Intradermal delivery of vaccines: potential benefits and current challenges

JK Hickling,[a] KR Jones,[a] M Friede,[b] D Zehrung,[c] D Chen[c] & D Kristensen[c]

Abstract Delivery of vaccine antigens to the dermis and/or epidermis of human skin (i.e. intradermal delivery) might be more efficient than injection into the muscle or subcutaneous tissue, thereby reducing the volumes of antigen. This is known as dose-sparing and has been demonstrated in clinical trials with some, but not all, vaccines. Dose-sparing could be beneficial to immunization programmes by potentially reducing the costs of purchase, distribution and storage of vaccines; increasing vaccine availability and effectiveness. The data obtained with intradermal delivery of some vaccines are encouraging and warrant further study and development; however significant gaps in knowledge and operational challenges such as reformulation, optimizing vaccine presentation and development of novel devices to aid intradermal vaccine delivery need to be addressed. Modelling of the costs and potential savings resulting from intradermal delivery should be done to provide realistic expectations of the potential benefits and to support cases for investment. Implementation and uptake of intradermal vaccine delivery requires further research and development, which depends upon collaboration between multiple stakeholders in the field of vaccination.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Most vaccines are delivered by the intramuscular or subcutaneous routes using a needle and syringe; the intradermal route is only widely used for the administration of Bacille Calmette-Guérin and rabies vaccines. However there is renewed interest in intradermal vaccine delivery, driven by the fact that the dermis and epidermis of human skin are rich in antigen-presenting cells, suggesting that delivery of vaccines to these layers, rather than to muscle or subcutaneous tissue, should be more efficient and induce protective immune responses with smaller amounts of vaccine antigen.[1]

Clinical trials investigating intradermal delivery and its potential for dose-sparing have been conducted with several different vaccines, with variable results. These have been reviewed in a recent report from the Program for Appropriate Technology in Health (PATH) and the World Health Organization (WHO).[2] For some vaccines, there has been a clear demonstration of dose-sparing by intradermal delivery; however, there are several gaps in knowledge as well as developmental and operational challenges to overcome if the benefits of using intradermal delivery are to be fully realized.

Potential benefits

Dose-sparing arising from intradermal delivery of vaccines could be beneficial to immunization programmes, particularly in resource-poor settings, by potentially reducing the per-injection cost (including transport and storage) of vaccines because more doses might be obtained from the existing vaccine presentation.

Dose-sparing might also "stretch" the availability of vaccines in cases where supply is limited by manufacturing capacity. This is probably most relevant for pandemic influenza vaccines where global production capacity limits access to a vaccine at the start of a pandemic.[3] In 2009, H1N1 vaccine was not available in most low-income countries until 8 months after WHO's declaration of the influenza pandemic.[4]

Other vaccines with potential supply constraints include yellow fever and inactivated poliovirus vaccines.[5,6] The level of demand for inactivated poliovirus vaccine in the period following eradication of wild-type polioviruses and the end of the use of oral poliovirus vaccines is uncertain, but modelling suggests that there could be a "demand spike" and supply shortage of inactivated poliovirus vaccine during this period.[6]

New delivery devices

New devices for easier, more reliable intradermal delivery as alternatives to the currently used Mantoux technique are being developed.[2,7] Some of the devices such as disposable-syringe jet injectors are needle-free and could therefore reduce or eliminate needlestick injuries and the costs associated with their treatment, estimated at US$ 535 million per year worldwide.[8] Other intradermal delivery devices such as microneedle patches are likely to occupy less volume than vials or prefilled syringes, thereby reducing demands on cold-chain capacity.

Current clinical research

The recent PATH and WHO report reviewed more than 90 clinical trials of intradermal delivery with vaccines against 11 diseases.[2] For some vaccines, notably influenza and rabies vaccines, intradermal delivery of reduced doses resulted in equivalent immune responses to the standard dose delivered by the standard route. Data from trials with hepatitis B vaccine were more variable, but also regarded as encouraging.[9] Promising data demonstrating dose-sparing have also been obtained with other vaccines including inactivated poliovirus, yellow fever and hepatitis A vaccines.[2]

[a] Working in Tandem Ltd, Cambridge, England.
[b] Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland.
[c] Program for Appropriate Technology in Health (PATH), PO Box 900922, Seattle, WA, 98109, United States of America.
Correspondence to Darin Zehrung (e-mail: dzehrung@path.org)
(*Submitted: 5 May 2010 – Revised version received: 1 November 2010 – Accepted: 2 November 2010 – Published online: 5 January 2011*)

