Evidence and guidance on vaccine safety and effectiveness in subpopulations

INAUGURALDISSERTATION
zur
Erlangung der Würde eines Doktors der Philosophie

vorgelegt der
Philosophisch-Naturwissenschaftlichen Fakultät
der Universität Basel

von

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Basel, 2011

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Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät auf Antrag von

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Basel, den 9. Dezember 2008

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Table of Contents

1 Summary 1

2 Résumé 5

3 Zusammenfassung 9

4 Abbreviations 13

5 Introduction 15

5.1 Vaccines 15

5.2 Vaccine Safety 20

5.3 Influenza and influenza vaccines 25

5.4 Tuberculosis and BCG vaccines 30

5.5 The issue of subpopulations 33

5.6 Summary 36

5.7 References 38

6 Rationale, aim and specific objectives 49

6.1 Rationale 49

6.2 Aim 49

6.3 Specific objectives 49

7 Influenza vaccination in pregnancy: current evidence and selected national policies 51

7.1 Abstract 52

7.2 Introduction 53

7.3 Search strategy and selection criteria 53

7.4 The risks of influenza viral infection in pregnancy 54

7.4.1 Risk of seasonal influenza in pregnant women 54

7.4.2 Risk to pregnant women with comorbidities 56

7.4.3 Risk to pregnant women in pandemics 57

7.4.4 Risk to the fetus from maternal infection 58

7.4.5 Risk to the neonate from maternal infection 59

7.5 The benefits and risks of influenza vaccination in pregnancy 59

7.5.1 Evidence for influenza vaccine immunogenicity in pregnancy 59

7.5.2 Evidence for influenza vaccine efficacy & effectiveness in pregnancy 60

7.5.3 Evidence for influenza vaccine safety in pregnancy 61

7.5.4 Other potential risks from influenza vaccination in pregnancy 63

7.6 UK data: Yellow Card reporting 1994–2004 64
7.7 Recommendations from WHO and selected countries 65
7.8 Discussion 66
7.9 Conclusions 67
7.10 Contributors & Acknowledgements 68
7.11 References 69

8a A systematic review of the risk of disseminated BCG disease in HIV-infected infants 75
8a.1 Abstract 76
8a.2 Background 77
8a.3 Methodology 79
8a.4 The risk of disseminated BCG disease in HIV-infected infants 79
8a.5 Background risk of disseminated BCG disease in HIV-infected infants 83
8a.6 Limited data on BCG efficacy in HIV-infected and HIV-exposed children.. 83
8a.7 Improving surveillance and reporting of BCG vaccine-related adverse events 84
8a.8 BCG vaccination policy in industrialized countries 85
8a.9 BCG vaccination policy and disseminated BCG disease surveillance in Canada 85
8a.10 Towards a selective BCG vaccination program in resource-limited countries 86
8a.11 Research priorities regarding alternative strategies to prevent tuberculosis in HIV-infected and HIV-exposed infants 88
8a.12 Discussion 91
8a.13 Summary 92
8a.14 Contributors & Acknowledgements 93
8a.15 References 94

8b Making BCG vaccination programmes safer in the HIV era 103
8b.1 Comment 104
8b.2 References 107

9 Review of the management of BCG-related adverse events following immunization 109
9.1 Introduction 110

9.2 Materials and Methods 111
9.2.1 Identification of data 111
9.2.2 Inclusion and exclusion criteria 112
9.2.3 Case definition and disease classification 112
9.3 Results 114
9.3.1 Normal BCG reactions 114
9.3.2 Management of BCG adverse events by disease classification .. 115
9.3.2.1 Local disease 116
9.3.2.2 Regional disease 116
9.3.2.3 Distant disease 117
9.3.2.4 Disseminated BCG disease 119
9.3.2.5 Immune Reconstitution Inflammatory Syndrome 119
9.3.3 Further key issues on managing BCG-related AEFI 127
9.3.3.1 Transmission of BCG disease 127
9.3.3.2 Laboratory diagnosis 127
9.3.3.3 Anti-tubercular drug resistance 128
9.4 Discussion..... 129
9.5 References 132

10 Discussion and Conclusions 139
10.1 Influenza and inactivated influenza vaccines in pregnancy 141
10.2 Tuberculosis and BCG vaccines in HIV-infected children..... 146
10.3 Management of BCG-related adverse events 151
10.4 Immunisation programmes 152
10.5 Public perception and risk communication 153
10.6 Conclusions 155
10.7 References 157

11 Appendix: Authors' Reply 167

12 Acknowledgements 173

1 Summary

Background

Vaccines against infectious diseases are given worldwide and provide one of the most effective and cost-effective interventions available in public health. The goal of any preventive vaccination is to attain effective protection by deliberate means against a potentially disabling or lethal disease, using an acceptable intervention causing minimal adverse events. As with any medicinal product, no vaccine is completely effective or completely safe.

Many vaccines are provided routinely to the general population, particularly those given in childhood. In certain subpopulations, the vaccination or the natural disease may pose a higher risk. It is essential to identify vaccine effects in subpopulations in order to maximise both vaccine safety and effectiveness in public health programs. Gathering and summarising the evidence from pre- and post-licensing surveillance, pharmacovigilance systems and epidemiological studies become essential tasks in determining the specific risk-benefit profile of a vaccine in subpopulations, and in recognising more fully the spectrum of vaccine-related adverse events.

This dissertation synthesises evidence for safety and effectiveness of vaccines against influenza and tuberculosis in pregnant women and in HIV-infected children, respectively, through reviews of the available published and unpublished literature, and an analysis of immunisation policies.

Objectives

1. Describe and analyse the risk-benefit of inactivated influenza vaccination in pregnant women, and to compare different national policies.
2. Assess systematically the risk of live attenuated BCG vaccines in HIV-infected infants and perform a meta-analysis on the risk of disseminated BCG disease.
3. Combine and synthesise the available evidence on the management of BCG-related adverse events, towards establishing therapeutic guidelines.
4. Based on these findings, to provide insights on the implications for influenza and BCG vaccine policies in pregnant women and HIV-infected children, respectively.

Findings

In Chapters 7 and 11, the issue of inactivated influenza vaccines in pregnancy is examined. Historical reports and epidemiological evidence following two pandemics during the 20th century documented high influenza-related mortality (about 50%) and severe sequelae in pregnant women. During annual influenza seasons, the largest cohort studies have shown excess influenza-attributed hospitalisations in pregnant women, with an excess admission rate similar to that of non-pregnant women with chronic medical conditions, a higher-risk subgroup for whom influenza vaccination is commonly recommended. The risk of influenza-related hospital admissions during the influenza season increased in the presence of comorbidities and advancing gestational weeks, with the excess rates highest in the third trimester. A small randomised clinical trial with women receiving influenza vaccine in the third trimester showed a reduction in influenza-like illness and laboratory-confirmed febrile influenza illness in their infants. There are few available studies on influenza vaccine safety in pregnancy, but those available have not indicated any serious adverse effects. Several countries have moved to provide national immunisation recommendations identifying pregnant women as a high-risk group targeted for inactivated influenza vaccination. Robust surveillance mechanisms are warranted, with long term follow up of outcomes in settings where vaccination in pregnancy is recommended.

The issue of safety and effectiveness of live attenuated BCG vaccine in the paediatric HIV-infected subpopulation was addressed through review, meta-analysis and commentary in Chapter 8a/8b. BCG vaccine's main benefit of effectiveness against disseminated forms of tuberculosis in HIV-uninfected children has not been determined or adequately studied in the HIV-infected subpopulation. Based on international studies, the pooled risk estimate of the incidence of disseminated BCG disease in the HIV-infected sub-population was 979 per 100,000 (95% CI: 564 to 1506) HIV-infected vaccinees, or about 1%. This risk is more than one thousand-fold higher than in HIV-negative children. WHO changed recommendations in 2007 and made BCG vaccine a contraindication in HIV-infected individuals, if the HIV-infected status is known. There are several operational challenges in the implementation of a selective BCG vaccination program based on HIV status for resource-poor, high-risk countries. Efforts to reduce BCG vaccination in HIV-infected children should be made feasible in

settings where early infant HIV testing and HIV prevention and treatment programs are scaled up.

With over 80 years of experience with BCG vaccination, a spectrum of related adverse events is described. Chapter 9 addresses the issue further by reviewing the evidence for clinical management of iatrogenic BCG disease in children. An early and pivotal decision point for management is the assessment of the affected individual's immune status, as immunosuppressed individuals have a higher likelihood of severe and serious BCG disease although often presenting with non-specific signs. In general, local and regional BCG disease in immunocompetent individuals can be managed conservatively.

Conclusions

The findings from this dissertation contribute towards a fuller understanding of the risk-benefit profiles of two major vaccines given worldwide. The first review summarised the available body of evidence and determined that in previous years, certain influenza viral strains have posed a higher risk of morbidity and mortality in pregnancy. Available data are limited, but have not pointed to any serious adverse effects from inactivated influenza vaccination in pregnancy. Larger studies with laboratory-confirmed influenza outcomes and long-term data in specialised vaccination registries are warranted. The second review calculated the first pooled risk estimate of disseminated BCG disease in HIV-infected infants, through a systematic review and meta-analysis of hospital-based studies, and outlined the challenges in implementing safer, selective BCG vaccination programs for settings with low resources and high HIV endemicity. Operational research needs to be conducted to evaluate such major vaccine policy transitions. The third major review in this dissertation provided a synthesis of evidence-based management of BCG-related adverse events, towards establishing standard guidelines that improve case management.

Ongoing assessments of the current evidence for a vaccine's risk-benefit in subpopulations, as contained in these reviews, are clearly essential for updating vaccine indications and contraindications, and in identifying gaps in research. These assessments allow for re-examining of vaccine policy which, in the end, strengthen the rationale and responsibilities of immunisation programmes that are well understood and acceptable to the public.

2 Résumé

Contexte

Les vaccins contre les maladies infectieuses sont distribués à l'échelle mondiale et constituent une des interventions les plus efficaces et rentables disponible en santé publique. L'objectif de toute vaccination préventive est d'atteindre une protection efficace par des moyens spécifiques contre une maladie potentiellement invalidante ou mortelle, en ayant recours à une intervention acceptable causant le minimum d'effets indésirables. Comme pour tout produit médical, aucun vaccin n'est complètement efficace ni complètement sûr.

De nombreux vaccins sont couramment distribués à la population, en particulier ceux administrés durant l'enfance. Dans certaines sous-populations, la vaccination ou la maladie survenant naturellement peut présenter un plus grand risque. Il est essentiel d'identifier les effets des vaccins dans les différentes sous-populations afin de maximiser la sécurité des vaccins et leur efficacité dans les programmes de santé publique. Le regroupement et la synthèse des observations obtenues durant les suivis qui précèdent et suivent l'obtention de la licence de commercialisation, ainsi que les observations issues des systèmes de pharmacovigilance et des études épidémiologiques, sont des tâches essentielles pour déterminer le rapport spécifique risque-bénéfice d'un vaccin dans différentes sous-populations, et pour connaître de manière plus complète le spectre des effets indésirables liés au vaccin.

Cette thèse synthétise les observations sur la sécurité et l'efficacité des vaccins contre la grippe chez les femmes enceintes et contre la tuberculose chez les enfants infectés par le VIH grâce à une étude systématique de la littérature disponible, publiée ou non, et à une analyse des politiques d'immunisation.

Objectifs

1. Décrire et analyser le rapport risque-bénéfice des vaccins inactivés contre la grippe chez les femmes enceintes et comparer les différentes directives nationales.

2. Evaluer systématiquement le risque des vaccins BCG vivants atténués chez des nourrissons infectés par le VIH et effectuer une méta-analyse du risque de maladie BCG systémique.
3. Combiner et faire une évaluation synthétique des informations disponibles sur la gestion des effets indésirables liés au BCG, en vue d'établir des directives thérapeutiques.
4. Sur la base de ces résultats, fournir un aperçu et un commentaire critique sur les implications des politiques contre la grippe et le vaccin BCG, respectivement chez les femmes enceintes et les enfants infectés par le VIH.

Résultats

Les chapitres 7 et 11 traitent la problématique des vaccins inactivés contre la grippe durant la grossesse. Des rapports historiques et des observations épidémiologiques qui ont suivi deux pandémies du 20^{e} siècle révèlent une haute mortalité liée à la grippe (jusqu'à 50%) et de graves séquelles chez les femmes enceintes. Durant les périodes saisonnières de grippe, les plus grandes études de cohorte montrent un excédent de cas d'hospitalisation attribués à la grippe chez les femmes enceintes. L'excédent de ce taux d'admission est similaire à celui des femmes qui ne sont pas enceintes mais souffrant de maladies chroniques, sous-groupe qui présente un risque plus élevé et pour lequel la vaccination est couramment recommandée. Le risque d'hospitalisation, lié à la grippe saisonnière, augmente en présence de comorbidités et lors d'un stade de grossesse avancée, le taux d'excès le plus élevé se situant au troisième trimestre. Un essai clinique réalisé sur un échantillon restreint de femmes, prises au hasard et recevant un vaccin contre la grippe durant le troisième trimestre, montre une réduction des cas de maladies ressemblant à la grippe et des cas de grippe fébrile confirmés par laboratoire chez leurs nourrissons. Il y a peu d'études disponibles sur la sécurité de la vaccination contre la grippe durant la grossesse, mais celles disponibles n'indiquent aucun effet indésirable grave. Plusieurs pays fournissent actuellement des recommandations nationales concernant l'immunisation et considèrent les femmes enceintes comme un groupe à haut risque devant recevoir un vaccin inactivé contre la grippe. De sérieux systèmes de surveillance, avec un suivi des résultats sur le long terme, sont justifiés dans les contextes où la vaccination contre la grippe durant la grossesse est recommandée.

La problématique de la sécurité et de l'efficacité du vaccin BCG vivant atténué parmi la sous-population pédiatrique infectée par le VIH est traitée dans les chapitres 8a et 8b sous la forme d'une analyse systématique de la littérature, d'une méta-analyse et d'un commentaire critique. L'utilité du vaccin BCG en relation avec son efficacité contre les formes systémiques de tuberculoses a été étudiée parmi les enfants non-infectés par le VIH, mais n'a pas été déterminée ou étudiée convenablement dans la sous-population pédiatrique infectée par le VIH. Sur la base d'études internationales, l'estimation du risque résumé de l'incidence de la maladie BCG systémique parmi la sous-population infectée VIH a été évaluée à 979 pour 100'000 (IC 95%: 564 à 1'506) individus vaccinés, soit environ 1%. Ce risque est plus de mille fois plus élevé que chez les enfants séronégatifs. L'OMS a changé de recommandations en 2007 et considère désormais le vaccin BCG comme une contre-indication chez les personnes infectées par le VIH, si leur statut d'infection au VIH est connu. La mise en œuvre d'un programme de vaccination BCG sélectif basé sur le statut VIH présente plusieurs défis opérationnels pour les pays pauvres et à haut risque. Des efforts pour diminuer la vaccination BCG chez les enfants infectés par le VIH devraient être rendus possibles dans les situations où des tests VIH sont effectués chez les nourrissons et où des programmes de prévention VIH et de traitement sont prévus.

Plus de 80 années d'expérience dans la vaccination BCG ont permis de décrire un spectre d'effets indésirables liés à ce vaccin. Le chapitre 9 évalue de manière plus approfondie cette problématique par une étude des informations sur la gestion clinique des maladies BCG iatrogéniques chez les enfants. Un point clé de la gestion est l'évaluation du statut immunitaire de l'individu affecté, étant donné que les personnes dont le système immunitaire est déficient ont une probabilité plus élevée de développer des maladies BCG graves bien qu'elles présentent souvent des signes non-spécifiques. De manière générale, la maladie BCG locale et régionale chez les individus immuno-compétents peut être approchée de manière conservative.

Conclusions

Les résultats de cette thèse contribuent à une meilleure compréhension du rapport risque-bénéfice de deux des principaux vaccins distribués à l'échelle mondiale. La pre-mière partie de cette recherche résume les informations disponibles et met en évidence

que, durant des années, certaines souches de virus de la grippe ont présenté un risque de morbidité et de mortalité plus élevé durant la grossesse. Les données disponibles sont limitées mais n'ont pas révélé d'effets indésirables graves dus aux vaccins inactivés contre la grippe durant la grossesse. Des études de plus grande envergure avec des résultats confirmés en laboratoire ainsi que des données sur le long terme concernant des aspects particuliers de la vaccination sont nécessaires. Le deuxième volet de cette thèse calcule la première estimation du risque résumé de maladie BCG systémique chez les nourrissons infectés par le VIH, par une étude systématique de la littérature et une méta-analyse des études réalisées dans les hôpitaux. Ce volet insiste sur les défis de la mise en œuvre de programmes de vaccination BCG plus sûrs et sélectifs pour des régions à faibles ressources et présentant une endémicité du VIH élevée. Il est nécessaire de conduire des recherches opérationnelles afin d'évaluer de telles transitions dans les politiques de vaccination. La troisième partie de cette thèse fournit une synthèse de la gestion des effets indésirables observés liés au BCG, en vue d'établir des directives standard qui améliorent la gestion de la situation selon les cas.

