the potential improvement in vaccination with prefilled syringe (PFS) compared to SDV and MDV (single and multidose vials) in Indian private market is the objective of this paper.
Method: An observational, open label, randomized 2-phase time and motion study involved comparison in terms of efficiency associated with the vaccine administration process (preparation, injection, and disposal) and rate of handling errors with safety implications.
Setting: Five Indian pediatric vaccination centers.
Participants: Forty vaccinators (8 per center). 10 observers.
Main outcome measures: Time taken for each activity cycle; frequency of errors observed (Phase 1); time for 10 consecutive injections (Phase 2).
Results: The mean time required to perform a vaccination with PFS was 47.6 ± 11.7 s and was twice as fast as with vials ($p < 0.0001$). The mean number of handling errors with PFS was 1.1 ± 1.7 and was 3 times fewer than with vials ($p < 0.0001$).
Conclusions: Compared with vials, PFS are productivity enhancers, as they decrease time required to perform vaccinations and reduce wastage. PFS are also risk reducers, as they reduced the occurrence of handling errors and associated health hazard risks by a factor of 3.

Actual cost comparison was not part of the study. But this study has shown that use of PFS is associated with cost reduction in terms of saving time correlated with man hours and reducing wastage.

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2212-8328/$ – see front matter
http://dx.doi.org/10.1016/j.pid.2013.11.005

1. Introduction

Globally, vaccines are distributed in three main presentations: vials, which can be single dose vial (SDV) or multidose vials (MDV), and prefilled syringes (PFSs). In India, predominantly MDVs are used, but PFSs have gained market share over the last few years in the private market.

Comparing MDV, PFS offer advantages in speed, disposal, wastage and patient safety, owing to premeasured accurate doses that reduce dosing errors and risk of microbial contamination.[1–3]

PFS vaccines come without preservative with minimal overfilling unlike MDV. The limitations of PFS are in terms of large storage space in cold chain maintenance and slightly high cost per dose. Use of MDV is cheaper, but using MDVs can be more time consuming for the healthcare worker, leading to higher administration costs with more potential for dosing and handling errors and contamination.

Here, we study the vaccine presentation globally with various study data. Considering the proportion of unsafe injection practices in India, to evaluate the potential improvement in vaccination with PFS compared to SDV and MDV in Indian private market is the objective of this review article. This is an attempt to improve injection practices in India.

2. Global data of evaluation of vaccine presentation (vial versus PFS)

Prior studies comparing MDVs and PFSs have been conducted in other countries. A study conducted by Scheifele and colleagues[4] in Canada demonstrated that PFSs could save nurses' time in mass immunization clinics. In this Canadian study, for 1000 vaccine doses, vials took 36 nurse hours as against 27 nurse hours of syringes. This study clearly demonstrated that, compared with multidose vials, pre-filled syringes reduced nursing service time by 9 person-hours per 1000 doses, reducing labor costs by 25–33%.[4]

The observational study conducted by Johns Hopkins University, USA has found vaccinating with MDVs took 37.3 s longer than with PFSs.[5]

As per study conducted by Pellissier et al,[6] total nurse time associated with vaccine administration decreased by 2.4 and 1.7 min per shot eliminated in the examination room setting ($P = 0.006$) and in the injection room setting ($P < 0.001$), respectively. Significant time savings were realized for activities associated with vaccine preparation, vaccine injection, and administrative duties.[6]

Study conducted by Szilagyi et al, documented 1–2 min directly related to preparing and administering vaccines, as estimated by nurses or physicians.[7]

2.1. The Indian time and motion study

The study which was done in 2011/12 at five Indian pediatric vaccination centers with forty vaccinators and 10 observers, demonstrated advantages of PFS versus vials. The key advantage of this investigation over these studies lay in directly observing vaccinators rather than asking practitioners to estimate times via interviews or questionnaires.[7,8]

3. Materials and methods

3.1. Design

The study included 2 phases. In Phase 1, for each of the 9 injections (3 with each vaccine delivery system performed on dummy arm & in a randomized crossover order), an observer manually recorded the duration of the activity cycles with a stopwatch and noted potential handling errors. In Phase 2, observers recorded the time taken to perform 10 consecutive injections with each kind of vaccination delivery technology. The time required for vaccine delivery was divided into activity cycles depending on the vaccine delivery device used (Table 1).

