Single-dose versus multi-dose vaccine vials for immunization programmes in developing countries

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Abstract Excessive vaccine wastage and safety concerns have prompted the international health community to develop and supply vaccines in formats other than the standard multi-dose vial. This article presents a programmatic and economic comparison of the major differences between the multi-dose vials and single-dose formats used for immunization services in developing countries.

Multi-dose vials, in general, sell at a lower per-dose price and occupy less cold-chain capacity than single-dose formats. However, higher wastage rates may offset these benefits, especially for more expensive vaccines. Single-dose formats offer several important programmatic benefits, such as increased vaccination opportunities and improved vaccine safety. One single-dose format, the prefilled auto-disable (AD) device, provides additional injection safety and convenience features because it physically combines the vaccine and AD syringe.

Selecting the appropriate vaccine presentation will depend on many factors. However, multi-dose vials are likely to be most appropriate for cheaper vaccines and in settings where cold-chain storage capacity is restricted. Single-dose formats will be most appropriate for more expensive vaccines and where there are problems with unsafe injection practices. Prefilled AD injection devices will be particularly useful in expanding outreach services while eliminating the possibility of needle reuse.

Keywords Vaccines/administration and dosage/economics; Dosage forms; Injections/standards; Immunization programs; Comparative study; Developing countries (*source: MeSH, NLM*).

Mots clés Vaccins/administration et posologie/économie; Forme pharmaceutique; Injection/normes; Programmes de vaccination; Etude comparative; Pays en développement (*source: MeSH, INSERM*).

Palabras clave Vacunas/administración y dosificación/economía; Formas de dosificación; Inyecciones/normas; Programas de inmunización; Estudio comparativo; Países en desarrollo (*fuente: DeCS, BIREME*).

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Introduction

Immunization programmes save millions of lives every year worldwide (*1*). Vaccination is heralded as one of the most cost-effective medical interventions (*2*). However, nearly 25 years after WHO established the Expanded Programme on Immunization (EPI), it was estimated that in 2000, about 37 million children worldwide did not receive routine immunization during their first year of life (*3*). At the end of the 1990s, a decade that saw declining vaccination coverage rates (*4*), vaccine-preventable diseases killed nearly 3 million people, most of whom were children, every year (*3*, *5*).

Fortunately, immunization services have entered a new era, with an expanding selection of vaccines, safer injection syringes, and increased support from international organizations and donor agencies. Auto-disable (AD) syringes are quickly replacing reusable sterilizable syringes for vaccinations (*6*, *7*). With the founding of the Global Alliance for Vaccines and Immunization (GAVI) and the Vaccine Fund (*8*, *9*), over US$ 1 billion have been committed to support immunization in 60 of the world's poorest countries over the next 5 years (*10*).

The increasing focus on immunization programmes is accompanied by increased scrutiny on the way vaccines are packaged. In 2000, approximately 80% of vaccinations administered globally were supplied in multi-dose vials (*11*), but new concerns have arisen regarding the safety and cost-effectiveness of multi-dose vaccine vials. Increasing attention on safety, wastage reduction, and programmatic benefits has led to more options in vaccine vial size and packing (J. Vose, unpublished). Some vaccines, such as hepatitis B and tetanus

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toxoid (TT), may soon become widely available in prefilled AD devices.

The objective of this article is to present a comprehensive analysis and review of the major programmatic and economic issues affecting the use of single-dose and multi-dose vaccine vials in developing countries. The issues are presented systematically, from vaccine production to waste disposal.

Comparison of single-dose and multi-dose vaccine formats

Definitions

The term multi-dose vial is used in this paper to describe the common glass vial that is available in many sizes, including 2-dose, 6-dose, 10-dose, 20-dose, and others. Most childhood immunizations come in 10-dose or 20-dose vials; we have used 10-dose for comparison purposes in this review. Multi-dose vials are used for liquid (including oral polio, DPT, TT, hepatitis B) and lyophilized (including Bacille Calmette–Guérin (BCG) and measles) vaccines.

Single-dose formats include single-dose vials used for both liquid and lyophilized vaccines and prefilled AD devices. Prefilled AD devices refer to a specific type of single-dose format where a single dose of vaccine is prefilled into an AD injection device. These devices are used for liquid vaccines only. Ampoules are not included in this discussion.