Des évaluations continues des observations actuelles pour établir le rapport risque-bénéfice d'un vaccin dans différentes sous-populations, telles que celles traitées dans cette thèse, sont absolument essentielles pour mettre à jour les indications et les contre-indications pour les vaccins, et pour identifier les lacunes dans la recherche. Ces évaluations permettent le ré-examen de la politique des vaccins et, finalement, renforcent la raison d'être et les responsabilités de programmes d'immunisation bien compris et acceptables par le public.

3 Zusammenfassung

Hintergrund

Impfstoffe gegen Infektionskrankheiten werden weltweit eingesetzt und stellen eine der wirksamsten und kostengünstigsten Interventionsmöglichkeiten des öffentlichen Gesundheitswesens dar. Das Ziel jeder vorbeugenden Impfung ist es, durch den bewussten Einsatz von Mitteln einen wirksamen Schutz vor potentiell behindernden oder tödlichen Krankheiten zu erreichen, wobei der Eingriff tragbar und mit minimalen unerwünschten Erscheinungen (nachteilige Nebenwirkungen) verbunden sein soll. Wie andere medizinische Produkte sind auch Impfstoffe weder vollkommen wirksam noch vollends sicher.

Viele Impfstoffe werden routinemässig in der Bevölkerung eingesetzt, insbesondere während der Kindheit. Für bestimmte Subpopulationen allerdings können die natürlichen Krankheiten und/oder die entsprechende Impfung mit einem höheren Risiko bezüglich nachteiliger (Neben-)Effekte behaftet sein als für die Allgemeinheit. Um eine maximale Sicherheit und Wirksamkeit von Impfstoffen (und anderer präventiver Strategien) in Programmen der öffentlichen Gesundheitsversorgung erreichen zu können, ist es unerlässlich, die Folgen einer Krankheit und die entsprechenden Impffolgen spezifisch für Subpopulationen zu identifizieren. Wesentlich für das Erstellen eines spezifischen Risiko-Nutzen-Profils eines Impfstoffes für bestimmte Bevölkerungsgruppen, und entscheidend für ein umfassendes Verständnis des Spektrums unerwünschter (negativer) Impferscheinungen ist die Erfassung und Auswertung wissenschaftlicher Nachweise aus allen Stufen der Arzneimittelüberwachung während des Zulassungsverfahrens, nach Inverkehrbringen, aus Pharmakovigilanzsystemen und aus epidemiologischen Studien.

In der vorliegenden Dissertation werden - mittels Reviews der vorhandenen publizierten und unpublizierten Literatur - die nachweisbare Wirksamkeit und Sicherheit des Einsatzes von Influenza-Impfstoffen bei schwangeren Frauen und Tuberkulose-Impfstoffen bei HIV-infizierten Kindern dargestellt, verbunden mit einer Analyse der entsprechenden Immunisierungsstrategien bzw. -politiken.

Ziele

1. Risiko-Nutzen-Analyse der Impfung schwangerer Frauen mit inaktiviertem Influenza-Impfstoff und Vergleich verschiedener nationaler Strategien.
2. Systematische Bewertung des Risikos attenuierter BCG-Lebendvakzinen bei HIV-infizierten Kindern und Durchführung einer Meta-Analyse des Risikos einer disseminierten BCG-Infektion.
3. Zusammenfassende Auswertung der vorhandenen Datenlage zum Management BCG-bedingter unerwünschter Erscheinungen (nachteiliger Nebenwirkungen) im Hinblick auf die Erarbeitung von Therapie-Richtlinien.
4. Eine auf diese Ergebnisse gestützte Darstellung der Erkenntnisse und Beurteilung der Tragweite von Influenza-Impfstragtegien bei schwangeren Frauen und BCG-Impfstrategien bei HIV-infizierten Kinder.

Ergebnisse

In den Kapiteln 7 und 11 wird die Problematik des Einsatzes von inaktivierten Influenza-Vakzinen während der Schwangerschaft untersucht. Historische Berichte und epidemiologische Befunde aus zwei Pandemien des 20. Jahrhunderts dokumentieren eine hohe Influenza-bedingte Mortalität (bis zu 50%) und schwere Folgekomplikationen bei schwangeren Frauen. Während der jährlich auftretenden saisonalen Influenza werden gemäss den breitesten Kohort-Studien besonders häufig schwangere Frauen wegen Grippe hopsitalisiert; ihre Exzess-Eintrittsrate ist vergleichbar mit jener nicht schwangerer Frauen, die an einer chronischen Krankheit leiden, wobei letztere als Risiko-Gruppe gelten, für die Influenza-Impfungen im Allgemeinen empfohlen wird. Das Risiko von Influenza-bedingten Spitaleintritten während einer Grippewelle ist erhöht im Fall von Komorbiditäten und während fortgeschrittener Schwangerschaft, wobei die höchsten Exzess-Raten während des dritten Trimesters festzustellen waren. Eine kleine, randomisierte klinische Studie mit Frauen, die im dritten Trimester gegen Grippe geimpft wurden, liess weniger Fälle von grippeähnlichen und von durch Laborbefunde bestätigten fieberhaften Influenza-Erkrankungen bei deren Kleinkindern erkennen. Zur Impfstoff-Sicherheit beim Einsatz von Influenza-Vakzinen während der Schwangerschaft existieren nur wenige Studien. Aus diesen ergeben sich jedoch keine Hinweise auf schwerwiegende unerwünschte Impferscheinungen bzw. Nebenwirkungen. Verschiedene Länder sind dazu übergegangen, in nationalen Immunisierungsemp-

fehlungen schwangere Frauen als eine stark gefährdete Gruppe und damit als Zielgruppe für inaktivierte Influenza-Impfungen zu identifizieren. Wo Impfungen während der Schwangerschaft empfohlen werden, sind stabile Überwachungsmechanismen mit der Erfassung von Langzeitfolgen zur gewährleisten.

Dem Problemkreis Sicherheit und Wirksamkeit attenuierter BCG-Lebendimpfstoffe in der pädiatrischen, HIV-infizierten Subpopulation widmen sich ihm Rahmen eines systematischen Reviews, einer Meta-Analyse und eines Kommentars die Kapitel 8a und 8b. Ob der BCG-Impfstoff auch gegen disseminierte Formen von Tuberkulose bei HIV-infizierten Kindern wirksam ist, wurde bislang nicht adäquat untersucht. Diese Wirkung gilt bei nicht HIV-infizierten Kindern als Hauptverdienst des Vakzins. Gestützt auf internationale Studien wurde in einer zusammengefassten Risikoschätzung die Wahrscheinlichkeit des Eintretens einer disseminierten BCG-Erkrankung in der HIV-infizierten Subpopulation auf 979 pro 100'000 (95% KI: 564 bis 1'506) HIV-infizierte Geimpfte berechnet, oder ungefähr 1%. Dieses Risiko ist mehr als tausendmal höher als für HIV-negative Kinder. Die WHO änderte ihre Empfehlungen im Jahr 2007 und erklärte BCG-Impfungen als kontraindiziert für HIV-infizierten Menschen, sofern der HIV-Infektionsstatus bekannt ist. Für ressourcenarme Hochrisiko-Länder ergeben sich verschiedene operative Herausforderungen bei der Implementierung eines selektiven BCG-Impfprogramms, will man den HIV-Status berücksichtigen. Bestrebungen, BCG-Impfungen in HIV-infizierten Kindern zu reduzieren, sollten Hand in Hand gehen mit dem Ausbau der HIV-Diagnostik im frühen Kindesalter und dem Angebot von HIV-Präventions- und Behandlungsprogrammen.

Nach über 80 Jahren Erfahrung mit BCG-Impfungen ist ein Spektrum von begleitenden unerwünschten Impferscheinungen beschrieben. Das Kapitel 9 befasst sich weiter mit diesem Thema in Form einer Review der Behandlungsansätze und -verläufe iatrogener BCG-Erkrankungen bei Kindern. Ein früher und zentraler Entscheidpunkt im Behandlungsverlauf ist die Untersuchung des Immunstatus des Patienten, zumal Immunsupprimierte besonders gefährdet sind für eine schwerwiegende, wenn auch im Krankheitsbild unspezifische BCG-Erkrankung. Bei immunkompetenten Patienten ist eine konservative Behandlung lokaler und regionaler BCG-Erkrankungen in der Regel ausreichend.

Schlussfolgerungen

Die Ergebnisse dieser Dissertation tragen zu einem umfassenderen Verständnis des Risiko-Nutzen-Profiles von zwei bedeutenden Impfstoffen bei, die weltweit eingesetzt werden. Das erste Review wertet den verfügbaren Pulk von wissenschaftlichen Belegen aus und zeigt auf, dass in früheren Jahren gewisse Influenza-Virus-Stämme ein höheres Morbiditäts- und Mortalitätsrisiko während der Schwangerschaft darstellten. Verfügbare Daten sind zwar beschränkt, aus ihnen ergeben sich jedoch keine Hinweise auf irgendwelche ernsthaften nachteiligen Effekte infolge inaktivierter Influenza-Impfungen während der Schwangerschaft. Breiter angelegte Studien mit laborgestützten Influenza-Diagnostik und eine Erfassung von Langzeitdaten in spezialisierten Impfregistern sind vonnöten. Im zweiten Review wird mittels einer systematischen Auswertung und einer Meta-Analyse spitalbasierter Studien die erste zusammengefasste Risikoschätzung für disseminierte BCG-Erkrankungen in HIV-infizierten Kleinkindern errechnet. Das Review skizziert die Herausforderungen der Umsetzung sichererer selektiver BCG-Impfprogramme in Gebieten, die knapp an Ressourcen sind und in denen HIV hochendemisch ist. Operationale Untersuchen müssen durchgeführt werden, um derart bedeutende Wechsel der Impfstrategie zu evaluieren. Das dritte grössere Review in dieser Dissertation bietet eine Darstellung eines evidenzbasierten Managements BCG-bedingter nachteiliger Nebenwirkungen im Hinblick auf die Erarbeitung von standardisierten Therapie-Richtlinien.

Wie in den Reviews gezeigt, sind kontinuierliche Bewertungen neuer wissenschaftlicher Nachweise unerlässlich für ein zielgruppenspezifisches Risiko-Nutzen-Profil eines Impfstoffs. Sie sind essentiell für die Aktualisierung von Anwendungsgebieten und Kontraindikationen von Vakzinen sowie zur Identifizierung von entsprechenden Forschungslücken. Diese Bewertungen erlauben es, Impfstrategien ständig zu überprüfen und dadurch letztlich die argumentative Begründung und die Verantwortlichkeiten zu stärken für Impfprogramme, die von der Öffentlichkeit verstanden und akzeptiert werden.

4 Abbreviations

AEFI	Adverse event following immunization
AFB	Acid fast bacilli
AIDS	Acquired immune deficiency syndrome
ARR	Adjusted relative risk
ART	Antiretroviral therapy
dBCG	Disseminated BCG disease
BCG	Bacille Calmette-Guérin
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
EPI	Expanded Programme on Immunization
GACVS	Global Advisory Committee on Vaccine Safety
GAVI	Global Alliance for Vaccines and Immunization
GBS	Guillain-Barré syndrome
GIVS	Global Immunization Vision and Strategy 2006-2015
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
H	Haemagglutinin
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPT	Isoniazid preventive therapy
IRIS	Immune reconstitution inflammatory syndrome
IUATLD	International Union Against Tuberculosis and Lung Disease
M. bovis	*Mycobacterium bovis*
M. tuberculosis	*Mycobacterium tuberculosis*
MDR	Multi-drug resistance
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MTBC	*Mycobacterium tuberculosis* complex
N	Neuraminidase
OR	Odds ratio
PCR	Polymerase chain reaction
PID	Primary immunodeficiency disorder
RCT	Randomised controlled trial
RD1	Region-of-difference 1
SCID	Severe combined immunodeficiency
UCI	Universal Childhood Immunization
UMC	Uppsala Monitoring Centre
UNICEF	United Nations Children's Fund
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization
WHO-ART	WHO Adverse Reaction Terminology
XDR	Extensively drug-resistant

5 Introduction

This dissertation examines post-licensing vaccine safety and effectiveness against two major respiratory diseases in specific subpopulations, with emphasis on safety. First, inactivated influenza vaccination in pregnant women is reviewed, and a comparison is made of national influenza vaccine policies. Second, a systematic review is conducted and the pooled risk estimate calculated on the risk of disseminated disease from bacille Calmette-Guérin (BCG) vaccination in infants infected with human immunodeficiency virus (HIV). Potential impacts on immunisation programmes are considered for settings with different burdens of disease and levels of resources. Third, a review of the evidence-based management of BCG-related adverse events is performed, towards developing useful guidelines for healthcare providers. An introduction and historical background are provided on vaccines, vaccine development, national immunisation policy and programmes, vaccine safety and surveillance, clinical disease and epidemiology of influenza and tuberculosis, the current influenza and BCG vaccines, and the pregnant and HIV-infected infant subpopulations, which form the basis of enquiry.

5.1 Vaccines

History and development

Vaccines are biological medicines derived from living organisms and their products, which are not easily characterised molecularly, as compared with chemical or synthesised drugs. The manufacturing process of medical products obtained from complex living organisms requires additional safeguards due to inherent variability and lack of full characterisation of source materials. Vaccines, like other complex biologicals such as blood and cell tissue products, are regulated by international standards to ensure the highest quality and safety of biological products are achieved (Shin *et al.* 2007; WHO 2007c).

The aim of vaccination against an infectious disease is to induce an appropriate and effective immune response that protects against a clinically significant disease upon natural exposure. Vaccines have been called one of modern medicine's miracles, with a leading impact in reducing mortality and morbidity worldwide (Henderson 1997). A prominent success was the eradication of smallpox disease (certified in 1979) through

global mass vaccination, signifying the first and only eradication of a human infectious disease.

The term "vaccination" originated with the act of inoculation (*in oculus,* Latin for "into a bud" (Last 2001)) of vaccinia (cowpox) viral materials that offers immune cross-protection against variola (smallpox) disease in humans. Principles of smallpox vaccination existed centuries ago, but in the late 1700s was most famously and convincingly introduced in Europe by Jenner, who is considered the founder of vaccinology and immunology; there were several lesser known predecessors who also conducted vaccinations against smallpox, such as Boylston, Jesty and Rabaut-Pommier (Theodorides 1979; Pead 2003; Riedel 2005).

Scientific research classically follows the path from etiologic discovery of a new, serious pathogen to investigation of methods to propagate the pathogen in the laboratory. Products of the pathogen are then used to try and induce appropriate long-term immune responses for an effective and safe vaccine. An early debt is owed to Pasteur's experiments and serendipitous discoveries that led to one of the founding principles of vaccine development. The first actively manufactured vaccines were developed by attenuation of the live pathogen, at that time by in vitro serial passage. Teams led by Salmon, Smith and Roux followed with the development of completely inactivated (killed pathogen) vaccines. Further discovery of extracellular bacterial toxins led to the development of toxoid (inactivated toxin) vaccines in the early 20th century. Over the past 50 years, major advances have accelerated vaccine development, starting with cell culture passage, the ability to purify and extract components of the pathogens for subunit vaccines, the ability to conjugate proteins with polysaccharides to improve immune responses in infants, and most recently, vaccine technologies using recombinant DNA and novel vaccine delivery systems (Hilleman 2000; Plotkin 2005).

Thus, in general there are four ways vaccines have been or are being developed: by inactivated or killed organisms; attenuated live organisms; toxoids; or purified subunits (eg proteins, glycoproteins, carbohydrates) of the pathogen. The biological goal of vaccination is to achieve an appropriate and effective host memory immune response. An effective vaccine can require three components: 1) a suitable antigen from the pathogen; 2) an immune potentiator (also known as an adjuvant) may be required

to assist in activating the innate immune system to generate long-term adaptive immune responses against the antigen; and 3) a delivery system to help present and distribute antigens (with or without immune potentiators) to the target cells of the immune system (Pashine *et al.* 2005).