The health hazard risk (HHR) evaluation tool was built by BDM- PS (Becton Dickinson Medical – Pharmaceutical systems) and validated by the principal investigator. The HHR score was calculated, for each activity cycle and in total, by multiplying the observed error frequency by a theoretical severity score (determined in the study protocol).

3.2. Vaccinators

The study was conducted at 5 centers (Mumbai, Hyderabad, Bengaluru, Delhi and Kolkata). Forty vaccinators (8 at each center), of both genders, with at least two years of professional experience delivering vaccines in children and/or adults, were recruited. Vaccinators were not centers employees. The study also included observers whom were met for the first time. There was a potential influence of observation to vaccinator behavior but logically equivalent for the three compared systems (PFS, SDV, and MDV).

3.3. Waste weight

Waste management is a significant part of cost evaluation; therefore, vaccine dose wastage with MDVs was measured after Phase 2 by counting the number of doses obtained per MDV. Supplementary MDVs were provided, if necessary, to allow vaccinators to prepare 10 doses.

3.4. Ethics

All participants were volunteers and agreed to participate in the study. Oral informed consent was taken.

3.5. Statistics

To have a margin in case of non-evaluable injections, a final sample size (observed injection) of 1560, i.e. 520 for each delivery system option, was targeted. Statistical analysis was performed using SAS 9.2. The significance level was 0.05 (2-sided). *Descriptive statistics were calculated for all continuous and categorical data.*

Table 1 – Description of activity cycle per tested system.

Prefilled syringe (PFS)	Single dose vial (SDV)	Multidose vial (MDV)
1. Assembling the equipment and supplies from the refrigerator onto working table		
One PFS, one swab	One vial, one disposable syringe (1 ml), two needles, two swabs	
2. Open the primary packaging		
Open the primary packaging of the PFS	Open the vial, the packaging of syringe, needle, and assembly	
3. Preparation for injection		
Check the prefilled content (cloudiness, particulate matter)	Disinfect the vial stopper with swab	
Remove air bubbles by tapping, if any	Insert needle with syringe in the vial	
	Withdraw required amount of solution; Remove syringe & needle assembly for the vial	
	Replace the needle shield on the needle and tap the syringe to dislodge any air bubble, expel air, and check dose	
	Remove the first needle and discard in sharp collector provided	
	Correctly assembly the second needle on the hand filled disposable syringe	
4. Injection procedure: – (inserting – administration–removal)		
	Prepare simulated skin (swab the foam pad surface)	
	Insert the syringe with needle at 90° angle	
	Complete fluid injection in the muscular tissue (foam pad)	
	Verify that dose has been fully injected by inspecting syringe	
	Remove needle from the muscle tissue (foam pad)	
5. Discarding the used material		
Discard the used PFS in designated bin	Discard the SDV in designated bin	Replace the MDV in refrigerator or discard the
Discard the swab(s) in BMW container	Discard the used disposable syringe in sharp collector	MDV in designated bin if non reusable or finished
Discard the general waste in designated bin	Discard the swab(s) in BMW container	Discard the used disposable syringe in sharp collector
	Discard the general waste in designated bin	Discard the swab(s) in BMW container
		Discard the general waste in designated bin

3.6. *Potential limitation and biases*

The main limitation of this study was that it focused entirely on the efficiency of the vaccination system. Actual cost comparison of each vaccine delivery technique was not part of study.

The limitations about use of PFS in terms of large storage space in cold chain maintenance is another important aspect.

Another issue could be the simulated injection process to the 'real-life' clinic setting, as behavior and interaction will be different.

4. Results

4.1. *Comparison of PFS versus SDV and MDV*

4.1.1. *Time & motion evaluation (Phase 1)*

The time to perform the whole vaccination is 2 times faster with PFS (47.6 s) than with SDV (99.8 s) and MDV (100.5 s) ($p < 0.0001$) (Fig. 1). Time savings observed with PFSs were due to reduction in all activity cycle durations except injection (Table 2).

4.1.2. *Vaccinator productivity (Phase 2)*

The required time for 10 simulated injections is shorter with PFS than SDV and MDV ($p < 0{,}0001$), respectively 7 min, 14 min and 13.6 min, i.e. 2 times faster with PFS.