Vaccine manufacturing costs

The manufacturing costs of the various vaccine formats are separated into three categories (see Table 1). In all categories single-dose formats are more costly than multi-dose vials, for three main reasons. First, filling costs for single-dose vials are higher than those for multi-dose vials because single-dose vials can be filled with fewer doses per minute. By one estimate, filling costs per dose for single-dose liquid vaccine vials are approximately three times higher than for 10-dose vials (P. Heyman, BD Pharmaceutical Systems R&D, personal communication, 2000). The difference in filling costs is amplified with lyophilized vaccines because single-dose vials occupy significantly more space during lyophilization — an expensive process that usually lasts several days.

Second, vaccine overfill is necessary when filling syringes so that the syringe can be filled with an entire dose of vaccine. Single-dose vials require more vaccine overfill per dose than do multi-dose vials. Prefilled AD devices require less overfill than single- or multi-dose vials.

Third, packaging costs include glass, metal, rubber, labels, and vaccine vial monitors (VVMs). With multi-dose vials these costs are shared across many doses and thus have a lower per-dose cost for packaging materials.

Overall, manufacturing costs for single-dose formats are about 2.5 times greater than the costs of packaging 10-dose vials; however, this difference does not include the vaccine price (Table 1). For expensive vaccines the difference in manufacturing costs will represent only a small portion of the total packaged-vaccine price, whereas for inexpensive vaccines manufacturing costs may be the primary price component.

Vaccine distribution

The primary vaccine distribution issues affected by vial size are inventory logistics and cold-chain capacity. The use of single-dose formats may simplify logistical complications of cold chain distribution but it may also increase cold-chain capacity requirements. For example, vaccine tracking and inventory logistics are simplified with single-dose formats. They reduce the need for health workers to round dose calculations or estimate high wastage rates associated with multi-dose vials. In addition, vaccine stock-outs, which can be caused by unanticipated high wastage rates, may be reduced with the use of single-dose formats. Prefilled AD devices further simplify immunization logistics by providing one dose of vaccine and one syringe together.

In addition, single-dose vials occupy a larger cold-chain volume per dose. For liquid vaccines, the packed volume per dose for single-dose vials is approximately six times greater than for 10-dose vials (Table 2) (*12*). However, comparisons of cold-chain impact must account for differences in vaccine wastage rates: if multi-dose wastage rates are 50%, then half the cold-chain volume is being used for vaccines that will not be delivered. Replacing 10-dose vials (50% wastage) with single-dose vials (5% wastage) would result in a threefold, rather than sixfold, difference in actual cold-chain volume. Prefilled AD devices occupy 30% more cold chain volume than single-dose vials.

Vaccine safety

Vial size affects injection safety in terms of contamination and reuse. Single-dose vials reduce many of the contamination risks of multi-dose vials, but only prefilled AD devices protect against syringe reuse.

Vial contamination can occur when an unsterile needle is inserted into a multi-dose vial. Multi-dose vials can also become contaminated from the practice of leaving a needle in

Table 1. **Estimated manufacturing costs per dose, including an injection device and excluding the cost of vaccine solution, for 10-dose vials, 1-dose vials, and a prefilled AD device by a hypothetical vaccine producer in a developing country**

	Manufacturing costs (US$)[a]		
	10-dose vial	**1-dose vial**	**Prefilled AD device**
Production (labour and equipment)[b]	0.015	0.040	0.042
Material packaging and syringe[c]	0.090	0.217	0.200
Vaccine overfill adjustment (%)[d]	100	113	98
Total manufacturing cost	**0.105**	**0.257**	**0.242**

[a] Based on a production rate of 120 units/minute, with manual inspection and packaging, and a US$ 5000/year direct labour rate.
[b] Includes quality control tests, facility and utility costs, and equipment depreciation, based on a 10-year life span for all manufacturing equipment.
[c] All costs include vial/device, stopper, aluminum crimp seal, label, carton or pouch, box, and a US$ 0.04 vaccine vial monitor. Vials include a US$ 0.07 auto-disable syringe.
[d] Based on recommended levels of overfill for injectable vaccines.