In addition to antigens, and sterile water or saline, vaccines contain several ingredients that are introduced during the production process and that are also scrutinised for reactogenicity and vaccine-related adverse events. These include solvents such as glycerin, detergents such as triton N-101, stabilisers such as sorbitol, preservatives such as thiomersal and adjuvants such as aluminium phosphate. Vaccines may also contain trace amounts of materials from growth media (eg. ovalbumin from embryonated chicken eggs). Comprehensive lists of excipients and growth media used in vaccine production are available (CDC 2008). Certain compounds can be introduced at different points during the manufacturing process for different purposes, such as thiomersal (sodium ethylmercurithiosalicylate) which may be used to inactivate the pathogen, or introduced during production to reduce bacterial and fungal contamination, or only added to the final product as a preservative in multidose vaccine vials.

Recent, rapid technologies for vaccine development are exemplified by current research on adjuvants. For over 70 years, the main licensed and available adjuvants were aluminium salts adsorbed with antigens; the mechanisms of immune potentiation were incompletely understood (HogenEsch 2002). Newer technologies have permitted vaccines based on fewer and more purified antigens having low inherent immunogenicity. This led to the need for new adjuvants that can provide a more effective and targeted immune response, improve safety and decrease reactogenicity (Kenney & Edelman 2003; Sesardic & Dobbelaer 2004). For example, MF59^{TM} is a recently licensed, oil-in-water emulsion that was tested as an adjuvant in split and subunit influenza vaccines (Schultze *et al.* 2008).

There are now dozens of potential vaccines in the pipeline applying novel technologies and many licensed vaccines have received updating according to safer and more modern methods of vaccine manufacturing. Half of all vaccines now licensed were developed in the past 25 years (Ulmer *et al.* 2006).

The number of different vaccines given in immunisation programmes has increased, but the total exposure to vaccine antigens has sharply decreased because of newer technologies developing more purified products. As a comparison, in the 1960s the total immunogenic proteins contained in 5 recommended vaccines was ~3017, whereas the current sum for 11 currently recommended vaccines (including these 5) is ~126 proteins (Offit *et al.* 2002). The reduction in vaccine antigen exposure is mainly due to the development of acellular pertussis vaccine, although whole-cell pertussis is still used in many countries worldwide.

In addition to improved technologies, it is important to note that vaccine manufacturing has also become safer with the increasing number of national regulatory agencies, which provide manufacturing oversight and rigorous requirements including independent laboratory testing of vaccine lots. The early history of vaccine production carries examples of major accidents from vaccine manufacturing that affected patients, and such past unfortunate errors are considered increasingly remote (Duclos *et al.* 2005).

The history of BCG vaccines includes a grave manufacturing error. In 1930, 72 of 250 children in Lübeck, Germany died of tuberculosis following peroral BCG vaccination. It was later discovered that during production, the BCG vaccine suspension was contaminated with *Mycobacteria tuberculosis*. After this accident, a general manufacturing principle arose that BCG for vaccine use would never again be maintained in a laboratory having other mycobacterial cultures (Comstock 1994).

The fragility of annual supplies of influenza vaccines was shown when regulators shut down a major vaccine production plant near Liverpool, United Kingdom in 2004, due to breaches in good manufacturing practices. During inspection, some vaccine batches were found to be contaminated with gram-negative bacteria including *Serratia*. The suspension resulted in the loss of 48 million doses of influenza vaccine, which was nearly half the expected US vaccine supply for that winter. Sterility issues continued with the closure of a second plant in Marburg, Germany, and the loss of 12 million more doses in 2005. The lessons learnt included the need to support several vaccine suppliers and to improve the collaboration and communication among international regulatory agencies to safeguard vaccine quality during production (FDA 2004; Sheridan 2005; Wilkie 2005).

Global immunisation programmes and strategies

It is important to consider the major initiatives that established vaccinations as an integral component of primary healthcare worldwide. The concerted effort of vaccination campaigns worldwide to eradicate smallpox was a major influence. By 1974, buoyed by the impending successful eradication, the Expanded Programme on Immunization (EPI) was proposed as the next step in global immunisation. Member states at the World Health Assembly aimed to reduce vaccine-preventable deaths in childhood by establishing long-term immunisation programmes (Henderson 1997). The EPI would routinely provide (originally) six vaccines to the general population: BCG, polio, measles, pertussis, tetanus toxoid, and diphtheria toxoid, according to a suggested immunisation schedule that has hardly changed to this day. In the 1970s, less than 5% of the world's children received these vaccines (Hardon & Blume 2005). As countries began establishing national immunisation programmes, global vaccination efforts were boosted by a reaffirmation by countries in 1984 to accelerate EPI towards the "Universal Childhood Immunization" (UCI) target of 80% coverage worldwide by 1990. Further funds and motivation arrived in 1988, when the World Health Assembly resolved to target polio as the next disease for global eradication through vaccination.

The overall UCI target of 80% global coverage was reached in the 1990s, but disaggregated data revealed that coverage was not uniformly distributed and the target was not reached in more than half of countries (Hardon & Blume 2005). EPI vaccines were clearly underused. The EPI prevented 3 million pediatric deaths annually but one quarter of the world's children still remained unvaccinated. The number of deaths prevented by EPI vaccines could have been potentially doubled (Kapp 2002). Disconnected immunisation services in developing countries have highlighted the increasing disparity and the "unused potential" of vaccination as an effective life-saving intervention, without even considering the addition of new and costlier vaccines to the programme (Keegan & Bilous 2004).

With 130 million children born each year, the momentum for sustained immunisation coverage is a continual challenge. There is currently an unprecedented mobilisation of financial resources to boost immunisation programmes in developing countries. The global value of vaccines is recognised, and public and private sectors have partnered to form the Global Alliance for Vaccines and Immunizations (GAVI) and the Global

Fund for Children's Vaccines. The aims are to strengthen immunisation services by sustaining and improving the global commitment for high coverage and ensuring long-term funds and secure vaccine supplies (Wittet 2000). The Global Immunization Vision and Strategy, developed by the World Health Organization (WHO) and United Nations Children's Fund (UNICEF), anticipates more than 20 new or improved licensed vaccines by 2015, and lists four main goals: increasing global coverage to 90%, ensuring access for eligible populations within 5 years of introducing new vaccines into programmes, integrating immunisation with health systems and surveillance, and understanding global interdependence of immunisations. Of importance is a specific aim (Strategy 5) addressing all aspects of safe immunisation, and to establish surveillance and appropriate timely response to adverse events following immunisation (WHO/UNICEF 2005a).

5.2 Vaccine safety

Monitoring vaccine safety is an integral part of immunisation programmes. Vaccine pharmacovigilance, also called "vaccinovigilance" (Lankinen *et al.* 2004), is described as "the science and activities relating to the detection, assessment, understanding, prevention, and communication of adverse events following immunization, or of any other vaccine- or immunization-related issues" (CIOMS 2007). This also includes monitoring aspects of safe immunisation practices to ensure the quality of vaccines produced, proper storage, safe injection, and appropriate handling and disposal of vaccine-related products.

Terminology and Case definitions

There are several important terms used in vaccine safety. An *adverse event following immunization* (AEFI) is defined as "an untoward medical event temporally associated with immunization that causes concern and is believed to be caused by immunization but might not be actually caused by the vaccine or the immunization process" (Duclos *et al.* 2005).

A *signal* is described as "reported information on possible causal relationship between AEFI and vaccine; relationship previously unknown or incompletely documented" (WHO 2008a). A signal may be a single event or a cluster of events that require clinical and epidemiological investigation.

Commonly used adjectives to describe frequency of the adverse event have also been standardised: "*very common*" ≥ 1 in 10; "*common*" ≥1 in 100 and <1 in 10; "*uncommon*" ≥1 in 1000 and <1 in 100; "*rare*" ≥ 1 in 10,000 and <1 in 1000; and "*very rare*" <1 in 10,000 (CIOMS 2005).

Finally, a distinction is also made in describing a "serious" event for regulatory reporting. A *serious* AEFI results in a life-threatening or fatal condition, hospital admission or prolongation of hospitalisation, or a persistent or significant disability. A *severe* AEFI is not synonymous and is not a term used in classification and reporting of serious AEFI. Severity describes not the event itself but the intensity, which may be graded as mild, moderate or severe, and does not indicate the seriousness of the medical condition. An example commonly given is a severe headache, which indicates high intensity but not necessarily serious medial consequence (ICH 1994).

The need for standardised terminology to describe vaccine-related adverse events was recognized by WHO and the Council for International Organizations of Medical Sciences (CIOMS), with joint efforts made to provide clear, consistent definitions of vaccine-related adverse reactions in order to improve the quality, comparability, and signal detection from the variety of sources of safety data available. Some definitions and standards for reporting safety data and adverse events management were outlined in 1994 by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), as an essential component of good practices in all clinical investigations, and applicable to adverse events from biologicals or chemical drugs (ICH 1994).

Clinical terminology has been standardized by international dictionaries for pharmacovigilance used by regulatory authorities and industry, such as the WHO-Adverse Reaction Terminology (WHO-ART, www.umc-products.com) and the Medical Dictionary for Regulatory Activities (MedDRA www.meddramsso.com).

WHO developed a number of case definitions of AEFI (WPRO 1999), but there are many remaining AEFI that are not defined. In 2000, a global network of scientists in academia, industry and governmental agencies launched The Brighton Collaboration (www.brightoncollaboration.org), and assigned volunteer working groups to the task

of forming a standardised case definition for up to 100 known vaccine-related AEFI (Bonhoeffer *et al.* 2002). The aim is to develop globally accepted definitions to improve the quality of vaccine safety data collection, analysis and reporting. So far, over 20 Brighton case definitions of vaccine-related adverse events have been published.

Pre-licensing safety data collection and reporting

Even with the largest pre-licensing randomised controlled trials (RCTs), there will be limits in the representativeness of the study population and in adverse events detection. Potentially vulnerable groups may have little representation or are actively excluded from participation in these trials, resulting in little or no data on these groups prior to vaccine licensing. Analyses of subgroups that are included in the study may also be limited for several methodological reasons.

Assessment of safety is inherently more difficult than efficacy, because safety is not measured by the presence but inferred by the absence of reported events. For example, a Phase III trial of 10^5 subjects is well powered to determine vaccine efficacy. To assess safety, 10^5 will likely detect events occurring more often than 1 in 33,333 doses. This follows the so-called Rule of Three or Hanley's formula, where 3/N (or 3/(N+1) (Jovanovic & Levy 1997)) approximates the upper limit of the 95% confidence interval for an unknown binomial probability having no events occurring in N independent observations, if N>30 (Hanley & Lippman-Hand 1983; Eypasch *et al.* 1995). The trial is unlikely to capture events that are less frequent, nor can it capture events with a delayed onset beyond the usual study period of 42 days. Even a single serious adverse event in a clinical trial serves as a signal of a potential vaccine-related AEFI that requires careful assessment for causality and further studies. There have been some examples after licensing of serious adverse events determined to be linked through observational studies and vaccine pharmacovigilance systems, such as rhesus rotavirus vaccine and the risk of intussusception (Offit *et al.* 2008).

In addition to limitations in study design, there are issues of reporting. As part of regulatory requirements, the conduct of trials requires an increasingly comprehensive collection of safety data. These data, however, are often not publicly accessible or well explained in the eventual scientific publications. A systematic review on the reporting of chemical drug adverse events in RCTs, found the safety content lacking in several

areas of medical research published up to the mid 1990s. The inadequacy of reporting was both quantitative, with the average allocated written space was one third of a single page; and qualitative, with more than 60% of RCTs were assessed as having insufficient safety reporting, such as lack of grading of severity or the lack of reporting negative results (Gellin & Schaffner 2001; Ioannidis & Lau 2001).

Since these limitations were recognised, the opportunity to assess vaccine and drug safety data in current phase III clinical trials has improved. Depending on the indication, larger study samples approaching $N=10^6$ and more extensive safety data collection and analysis are required prior to submission of a new vaccine or drug for licensing approval. Safety of an intervention is measured in the entire trial population, in contrast to earlier trials, where assessments were often limited to common (minor) reactions or only assessed in a subsample (Duclos *et al.* 2005).

Post-licensing safety data and surveillance systems

For these above reasons, vaccine safety data obtained from post-licensing observational studies are important, particularly for recently licensed medicinal products and in determining specific effects in subpopulations. Furthermore, non-controlled observational studies may be the most appropriate design, as ethical issues are raised in controlled studies after a new vaccine has been licensed, determined beneficial and widely recommended (Ioannidis *et al.* 2001). In addition to classic cohort and case-control studies, risk-interval and self-controlled case series are two alternative study designs used to evaluate vaccine safety, each having different study limitations (Glanz *et al.* 2006; Whitaker *et al.* 2006). Actively conducted studies are essential because of the limitations of post-licensing passive surveillance systems (Fontanarosa *et al.* 2004; Varricchio *et al.* 2004).

In 2004, only 68% of all countries had a national system to report AEFI (WHO/UNICEF 2005b). Of those existing in non-industrialised countries, only 25% are considered to be adequately functioning (WHO 2006c). Most industrialised countries have both a general passive scheme (such as UK's Yellow Card reporting or the US Vaccine Adverse Events Reporting System (VAERS) (Chen *et al.* 1994)), that is augmented by epidemiological studies and active surveillance registries, for example to monitor new vaccines or new indications of current vaccines. However, a recent survey of European

vaccinovigilance systems found many gaps in AEFI reporting and analysis even in industrialised countries (Lankinen *et al.* 2004). Passive surveillance databases can provide a valuable source for signal detection from computer-based data-mining programmes (Niu *et al.* 2001).

To augment passive surveillance, large, population-based health databases are also examined as another important source of vaccine safety data. With the increasing computerisation of medical records, there are now administrative longitudinal electronic databases available that link patient health records, including their vaccination history. Retrospective studies and signal detection programmes can then be conducted (Chen *et al.* 1997). Linked electronic databases that can monitor vaccine safety have been shown to be feasible in lower income settings (Ali *et al.* 2005).

Conducting an AEFI investigation shares several similarities with an outbreak investigation of an unconfirmed disease in a single case or cluster of cases. The main goals are chiefly to determine if the AEFI is causally related to the vaccine or if there are programmatic concerns; to manage the situation in a timely, appropriate and transparent manner; and to communicate findings well to maintain public confidence (WHO 2008b). A main challenge is timely collection and analysis of available evidence to determine if there is a causal association between the vaccine and the adverse event, and there can be delays before careful conclusions are reached. Causes of AEFI can be categorised in one of five groups: the AEFI may be due to a "true" adverse event from inherent properties of the vaccine (it may be then called a vaccine "reaction"); from programmatic errors related to vaccine storage, dose preparation, or administration; from reactions related to receiving the injection (an injection reaction); coincidental only and unrelated; finally, the cause may remain undetermined (WHO 2008a).

WHO recognised the need to respond to global vaccine safety issues in a timely, efficient manner. In 1999, WHO established the Global Advisory Committee on Vaccine Safety (GACVS, www.who.int/vaccine_safety/en). GACVS is an active scientific advisory that convenes to make independent expert assessments on topical vaccine safety issues (Folb *et al.* 2004). GACVS has published a substantial number of conclusions on vaccine safety issues that have influenced global and national vaccine policies (Duclos *et al.* 2005).

WHO also established an international pharmacovigilance database (WHO 2006b). Following the thalidomide disaster, in 1968 the WHO Programme for International Drug Monitoring was set up initially for chemical drugs, then expanded to include AEFI in the 1990s, relying upon spontaneous adverse event reporting from countries. The database is physically maintained by WHO's collaborating centre in Sweden, known as the Uppsala Monitoring Centre (UMC). An analysis of the UMC database up to 2005 revealed that 10% of reports are related to AEFI, and that just three countries – the United States, United Kingdom and Canada - have contributed 82.1% of all AEFI reports. The average time between the event onset date and the UMC report date was 2.4 years database (Letourneau *et al.* 2008). Some countries' national pharmacovigilance centres are clearly disconnected from EPI, indicated by discrepancies in AEFI data reported on UMC forms and the duplicate data requested by WHO/UNICEF on annual EPI monitoring forms (WHO 2006c). This indicates several areas to tackle, such as streamlining and harmonising reporting to WHO, establishing AEFI nosologic codes, improving timeliness and signal detection of AEFI, and building a truly international database. WHO also aims to support the establishment of networks of national post-marketing surveillance specifically for newly licensed vaccines and recognises the need for networks in non-industrialised countries (Bentsi-Enchill 2007).

5.3 Influenza and influenza vaccination

Certain subpopulations are at higher risk from influenza-related complications and are targeted for vaccination. There is a need to review the safety and effectiveness of influenza vaccine safety in the pregnant subpopulation. An overview of influenza, clinical disease and epidemiology and inactivated vaccines is now provided.