Results from clinical trials published since the completion of the report provide further evidence for dose-sparing using the intradermal route. One study compared equivalent doses of modified vaccinia Ankara delivered by subcutaneous, intramuscular and intradermal routes; equivalent immune responses and protection against vaccinia-virus challenge were induced with intradermal doses ten-fold lower than those delivered by intramuscular or subcutaneous injection.[10,11]

Two recently published trials of intradermal delivery of reduced (20%) doses of inactivated poliovirus vaccines have reported contrasting results: one trial found that reduced intradermal doses administered to infants aged 2, 4 and 6 months induced similar rates of seroconversion but lower mean antibody titres, compared with intramuscular injection;[12] however a similar study administered the vaccine at 6, 10 and 14 weeks of age and observed inferior seroconversion rates with reduced intradermal doses.[13]

Trials of intradermal immunization with seasonal and pandemic influenza vaccines have also been reported in the past year. Dose-sparing was not observed with a nonadjuvanted, subvirion H5N1 vaccine,[14] whereas a 60% intradermal dose of a trivalent seasonal flu vaccine resulted in similar immunogenicity as a standard dose delivered intramuscularly.[15]

Some rabies vaccines are already delivered using intradermal regimens using needle and syringe.[16,17] Recently, a new intradermal injection device (Soluvia™, Becton Dickinson, Franklin Lakes, NJ, United States of America) was evaluated for intradermal delivery of rabies vaccine; intradermal administration of a 25% dose of rabies vaccine resulted in equivalent antibody titres and seroconversion rates to the full dose delivered intramuscularly. The same study also evaluated an epidermal vaccination device (Onvax™, Becton Dickinson) that did not induce an immune response in the recipients.[18]

Recent vaccine approvals

A new presentation of a split, trivalent seasonal influenza vaccine, Intanza® (sanofi pasteur, Lyon, France) has been developed for intradermal immunization. The vaccine is delivered using the Soluvia™ device, a prefilled syringe with a single needle that is 1.5 mm in length.[19,20] Immune responses equivalent to those induced by the standard regimen can be achieved using this device and 60% of the standard dose of influenza vaccine.[21,22] A reduced-dose formulation (9-μg haemagglutinin rather than the standard 15-μg haemagglutinin) for use in healthy adults and a 15-μg haemagglutinin formulation for intradermal delivery in adults aged ≥ 60 years have been approved in Australia, Europe and New Zealand.[23–25]

Knowledge gaps

Despite the number of clinical trials conducted, there is still a lack of certainty whether intradermal delivery offers significant immunological advantages compared with intramuscular or subcutaneous delivery. Very few trials have compared equivalent doses (amounts of antigen) delivered by the different routes and, as such, do not permit direct comparison of relative immunological efficacy of the different methods; the recent studies with modified vaccinia Ankara are notable exceptions.[10,11] Most trials have aimed only to determine whether reduced intradermal doses were able to induce a sufficient or non-inferior immune response compared with the standard regimen. In these cases it is possible that a reduced dose delivered by the standard route would also have resulted in an equivalent immune response, as has been reported with some influenza vaccines.[26,27] Furthermore, the majority of dose-sparing trials have for reasons of practical simplicity delivered 10% or 20% of the standard dose intradermally. Finer dose-titrations such as those performed with influenza vaccines have shown that less-dramatic reductions in dose, such as a 40% reduction, might be more realistic.[22] To address these concerns, future studies should compare equivalent antigen doses given by the intradermal and standard route and, if possible, establish a dose–response relationship to determine whether any dose-sparing effect observed is simply due to using doses of antigen from the plateau-portion of the dose–response curve.

Which vaccines?

For any vaccine, the drivers for changing to the intradermal route, such as the need for dose-sparing to reduce costs and "stretch" the available manufacturing capacity, have to be assessed, but the suitability of the vaccine type and formulation for administration by this route also need to be considered.

Live-attenuated vaccines have been successfully delivered intradermally and should be good candidates for intradermal delivery providing that appropriate formulations can be developed.[2] Reduced doses of inactivated whole-virion vaccines, such as rabies and inactivated poliovirus vaccines, have also shown satisfactory immunogenicity when delivered intradermally. Inactivated whole-virion influenza vaccines might also be suitable because they have intrinsic immune-stimulating sequences, which might avoid the need for additional adjuvants.[28] There are no published clinical data regarding intradermal delivery of polysaccharide conjugate vaccines, which include meningococcal and pneumococcal conjugate vaccines, yet evaluation would be worthwhile particularly because high cost has limited the introduction of pneumococcal conjugate vaccines in some low-resource countries.[29]

Vaccines that contain aluminium-based or oil-in-water adjuvants are likely to have unacceptable local reactogenicity following intradermal administration. Clinical trials of intradermal delivery of vaccines formulated with these or novel adjuvants are needed.