Table 2. **Average cold chain volume per delivered dose for liquid vaccines in the cold chain with no, moderate, and high levels of vaccine wastage for 10-, 2-, and 1-dose vials and prefilled AD[a] device[b]**

Vial format	Storage volume per dose (cm^3)		
	No wastage	Moderate wastage[c]	High wastage[d]
10-dose vial	3	4	6
2-dose vial	8	9	10
1-dose vial	19	20	21
Prefilled AD device	25	26	27

[a] AD = auto-disable.
[b] Average packed volumes of 0.5 ml dose liquid vaccines listed in Ref. *12*.
[c] Assumes 25% vaccine wastage for 10-dose vials, 10% wastage for 2-dose vials, and 5% wastage for 1-dose vials and prefilled AD device.
[d] Assumes 50% vaccine wastage for 10-dose vials, 20% wastage for 2-dose vials, and 10% wastage for 1-dose vials and prefilled AD device.

the septum and reusing it to draw several consecutive doses from the same vial. Single-dose vials avoid these contamination risks and reduce the likelihood of a lyophilized vaccine reconstituted for more than six hours being delivered.

Thiomersal is added to many common liquid vaccines packaged in multi-dose vials to prevent microbial growth (*13*). A recent WHO review "found no scientific evidence of toxicity from thiomersal-containing vaccines" (*14*). WHO "strongly affirms that vaccines containing thiomersal continue to be used for maintaining safe immunization" (*14*). Nonetheless, the use of thiomersal remains controversial since some research has suggested that repeated immunization with thiomersal-containing vaccines might result in mercury doses above recommended levels (*15*). To avoid this, several vaccines have recently been developed that contain no, or only trace amounts of, thiomersal (*16*, *17*). These vaccines are available only in single-dose formats. Multi-dose vials continue to require microbial protection because they are more likely to become contaminated via multiple needle entries.

Prefilled AD devices take further steps toward improved injection safety. Since an AD syringe is integral to the vaccine package, the use of an AD syringe is guaranteed. Other vaccine packaging formats rely on the adequate supply of AD syringes, bundled with vaccines, as well as user compliance in electing to use an AD syringe.

Syringe requirements

For countries using AD syringes, the use of single-dose vials requires more syringes for reconstituting lyophilized vaccines, as one AD syringe is used to reconstitute each lyophilized vaccine vial and another is needed to administer each injection. Vaccine reconstitution and injection of 10 patients from a 10-dose measles vial requires one mixing syringe and 10 AD syringes. If single-dose vials were used, 20 AD syringes would be used.

Vaccine wastage

Vaccine wastage (the amount of discarded efficacious vaccine) is a major economic consideration for most developing countries. In 1992, WHO estimated that the amount of vaccine wasted (60%) accounted for more vaccine than was administered (*18*). In 1994, after switching to smaller multi-dose vials, vaccine wastage rates in some areas were reduced to 45% of vaccine demand (*17*). Single-dose vials reduce vaccine wastage because the entire vial contents are administered immediately after opening each vial. Although per-dose prices of vaccines in multi-dose vials are lower than single-dose prices, even moderate wastage rates can quickly negate that price advantage. Fig. 1 shows that single-dose vials provide a price advantage over 10-dose vials if 10-dose vial wastage is greater than 44% (based on current hepatitis B vaccine prices and varying wastage rates for 10-dose vials). A recent study in Indonesia found that switching from 5-dose vials of hepatitis B vaccine to a prefilled AD device reduced vaccine costs when 5-dose vial wastage rates were above 25% (*19*).

Coverage rates

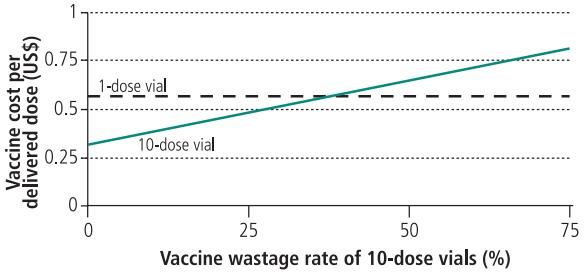
Although opening a multi-dose vial to administer a single vaccine dose contributes to vaccine wastage, a health worker's reluctance to open multi-dose vials for only a few children leads to missed opportunities and lower coverage rates. In a review of 79 studies, Hutchins et al. found that health workers' fear of vaccine wastage was one of four major reasons for missed opportunities, and it may account for 16% of all missed opportunities in developing countries (*20*). The use of single-dose vials eliminates health workers' concerns about vaccine wastage and therefore may reduce such missed opportunities and increase immunization coverage rates for all vaccines.