Clinical disease and epidemiology

Influenza viruses are single-stranded RNA viruses (Family: *Orthomyxoviridae*), with three genera affecting humans, classified according to major antigens as *Influenzavirus A, B,* or *C*. Types A and B are considered of main clinical importance, causing serious respiratory illnesses and epidemics. Type A is largely responsible for severe epidemics and pandemics. Only A viruses are subtyped by distinct differences in two glycoprotein spikes on the viral surface: haemaglutinin (H), with subtypes identified from H1 to H16; and neuraminidase (N), subtyped from N1 to N9 (Cox & Subbarao 1999; Nicholson *et al.* 2003; Fouchier *et al.* 2005). Only certain H and N subtypes are known

to infect humans and other mammals, whereas all subtypes have infected wild avian species, as birds are likely the evolutionary hosts for the A viruses.

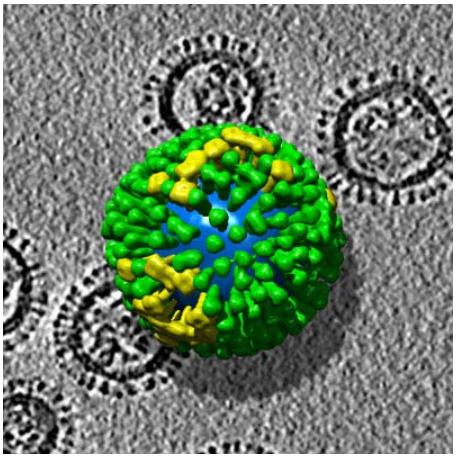

Figure 1:
3D electron tomography of the influenza virus (120 nm)

Haemagglutinin spikes are in green; neuraminidase spikes are in yellow. Reproduced with permission from Alasdair Steven.

The etiology of influenza was only discovered and transmission confirmed with swine influenza in 1930 by Shopes and the type A virus conclusively determined in human infections by Smith and colleagues in 1933, with demonstration of direct transmission of disease from infected human nasopharyngeal washings to ferrets (Smith *et al.* 1933; Taubenberger *et al.* 2007). Influenza types B and C were later discovered in 1940 and 1950 (Hilleman 2002).

Human influenza is a contagious respiratory disease that, after an incubation of 1-5 days, classically presents as a sudden onset of fever, chills, dry cough, muscle pain (myalgia) and diarrhoea. Human-to-human transmission of influenza occurs in three ways: from airborne droplet nuclei, from large droplets (> 10 μm) produced when coughing or sneezing, or from contact transmission that is direct (person-to-person) or indirect (fomites) (Salgado *et al.* 2002; Bridges *et al.* 2003). It is important to note that influenza exposure and infection affects individuals differently, ranging from subclinical to life-threatening illness. Primary influenza pneumonia usually presents early during the course, with dry cough becoming productive and haemorrhagic, and with increasing respiratory distress. A secondary bacterial pneumonia can occur usually during the convalescent period, commonly caused by *H. influenzae, Streptococcus pneumoniae,* and *Staphylococcus aureus*. Influenza can affect many organs, and is notably associated with serious neurological complications (Guillain-Barré syndrome, Reye's syndrome, other encephalopathies and myelitis) and muscular inflammatory diseases (myocarditis and myositis) (Cox & Subbarao 1999; Turner *et al.* 2003). De-

tailed clinical case descriptions of influenza disease and complications in pregnancy have been described for both influenza type A and B (Parkins *et al.* 2007; Yusuf *et al.* 2007).

Influenza pandemics have occurred probably much earlier, but in recorded western history, there were 13 probable or possible pandemics (global outbreaks) since the 17th century (Potter 2001). Three pandemics occurred during the 20th century, all by subtypes of influenza A: 1918/9 (H1N1), 1957/8 (H2N2) and 1968/9 (H3N2), while severe but less widespread epidemics (or "pseudopandemics") occurred in 1947/8, 1975/6 and 1989/9 (Nicholson *et al.* 2003; Kilbourne 2006). The pandemic between 1918-20 is estimated to have killed 20 to 50 million people worldwide, and was one of the most devastating infectious disease events in history (Johnson & Mueller 2002).

Influenza is one of the major infectious diseases in the world, having an enormous socioeconomic toll. An estimated 5-15% of the population is infected during average yearly epidemics, leading to severe respiratory illness in 3 to 5 million people and 250,000 to 500,000 deaths worldwide, occurring mainly in those >65 years of age (WHO 2003). The disease burden and affected higher-risk subpopulations are thought to be similar worldwide, although much less is known about its impact in many non-industrialised countries (WHO 2005a). Measures to assess mortality and morbidity from influenza are considered to underestimate the true burden. Influenza circulates among other respiratory pathogens and causes non-specific exacerbations of cardiopulmonary diseases, leading to "hidden" deaths from influenza (Nicholson *et al.* 2003). Antigenic variation, level of protective immunity in the population and the virulence of the strain (Cox & Subbarao 1999) are some key factors in determining the impact of influenza epidemics.

There are several vulnerable subpopulations with increased likelihood of influenza complications and death (WHO 2005a). These include the elderly, those in acute and long-term care facilities, or individuals with immunocompromising or chronic conditions (Salgado *et al.* 2002). For many years there have been scientific discussions whether there is sufficient evidence to include pregnancy as a higher risk condition for complications from pandemic and seasonal influenza (MacDonald *et al.* 2004). This open question was the basis of one of the reviews in this dissertation.

Young children are “efficient transmitters” of the infection, having the highest attack rates and are prolonged viral shedders (WHO 2005a). Influenza-attributed hospitalisation rates for cardiopulmonary were highest in infants under 12 months of age in the United States (Neuzil *et al.* 2000). This was supported by similar findings for children under 5 years using laboratory-confirmed influenza in Germany (Weigl *et al.* 2002). Although estimated influenza-related mortality is highest in those aged over 65 years (Thompson *et al.* 2003), laboratory-confirmed influenza mortality in children is substantial; during the 2003/4 season, of 153 laboratory-confirmed influenza deaths in US children (mainly from pneumonia, bronchiolitis, and encephalopathy), the highest mortality rate was in infants < 6 months old at 0.88 per 100,000 (Bhat *et al.* 2005).

Inactivated influenza vaccines

Vaccination is considered the mainstay of preventing influenza and mitigating the impact of outbreaks (Germann *et al.* 2006; WHO 2008c). In the 1930s, the successful propagation of the virus in the allantois of embryonated chicken eggs soon led to the development of the first crude, inactivated influenza vaccines (Bramwell & Perrie 2005). These were initially used to vaccinate American military staff.

Inactivated influenza vaccines are given as an intramuscular injection. The inactivated vaccines against seasonal influenza are trivalent, composed of antigens of 3 different influenza strains (usually two influenza type A strains, and one type B). Each antigen contained in the vaccine is classified by its lineage: “serotype/geographic origin/strain number/year first isolated (subtype)”, such as A/New Caledonia/20/99 (H1N1). One of the reasons for the epidemic nature of influenza is the frequent mutation in the viral surface antigens. Immunity from exposure to previous influenza antigens can offer some or no protection against infection by other strains. One factor in the effectiveness of vaccination is how well the selected antigens contained in the vaccine correspond with the antigens of circulating wildtype strains. Vaccine mismatch and reduced vaccine effectiveness due to antigenic variation has been recognised for many years (Francis *et al.* 1947). The frequency of viral mutations is reflected by the fact that WHO has recommended a change in composition of the annual influenza vaccine nearly every year since 1972.

There is an internationally accepted process for deciding upon the composition of annual influenza vaccines for the upcoming season for each of the hemispheres (WHO 2008c). A strict timeline is met each year following the decision on the predicted circulating strains and the production of adequate vaccine supplies for the next winter season. The process takes up to 6 months for manufacturers to produce 250-300 million vaccine doses from about the same number of embryonated chicken eggs. Worldwide annual capacity is constrained by egg-based vaccine production and manufacturing infrastructure (Ulmer *et al.* 2006). Vaccination coverage is considered paramount for influenza control. In the event of a pandemic, influenza vaccine production is a critical issue and an unprecedented number of doses will be urgently needed. There are efforts to increase manufacturing capacity and to develop novel, non egg-based production of influenza vaccines to maximize efficiency and safeguard supplies and quality (Bramwell & Perrie 2005; WHO 2005b).

Of serious adverse events following influenza vaccination, the risk of anaphylaxis is very rare (one study estimated 0.025 per 100,000) (Prosser *et al.* 2005). In 1976-7 a rise in cases of Guillain-Barré syndrome (GBS) was noted about 6-8 weeks after influenza vaccination. GBS is an acute, autoimmune demyelination of peripheral nerves, presenting as progressive ascending paralysis, requiring hospitalisation and often ventilatory support. With adequate supportive care, recovery is usually full after several weeks. The concern that GBS was an influenza-related AEFI led to the suspension of mass "swine flu" vaccine campaigns in the United States, which had been conducted following concerns that the 1976/7 circulating influenza strain would trigger the next pandemic (this did not occur). A total of 581 GBS cases was reported, and an authoritative US review concluded there was evidence favouring a causal link between the 1976/7 influenza vaccine and GBS. The estimated vaccine-related excess GBS was 0.6 per 100,000 above the estimated baseline incidence of 1-2 cases per 100,000. The excess risk remained substantially lower than the annual number of excess deaths attributed to influenza (Institute of Medicine 2004). One hypothesis is that during vaccine manufacturing using fertilised chicken eggs, the vaccine product may have been contaminated with *Campylobacter jejuni* (an endemic bacterial infection harboured in about 50% of chickens). Exposure to *C. jejuni* in humans is known to be associated with GBS (Marwick 2003; Haber *et al.* 2004;

Prosser *et al.* 2005). Since the swine flu vaccine, GBS has been listed as a possible adverse event from influenza vaccine.

5.4 Tuberculosis and BCG vaccines

Clinical disease and epidemiology

Human tuberculosis is an infectious disease primarily caused by *Mycobacterium tuberculosis.* Mycobacteria are slow-growing intracellular, atoxic, aerobic acid-fast bacilli. Human tuberculosis is less commonly caused by other closely related mycobacteria that mainly infect other mammals: *M. bovis, M. africanum, M. canetti, M. microti, M. caprae* and *M. pinipedii.* All these mycobacterial species causing tuberculosis in immunocompetent humans are considered members of the "*M. tuberculosis* complex" (MTBC) (Wirth *et al.* 2008). MTBC are distinguished from environmental mycobacterial species that can cause opportunistic disease in humans with immunodeficiencies, but are usually non-pathogenic in individuals with normal immune systems.

Most immunocompetent individuals are able to contain a primary *M. tuberculosis* infection and remain asymptomatic. About 90% of infected immunocompetent individuals will have latent tuberculosis without progression to reactivated tuberculosis in their lifetime. In contrast, tuberculosis progresses to active disease in about 50% of HIV-infected adults (WHO 2004c). Persistence of latent tuberculosis arises from the co-existence and co-evolution *M. tuberculosis* and the human host for thousands of years, and is one of the main obstacles to eliminate tuberculosis. Reactivation disease most commonly occurs as pulmonary tuberculosis in adults, which is the main infectious form. Classic presentation is cough, blood in sputum (haemoptysis), fever, sweats, and weight loss. Any organ system may be affected by tuberculosis, with the most serious forms of tuberculosis being disseminated disease and tubercular meningitis, which can occur at any age but are highest in young children.

Tuberculosis is the most common cause of death from a curable infectious disease. One third of the world's population is latently infected and an estimated 8.9 million new cases of tuberculosis disease occur each year. WHO declared tuberculosis a global health emergency in 2003 and emphasised two years later the situation was dire in Africa, which has 13 of the 15 countries with the highest annual incidence of tuberculosis

(>300/100,000) and where an estimated 1500 deaths from tuberculosis occur each day (WHO 2005c; Dye 2006; WHO 2007b). Global incidence of tuberculosis is on the rise, fueled by the HIV epidemic. Tuberculosis co-infection is now the leading cause of HIV-related morbidity and mortality. There is also an increasing number of individuals with multidrug-resistant (MDR) tuberculosis who are non-responsive to isoniazid or rifampicin, two first-line antitubercular drugs. Even more alarming is the emergence since 2006 of extensively drug-resistant (XDR) tuberculosis in several regions of the world, particularly seen in HIV-infected individuals. XDR *M. tuberculosis* strains have additional resistance to three of the six classes of second-line antitubercular agents, which severely restrict options for curative therapy (WHO 2007a).

Although tuberculosis in children can represent a substantial proportion of the total caseload and is associated with a more aggressive course, research in childhood tuberculosis is neglected (WHO 2006a). In a cohort of HIV-infected Ivorian children the cumulative incidence of tuberculosis by 3-years follow up was 5930 per 100,000, indicating the high risk of progression of tuberculosis disease in HIV-infected children (Elenga *et al.* 2005).

BCG vaccines

BCG is the oldest live attenuated vaccine still in use and the most widely given, with more than 3 billion individuals vaccinated since first use (Andersen & Doherty 2005). The story of BCG vaccine began more than 100 years ago. A *M. bovis* strain was isolated by Nocard and passaged in vitro for over a decade by Calmette and Guérin. After 230 passages, the organism had adequately attenuated to the sub-species named *M. bovis bacille Calmette-Guérin,* or BCG. The first human vaccination was in 1921 when Weill-Hallé administered a suspension of live BCG perorally to a tuberculosis-exposed infant who remained tuberculosis-free (Grange *et al.* 1983; Comstock 1994). It is now known that the selected *M. bovis* organism attenuated to BCG from the loss of genetic material mainly in RD-1 (region of difference-1) and RD-2 (Behr *et al.* 1999). BCG exemplifies the increased complexity and inherent variability of biological medicines. In the 1920s, daughter strains of BCG were shared with several laboratories around the world, and propagated by > 1000 serial cultures for 30 additional years prior to BCG seed lots being preserved by lyophilisation. This has resulted in several BCG vaccine

strains manufactured in the world with substantial genetic variation, which can translate to differences in effectiveness and related AEFI.

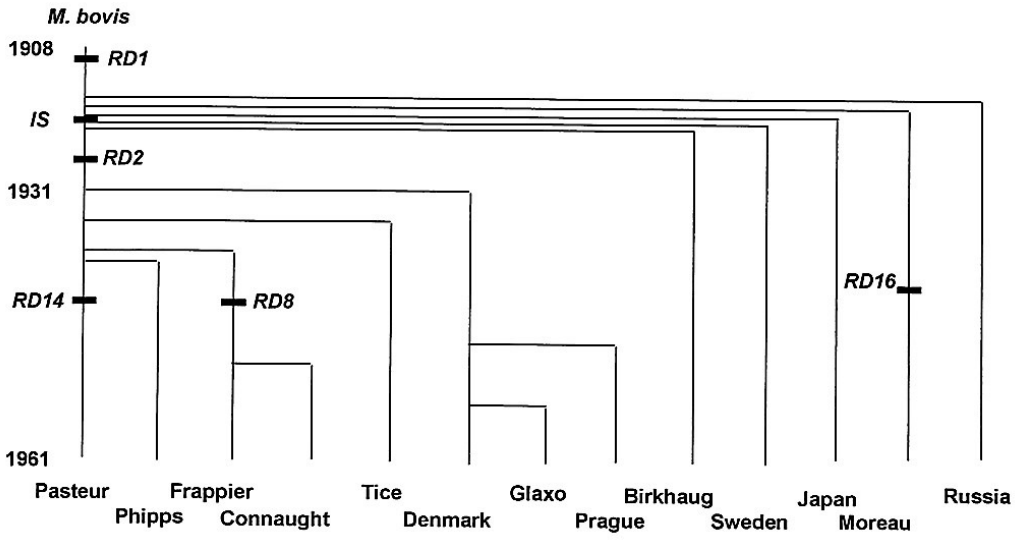

Figure 2: History of BCG geneology.
Vertical axis is time, horizontal lines indicate geographic location (and name) of BCG strains being propagated. RD indicates regions of genetic deletion. Reproduced from Behr *et al. 1999*.

BCG effectiveness against adult pulmonary tuberculosis has been observed to range from 0 to 80% depending on country, thus a summary efficacy rate is inappropriate. It remains unclear to what extent BCG vaccines prevent primary infection with *M. tuberculosis* or reactivation of latent pulmonary disease. Lower effectiveness may be partially explained by increased exposure to environmental mycobacteria in tropical settings (Fine 2001). The landmark large-scale field trial in Chingleput found 0% or even a negative BCG efficacy in preventing culture-positive adult pulmonary tuberculosis in HIV-uninfected adults followed for 15 years (Tuberculosis Research Centre (ICMR) Chennai 1999). The Malawi trial confirmed similar findings and also raised concern for the small HIV-infected adult subgroup included in the trial, whose risk of pulmonary tuberculosis possibly even increased after BCG revaccination (Karonga Prevention Trial Group 1996; Rieder 1996).