Potential benefits

Realistic estimates of the cost savings that might be achieved by ID dose-sparing have not been established for most vaccines, especially those that might be relevant to routine immunization in low- and middle-resource countries.

Cell-culture-produced rabies vaccines are expensive and are used in complex, multi-dose schedules for post-exposure prophylaxis. A limited number of cell-culture-derived rabies vaccines and two intradermal immunization regimens are already recommended by WHO.[16,17] The overall costs involved in administering post-exposure prophylaxis using intramuscular or intradermal regimens in different clinic settings in India have been compared.[30] Although significant savings were achieved with intradermal regimens, reducing the dose to 20% of the intramuscular dose did not reduce the overall costs by 80%, instead savings of 15–38% were obtained, depending on the setting. Intradermal regimens that used 10% rather than 20% of the standard dose resulted in a further reduction in costs of only 9–15%. Furthermore, the estimates did not include costs resulting from vaccine wastage, which were expected to be higher in intradermal regimens.

This example reinforces the point that the cost of manufacturing a vaccine is only a proportion of the overall cost of delivering each dose; furthermore, vaccine manufacturers will not necessarily pass on the full savings arising from a reduction in antigen content per dose. Novel devices for intradermal delivery are likely to be more expensive than needles and syringes, and immunization programmes using new devices will also incur the costs of retraining health workers.

A major benefit of changing to needle-free devices is a reduction in the direct health-care and societal costs resulting from needlestick injuries, although this is difficult to quantify in financial terms.[8,31] A reduction in the use of sharps and their associated costs could also be achieved, possibly more easily, by using needle-free delivery devices such as disposable-syringe jet injectors, without changing the route or dose of vaccine administered.

The incremental costs associated with changing some routine childhood vaccinations in Brazil, India and South Africa to intradermal delivery of reduced (20%) doses have been modelled.[32] For India and South Africa, the model indicated that intradermal delivery of reduced doses of hepatitis B vaccine using disposable-syringe jet injectors would increase the overall costs per fully-immunized child by US$ 0.45 and by US$ 0.76, respectively; hepatitis B vaccine is only one of five or six infant vaccines routinely administered in these two countries. In contrast, in Brazil, the model indicated that intradermal reduced doses of hepatitis B and yellow fever vaccines would reduce overall costs per fully-immunized child by US$ 0.11. Although antigen content of the vaccines delivered intradermally was reduced by 80%, the model assumed that prices were only reduced by 20%. The model did not include costs associated with treatment of bloodborne infections transmitted by sharps.

PATH has modelled the potential incremental costs of routine immunization with inactivated poliovirus vaccines in India. This analysis assumed that the full cost savings resulting from reduced antigen content were passed on by manufacturers and included estimates for costs due to transmission of bloodborne infection. In this case, delivery of a 20% intradermal dose with either needle and syringe or disposable-syringe jet injectors could result in cost savings of 71–73% per immunized child.[33]

In applications where it is warranted, significant investment by vaccine manufacturers and other stakeholders will be required to change the route of vaccine delivery. It is important, therefore, to model accurately the costs involved to determine the potential benefits and to support the case for investment. Decisions should be based on cost modelling and economic analysis, with continual improvement of inputs and assumptions.

Challenges

Changing the delivery route and dose for a vaccine is not a straightforward task, and several challenges and operational issues need to be addressed.

Demonstration of efficacy

The applicability and benefits of intradermal administration will vary among vaccines; it cannot be assumed that reduced intradermal doses will be efficacious in all cases. Even when there is dose-sparing, it might not be with a dose as low as 20% or 10% of the standard dose. The degree of dose-sparing that can be achieved will need to be determined for each vaccine in non-inferiority trials. It will also be important to maintain a "margin of safety" to ensure adequate immunogenicity across the whole target population and to ensure the potency of the reduced dose is sufficient to induce protection at the end of the vaccine's shelf life.

Reformulation

Intradermal doses of 20% of a standard 0.5 ml dose or 10% of a 1.0 ml dose might not require reformulation; 0.1 ml of the existing formulation could easily be administered, as is the usual practice in clinical trials of intradermal delivery. If more antigen per dose is required, then the vaccine will need to be concentrated so that it can be delivered in the smaller volume. In the development of Intanza®, which contains 60% of the standard amount of antigen in 20% of the volume, there were challenges filling the device with a small volume as well as adjusting vaccine concentration and viscosity.[34] Even if there is no need to adjust the concentration of the vaccine, it might be necessary to incorporate a preservative into the formulation if dose-sparing means that more than one dose can be obtained per vial.