Prefilled AD devices may further improve coverage rates due to their acceptability and ease of use in outreach services (*21*, *22*). The use of a prefilled AD device in Indonesia has recently enabled the nationwide home delivery of a hepatitis B birth dose due to its safety, convenience, and transportability for outreach services (*19*). The United Nations Children's Fund (UNICEF) has recently begun using a prefilled AD device to extend the coverage of its TT campaigns. The devices allow minimally trained health workers to deliver accurate and safe immunizations within their communities. Several studies have shown that injection recipients and their parents prefer the smaller size and quicker preparation of these prefilled devices (*16*, *21*, *22*).

Medical waste

Single-dose vials generate a larger total volume of contaminated medical waste per dose than multi-dose vials (Table 3).

Fig. 1. **The impact of vaccine wastage on cost per delivered dose of hepatitis B vaccine: comparison of 1-dose vials with no wastage with 10-dose vials at varying wastage rates[a]**



[a] Prices from UNICEF 2002 Vaccine Projections as of 2 July 2002. Weighted average price per dose for recombinant hepatitis B vaccine: 1-dose vial, US$ 0.57; 10-dose vial, US$ 0.32.

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Table 3. **Average medical waste volume per dose for liquid vaccines by sharps and non-sharps waste, assuming moderate vaccine wastage rates[a], for 10- and 1-dose vials and a prefilled AD[b] device**

Vial format	Waste volume per dose (cm^3)		
	Sharps waste[c]	Non-sharps (vial) waste[d]	Total waste
10-dose vial	50	4	54
1-dose vial	50	20	70
Prefilled AD device	26	0	26

[a] Assumes 25% vaccine wastage for 10-dose vials and 5% wastage for 1-dose vials and prefilled AD devices.
[b] AD = auto-disable.
[c] Average packed volume per 0.5 ml auto-disable syringe among the four suppliers listed in Product Information Sheets, 2000 (*25*) and volume of Uniject™ device as reported by Becton Dickinson.
[d] Average packed volumes of 0.5 ml dose liquid vaccines listed in Ref. *12*.

For liquid vaccines, there is no difference in the volume of sharps waste. For lyophilized vaccines, however, single-dose vials generate almost twice as much sharps waste per dose as 10-dose vials, because a second syringe must be used to reconstitute each dose. Disposed vial volume is approximately 2–5 times greater for single-dose vials; however, vial disposal does not present the same risk as sharps disposal. Compared with single-dose vials with an AD syringe, prefilled AD devices decrease the total volume of contaminated medical waste by over 60%.

Discussion

Single-dose and multi-dose vials each have certain programmatic and economic advantages (Table 4), but the relative importance of these benefits varies according to several factors. Although vaccine wastage is easily quantifiable in economic terms, other issues are more difficult to put into monetary figures. These include safety, increased coverage, and other programmatic benefits. In certain situations, such as switching from multi-dose vials to single-dose vials where wastage of an expensive vaccine is high, cost savings would be obvious; thus safety and programmatic benefits would be "free" additional benefits. In other situations, there could be increased costs in switching to single-dose vials that would have to be weighed against the value of increased injection safety or programme enhancements. Such cost-benefit trade-offs can be difficult to evaluate, especially where short-term costs are the primary decision-making criteria. Nonetheless, the relative advantages of different vaccine formats should be considered in light of each country's individual problems, opportunities, and goals.

Although the impact of vial size on wastage may be easily quantifiable, the implications of cold chain capacity assessments may be less obvious: careful analysis of distribution options is important. A large proportion of existing cold chain capacity is currently lost to high vaccine wastage. Utilization of excess cold chain capacity or more frequent distribution of vaccines can minimize the impact of the high volume of single-dose vials. In recent large-scale introductions of a prefilled AD device in Indonesia, increasing the distribution frequency from once to twice a month was found to easily absorb the increased volume (*23*). Finally, innovative distribution schemes such as removing heat-stable vaccines from certain segments of the cold chain could expand distribution capacity.