Few studies have examined BCG effectiveness in HIV-infected adults and findings are inconsistent. There is limited evidence that BCG provided to HIV-uninfected infants may protect against later disseminated tuberculosis in those who later acquire HIV/AIDS in adulthood (Marsh *et al.* 1997). However, childhood BCG vaccination

did not appear to protect HIV-infected adults against extrapulmonary tuberculosis (Arbelaez *et al.* 2000). The limitations of these studies on BCG effectiveness in HIV-infected adults include their retrospective nature, small sample size, the potential bias from selective non-vaccination and the suboptimal choice of BCG scarring as a surrogate indicator for vaccine-induced immunity.

The WHO rationale for BCG vaccination is based on the consistent, reasonable protection against serious forms of primary, progressive tuberculosis in the general pediatric population (WHO 1980; Brimnes 2008). A meta-analysis found summary protection against meningeal and military tuberculosis of 86% (95% CI: 65-95%) from RCTs and 75% (95% CI: 61-84) from case-control studies (Rodrigues *et al.* 1993). Another calculated a pooled vaccine efficacy of 74% (95% CI: 62-83%) against all forms of childhood tuberculosis from RCTs and 52% (95% CI: 38-64%) from case-control studies (Colditz *et al.* 1995). Since the inception of the EPI, WHO has recommended BCG at or soon after birth in countries with high tuberculosis burdens (WHO 2004b).

Currently BCG is part of immunisation programmes in over 150 countries endemic for tuberculosis. In contrast, most industrialised countries offer BCG selectively to high-risk subpopulations rather than routinely. There are guidelines to consider such shifts in BCG vaccine policy if epidemiological indicators of low-burden tuberculosis are met (IUATLD 1994). In 2008, a global mapping exercise was initiated in order to document changes in BCG policies and practices for each country (www.bcgatlas.org).

As BCG vaccination has not demonstrated a major impact against spread of infection, this vaccine does not have a substantial role in tuberculosis control strategies (WHO 2004a). With the spectre of MDR and XDR tuberculosis and a currently limited armamentarium of effective anti-tubercular drugs, it is clear that a tuberculosis vaccine is needed that effectively prevents reactivation disease to have an impact on disease control, and particularly one that is proven effective and safe in HIV-infected individuals, a subpopulation facing one of the highest risks from tuberculosis.

5.5 The issue of subpopulations

Pregnant women and HIV-infected children are two subpopulations examined in this dissertation. There may be little pre-licensing data on a chemical drug or vaccine's

profile in subpopulations, although certain groups may be more vulnerable to the disease. As described, post-licensing studies that evaluate subpopulations provide vital information because these groups are often excluded in clinical trials as well as neglected in drug development (Fisk & Atun 2008). The immunological mechanisms of vaccine safety and effectiveness play a key underlying role in the differential risk of adverse events from the natural disease or from the vaccination in certain subpopulations.

Subpopulation of pregnant women

Pregnancy is an altered immune state. Several physiological and immunological changes occur in pregnant women, with immune tolerance mechanisms to the foreign paternal antigens in the fetal allograft. These changes are not well understood, but a shift from cell-mediated adaptive immunity to innate immunity occurs. This relative imbalance in immune response may explain the increased morbidity seen in pregnant women with some infections, particularly intracellular pathogens (Sacks *et al.* 1999). There are several infectious diseases in pregnancy that also are known to carry a risk of fetal malformations, including varicella, rubella, syphilis, cytomegalovirus, and parvovirus B19 infections (Price 2008).

During pregnancy, embryonic organogenesis and fetal development take place in a programmed sequence of events. Research in teratology aims to define periods of risk and the outcomes related to the timing of an insult during gestation. An area of investigation explores how insults to intrauterine programming or in early childhood may predispose to certain health conditions in later life (Brent 2006; Price 2008).

It is well known that passive immunity with maternal pathogen-specific antibodies acquired from transplacental and lactational transfer offers protection to the newborn against infectious diseases in the vulnerable first months of life (Munoz & Englund 2001). Newborns are particularly susceptible to infections because of reduced, age-dependent antibody responses to a range of pathogens. Most of the world's neonatal deaths occur in poor countries, and infectious diseases are the leading cause (Anon 1999). In general, vaccination in early infancy also does not induce strong antibody responses, due to immunological immaturity as well as the persistence and interference of maternal antibodies. Vaccination in early life can, however, provide immunological priming that can lead to improved responses against later antigen-specific exposures

(Siegrist 2001). Except for BCG, all other current vaccines administered before the age of 6 months require repeated doses.

Inactivated vaccination in pregnancy and passive transfer of vaccine-derived maternal antibodies is considered a potential alternative means of protecting young infants (Healy & Baker 2006). Such a strategy has been called the "quintessence" of preventive medicine (Brent 2003). For several decades, tetanus toxoid vaccination during pregnancy has been considered a safe, effective EPI strategy to prevent neonatal tetanus in endemic countries (Roper *et al.* 2007). Despite this long-standing example, there remain several scientific, societal, legal and regulatory barriers to provide vaccines in pregnancy, particularly in industrialised countries (Glezen 2003).

Live attenuated vaccines are contraindicated in pregnancy due to concern that live vaccine strain replication in the maternal host and "vaccinemia" can potentially infect the placenta and fetus, leading to adverse pregnancy outcomes. Cases of fetal infection have been well documented after live attenuated rubella vaccine was given inadvertently in pregnancy (Hofmann *et al.* 2000; Hamkar *et al.* 2006). There have been no documented cases of congenital rubella syndrome, however, from inadvertent maternal vaccination or congenital adverse events from any other live attenuated vaccination except for smallpox. About 50 documented cases of fetal vaccinia have been reported worldwide, with some cases leading to fetal or neonatal death (Napolitano *et al.* 2004).

Subpopulation of HIV-infected and primary immunosuppressed children

Limited information is available about safety and effectiveness of most vaccines in the HIV-infected immunocompromised subpopulation (Clements *et al.* 1987; Moss *et al.* 2003). Immunodeficiency is defined as either primary immunodeficiency disorders (PIDs) or secondary, with HIV being one form of acquired immunosuppression (others include leukaemia, lymphoma, generalised malignancies, or drug-induced such as high-dose steroids or chemotherapy). Each disorder has its own underlying immunopathogenic mechanisms. Because the immune system is very complex, there are potential deficiencies with a variety of different mechanisms, such as abnormal function of white blood cells or the complement system. New PIDs continue to be discovered. Since the first was identified in the 1950s, the molecular basis of more than 100 PIDs

are now known. Although PIDs form a heterogenous group, there are less than 20 disorders that account for most cases (Lindegren *et al.* 2004).

In general in industrialised countries, live vaccines are contraindicated in immunocompromised individuals, out of concern that replication of the vaccine strain may occur unchecked and lead to serious vaccine-induced infections. One of the complicating features of HIV is that left untreated, the immune dysfunction from HIV is progressive. Uncertainty remains if there is an early safe window in which to administer live attenuated vaccines. Current guidelines for live measles vaccination in industrialised countries, for example, are based on a threshold age-specific $CD4^+$ count in HIV-infected children (Department of Health 2006). Inactivated vaccines are empirically considered safe; there have been some conflicting reports of viral load increasing transiently after inactivated influenza vaccination in HIV-infected adults (Stanley *et al.* 1996), but the clinical relevance has not been demonstrated. Immune responses in the immunodeficient vaccinee are related to the level of suppression. In general, responses to live or inactivated vaccines are reduced.

Prior to the HIV epidemic, disseminated BCG disease (dBCG) were known to occur (Lotte *et al.* 1984), almost exclusively in children with primary cellular immunodeficiencies. Retrospective reviews have defined a group of PIDs associated with dBCG: Severe combined immunodeficiency (SCID), chronic granulomatous disease, partial or complete Di George syndrome, and partial or complete interferon gamma deficiencies have been found to be at increased risk of opportunistic mycobacterial infections, among other infections (Casanova *et al.* 1996; Afshar Paiman *et al.* 2006; Liberek *et al.* 2006).

5.6 Summary

The field of vaccinology has seen major public health successes and technological advancements over its 200 years. Vaccines are valued as essential, cost-effective interventions in global public health and there are many novel vaccine candidates on the horizon. Like other medical interventions, a vaccine has benefits and risks. Safety information of a new vaccine is limited by pre-licensing studies that are insufficiently powered to assess safety or that report on adverse events incompletely. Subpopulations suspected of having a special vaccine risk-benefit profile may not be represented in

trials, or are actively excluded, or arise later as a concern, such as with HIV infection. Post-licensing surveillance studies and pharmacovigilance systems are thus crucial in providing more complete information on safety and effectiveness.

Influenza and tuberculosis are respiratory infections having enormous global health impacts. Pregnant women and HIV-infected subpopulations are groups known to be vulnerable to certain infectious diseases. The risk-benefit profile of inactivated influenza vaccines in pregnancy and of live attenuated BCG vaccination in HIV-infected children are important research questions for full consideration. Continual, careful appraisal of the evidence for vaccine safety informs policy and upholds the public trust placed in immunisation programmes.

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6 Rationale, aim and specific objectives

6.1 Rationale

It is essential to continually gather and evaluate current evidence to improve understanding of a vaccine's risk-benefit profile and to inform vaccine policy and practice. The dissertational research areas were topical and conducted during recent changes to WHO vaccine policy recommendations. Countries are in the process of evaluating national influenza vaccine policies, spurred also by WHO guidance to prepare pandemic plans that include identifying higher-risk groups for priority vaccination. BCG vaccine safety concerns in HIV-infected children have been raised in light of accumulating evidence, and a full review of BCG's risk-benefit profile in this subpopulation was warranted.

6.2 Aim

The aim is to contribute towards informed policy and practices in immunisation by synthesising current available evidence through systematic reviews on the safety and effectiveness of vaccines against influenza and tuberculosis in specific subpopulations.

6.3 Specific Objectives

- To assess the evidence of the risks and benefits of inactivated influenza vaccines in pregnant women, and compare different national vaccine policies.

- To assess the evidence of the risks and benefits of live attenuated BCG vaccines in HIV-infected infants, to perform a meta-analysis for a pooled risk estimate of disseminated BCG disease in this subpopulation, and to consider implications in settings with different levels of resources and burdens of disease.

- To collate and assess the current available evidence for management of the spectrum of BCG-related adverse events following immunisation, with the aim of contributing to useful evidence-based guidance for health care providers.

- Based on a synthesis of these findings, to provide useful commentary on influenza and BCG vaccine policies for pregnant women and HIV-infected infants, respectively, and to identify further research areas to improve the study of vaccine safety in subpopulations.

7 Influenza vaccination in pregnancy: current evidence and selected national policies

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All authors declare there are no conflicts of interest.

*Footnotes:

All references to influenza vaccines in this review refer to inactivated vaccines only. "Co-morbidity" is used to describe medical conditions which are associated with increased risk of influenza-related complications.

This manuscript was published in:

The Lancet Infectious Diseases (2008): **8**(1):44-52

7.1 Abstract

In several countries, pregnant women are recommended seasonal influenza vaccination and identified as a priority group for vaccination in the event of a pandemic. We review the evidence for the risks of influenza and the risks and benefits of seasonal influenza vaccination in pregnancy. Data on influenza vaccine safety in pregnancy are inadequate, but the few published studies report no serious side-effects in women or their infants, including no indication of harm from vaccination in the first trimester. National policies differ widely, mainly because of the limited data available, particularly on vaccination in the first trimester. The evidence of excess morbidity during seasonal influenza supports vaccinating healthy pregnant women in the second or third trimester and those with comorbidities in any trimester. The evidence of excess mortality in two previous influenza pandemics supports vaccinating in any trimester during a pandemic.

Keywords

Influenza; influenza vaccines; adverse effects; pregnancy; pregnancy complications; pregnancy trimesters; infant, newborn; health policy; risk assessment

7.2 Introduction

Certain population groups are known to be at higher risk of morbidity and mortality from influenza infection. Pregnancy is considered to be one of the conditions conferring increased risk; however, several countries, including the UK and Germany, do not routinely vaccinate in pregnancy,[1,2] whereas others, such as the USA and Canada, recommend vaccinating healthy pregnant women regardless of trimester.[3,4] In Australia, the vaccine is offered to healthy pregnant women in any trimester who will be in the second or third trimester during the influenza season.[5] WHO's current position paper recommends that all pregnant women should be immunised during the influenza season.[6] There has been no indication that inactivated vaccines given during pregnancy harm the fetus; however, safety data are limited.

Information on the burden of disease from seasonal influenza in healthy pregnant women is also limited. This is by contrast with the possible burden that may occur in an influenza pandemic, which is of international concern.[7] The 2005 UK Health Departments' Influenza Pandemic Contingency Plan[8] identified pregnant women in the third trimester as a provisional priority group for immunisation, recognising that morbidity and mortality patterns from a new pandemic strain cannot be predicted.

We examine the risks from both seasonal and pandemic influenza infection together with the benefits and risks of inactivated vaccine to the mother and fetus. The UK Yellow Card data (the UK's passive reporting system on adverse events associated with medicines), current WHO recommendations, and the policies of selected countries are also reviewed. All references to influenza vaccines in this Review refer to inactivated vaccines only. “Comorbidity” is used to describe medical conditions that are associated with increased risk of influenza-related complications.

7.3 Search strategy and selection criteria

Data for this Review were identified by searches of the PubMed database without date restriction up to August, 2007, for relevant articles in English, with the following medical subject headings: (1)“influenza, human” OR “influenza A virus”, (2) “influenza vaccine”, (3) “pregnancy”, “pregnancy trimesters”, OR “pregnancy outcome”, OR “pregnancy maintenance”, OR “pregnancy complications”, alone and in combination with major topic subheadings: “administration and dosage”, “adverse effects”, “contra-

indications", "epidemiology", "immunology", "mortality", "pathology", "prevention and control", "therapeutic use", "therapy", or "toxicity". The Cochrane Library and System for Information on Grey Literature in Europe (SIGLE) and selected countries' influenza vaccination policies were also searched. Bibliographies of key articles and the authors' own extensive files were reviewed. Citation hits were found through the Web of Science. This study obtained permission from the UK Medicines and Healthcare products Regulatory Agency to review a summary of Yellow Card reports from June, 1994, to June, 2004.

7.4 The risks of influenza viral infection in pregnancy

7.4.1 Risk of seasonal influenza in pregnant women

Women are commonly exposed to influenza during pregnancy. 11% of 1659 women in the 1993/94 influenza season in the UK had a four-fold rise in antibody titres indicative of new influenza infections.[9] Following the 1989/90 severe influenza season in the UK, a one in 15 random sample of records of all fatal cases was compared with a "regular" season in 1985/86.[10] Using these methods, eight deaths in pregnant women were counted in the severe season and two in the regular season, suggesting a four times higher risk of death during a severe influenza season. These figures were extrapolated to an excess of 90 deaths in pregnant women out of the 25 185 total excess deaths estimated in the 1989/90 influenza season.[11]

Although several observational studies using routine hospital admission data have noted a higher risk of hospital admission in pregnancy with influenza-like illness, the precise level of risk and the extent that risk varies by trimester are unclear because of varying outcome definitions and difficulty in controlling for unknown underlying morbidity. In one of the first observational studies, directly standardised rates of acute cardiorespiratory illness in hospitalised pregnant women with no known comorbidities were compared with those in hospitalised postpartum women in the winter when influenza was not circulating, using Tennessee Medicaid data from 1974-93.[12] Peri-influenza season rates were subtracted from those in the influenza period to obtain excess hospital admission rates attributable to influenza. Women in the second and third trimesters had excess hospital admission rates of 6.32 (95% CI 2.90-9.74) and 10.48 (6.70-14.26) per 10 000 woman-months, respectively. Women in the first trimester and

women in the postpartum period had excess hospital admission rates of only 3.06 (0.44-5.68) and 1.16 (-0.09 to 2.42) per 10 000 woman-months, respectively, similar to the rate in non-pregnant women of 1.91 (1.51-2.31) per 10 000 woman-months. The excess hospital admission rate attributable to influenza in healthy women in the last trimester was equivalent to that seen in non-pregnant women with chronic medical conditions.[13] Medicaid provides health care for those without personal insurance and poorer sociodemographic groups are therefore over-represented in this population. Residual confounding - eg, by tobacco - is likely to bias upwards any effect observed.