4.1.3. *Handling errors (Phase 1) and Health Hazard Risk Evaluation (HHRE)*

Total 334 errors were recorded (Table 3) .The number of handling errors with PFS (**43 errors** i.e. an error rate of **3.6% for 120 injections) was 3 times smaller** than with vials (with SDV, a total of **154 errors** i.e. an error rate of **8.5%**, with MDV, a total of **137 errors** i.e. an error rate of **7.6% for 120 injections).** ($p < 0.0001$).

Total HHRE score is 3 times smaller with PFS (3.0 than with MDV (9.9) and SDV (10.5) ($p < 0.002$)).

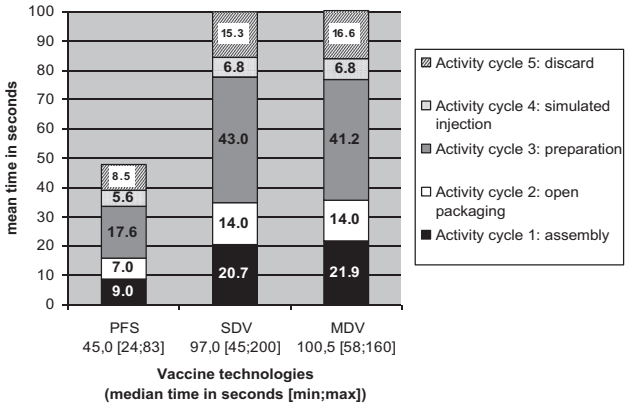

Fig. 1 – Mean time required per injection.

Table 2 – Mean required time at total and per activity cycle.

Time to perform (in s):	Vaccination technique			*p* Value (Tukey's adjustment)		
	PFS (*N* = 120)	SDV (*N* = 120)	MDV (*N* = 120)	PFS versus SDV	PFS versus MDV	SDV versus MDV
The whole vaccination						
LS[a] Means	42.7	95.6	96.1			
95%CI	[29.2; 56.2]	[82.1; 109.0]	[82.6; 109.6]	**< 0.0001**	**< 0.0001**	0.9542
Activity cycle 1: assembling						
LS Means	8.9	20.8	21.8			
95%CI	[5.9; 12.0]	[17.7; 23.9]	[18.7; 24.9]	**< 0.0001**	**< 0.0001**	0.2320
Activity cycle 2: open packaging						
LS Means	6.1	13.1	13.1			
95%CI	[3.8; 8.3]	[10.8; 15.3]	[10.8; 15.3]	**< 0.0001**	**< 0.0001**	0.9976
Activity cycle 3: preparation						
LS Means	14.0	40.0	37.8			
95%CI	[6.2; 21.9]	[32.1; 47.8]	[30.0; 45.7]	**< 0.0001**	**< 0.0001**	0.2281
Activity cycle 4: simulated injection						
LS Means	5.4	6.6	6.8			
95%CI	[3.8; 7.1]	[5.0; 8.3]	[5.1; 8.5]	**< 0.0001**	**< 0.0001**	0.8746
Activity cycle 5: discarding						
LS Means	8.2	15.1	16.6			
95%CI	[5.6; 10.8]	[12.5; 17.7]	[14.0; 19.1]	**< 0.0001**	**< 0.0001**	**0.0151**

[a] LS = Least Squares means (means estimated by Least Square Method).

4.1.4. *Number of doses obtainable and wastage with MDV (Phase 2)*

In mean, to deliver 10 doses, 1.35 MDV wherever required (54 MDV to perform 400 doses). Vaccine waste was higher (35%) with multidose vials (MDV).

The mean vaccine dose wastage with MDV is 0.52 g ± 0.48 g (min = 0; max = 2.7).

4.2. *Comparison between SDV and MDV*

No statistically significant differences were observed between SDVs and MDVs for any parameter.

5. Discussion

The study finding of mean required time to deliver one vaccine dose with a PFS (approximately 48 s) is consistent with the results of a previous time and motion study conducted in India (46 s).[9]

The shorter vaccination time related to PFSs resulted in a 2-fold vaccinator productivity increase. Although this was recorded in observed simulated conditions, the finding is supported by Scheifele et al, who found a 9-h working-time reduction using PFSs versus vials for delivery of 1000

Table 3 – Number of handling errors at total and per activity cycle (Phase 1).