An important limitation to this analysis is the paucity of information on many aspects of immunization costs that are specifically related to the cost savings associated with greater programme efficiencies and new safe injection technologies (*19*). Although this review may not have addressed all possible situations and perspectives, we have attempted to capture salient issues faced by developing countries. Each country must evaluate the programmatic and economic relevance of these issues within the context of its immunization services and available resources. Although this paper has used 1- and 10-dose vials for examples, some vaccines are offered in 2-, 5-, and 6-dose vials. These intermediate sizes may offer some of the advantages of reduced wastage attributable to single-dose vials, along with some of the cold chain and price advantages offered by 10- or 20-dose vials.

Table 4. **Comparison of the major programmatic and economic advantages of single-dose versus multi-dose vaccine vials for immunization programmes in developing countries**

	Major programmatic and economic advantages	
	Single-dose formats	Multi-dose vials
Production		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 Eliminates use of thiomersal Ensures more accurate dose delivery	
Syringe usage		Requires fewer reconstitution syringes
Vaccine wastage	Significantly less vaccine wastage	
Coverage rates	Facilitates innovative outreach strategies	
Medical waste		Smaller medical waste volume[a]

[a] Prefilled auto-disable device has less waste volume than multi-dose vial.

Several general recommendations can be made from this review. First, multi-dose vials appear to be most appropriate for less expensive vaccines (e.g. DPT, BCG), and in situations where cold chain systems are severely limited. Well-managed immunization programmes, with reasonable injection safety, may be well suited to the continued use of multi-dose vials.

Second, single-dose vials, in addition to reduced wastage, offer crucial programmatic benefits, such as increased safety and improved coverage rates. The value of these benefits should be weighed against the possibility of higher vaccine or distribution costs, especially for low-cost vaccines. Single-dose vials will be more cost-effective for expensive vaccines in areas with considerable vaccine wastage. The introduction of single-dose vials would benefit from flexible logistics management to increase utilization of cold-chain capacity. Otherwise, investments in cold-chain infrastructure may be required.

Third, prefilled single-dose devices are comparable to single-dose vials in wastage-reduction benefits and cold-chain impact; however, they enable programmatic opportunities in regions with unsafe injection practices, low coverage rates, limited health infrastructure, and in areas trying to improve outreach services.

To optimize the benefits of vaccine format, a mix of strategies is likely to be most effective. Differences in vaccine cost, programmatic weaknesses, or outreach strategy may support the use of different presentations for different vaccines. Some programmes will find benefits in using different presentations of the same vaccine, such as multi-dose vials in a high-volume clinical setting and prefilled AD devices for extended outreach. As international agencies continue purchasing vaccines, attention should be focused on supplying presentations that are most suitable and economically feasible for each country's specific needs and opportunities. Doing so would enhance the cost-effectiveness and health impact of immunization programmes. ■

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Résumé

Flacons monodoses ou multidoses pour les programmes de vaccination des pays en développement

Pour remédier au gaspillage de vaccin et résoudre les problèmes de sécurité, les responsables sanitaires internationaux ont été amenés à conditionner et fournir les vaccins autrement qu'en flacons multidoses standard. Le présent article compare les avantages programmatiques et économiques des flacons multidoses et monodoses utilisés pour la vaccination dans les pays en développement.

Dans le cas des flacons multidoses, la dose revient généralement moins cher et la capacité de la chaîne du froid utilisée est inférieure. En contrepartie, le taux de gaspillage est plus élevé, en particulier pour les vaccins plus chers. Les monodoses présentent plusieurs avantages programmatiques importants, et notamment des possibilités de vaccination accrues et une meilleure sécurité des vaccins. Le dispositif autobloquant prérempli, présentation monodose, offre une sécurité et une commodité accrues car il associe physiquement le vaccin et la seringue autobloquante.

Le choix de la présentation appropriée d'un vaccin dépendra de nombreux facteurs. Les flacons multidoses seront toutefois mieux adaptés pour les vaccins moins chers et là où les capacités de stockage de la chaîne du froid sont limitées. Les monodoses conviendront particulièrement pour les vaccins plus coûteux et là où la sécurité des injections pose des problèmes. Les dispositifs d'injection autobloquants préremplis seront surtout utiles pour étendre la couverture des personnes insuffisamment desservies, et rendre impossible le réemploi des aiguilles.