Excess hospital admission rates attributable to influenza were calculated by similar methods in a 1990-2002 population-based record linkage study of 134 188 pregnant women from Nova Scotia.[14] Rates of hospital admission and medical visits during defined influenza, peri-influenza, and non-influenza seasons were compared per trimester. The influenza-attributable excess rates of hospital admissions because of respiratory illness were 1.1 (-0.1 to 2.3), 0.4 (-1.1 to 1.9), and 2.0 (-0.3 to 4.3) per 10 000 healthy woman-months in the first, second, and third trimesters, respectively, after subtracting the background peri-influenza season rates. The results from this study were lower than those from the Tennessee study, which could partly be explained by the conservative definition of hospitalisation (admissions that included delivery were omitted, as were admissions for asthma exacerbation without influenza-related diagnostic codes); adjustments for confounders such as smoking and socioeconomic status made no difference to the risk of hospital admission.

Two other studies examined outpatient medical visits reported in US health maintenance organisation (HMO) databases as opposed to hospital admissions.[15,16] The first, on a small study population from a Washington HMO, examined rate differences in influenza-like illness diagnosed in an inpatient or outpatient visit, compared with influenza-unexposed weeks in healthy pregnant women during defined weeks when influenza circulated from 1991-97. Excess rates attributable to influenza were 5.8, 9.8, 14.1, and 11.0 per 10 000 woman-weeks in the first, second, and third trimesters, and postpartum period, respectively, but with only 5.4% of episodes considered severe - eg, pneumonia or requiring an emergency visit.[15] Low admission rates for influenza and pneumonia in pregnancy were also noted in another HMO dataset.[17]

In the second study, Oregon HMO data were used to compare outpatient medical visits for acute respiratory disease in pregnant women with non-pregnant women. Four severe influenza seasons (1975, 1976, 1978, 1979) and one regular season (1977) were included.[16] During the 1978 season, influenza A H1N1 reappeared, a subtype that had not circulated for 20 years. Pregnant women had a significant excess rate of medical visits of 48.1 per 1000 visits categorised as influenza, pneumonia, upper respiratory illness, and respiratory symptoms. By contrast, pregnant women did not have an excess acute respiratory disease rate in the 1975, 1976, and 1979 seasons when predominant circulating strains were all H3N2 variants. This finding suggests that different strains or previous exposure to subtypes could selectively affect the impact of an influenza season. Nearly all acute respiratory disease medical encounters were supernumerary visits and therefore not attributable to increased opportunity to report a respiratory illness during the regular prenatal encounters.

Secondary effects of influenza-like illness or pneumonia in pregnancy on the fetus were examined in 6 277 508 hospital admissions for pregnant women, representing a 20% sample of US public hospitals from 1998-2002.[18] 2.3% of hospital admissions during influenza seasons included pneumonia or influenza compared with 1.2% during the rest of the year, excluding hospital stays in which a delivery occurred. Hospitalised pregnant women with respiratory illness had higher odds of preterm delivery, fetal distress, and caesarean section (adjusted odds ratios (OR) 4.08 [95% CI 3.57-4.67], 2.48 [1.84-3.35], and 3.91 [3.48-4.39], respectively) compared with hospitalised pregnant women without respiratory illness.

7.4.2 Risk to pregnant women with comorbidities

In the US public hospitals study of admissions for pregnancy and respiratory illness, pregnant women with a comorbid condition were three times more likely to have a respiratory illness compared with healthy pregnant women (OR 3.2 [3.0-3.5]) during defined influenza months (1998-2002).[18] In a separate cohort analysis of 297 pregnant women with respiratory hospitalisation in the Tennessee Medicaid database (1985-93), pregnant women with a history of asthma had the highest rate of respiratory hospital admission at 597 per 10 000 (OR 10.63 [8.18-13.83]) compared with pregnant women without comorbidities during defined influenza seasons.[19] Most recently, nearly 13 500

pregnant women with one or more comorbidities were reviewed in the Nova Scotia study (1990-2002).[14] Their influenza-attributable rate of hospital admission was 3.9 (-6.4 to 14.2), 6.7 (-4.1 to 17.5), and 35.6 (21.1 to 50.1) per 10 000 woman-months for the first, second, and third trimesters, respectively, when comparing influenza and peri-influenza seasons. Based on an average season of 3.4 influenza-exposed months during the study, excess hospital admissions during the third trimester would occur in 121 per 10 000 pregnant women with comorbidities and in 6.8 per 10 000 healthy pregnant women.

7.4.3 Risk to pregnant women in pandemics

During the influenza pandemic of 1918/19, more than 20 million people died, with pregnant women among those at high risk for complications or death. For example, 1350 pregnant women diagnosed with influenza were ascertained from a mail survey of members of the American obstetrical societies and all physicians in Maryland.[20] Overall, the case fatality rate was 27%, but all deaths occurred within the 678 cases complicated by pneumonia. The case fatality rate within the pneumonia subgroup was 54%. A similarly high rate was noted in Chicago (IL, USA) in 101 hospitalised pregnant women with influenza illness complicated by pneumonia compared with a 32% case fatality rate in 2053 non-pregnant patients admitted with pneumonia in the same 7-week period.[21]

Eickhoff and colleagues[22] noted in 1961 that "An association of influenza-associated deaths and pregnancy is a common clinical impression". For instance, of a total of 216 influenza deaths during the 1957/58 pandemic documented in New York City (NY, USA), 22 deaths were in unvaccinated pregnant women, only seven of whom had rheumatic heart disease.[23] Deaths from all causes in pregnant women were double the expected number compared with the number of deaths in pregnant women in the preceding 4 years. A similar doubling of risk of death from all causes in pregnancy compared with previous years was seen in England and Wales in 1957, where 12 of the 103 women aged 15-44 years who died from influenza were pregnant. These 12 deaths were within the 477 deaths reported to the Central Public Health Laboratory Service (now known as the Health Protection Agency), accounting for 3% of all excess deaths.[24] In Minnesota, USA, 11 deaths in unvaccinated pregnant women accounted

for over half of this state's deaths in women of child-bearing age during the 1957/58 pandemic.[25] All fatal pregnant cases in this last study had fulminant, in most cases haemorrhagic, pulmonary oedema.

There is an absence of evidence of an increased risk of influenza-associated morbidity or mortality in pregnant women in the 1968/69 pandemic that had variable global impact. Previous immunity against the influenza A N2 neuraminidase of the 1968/69 pandemic strain possibly had a role in the different risk patterns observed.[26]

7.4.4 Risk to the fetus from maternal infection

In general, the viral risk to the fetus from maternal influenza infection is low, since transplacental transmission of influenza infection is rare. Although there have been one or two case reports of in-utero infection confirmed by viral culture at fetal autopsy,[27] a seroepidemiological study in Nottingham, UK, found no IgM anti-influenza antibodies or autoantibodies in the cord sera of 138 infants whose mothers had acute influenza infection confirmed by serology.[9] By contrast, a cluster of 12 fetal deaths within 3 weeks (eight spontaneous abortions and four stillbirths) was reported in one UK general practice where an average of 84 births and hence 12-14 fetal losses are expected per year. Serological evidence of exposure to influenza A during pregnancy was seen in all the 12 mothers, compared with none in nine randomly selected postpartum mothers of live babies born in the same time period and registered with the same practice.[28]

There is a lack of clear evidence for an association between maternal influenza infection or influenza-induced maternal high fever and congenital abnormalities in human beings. Influenza infection induces pyrexia greater than 37.8°C in 50-100% of cases, usually persisting for 3 days (up to 5 days) with a range between 38°C and 40°C.[11] Suggestions of a teratogenic link with pyrexia are difficult to discern in the presence of important causes such as genetic disease or drugs. There are few studies[29] assessing the risk to the fetus using serological confirmation of maternal influenza infection, which is a major limitation when up to half of influenza infections are mild or subclinical.

7.4.5 Risk to the neonate from maternal infection

Infants are at high risk of morbidity from influenza. In a prospective cohort study in three American counties, 160 (5.7%) of 2797 children under the age of 5 years presenting to selected clinics and hospitals with respiratory illness in 2000-04 had positive nasal or throat viral swabs for influenza.[30] Hospital admission rates for laboratory-confirmed influenza in children aged 0-5 months, 6-23 months, and 24-59 months were 4.5 (3.4-5.5), 0.9 (0.7-1.2), and 0.3 (0.2-0.5), respectively, per 1000 children. The rates of influenza in non-hospitalised young children revealed a different trend. Children aged 0-5 months had the lowest annual rates of outpatient clinic visits and laboratory-confirmed influenza, whereas those aged 6-23 months had the highest. Other cohort studies of hospital admissions with laboratory-confirmed diagnoses suggest a rate of about 2 per 1000 children under 12 months of age; however, with only 60-70% of admissions being laboratory investigated, there is scope for biased ascertainment of virologically proven cases and overestimation of the rates.[31,32] The differences in infant hospital admission rates in seasons with circulating influenza compared with no circulating influenza in the USA were of similar magnitude.[33]

7.5 The benefits and risks of influenza vaccination in pregnancy

The potential benefits of protecting against the increased risk from influenza in pregnancy need to be balanced against any actual or theoretical concerns of vaccination during pregnancy.

7.5.1 Evidence for influenza vaccine immunogenicity in pregnancy

The few serological studies on pregnant women suggest that antibody response to influenza vaccine is similar in pregnant and non-pregnant women.[34,35] Antibody response measured in 15 pregnant women 4-6 weeks following vaccination in the second or third trimester was similar to titres in non-pregnant vaccinated adults.[36] In a small randomised trial, maternal seroconversion to one or more antigens was seen in all 13 women given influenza vaccine in the last trimester of pregnancy and in none of 13 women who received tetanus toxoid in the control arm.[34]

7.5.2 Evidence for influenza vaccine efficacy and effectiveness in pregnancy

Based on evidence of higher risk of mortality in pregnant women from two previous influenza pandemics, it is assumed that vaccinating this population against a pandemic influenza strain will prevent a substantial number of deaths. The assumed benefits of vaccinating pregnant women against seasonal influenza include reduced maternal morbidity and the possibility of reduced mortality in a severe influenza season. An additional benefit of vaccinating a pregnant woman may be the reduced risk of clinically significant influenza illness in the young infant.

Early studies on healthy military recruits provide clear evidence of influenza vaccine efficacy and reduced morbidity in (non-pregnant) young adults.[37] A Cochrane systematic review concluded that inactivated influenza vaccines prevented 67% (51-78%) of serologically confirmed and 25% (13-35%) of clinically apparent cases in non-pregnant healthy adults.[38] Limitations of summarising across studies from 1966-2003 were acknowledged. For example, vaccine standardisation and composition changed in the same period. A separate systematic review found influenza vaccine efficacy to be even higher if summarised across more recent studies.[39]

In pregnant women, a recent randomised trial in Bangladesh found that influenza vaccine effectiveness against febrile respiratory illness in women immunised in the third trimester was 28% (4-46%).[40] Vaccine efficacy based on laboratory-confirmed influenza illness is awaited.[40]

Two studies have shown transplacental influenza-specific antibodies and some protectt-ion to infants from naturally acquired maternal influenza infection.[41, 42] The first study, from Texas, USA (1975-78), found that where cord blood influenza IgG titres were 1/8 or more, infants did not have laboratory-confirmed, clinically apparent acute influenza before 8 weeks of age.[41] The second study, from Florida, USA, followed 39 mother-infant pairs in the 1978/79 influenza season. Although no reduction in the rate of clinically apparent, serologically proven acute infection occurred in infants born to infected mothers, there was evidence to suggest that their respiratory illness was milder and with delayed onset.[42]

In 13 immunised pregnant women, vaccine-acquired influenza-specific maternal antibodies had high transplacental transfer ranging from 87% to 99%, depending on the IgG antibody.[34] The half-life of antibodies in the babies was 43-53 days, similar to the half-life of transplacental antibodies from naturally acquired maternal influenza infection.[34] The cord titres in 26 maternal-newborn serum pairs did not differ significantly if maternal vaccination occurred in the second or third trimester.[36]

Results from the small Bangladesh randomised trial in immunised pregnant women indicate protection against laboratory-confirmed febrile illness caused by influenza in the infants (vaccine efficacy 61% [9-84%]).[40] A 2003-05 database review from Texas found that infants under 6 months of age born to immunised pregnant women were less likely to have a medically attended acute respiratory illness (not laboratory confirmed) during the peak of the 2004/05 influenza season, when compared with those infants born to non-immunised pregnant women matched by age and date of delivery (10.9% *vs* 31%, p<0·001).[43] Two retrospective reviews (1997-2002[17] and 1995-2001[44]) from the USA using managed care databases did not find a reduction in the incidence of medically attended acute respiratory illness (not laboratory confirmed) in immunised mothers[17] or their infants.[17,44] Both studies were, however, based on easily measured but, by their nature, non-specific outcomes and they were also underpowered because of lower outcome rates or lower maternal vaccine coverage than expected.

7.5.3 Evidence for influenza vaccine safety in pregnancy

There are only a handful of studies on the safety of influenza immunisation in human pregnancy. Two studies have provided long-term data after first trimester vaccinations. The largest, from the USA, analysed 650 mother-child pairs registered within the US Collaborative Perinatal Project (1959-65) who had received influenza vaccine in the first trimester. The project followed 50 897 pregnant women at more than 20 weeks' gestation attending antenatal clinics in several US hospitals. The main aim was to examine factors in pregnancy related to cerebral palsy and other damage to the central nervous system.[45] The immunised cohort was exposed to some or all of these immunisations: trivalent inactivated influenza, oral polio, inactivated polio, tetanus toxoid, and diphtheria toxoid vaccines. In the first week of life and at 12 months of age the children were assessed by a paediatrician and at 4, 8, 12, and 24 months of age their mothers were interviewed. Thereafter, the children were followed for deaths up to the

age of 4 years (autopsy data were available on just over 80% of deaths) and followed up to the age of 7 years for hearing impairment, learning disabilities, and malformations. Influenza vaccination was not associated with any excess minor or major malformations.[46] Based on a total of 2291 pregnant women vaccinated in all trimesters in the same study, there was no evidence for an excess incidence of childhood malignancies up to 1 year of age and cancer mortality up to 4 years of age.[47]

A smaller study (1976-77) found no difference between 41 mothers vaccinated in the first trimester and 517 non-vaccinees followed up at 8 weeks for physical and neurological development or maternal, perinatal, or infant complications.[48] Similarly, no differences were noted in 58 women vaccinated in the second and 77 women vaccinated in the third trimester.[48] There were no serious adverse events in the vaccinated group with an incidence of side-effects (eg, fever, headache, myalgias) under 3%.

Further evidence of vaccine safety in the second and third trimesters is available from a third more recent, historical cohort database study of five influenza seasons in Texas (1998-2003). No serious adverse events were noted up to 42 days post-vaccination in 252 pregnant women immunised in the second or third trimester, and there were no differences in outcomes of pregnancy or infant hospital admissions up to 6 months of age compared with matched, unvaccinated healthy controls.[49] Information on two further years (2004-05) were recently reported with similar follow-up of infants to 6 months of age.[43] In this larger study no serious adverse events in pregnancy were detected in 1006 vaccinated pregnant women compared with 1495 matched unvaccinated pregnant controls.

Other studies have only looked at immediate post-vaccine adverse events. Some safety studies followed the US experience of mass immunisation with swine influenza vaccine in 1976. One study followed 11 pregnant women vaccinated in the second trimester and 45 women vaccinated in the third trimester.[36] 40 of the 56 women were followed for 24 h after immunisation. Seven vaccinated pregnant women had side-effects, of whom three reported mild fever. Other side-effects included coryza, influenza-like symptoms, headache, and dizziness. The type and number of vaccine reactions were described as similar to other clinical trials, and pregnancy outcomes as identical to controls.

Finally, in the randomised immunogenicity trial during the 1988/89 season, 30 healthy women in the third trimester received either trivalent influenza or tetanus toxoid vaccine. No significant reactogenicity was noted in any recipient, including fever, pain, or health-care seeking.[34]

7.5.4 Other potential risks from influenza vaccination in pregnancy

By contrast with the risk of fever from naturally acquired maternal infection, a low-grade fever rarely occurs in response to influenza vaccination. In one study, 1·3% of 189 vaccinated pregnant women had a temperature of more than 37.8°C, which lasted between 1 and 2 days.[48] In view of the possible teratogenic effect of hyperthermia in pregnancy based on observations from animal models,[50] there may be a theoretical risk of teratogenicity from maternal pyrexia secondary to vaccination.[5] In trials of influenza vaccine in other, older populations, however, no difference in fever was noted in 904 patients in the active arm compared with 902 patients in the placebo control arm (1.3% *vs* 0.7%, p=0.15).[51] There is also the possibility of fetal hypoxia associated with maternal anaphylaxis, for example in reaction to the vaccine's egg protein or other constituents.