Descriptive analysis	Vaccination technologies			
	PFS (*N* = 40)	SDV (*N* = 40)	MDV (*N* = 40)	Total (*N* = 120)
Injections with 100% of steps correctly performed – *N* (%)				
0 injection/3	9 (22.5%)	27 (67.5%)	25 (62.5%)	61 (50.8%)
1 injection/3	4 (10.0%)	3 (7.5%)	3 (7.5%)	10 (8.3%)
2 injections/3	0 (0.0%)	5 (12.5%)	5 (12.5%)	10 (8.3%)
3 injections/3	27 (67.5%)	5 (12.5%)	7 (17.5%)	39 (32.5%)
Number of errors during the 3 injections				
Mean (±SD)	1.1 (±1.7)	3.9 (±3.1)	3.4 (±2.5)	2.8 (±2.8)
Median	0.0	3.0	3.0	3.0
Min-Max	[0.0; 6.0]	[0.0; 17.0]	[0.0; 9.0]	[0.0; 17.0]
Handling errors	**PFS (*N* = 120)**	**SDV (*N* = 120)**	**MDV (*N* = 120)**	**Total (*N* = 360)**
Disinfect vial stopper with the swab		27	17	44
Insert needle with syringe in vial		0	1	1
First needle replacement (replace needle shield, assembly of second needle)		47	27	74
Prepare simulated skin	1	3	6	10
Needle at 90° angle	32	34	36	102
Inspect syringe after injection (complete dose)	9	37	36	82
Replace MDV in refrigerator			11	11
Discard vial or general wastage in correct bin	0	5	2	7
Discard swab	1	1	1	3
Total	**43**	**154**	**137**	**334**

influenza doses.[4] Extrapolating our results in the context of an Indian vaccination campaign, the time saving achieved by replacing MDVs with PFSs would be 13 h per 1000 injections. According to Wiedenmayer et al, in a previous time and motion study based on the Institute of Child Health in Calcutta, a 50-s time saving per vaccination translates to a global delivery time saving of about 107,000 working days per year.[9]

As per the study conducted by Johns Hopkins University, the cost of administering 1000 immunizations in 2009 using PFS was marginally high (US$0.32 per dose administered) compared to MDV. This excludes the acquisition cost of the vaccine which is significant factor in the vaccine administration cost.[5] An European study in 1996 compared prefilled disposable syringes with conventional vial-based systems for parenteral injections and revealed that PFSs led to a cost reduction of 1.5 French Francs (or 1996 GB£0.15) per injection as it saves time.[3]

The economic decision rests on whether there are improved uses for the valuable resource of healthcare worker time, especially of nurses. However, in Indian set up, because of cost limitation and large cold chain storage requirement, PFS has limitation in the public healthcare sector.

Finally, this study highlighted the important issue of vaccine wastage with MDVs. Despite MDV overfilling, 35% of MDVs delivered only 9 doses, necessitating the opening of additional vials for the tenth vaccination. This result is concordant with a previous study which demonstrated that 10-dose vaccine vials delivered an average of 7.3–8.8 × 0.5 mL doses per vial, depending on the type of disposable syringe used.[10] UNICEF data for Indian study proved that wastage was due to inability to draw the number of doses in a vial and poor reconstitution practices preparation etc.[11]

In this review, the safety advantages of PFSs are also confirmed as the handling error rate and the HHR were substantially lower with PFSs than with vials. Indian study, study from Johns Hopkins University, USA[5] confirm that with PFS, handling errors are much less as compared to vials.

5.1. *Safety*

Safety is a prime concern in vaccination. Paradoxically, there is distinctive variation in the way vaccines are administered, reflecting particularities in safe injection practices.

5.2. *What is the current status of injection practices in India[12]?*

IPEN study group, revealed that

- Of the total injections, 62.9% (95%CI: 60.7–65.0) were unsafe.

5.3. *Unsafe injections*

- Of all the injections administered in India, one third [31.6%; 95%CI 29.4–33.0] carried a potential risk of transmitting blood borne virus (use of syringes and needles that were inadequately sterile and/or reuse of plastic syringe).[12]
- Unsafe injection due to faulty technique was observed in 53.1 percent [95%CI 50.8–55.4] of injections.[12]

The CDC identified as safety breaches the use of multidose medications that were accessed multiple times with non-sterile syringes and needles.[13] As per EPINET 2011 data,[14] injuries with disposable syringes were high (37.4%) as against with PFS (2.2%).