Vaccine presentation

One consequence of delivering a smaller volume per dose is that a single-dose vial presentation would effectively become a multi-dose vial, yielding perhaps 5 or 10 intradermal doses. Liquid vaccines with multi-dose vial presentations can contain preservatives so that unused vaccine can be stored more safely beyond the end of an immunization session.[35] Single-dose vials do not typically contain thiomersal or other preservatives. If dose-sparing allows multiple doses to be drawn from preservative-free vaccines in single-dose vials, unused vaccine would have to be discarded at the end of the immunization session. Computer modelling has shown that matching the number of doses per vial with the immunization session's size has a significant economic impact in terms of minimizing vaccine wastage as well as supply, storage and disposal costs.[36] For some vaccines and settings, fewer than five doses per vial would be the most cost-effective option. Therefore, alternative, smaller-volume presentations might be required, otherwise intradermal delivery might not yield the expected cost savings in settings where immunization session-sizes are small.

Regulatory issues

Intradermal delivery of fractional doses of an existing vaccine formulation intended for subcutaneous/intramuscular injection would have to be undertaken on an "off-label" basis. A licensing amendment between the relevant national regulatory authority and the vaccine producer would be needed to authorize official "on-label" use of fractional doses.[37] Alternatively, marketing approval for the new intradermal formulation and presentation of the vaccine would be needed.

For many existing vaccines, there might not be a sufficiently strong commercial incentive for manufacturers to undertake the expensive processes of reformulation, production of new presentations and application for marketing authorizations for a new delivery route. Novel vaccines might, therefore, be more likely candidates for intradermal delivery. This route should be evaluated early in research and development to avoid expensive retesting and redevelopment at a later stage. Unless there are strong drivers to use the intradermal route, vaccine manufacturers are likely to continue to use standard presentations and routes of delivery

even for new vaccines, thereby reducing risk from the development process.

Device development

Novel devices for simple, reliable and reproducible intradermal delivery of vaccines will be needed if this route is to be widely used. There are several different types of intradermal delivery devices in development.[1,2,7] However they cannot be developed in isolation; the device inventors require access to vaccines and collaboration with vaccine manufacturers to enable development, testing and approval of device/vaccine combinations.

In the shorter term, delivery technologies could include simple adapters fitted to existing needles and syringes to control the depth and angle of delivery, syringe-mounted arrays of hollow microneedles and needle-free disposable-syringe jet injectors.[2] Each of these approaches is compatible with existing liquid and lyophilized formulations and presentations and so should be simpler to introduce into immunization programmes than some other technologies.

Devices that are in earlier stages of development include skin-patches covered in microneedles coated with, or composed of, vaccine. Encouraging preclinical data have been obtained with several formats of this type of device.[38–40] Challenges remain in producing solid formulations of different types of vaccine antigens, developing methods for coating sufficient antigen onto the microneedles and controlling the reproducibility of antigen delivery. If these can be overcome, microneedle patches could provide several benefits in addition to dose-sparing, including small-packaged volumes and simplicity of use.

Conclusion

Data from clinical trials indicate that intradermal delivery of reduced doses of some, although not all, vaccines results in equivalent immune responses to the standard regimen. An increasing number of trials are producing data that support dose-sparing. However, there are significant operational challenges, such as reformulation, changing from a single- to a multiple-dose presentation, development of intradermal delivery devices and training health workers. Economic studies and modelling exercises have shown that cost savings should be achievable with intradermal immunization with some vaccines. These analyses are needed to help guide and support development and implementation of intradermal vaccine delivery as well as provide an indication of potential savings.

Research and development in all of these disciplines is required if the promise of intradermal delivery is to be realized; this will require collaboration between academic and clinical researchers, vaccine manufacturers, device developers, regulatory authorities, national immunization programmes and nongovernmental global health organizations. A careful evaluation of all aspects of this route of delivery for vaccines should continue to be a priority for global public health. ■

Acknowledgements

We thank Courtney Jarrahian and Kristina Lorensen for reviewing the manuscript and Emily Griswold for proofreading.

Funding: Work on this article by PATH staff members and consultants was supported by funding from the Bill & Melinda Gates Foundation. The authors had full control of all primary data.

Competing interests: None declared.