Other adverse events associated with influenza vaccine in the general population should also apply to pregnant women and include local reaction, headaches, and malaise. Antigenic determinants can change annually and manufacturers' formulations of influenza vaccines can also change and vary in safety profile, as seen with the 1976 swine influenza vaccine.

Finally, thiomersal, an organic mercury compound, has been used since the 1930s as a preservative in some vaccines, including influenza, to prevent contamination during the production process. Neither a UK retrospective cohort of more than 100 000 children[52] nor a UK prospective study of more than 14 000 children[53] followed from birth to more than 7 years of age found any causal association between thiomersal-containing vaccines and neurodevelopmental disorders. In 2001, the US Institute of Medicine (IOM) reviewed fetal exposure to mercury and found insufficient evidence to suggest a causal relation between vaccines containing thiomersal and neurodevelopmental disorders; however, the IOM considered the risk to be biologically plausible.[54] In 2004, the IOM reviewed cumulative paediatric exposure to thiomersal-containing vaccines (in-

cluding data from new population-based epidemiology studies), which led them to reject the hypothesis of a causal link between infants exposed to thiomersal-containing vaccines or the measles, mumps, and rubella vaccine and autism.[55] The European Medicines Agency also concluded there was no evidence of a risk of autism or speech disorders associated with the use of thiomersal-containing vaccines.[56] The Global Advisory Committee on Vaccine Safety (GACVS), an advisory body to WHO, concluded that there is currently no evidence of mercury toxicity from thiomersal in vaccines and no reason to change current immunisation practices on the grounds of safety, but noted the paucity of safety data for malnourished or preterm infants.[57]

The UK Health Departments, while noting the lack of evidence of toxicity, currently recommend use of the thiomersal-free vaccine in pregnant women, where this is available, based on the precautionary principle. If only thiomersal-containing vaccine is available, however, the benefit of vaccination is felt to outweigh any theoretical risk and the vaccine is not considered contraindicated in pregnant women.[1]

7.6 UK data: Yellow Card reporting 1994-2004

For this Review, the Post Licensing Division of the UK Medicines and Healthcare products Regulatory Agency (MHRA) searched the Yellow Card database from June 1, 1994 to June 22, 2004. A causal link between influenza vaccination and adverse events cannot be formed from these case reports and, as with other passive reporting schemes, inherent limitations in these systems include lack of information on the denominator, under-reporting, and incomplete information on confounders. Among 1366 reports of adverse reactions to influenza vaccine in 10 years, eight occurred in pregnancy. Seven of these eight cases were vaccinated in the first trimester. Six of the pregnant women were documented as having a medical history of asthma (four women), pleurisy (one), or diabetes (one). Four women received other medications, of whom two were exposed to other vaccines; the remaining four cases did not provide medication history. The adverse outcomes reported were one stillbirth, three spontaneous abortions, and three cases of fetal growth retardation, of which two delivered prematurely. The eighth case was a congenital urinary tract anomaly at an 18-week ultrasound scan that resolved or was artifactual, since the outcome was a healthy delivery and normal postnatal renal

scan. In view of the reporting and denominator limitations to these data, firm conclusions cannot be made from these eight case reports.

7.7 Recommendations from WHO and selected countries

In 2004 and 2006, the GACVS recommended that authorities reconsider their national policies and review the risk-benefit of influenza vaccination in pregnancy, "given the high risk to the mother - and thus to the fetus - of the disease itself and the likely small risk to mother and fetus of the inactivated influenza vaccine".[58,59] The 2005 WHO position paper contains a stronger statement that "influenza vaccination in pregnancy is considered safe and is recommended for all pregnant women during the influenza season" and it specifies that this recommendation aims to protect the mother as well as the infant in the first months of life.[6]

In the USA, influenza vaccine in pregnancy was considered safe and practised in the 1950s and 1960s. Official recommendation was provided in 1997 by the Advisory Committee on Immunization Practices (ACIP) for routine immunisation in the second or third trimester. The ACIP now recommends (since 2004) routine influenza vaccination in all trimesters for healthy pregnant women during the influenza season.[3] Canada's national advisory committee has expanded its recommendations to vaccinate women in all trimesters for the 2007-08 season.[4] In previous years, this practice was "encouraged" for any healthy pregnant Canadian woman wishing to avoid influenza morbidity, and explicitly recommended for women in the third trimester expecting to deliver during the influenza season, with the rationale that they were household contacts to their infants.[60] In Australia, vaccination is recommended for healthy women who will be in the second or third trimester during the influenza season, including those in the first trimester at the time of vaccination.[5] In the UK, vaccination is recommended for pregnant women with any condition listed as a high-risk comorbidity regardless of trimester, but no routine recommendation for healthy pregnant women has been made;[1] this policy is currently under review. Many countries, however, provide no routine recommendation to vaccinate in pregnancy. For example, Germany's Standing Commission on Vaccination (STIKO) does not routinely recommend influenza vaccine in pregnancy.[2 and 61] STIKO notes the safety evidence is incomplete but no teratogenic effect has been clearly identified. Although pregnancy is not considered as

a contraindication, STIKO recommends individual risk-benefit assessment and avoiding first trimester vaccination if there is no urgent indication.

7.8 Discussion

In two previous influenza pandemics (1918/19 and 1957/58), pregnant women were at higher risk of morbidity and mortality from influenza-related complications compared with non-pandemic years. In seasonal influenza, pregnant women are at increased risk of influenza-related hospital admission compared with non-pregnant or postpartum women during influenza-exposed periods and occasionally increased mortality in a severe season. This risk rises with increasing length of gestation, and even more strongly with comorbidity.

Research on influenza vaccines is limited in pregnant women. This population is excluded from controlled randomised trials and reproductive toxicity testing until now has not been a regulatory requirement for existing vaccines.[62] The few prospective studies of women immunised in the second or third trimester suggest the vaccine is safe.

Safety data for the use of any inactivated vaccine in pregnancy, particularly in the first trimester, are limited but have not clearly identified any risk to the fetus. Some reassurance is provided by the inactivated tetanus toxoid vaccines, for which there is more evidence for safety in pregnancy; these vaccines are widely used in all trimesters to prevent neonatal tetanus.[46, 63]

There is less evidence about harmful effects of seasonal influenza infection in healthy women in the first trimester compared with the second and third trimesters. A recommendation to routinely immunise healthy women in the first trimester remains determined more by theoretical risks and benefits than by available current evidence. A practical concern is spontaneous abortion, which occurs more often in early pregnancy and could be misattributed to the vaccine.

Vaccination of women before knowledge of a first trimester pregnancy does occur – perhaps more frequently in countries that recommend influenza vaccine for their health-care workforce - and there is no current evidence to suggest harm to the fetus. A recommendation to offer first trimester immunisation routinely would be strengthened

if future studies demonstrate adverse effects from early maternal influenza exposure. One seroepidemiological study provided evidence suggestive of a higher risk to the fetus of adult schizophrenia if maternal influenza exposure occurred in the first half of pregnancy.[29]

The USA reached just 16% influenza vaccination coverage of pregnant women in 2005.[3] Improvements in vaccine uptake will require practical efforts to reduce barriers and address any concerns of pregnant women and their health providers.[64]

Since the current evidence base to fully assess the risk-benefit of influenza immunisation in pregnancy is incomplete, countries have produced different recommendations. These guidelines do not apply to pandemic influenza, where pregnant women are expected to be at much higher risk of infection, disease, and mortality.

7.9 Conclusions

There is evidence to support seasonal influenza vaccination in pregnancy in two groups: healthy pregnant women in the second or third trimester and pregnant women with comorbidities in any trimester. There is also good evidence that pregnant women are more vulnerable during pandemic influenza. Further evaluation of the assumed benefits from maternal immunisation is needed. It is encouraging that the first randomised effectiveness trial of maternal influenza immunisation in the third trimester found significant protection to the mother from febrile respiratory illnesses and indirect protection to their young infants against clinically apparent and influenza-proven febrile respiratory illness.[40]

No serious adverse effects of influenza immunisation in pregnancy have been reported in the few published studies on vaccine safety. There are, however, limited data on safety in the first trimester. Furthermore, the risk from infection and hence the assumed benefit of vaccination in the first trimester are unclear. Influenza vaccines containing thiomersal are not contraindicated in pregnant women. Preference for the use of thiomersal-free influenza vaccines in pregnancy is a precautionary measure only. Further research on the risk of influenza in pregnancy and longer term safety data on influenza immunisation are needed. Consideration should be given to developing mechanisms for following up pregnancy outcomes after maternal immunisation to aug-

ment passive surveillance, particularly if national recommendations are broadened for this group.

7.10 Contributors & Acknowledgements

Tippi Mak wrote the first draft and with Punam Mangtani and Dina Pfeifer, designed the paper and critically evaluated the literature. John Watson and Jane Leese conceived the idea for the review and helped design the paper. All authors have contributed substantially to intellectual content, revisions and updates.

We thank several colleagues. Philip Bryan prepared the Yellow Card 10-year summary of data. He and Jane Woolley reviewed the manuscript on the use of Yellow Card data. Adwoa Bentsi-Enchill, Zaid Chalabi, Arlene Reynolds, and Karen Noakes reviewed an earlier manuscript and made valuable suggestions. Andreas Reich translated from German the influenza vaccine recommendations of Germany's Ständige Impfkommission (Standing Commission on Vaccination). Jaakko Kaprio and Marja Heinonen assisted our access to the doctoral dissertation of the late Olli P Heinonen.

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8a A systematic review and meta-analysis of the risk of disseminated BCG disease in HIV-infected infants

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No conflicts of interest declared. The views expressed in this article do not necessarily reflect the official positions of any of the agencies or institutions with which the authors are affiliated.

Working Paper

8a.1 Abstract

Attenuated, live bacille Calmette-Guérin (BCG) is the only currently licensed vaccine against tuberculosis. The WHO recently revised BCG vaccination recommendations, making HIV infection a full contraindication to BCG vaccination, even in highly tuberculosis-endemic settings. HIV-infected infants face an appreciably increased risk of disseminated BCG disease (dBCG), the most serious BCG vaccine-related adverse event. We performed a systematic review and calculated a pooled estimated risk of dBCG in vaccinated HIV-infected infants of 979 per 100,000 (95% CI: 564-1506 per 100,000). Implications of this policy revision are different in Canada and other low-burden countries, compared with resource-constrained countries with high incidences of HIV and tuberculosis. For the latter, we address the requirements to implement a selective BCG vaccination program based on the infant's HIV status. Local programs for immunization and the prevention of HIV and tuberculosis must be coordinated. Safer and more effective strategies should be investigated and existing programs strengthened in order to prevent tuberculosis in HIV-infected and HIV-exposed infants.

Keywords

BCG vaccines; infant, newborn, tuberculosis; HIV; AIDS-related opportunistic infections; immunization programs; risk factors, risk assessment, meta-analysis; review

8a.2 Background

In May 2007, WHO revised global vaccination recommendations for bacille Calmette-Guérin (BCG), following safety concerns in HIV-infected children.[1] The change in guidance has added complexity to the decision-making on whether to provide BCG vaccination, and affects approaches to childhood tuberculosis prevention and immunization programs worldwide.

Although contributing up to 25%[2] of the total tuberculosis caseload in high-burden countries, childhood tuberculosis has been called an "orphan disease"[3] when compared with the attention given to adult tuberculosis. Children under 3 years of age are the highest risk group for developing disseminated tuberculosis.[4] If co-infected with HIV, children have at least a 6-8 times higher risk of developing tuberculosis in settings with high tuberculosis burden.[5] In 2007, nearly 90% of the 350,000-540,000 children with new HIV infections were from sub-Saharan Africa, mainly due to mother-to-child transmission.[6]

BCG is the only currently licensed vaccine against tuberculosis. This vaccine was derived from a live attenuation of *Mycobacterium bovis* and has been used for 87 years. In 2005, BCG was part of immunization programs in over 150 reporting countries, including all African countries.[7] About 100 million doses are given each year worldwide. BCG vaccination in HIV-*uninfected* infants is effective,[8,9] cost effective,[10] and estimated to avert almost 40 cases of serious childhood tuberculosis per 100,000 doses, globally equivalent to about 30,000 cases of tuberculous meningitis and 11,000 cases of miliary tuberculosis.[10]

Until 2007, WHO advised countries with high tuberculosis incidence to provide a single dose of intradermal BCG vaccine at or soon after birth to all infants, including those who were HIV-infected but asymptomatic.[11] This longstanding routine policy was maintained during the escalation of the HIV epidemic. The rationale was based on the population risk of tuberculosis and the assumption that HIV-infected children would have a similar risk-benefit ratio from BCG vaccination as the general pediatric population, namely, BCG-induced protection against disseminated tuberculosis and a comparable low risk of serious BCG-related complications.

The most serious adverse event from BCG vaccination is systemic BCG disease, classified as "distant" (regional disease +1 remote site) or "disseminated" (regional disease + ≥2 remote sites (remote i.e. spleen or bone marrow), and here collectively referred to as "dBCG".[12] Nearly 30 years ago, the background estimated risk of dBCG in HIV-uninfected infant vaccinees in Europe was 0.429 per 100,000.[13] However, recent data provided in this review have indicated that this risk in HIV-infected infant vaccinees is more than a thousandfold higher than in the general pediatric population. The outcome of dBCG in HIV-infected children is poor, with an all-cause mortality of about 75%.[12,14-17]

In 2007, WHO responded to mounting risk data and made HIV infection a full contraindication to BCG vaccination, including in HIV-infected infants asymptomatic at birth and in settings with high tuberculosis burden.[1] This major revision was supported by the Global Advisory Committee on Vaccine Safety[18] and the Strategic Advisory Group of Experts,[19] both independent scientific advisory committees established by WHO.[20] The Box below shows the updated list of contraindications to BCG vaccine.

We conducted a systematic review and meta-analysis to estimate the risk of dBCG in HIV-infected infants. We further highlight several issues surrounding this full BCG vaccine contraindication and in particular, the feasibility of its implementation in HIV-endemic, resource-limited settings where maternal and infant HIV status is not routinely determined. Program requirements are outlined to allow for selective BCG vaccination programs based on maternal and infant HIV status in such settings. Policy implications in resource-rich, low-burden settings are also compared. In particular, we consider Canada's experience with BCG vaccination, which highlighted the need for robust surveillance and dBCG risk estimates in specific populations.

Box

WHO Contraindications to BCG Vaccination

- **Persons with HIV infection[§]**
- Persons with impaired immunity (known or suspected congenital immunodeficiency, leukemia, lymphoma or generalized malignant disease)*
- Persons under immunosuppressive treatment (corticosteroids, alkylating agents, antimetabolites, radiation)*
- In pregnancy*

[§] **Replacing WHO's previous recommendation that asymptomatic HIV-infected infants should receive BCG vaccine in settings with high tuberculosis burden (WHO 2007[1])**

8a.3 Methodology

We conducted a PubMed search of the literature (from Jan 1990 to July 2008) for English language articles with following strategy: ((HIV*) OR (Immunologic Deficiency Syndromes) OR (AIDS-Related Opportunistic Infections)) AND (Mycobacterium bovis* OR BCG OR "Guerin" OR "Calmette"), searched with and without the following limitation "(adverse effect*) OR ("injurious effect*" OR "undesirable effect*" OR "side effect*" OR "adverse reaction*" OR "adverse event*")". All available Abstracts and the bibliographies of selected articles were reviewed.

In order to calculate a pooled risk estimate of disseminated BCG disease (dBCG), we included all cohort studies of HIV-infected infants that assessed BCG-related adverse events. dBCG cases were counted if confirmed by biochemical or molecular methods; suspected dBCG cases without laboratory confirmation were not counted. With permission, we accessed materials collected for a global review of BCG vaccine-related adverse events conducted by WHO in 2005, which included published and unpublished studies, and search results from WHOLIS, the Uppsala Monitoring Center database. Congress proceedings, the authors' own libraries, Google Scholar and Web of Science citation hits of key articles were also reviewed. The meta-analysis was conducted using StatsDirect 2.6.8 software (StatsDirect Ltd, Cheshire, England).