5.3.1. *From the November 2012 CDC guidelines[15]*

Manufacturer-filled syringes are recommended instead of pre drawing vaccine. Manufacturer-filled syringes are labeled and prepared under sterile conditions that meet standards for proper storage and handling. They have been designed and tested to assure vaccine potency and sterility over prolonged storage times.

In summary, current literature and guidelines indicates that PFSs have the potential to be safer and more efficient than vials. But there have been no review from India to support a systematic comparison of vial and syringes with safety and efficiency parameters. The rationale for this review was to quantify benefits of PFS over vials with Indian study.

6. Conclusion

This review has shown that compared to vials, PFSs enhance productivity by decreasing the vaccination time and reducing waste of drug, also reduce risk. The number of handling errors and related HHR (heath hazard risk) with PFS were 3 times smaller than with vials as per Indian time and motion study.

Although MDVs require less space for cold storage and are cheaper, their use imposes higher staff time burdens with more potential for dosing and handling errors and contamination.

This work shows that use of PFS is more economic than MDVs as it reveals the longer average time required to prepare a dose of vaccine from an MDV. The small increment in the cost of PFS and storage requirements are likely to be the main reasons that practices have not yet completely switched to PFSs. In Mass vaccination, clinics would need to weigh the relative advantages of PFSs over MDVs, versus the full cost of both.

Vaccination in India still predominantly uses MDVs, but PFSs offer many advantages over MDVs in terms of efficiency and safety, especially considering the many opportunities for errors and contamination that the use of MDVs creates in vaccination. In Indian set up, health insurance is not covered by government and patients have to pay from their pockets. Hence additional increment in the cost of PFS application is constraint for public health sector. However, in the private healthcare sector, PFS has gained market share for its safety and efficiency benefits. Although there are issues surrounding policy and market pricing strategy related to vaccine, we expect to continue to see growth in the market share of PFSs in private sector. Our projection is based on survey about opinion and preference of vaccinators about prefilled syringe and vial and from our understanding of the market dynamics over the last few years. As the demand for PFSs increases manufacturers are expected to increase production capacity bringing cost down.

This has already been seen to a certain extent in the past decade. The price gap between PFSs and MDVs will diminish over the period of time.

Acknowledgements

The authors would like to thank the vaccinators who kindly allowed observing their work and routine. The authors would like to thank Frederic Mistretta (RCTS, statistician), and Anna Roubo (Aspen), Philippe Laurent and Florence Schwarzenbach, Alaknanda Dhotre (BD Pharmaceutical Systems, Medical Affairs) for their expert comments which helped in preparing this report.

Financial & competing interest disclosure

This work was initiated and conducted by the Indian Academy of Pediatrics Committee of Immunization. The study was funded by grant received by Becton Dickinson India Pvt. Ltd, Gurgaon.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

The authors state that the Time and Motion study did not involve any human being as subject. The study was done in simulated conditions using dummy arms for vaccination purpose. The dummy arm used resembled human skin with all the layers with same texture and consistency. The study was conducted as per the prevailing guideline for clinical trials with simulation technique and as per the protocol. (Hale et al 1996, Peck & Desjardins 1996, ECPM 1996, CDDS 1997,FDA 1999, Peck 1997b, Krall et al 1998.) The authors state that clinical study fulfills the criteria for exemption for human subject research as per 45 CFR 46.101(b). As per ICH–GCP guidelines, DCGI regulation, The Office for Human Research Protections (OHRP), IEC approval is mandatory only if human subjects are involved and not otherwise.

Time and Motion study was eligible for exemption from registration of the study as per guidelines as this was the small clinical study to determine the feasibility of a device using dummy arms. The study was conducted to quantify the existing benefits of device in the scientific and clinical manner. It was not aimed to find out new usage of the device. Hence exemption from registration was as per the guidelines.

Even though the IRB and registration exemption was applicable to the study as per the guidelines, the investigators obtained consent from each vaccinator to be part of the study.

Conflicts of interest

All authors have none to declare.

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