الملخص

إعطاء اللقاحات داخل الأدمة: فوائد ممكنة وتحديات راهنة

قد يكون إعطاء مستضدات اللقاح في الأدمة أو بشرة جلد الإنسان)مثل الحقن داخل الأدمة مباشرة) أكثر فاعلية من الحقن العضلي أو الحقن تحت الجلد، مما يعني خفض حجم المستضد. وهذا ما يعرف بالاقتصاد في الجرعة وهو ما أوضحته التجارب السريرية مع بعض اللقاحات، وليس كلها. وقد يكون للاقتصاد في الجرعة فائدة تكتسبها برامج التمنيع من حيث إمكانية خفض تكاليف الشراء، وتوزيع وتخزين اللقاحات، بالإضافة إلى زيادة توفيراللقاحات نفسها وارتفاع فعاليته.إن ما تم الحصول عليه من المعطيات الخاصة بإعطاء بعض اللقاحات عن طريق الأدمة معطيات مشجعة وتستحق أن تتم دراستها باستفاضة والعمل على تطويرها، ومع ذلك، هناك ثغرات يجب التصدي لها تتمثل في المعرفة والتحجيات العملية مثل إعادة الصياغة، والتوسع في تقديم أنواع اللقاحات وتطوير جهائز جديدة للمساعدة في تقديم اللقاح بالحقن في الأدمة. كما ينبغي وضع نموذج للتكلفة ومدى التوفير المحتمل الناجم عن الحقن داخل الأدمة لتقديم توقعات حقيقية للفائدة المحتملة ولدعم حالات الاستثمار. ويتطلب تنفيذ والعمل بإعطاء اللقاح داخل الأدمة المزيد من تطبيق وامتصاص لقاح الأدمة المزيد من البحث والتطوير وهذا يعتمد على التعاون بين العديد من أصحاب المصلحة العاملين في مجال التلقيح.

摘要

疫苗皮内接种:潜在益处和当前面临的挑战

疫苗抗原给药至人体皮肤的真皮层和/或表皮层(即皮内接种)可能较肌肉或皮下组织注射更为有效,这样能够降低抗原用量。这就是所谓的剂量节约,而且已有一些(但并非所有)疫苗在临床试验中获得验证。降低剂量可减少疫苗购买、配送和储存费用,从而有益于免疫接种计划;增加疫苗的可获得性和有效性。部分疫苗皮内接种获得的数据令人鼓舞,这值得进一步的研究和开发;但是现有知识和实践中仍有鸿沟需要弥补,例如改造剂型、优化疫苗抗原呈递以及开发新型疫苗皮内接种辅助器械。必须对皮内接种带来的成本及潜在节约进行建模,以便对潜在益处提供符合现实的期望值,并为争取投资提供支持案例。疫苗皮内接种的实施和开展需要进一步研究和开发,这取决于多方利益攸关者在疫苗接种领域中的合作。

Résumé

Injection intradermique de vaccins: les défis potentiels et les défis actuels

L'injection d'antigènes de vaccin dans le derme et/ou l'épiderme de la peau chez l'homme (appelée injection intradermique) peut s'avérer plus efficace qu'une injection dans le muscle ou dans le tissu sous-cutané, réduisant de ce fait les volumes d'antigène. C'est ce qu'on appelle l'utilisation parcimonieuse des doses, qui a été démontrée lors d'essais cliniques avec certains vaccins, mais pas tous. Cette limitation des doses pourrait être bénéfique aux programmes d'immunisation car elle pourrait diminuer les frais d'acquisition, de distribution et de stockage des vaccins, et augmenter par ailleurs leur disponibilité et leur efficacité. Les données obtenues avec l'injection intradermique de certains vaccins sont encourageantes et légitiment d'autres études et développements. Cependant, des écarts significatifs dans les connaissances et les enjeux opérationnels, comme la reformulation, l'optimisation de la présentation des vaccins et le développement de nouveaux dispositifs facilitant la distribution des vaccins intradermiques, doivent être abordés. Une modélisation des coûts et des économies potentielles provenant de l'injection intradermique doit être effectuée afin de proposer des prévisions réalistes des avantages potentiels et de plaider en faveur de l'investissement. La mise en œuvre et l'utilisation de l'injection intradermique des vaccins nécessitent des recherches et développements supplémentaires, dépendant de la collaboration entre de nombreuses parties prenantes dans le domaine de la vaccination.