Resumen

Viales monodosis frente a multidosis en los programas de vacunación en los países en desarrollo

El excesivo desperdicio de vacunas y la preocupación en torno a su seguridad han llevado a la comunidad sanitaria internacional a desarrollar y suministrar las vacunas en forma de preparaciones distintas del vial multidosis habitual. Este artículo describe en términos programáticos y económicos las principales diferencias entre los viales multidosis y las preparaciones monodosis asignadas a los servicios de inmunización en los países en desarrollo.

En general, los viales multidosis se venden a un precio inferior por dosis y exigen menos capacidad de cadena de frío que las preparaciones monodosis. Sin embargo, la mayor tasa de desperdicio puede contrarrestar esos beneficios, especialmente en el caso de las vacunas más costosas. Las preparaciones monodosis reportan varios beneficios programáticos importantes, como más oportunidades de vacunación y una mayor seguridad de la vacuna. Una preparación monodosis, el dispositivo prellenado autodestruible (AD), garantiza una mayor seguridad de las inyecciones y resulta bastante cómoda porque combina físicamente la vacuna y la jeringa autodestruible.

La selección de la presentación idónea de la vacuna dependerá de muchos factores. Sin embargo, los viales multidosis tenderán a ser los más apropiados para las vacunas más baratas y en los entornos con una limitada capacidad de almacenamiento de la cadena de frío. Las preparaciones monodosis serán las más idóneas para las vacunas más costosas y cuando las prácticas de inyección peligrosas sean un problema extendido. Los dispositivos prellenados AD, por último, serán particularmente útiles para ampliar el alcance de los servicios de extensión y evitar la posibilidad de reutilizar las agujas.

ملخص

موازنة استخدام العبوات الوحيدة الجرعة من اللقاح مع العبوات المتعددة الجرعات في برامج التمنيع في البلدان النامية

الخلاصة: لقد دفعت القضايا المتعلقة بهدر كميات كبيرة من اللقاحات ومأمونية اللقاحات بالمجتمع الدولي للإعداد والإمداد بأشكال صيدلانية للقاحات تختلف عن العبوات القياسية المتعددة الجرعات .ونستعرض في هذه المقالة مقارنة عملية واقتصادية للاختلافات الكبيرة بين العبوات المتعددة الجرعات وتلك الوحيدة الجرعة المستخدمة في خدمات التمنيع في البلدان النامية.

ويمكن القول بشكل عام إن سعر الجرعة الواحدة سيكون في العبوات المتعددة الجرعات أقل منه في العبوات الوحيدة الجرعة، كما أن الجرعة الواحدة ستشغل حيزاً أقل في سلسلة التبريد إذا كانت ضمن عبوة متعددة الجرعات مما ستأخذه فيما لو كانت في عبوة وحيدة الجرعة .إلا أن المعدلات العالية للهدر قد تغطي على هذه المنافع ولاسيما في اللقاحات الغالية الثمن، تقدم العبوات الوحيدة الجرعة منافع عملية هامة ومتعددة مثل زيادة فرص التلقيح وتحسين مأمونية اللقاح. كما أن أحد الأشكال الصيدلانية الوحيدة الجرعة وهي المحقنة المعبأة مسبقاً والذاتية التعطل ستوفر المزيد من السلامة في الحقن والملاءمة لأنها تشتمل في الوقت نفسه على كل من اللقاح والمحقنة معاً.

ويعتمد اختيار شكل العبوة الصيدلانية للقاح على عوامل متعددة، ومع ذلك فإن العبوات المتعددة الجرعات تبدو الأكثر ملاءمة للقاحات الأرخص ثمناً في المواقع التي تكون فيها إمكانية التخزين في سلسلة التبريد محدودة، فيما تبدو اللقاحات الوحيدة الجرعة أكثر ملاءمة للقاحات الوحيدة الجرعة وفي المواقع التي تنتشر فيها ممارسات الحقن المحفوفة بالمخاطر .أما الحقن المعبأة مسبقاً والذاتية التعطل فستكون ذات فائدة خاصة في الوصول إلى المناطق النائية مع ضمان عدم إعادة استخدام المحاقن ثانية.

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