Резюме

Внутрикожное введение вакцин: потенциальные преимущества и существующие проблемы

Введение антигенов вакцины в дерму и/или эпидермис человеческой кожи (т. е. внутрикожное введение) может быть более экономичным, чем инъекция в мышцу или подкожную ткань, так как снижает объем антигена. Эта практика известна как экономная дозировка и была продемонстрирована во время клинических испытаний на некоторых, хотя и не всех, вакцинах. Экономная дозировка могла бы принести пользу программам иммунизации благодаря потенциальному снижению затрат на закупку, распределение и хранение вакцин, а также благодаря повышению их доступности и эффективности. Полученные данные о внутрикожном введении некоторых вакцин являются обнадеживающими и требуют проведения дальнейших исследований и разработок. Вместе с тем необходимо устранить серьезные пробелы в знаниях и решить оперативные проблемы, такие как реформуляция, оптимизация расфасовки вакцины и разработка нового оборудования, призванного облегчить внутрикожное введение вакцины. Для формирования реалистичных ожиданий в отношении потенциальных выгод и для более убедительного обоснования инвестиций необходимо провести моделирование затрат и потенциальной экономии от внутрикожного введения вакцин. Внедрение и освоение внутрикожного введения вакцин требует дальнейших исследований и разработок, которые зависят от сотрудничества с многочисленными заинтересованными сторонами в сфере вакцинации.

Resumen

Administración de vacunas por vía intradérmica: posibles beneficios y retos actuales

La administración de los antígenos de una vacuna a través de la dermis y/o de la epidermis de la piel humana (es decir, la administración por vía intradérmica) podría resultar más eficaz que la inyección intramuscular o subcutánea, reduciendo de este modo los volúmenes de antígenos. Esta vía de administración permite reducir la dosis necesaria, según ha quedado demostrado mediante ensayos clínicos en algunas vacunas, aunque no en todas. La disminución de la dosis podría ser beneficiosa para los programas de inmunización, ya que se reducirían los gastos correspondientes a la compra, la distribución y el almacenamiento de las vacunas, al tiempo que se incrementaría su disponibilidad y eficacia. Los datos obtenidos sobre la administración de algunas vacunas por vía intradérmica están impulsando y justificando la necesidad de realizar más estudios y potenciar su desarrollo, si bien se han observado algunas lagunas de conocimiento y retos operativos como su reformulación, la optimización de su presentación y el desarrollo de nuevos dispositivos que ayuden a satisfacer las necesidades que conlleva la administración por vía intradérmica. Deberían crearse modelos de los costes y del posible ahorro que conllevaría la administración por vía intradérmica para poder ofrecer así unas expectativas realistas de los posibles beneficios y apoyar proyectos de inversión. La puesta en marcha y aplicación de la administración de vacunas por vía intradérmica exige más investigación y desarrollo, que dependen de la colaboración entre las numerosas partes implicadas dentro del ámbito de la inmunización.

References

1. Lambert PH, Laurent PE. Intradermal vaccine delivery: will new delivery systems transform vaccine administration? *Vaccine* 2008;26:3197–208. doi:10.1016/j.vaccine.2008.03.095 PMID:18486285
2. *Intradermal delivery of vaccines: a review of the literature and potential for development for use in low- and middle-income countries*. Seattle: Program for Appropriate Technology in Health (PATH); 2009. Available from: http://www.path.org/files/TS_opt_idd_review.pdf [accessed 16 December 2010].
3. Kieny MP, Costa A, Hombach J, Carrasco P, Pervikov Y, Salisbury D et al. A global pandemic influenza vaccine action plan. *Vaccine* 2006;24:6367–70. doi:10.1016/j.vaccine.2006.07.021 PMID:17240560
4. Partridge J, Kieny MP; World Health Organization H1N1 influenza vaccine Task Force. Global production of seasonal and pandemic (H1N1) influenza vaccines in 2009–2010 and comparison with previous estimates and global action plan targets. *Vaccine* 2010;28:4709–12. doi:10.1016/j.vaccine.2010.04.083 PMID:20488262
5. *Yellow fever initiative: providing an opportunity of a lifetime.* Geneva: World Health Organization; 2010. Available from: http://www.who.int/csr/disease/yellowfev/YFIbrochure.pdf [accessed 16 December 2010].

6. Oliver Wyman Inc. *Global post-eradication IPV supply and demand assessment: integrated findings.* Seattle: Bill & Melinda Gates Foundation; 2009. Available from: http://www.polioeradication.org/content/general/March%202009%20OW%20IPV%20Effort%20Report.pdf [accessed 16 December 2010].
7. Weniger BG, Papania MJ. Alternative vaccine delivery methods. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines*, 5th ed. Amsterdam: Elsevier; 2008:1357-92.
8. Miller MA, Pisani E. The cost of unsafe injections. *Bull World Health Organ* 1999;77:808–11. PMID:10593028
9. Sangaré L, Manhart L, Zehrung D, Wang CC. Intradermal hepatitis B vaccination: a systematic review and meta-analysis. *Vaccine* 2009;27:1777–86. doi:10.1016/j.vaccine.2009.01.043 PMID:19200451
10. Wilck MB, Seaman MS, Baden LR, Walsh SR, Grandpre LE, Devoy C et al. Safety and immunogenicity of modified vaccinia Ankara (ACAM3000): effect of dose and route of administration. *J Infect Dis* 2010;201:1361–70. doi:10.1086/651561 PMID:20350191
11. Seaman MS, Wilck MB, Baden LR, Walsh SR, Grandpre LE, Devoy C et al. Effect of vaccination with modified vaccinia Ankara (ACAM3000) on subsequent challenge with Dryvax. *J Infect Dis* 2010;201:1353–60. doi:10.1086/651560 PMID:20350190
12. Mohammed AJ, AlAwaidy S, Bawikar S, Kurup PJ, Elamir E, Shaban MMA et al. Fractional doses of inactivated poliovirus vaccine in Oman. *N Engl J Med* 2010;362:2351–9. doi:10.1056/NEJMoa0909383 PMID:20573923
13. Resik S, Tejeda A, Lago PM, Diaz M, Carmenates A, Sarmiento L et al. Randomized controlled clinical trial of fractional doses of inactivated poliovirus vaccine administered intradermally by needle-free device in Cuba. *J Infect Dis* 2010;201:1344–52. doi:10.1086/651611 PMID:20350164
14. Patel SM, Atmar RL, El Sahly HM, Cate TR, Keitel WA. A phase I evaluation of inactivated influenza A/H5N1 vaccine administered by the intradermal or the intramuscular route. *Vaccine* 2010;28:3025–9. doi:10.1016/j.vaccine.2009.10.152 PMID:19931380
15. Chi RC, Rock MT, Neuzil KM. Immunogenicity and safety of intradermal influenza vaccination in healthy older adults. *Clin Infect Dis* 2010;50:1331–8. doi:10.1086/652144 PMID:20377407
16. *WHO expert consultation on rabies* (WHO technical report series 931). Geneva: World Health Organization; 2005. Available from: http://www.who.int/rabies/trs931_%2006_05.pdf [accessed 16 December 2010].
17. World Health Organization. Rabies vaccines. WHO position paper. *Wkly Epidemiol Rec* 2007;82:425–35. PMID:18064757
18. Laurent PE, Bourhy H, Fantino M, Alchas P, Mikszta JA. Safety and efficacy of novel dermal and epidermal microneedle delivery systems for rabies vaccination in healthy adults. *Vaccine* 2010;28:5850–6. doi:10.1016/j.vaccine.2010.06.062 PMID:20600481
19. Alarcon JB, Hartley AW, Harvey NG, Mikszta JA. Preclinical evaluation of microneedle technology for intradermal delivery of influenza vaccines. *Clin Vaccine Immunol* 2007;14:375–81. doi:10.1128/CVI.00387-06 PMID:17329444
20. Laurent PE, Bonnet S, Alchas P, Regolini P, Mikszta JA, Pettis R et al. Evaluation of the clinical performance of a new intradermal vaccine administration technique and associated delivery system. *Vaccine* 2007;25:8833–42. doi:10.1016/j.vaccine.2007.10.020 PMID:18023942
21. Arnou R, Eavis P, Pardo JR, Ambrozaitis A, Kazek MP, Weber F. Immunogenicity, large scale safety and lot consistency of an intradermal influenza vaccine in adults aged 18–60 years: Randomized, controlled, phase III trial. *Hum Vaccin* 2010;6:346–54. doi:10.4161/hv.6.4.10961 PMID:20372053
22. Beran J, Ambrozaitis A, Laiskonis A, Mickuviene N, Bacart P, Calozet Y et al. Intradermal influenza vaccination of healthy adults using a new microinjection system: a 3-year randomised controlled safety and immunogenicity trial. *BMC Med* 2009;7:13. doi:10.1186/1741-7015-7-13 PMID:19341446
23. Committee for Medical Products for Human Use. *Summary of product characteristics* (Intanza 9microgram). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000957/WC500033852.pdf [accessed 16 December 2010].
24. Arnou R, Icardi G, De Decker M, Ambrozaitis A, Kazek MP, Weber F et al. Intradermal influenza vaccine for older adults: a randomized controlled multicenter phase III study. *Vaccine* 2009;27:7304–12. doi:10.1016/j.vaccine.2009.10.033 PMID:19849996
25. Australian Drug Evaluation Committee. ADEC 262nd meeting resolutions; resolution 9254. *Commonwealth of Australia Gazette* 2009;11. Available from: http://www.tga.gov.au/docs/html/adec/adec0262.htm [accessed 16 December 2010].
26. Treanor J, Keitel W, Belshe R, Campbell J, Schiff G, Zangwill K et al. Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. *Vaccine* 2002;20:1099–105. doi:10.1016/S0264-410X(01)00440-6 PMID:11803070
27. Belshe RB, Newman FK, Wilkins K, Graham IL, Babusis E, Ewell M et al. Comparative immunogenicity of trivalent influenza vaccine administered by intradermal or intramuscular route in healthy adults. *Vaccine* 2007;25:6755–63. doi:10.1016/j.vaccine.2007.06.066 PMID:17692438
28. Geeraedts F, Goutagny N, Hornung V, Severa M, de Haan A, Pool J et al. Superior immunogenicity of inactivated whole virus H5N1 influenza vaccine is primarily controlled by Toll-like receptor signalling. *PLoS Pathog* 2008;4:e1000138. PMID:18769719
29. World Health Organization. Worldwide progress in introducing pneumococcal conjugate vaccine, 2000–2008. *Wkly Epidemiol Rec* 2008;83:388–92. PMID:18949860
30. Goswami A, Plun-Favreau J, Nicoloyannis N, Sampath G, Siddiqui MN, Zinsou JA. The real cost of rabies post-exposure treatments. *Vaccine* 2005;23:2970–6. doi:10.1016/j.vaccine.2004.12.008 PMID:15811642
31. Ekwueme DU, Weniger BG, Chen RT. Model-based estimates of risks of disease transmission and economic costs of seven injection devices in sub-Saharan Africa. *Bull World Health Organ* 2002;80:859–70. PMID:12481207
32. Griffiths UK, Santos AC, Nundy N, Jacoby E, Matthias D. Incremental costs of introducing jet injection technology for delivery of routine childhood vaccinations: Comparative analysis from Brazil, India, and South Africa. *Vaccine* 2011;29:969–75. doi:10.1016/j.vaccine.2010.11.038 PMID:21115059
33. *Improving the affordability of inactivated poliovirus vaccines (IPV) for use in low- and middle-income countries: an economic analysis of strategies to reduce the cost of routine IPV immunization.* Seattle: Program for Appropriate Technology in Health (PATH); 2010. Available from: http://www.path.org/publications/details.php?i=1809 [accessed 16 December 2010].
34. Picot V. Intradermal immunization: an alternative route for vaccine administration. Articles as per sessions meeting report. *Vaccine* 2008;26(Suppl 9):S1–5. doi:10.1016/j.vaccine.2008.10.092 PMID:19268138
35. *The use of opened multi-dose vials of vaccine in subsequent immunization sessions.* Geneva: World Health Organization; 2000. Available from: http://www.who.int/vaccines-documents/DocsPDF99/www9924.pdf [accessed 16 December 2010].
36. Lee BY, Norman BA, Assi TM, Chen SI, Bailey RR, Rajgopal J et al. Single versus multi-dose vaccine vials: an economic computational model. *Vaccine* 2010;28:5292–300. doi:10.1016/j.vaccine.2010.05.048 PMID:20566395
37. *Report of a meeting on priorities for pneumococcal and Haemophilus influenzae type b (Hib) vaccine development, February 1999.* Geneva: World Health Organization; 2001. Available from: http://www.who.int/vaccines-documents/DocsPDF01/www530.pdf [accessed 16 December 2010].
38. Kim YC, Quan FS, Compans RW, Kang SM, Prausnitz MR. Formulation and coating of microneedles with inactivated influenza virus to improve vaccine stability and immunogenicity. *J Control Release* 2010;142:187–95. doi:10.1016/j.jconrel.2009.10.013 PMID:19840825
39. Sullivan SP, Koutsonanos DG, Del Pilar Martin M, Lee JW, Zarnitsyn V, Choi SO et al. Dissolving polymer microneedle patches for influenza vaccination. *Nat Med* 2010;16:915–20. doi:10.1038/nm.2182 PMID:20639891
40. Fernando GJP, Chen X, Prow TW, Crichton ML, Fairmaid EJ, Roberts MS et al. Potent immunity to low doses of influenza vaccine by probabilistic guided micro-targeted skin delivery in a mouse model. *PLoS One* 2010;5:e10266. doi:10.1371/journal.pone.0010266 PMID:20422002