8a.4 The risk of disseminated BCG disease in HIV-infected infants

We performed a systematic review with the aim to calculate a pooled risk estimate of dBCG in HIV-infected vaccinated infants based on the available literature. The diagnosis of dBCG usually requires tertiary health services. Limitations of hospital-based studies should be considered and include selection bias. For identified data presented only at conferences, limitations include potential lack of rigorous peer review. Finally, detection of dBCG improved after molecular diagnosis became available after about 1997.[21]

We identified a total of 14 hospital-based cohort studies on HIV-infected children, with 7 studies in 5 countries reporting dBCG cases.[14-17,22-24] (see Table) Two other studies were not considered; one study had a cohort < 5 HIV-infected BCG-vaccinated children[25] and the other had incomplete information.[26] The two studies from South

Africa provide the only population-based estimates of dBCG risk in HIV-infected infants from active surveillance and using denominators based on the estimated annual number of HIV-infected infants born in the province during the study period.[16,17] The first study from 2002-2004 was an estimate based on one reporting tertiary hospital.[16] The second study from 2004-2006 provided an improved population-based estimate based on three reporting provincial tertiary hospitals, and found an estimated population incidence of dBCG at 992 per 100,000 (95% Confidence Interval (CI): 567 to 1495 per 100,000).[17] This South African population estimate provided a comparator for the pooled estimate risk of studies included in the meta-analysis .

The remaining 10 international studies were all based on denominators of hospital cohorts and included in the meta-analysis. Four of these included studies reported cases of dBCG. An early, small study of 68 inadvertently-vaccinated HIV-infected infants were followed in a French hospital and had the highest rate of dBCG of nearly 3%.[22] Of 9 resulting BCG-related complications, 2 children had dBCG confirmed by biochemical methods or PCR testing for *M. tuberculosis* complex (MTBC). The second early study was published in a non-PubMed-indexed but internationally peer-reviewed journal.[23] Of 355 HIV-infected children admitted to a Thai hospital from 1989-94, 9 had BCG vaccine-related complications with one confirmed as dBCG and 5 with suspected but non-confirmed pulmonary lesions. Mycobacterial isolates were sent to the Johns Hopkins laboratory for biochemical speciation. Three more recent published abstracts from South American hospitals,[14,15,24] have further indicated the generalisability of an increased dBCG risk in vaccinated HIV-infected children. Five, mostly earlier studies of vaccinated HIV-infected children reported no dBCG cases.[27-31] The absence of dBCG cases in these studies may have occurred by chance, the small sample sizes (all cohorts were less than 50 HIV-infected children) and short follow-up period.

We performed a random-effects meta-analysis based on these 10 studies. (Figure 1) The pooled risk estimate of dBCG in hospitalized, HIV-infected infant vaccinees was 979 per 100,000 (95% CI: 564 to 1506 per 100,000), or about 1% of vaccinated HIV-infected infants. The estimate was stable, with the fixed-effects model producing the same result. There was no suggestion of publication bias using the Egger test (intercept =0.06, p=0.84) or heterogeneity of studies (Cochran Q (9) = 4.9, p=0.84, I^2 = 0%).

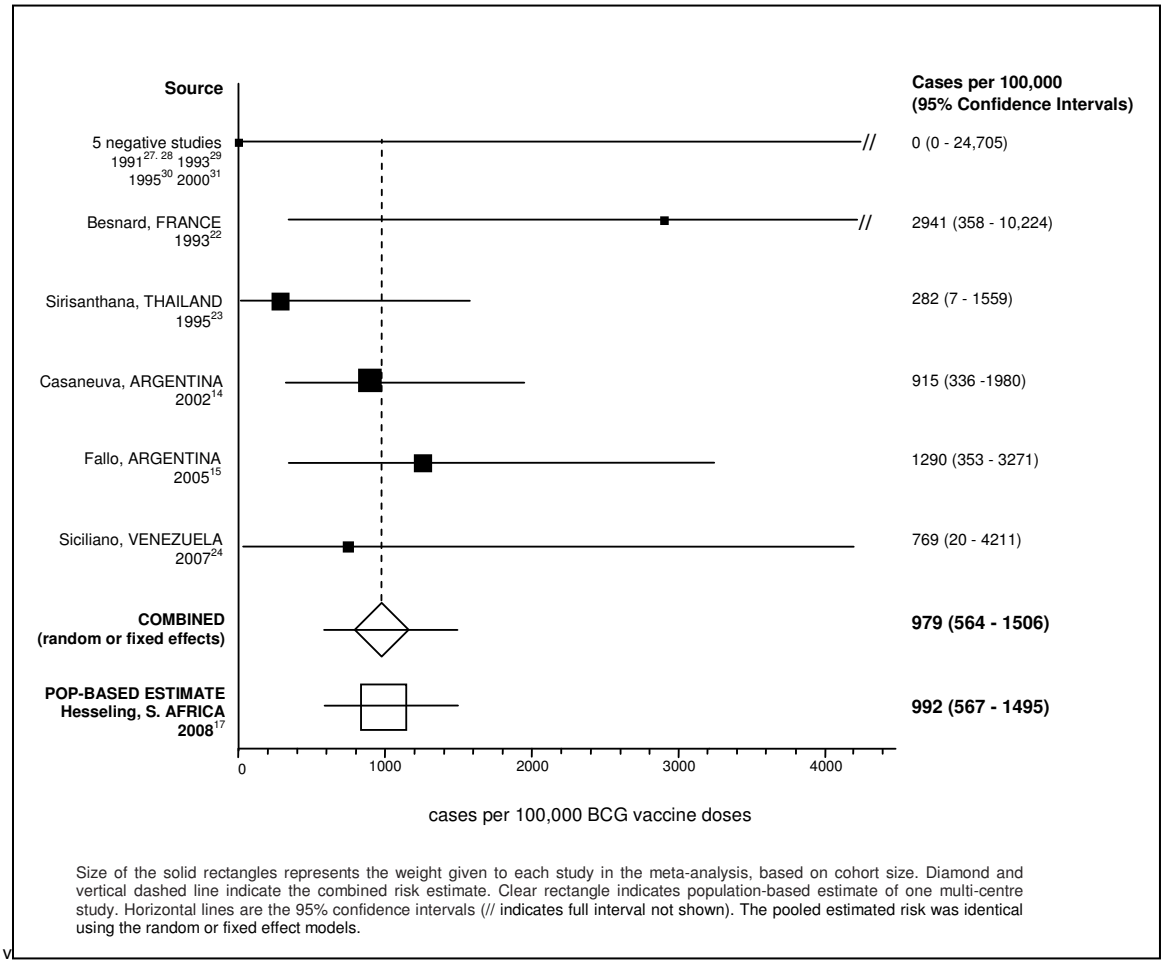
Table
Summary of studies reporting disseminated BCG disease (dBCG) in HIV-infected vaccinated infants

Year Authors (Country)	Type of study and duration Number of vaccinated HIV-infected children	Confirmed cases of dBCG	Number of confirmed dBCG cases in HIV-infected vaccinees per 100,000	Number of deaths in HIV-infected children with dBCG, during follow up period (% all-cause mortality)
1993 Besnard et al.[22] FRANCE	Prospective study, 1983-1993 Single hospital centre, 68 children	2	2941 per 100,000	2 (100%)
1995 Sirisanthana[23] THAILAND	Retrospective study, 1989-1994 Single hospital centre, 355 children	1	282 per 100,000	1 (100%)
2002 Casanueva et al.[14] ARGENTINA	Retrospective study, 1989-2001 9 hospital centres, 656 children	6	915 per 100,000	4 (67%) *
2005 Fallo et al.[15] ARGENTINA	Retrospective study, 1992–2004 Single hospital centre, 310 children	4	1290 per 100,000	3 (75%)
2007 Siciliano et al.[24] VENEZUELA	Prospective study, 2002-2004 Single hospital centre, 130 children	1	769 per 100,000	0
2007 Hesseling et al.[16] SOUTH AFRICA	Prospective, active surveillance, 2002-2004. Single hospital centre. Denominator = estimated provincial total newly HIV-infected infants.	7	110 to 417 per 100,000	6 (86%)
2008 Hesseling et al.[17] SOUTH AFRICA	Similar methodology as in 2007, now 3 reporting hospitals from 2004-2006	32	567 to 1495 per 100,000	25 (78.1%)

* personal communication

Figure 1

Pooled incidence of disseminated BCG disease in HIV-infected infants from hospital-based cohort studies



Size of the solid rectangles represents the weight given to each study in the meta-analysis, based on cohort size. Diamond and vertical dashed line indicate the combined risk estimate. Clear rectangle indicates population-based estimate of one multi-centre study. Horizontal lines are the 95% confidence intervals (// indicates full interval not shown). The pooled estimated risk was identical using the random or fixed effect models.

Our pooled risk estimate is nearly identical to the population-based estimate from South Africa.[17] Data from 5 different countries on dBCG in HIV-infected children shared several common features. At the time of dBCG diagnosis, children had significant CD4 depletion and were not receiving (or had only recently started) antiretroviral therapy. dBCG presents several months after vaccination (median age of 10 months; age range 5-36 months). In the more recently reported and larger cohorts of HIV-infected children, the all-cause mortality of the dBCG cases was 67-86%.

8a.5 Background risk of disseminated BCG disease in HIV-negative infants

The widely-cited background risk of dBCG in the general infant (HIV-negative) population is based on two large studies conducted in the pre-HIV era. The International Union Against Tuberculosis and Lung Disease (IUATLD) reviewed adverse events retrospectively from global reports (1948-1974)[32,33] and prospectively in six European countries (1979-1983).[13] The prospective study calculated an overall dBCG risk of 0.429 per 100,000 vaccinees.[13] This background European incidence of dBCG is mainly attributed to infants with rare primary immunodeficiencies (PIDs) that are also associated with higher risk of dBCG,[34-36] but not diagnosed before vaccinetion.

8a.6 Limited data on BCG efficacy in HIV-infected and HIV-exposed children

BCG efficacy in HIV-infected infants has not been adequately studied.[5,15] It is unknown if non-vaccinated HIV-infected infants could lose potential BCG-associated vaccination benefits that are characterized in the HIV-uninfected populations, including reduced protection against tuberculosis and other mycobacterial diseases,[37,38] potential reduced all-cause morbidity and mortality,[39] and enhanced immune response to other vaccines.[40] However the excess risk of dBCG is expected to outweigh any such potential benefits in HIV-infected children.

BCG vaccine efficacy in HIV-exposed infants (i.e. infants born to HIV-infected mothers) is also unknown. Most infants born to HIV-infected women will escape HIV infection themselves, but may have an increased risk of tuberculosis compared with HIV-unexposed infants. HIV-exposed infants have altered immune responses to mycobacteria[41] and a high risk of household tuberculosis exposure.[42] If BCG vaccination is determined to be effective in preventing tuberculosis in HIV-exposed but uninfected

infants, it is a concern that deferred or simply missed vaccination may lead to an increase of tuberculosis cases in this group.

The impact of changing immunization policy and its implementation therefore need to be carefully evaluated in countries with high tuberculosis and HIV endemicity where infants routinely receive BCG vaccination. If countries proceed to implement the revised recommendation hastily, a selective BCG vaccination program in settings with inadequate resources could potentially disrupt appropriate BCG vaccination of HIV-uninfected infants, who are the vast majority of infants. Avoiding dBCG in a considerably smaller number of HIV-infected infants should not be achieved at the cost of increased tuberculosis incidence in inadvertently non-vaccinated HIV-uninfected infants.

8a.7 Improving surveillance and reporting of BCG vaccine-related adverse events

Improved surveillance and new diagnostic tools have played important roles in identifying the increased risk of dBCG in HIV-infected children. Diagnosing and reporting dBCG depend on several factors: clinical suspicion, standard case definitions, adequate sampling, culture yields, laboratory facilities for definitive diagnosis of *M. bovis BCG*, and established mechanisms to report events. PCR-based speciation[21] now allows rapid definitive differentiation of *M. bovis BCG* from other species of the MTBC although in resource-limited countries, this capacity is mainly situated in tertiary centres.[12,14,15,24] Biochemical speciation is more readily available.

There are several reasons to expect that dBCG is underdiagnosed in most settings. In a 2002-2005 retrospective study, all routinely banked mycobacterial isolates were speciated following routine culture of samples obtained from 466 hospitalized children diagnosed and treated for "MTBC disease"; 25 cases (5.4%) had PCR-confirmed *M. bovis BCG* disease.[12] Of these 25 cases, 8 cases originally diagnosed as disseminated MTBC disease were retrospectively identified as dBCG. Only 298 children had their HIV status recorded; of the 108 children confirmed to be HIV-infected, 6 (5.6%) had dBCG. The 2 remaining dBCG cases that were retrospectively diagnosed occurred in children with PIDs.

With increasing awareness of the need for improved surveillance and reporting, the IUATLD's BCG Working Group was established in 2006 to coordinate surveillance activities and to support improved data generation on global BCG vaccine safety, efficacy and policy, especially in countries with high HIV and tuberculosis burdens and neonatal BCG vaccination programs. Consistent with this initiative, a recent European review of BCG vaccination policies and safety monitoring found substantial scope to improve surveillance mechanisms for serious BCG vaccine-related adverse events even in industrialized countries.[43]

8a.8 BCG vaccination policy in industrialized countries

In contrast with low-income countries, selective BCG vaccination of targeted higher-risk groups has been recommended, feasible, and established for years in wealthier low-burden countries. In many industrialized settings, BCG vaccination in infants at risk for HIV infection is explicitly contraindicated,[44,45] and BCG is postponed until testing HIV-negative, and often with repeated confirmation of negative status.[43,46]

In low-burden countries where selected infant populations are targeted for BCG vaccination and there is a low incidence of pediatric tuberculosis, the BCG risk-benefit margin narrows. For countries with falling tuberculosis incidence, IUATLD's epidemiological criteria[47] should be met before discontinuation of a routine BCG vaccinetion program in favour of individualized or selective vaccination strategies for high-risk groups. These criteria include an efficient notification system and a low annual tuberculosis incidence of 0.1%.[47] In addition, IUATLD criteria assume that the incidence of dBCG is rare, based on surveillance estimates of 0.429 cases per 100,000 vaccinations in HIV-negative European infant populations.[13]

8a.9 BCG vaccination policy and disseminated BCG disease surveillance in Canada

Canada's experience highlights several issues and the importance of rigorous surveillance for dBCG in targeted populations. In Canada, tuberculosis remained endemic among certain First Nation and Inuit reserves. Previously, Aboriginal infants in these communities were routinely BCG-vaccinated.[48] The Immunization Monitoring Program-Active (IMPACT), an active surveillance network of Canadian pediatric hospi-

tals, identified 21 children admitted for BCG-related adverse events between 1993-2002.[35] Of 6 dBCG cases, 5 were vaccinated Aboriginal children and the sixth case was an immigrant; all children subsequently died. Five had PIDs (severe combined immunodeficiency [SCID] or interferon-γ deficiency) and one child was HIV-infected. dBCG negatively affected the clinical management and eligibility for bone marrow transplantation, a potentially curative therapy for immune restoration in SCID patients.[49,50] Several other countries have also reported on children with a range of PIDs associated with dBCG, having similar complications and high all-cause mortality.[34,51,52]

The risk of dBCG in Canadian Aboriginal infants was estimated to be 20.5 per 100,000 doses (95% CI: 4.2-60 per 100,000), more than 40 times higher than the incidence estimated in European populations.[13] Based on these findings, Canada's National Advisory Committee on Immunization (NACI) recommended in 2004 that BCG no longer be offered routinely to infants on Aboriginal reserves. NACI recommended BCG only if certain criteria were met for poor tuberculosis control and management, and if maternal HIV status and family history of immunodeficiency were first determined.[44,48] Emphasis was placed on the mainstays of tuberculosis control and management such as early case detection, directly observed therapy, and surveillance. NACI stated that "BCG vaccine is intended only to prevent serious consequences of unrecognized infection in young children when tuberculosis identification and control programs are suboptimal."[48] With falling tuberculosis notification rates, several Canadian provinces and territories have discontinued routine BCG programs in favour of individualized decision-making.[53]

Canadian Aboriginals appear to have an unexpectedly higher incidence of PIDs and therefore higher risk of dBCG. Rigorous surveillance of vaccine-related adverse events was essential in influencing BCG policy in Canada, and demonstrated the need to determine population-specific estimates for dBCG incidence.

8a.10 Towards a selective BCG vaccination program in resource-limited countries?

In resource-limited countries facing high tuberculosis and HIV burdens, it has been routine practice for HIV-exposed newborns to receive BCG vaccination. The former

WHO recommendation to vaccinate only asymptomatic HIV-infected infants had limited practical application, since most infants acquiring HIV infection are asymptomatic at birth.

WHO revised guidance now makes the infant's HIV status a determinant of BCG vaccination, *if the status is known*. Until local programs are able to implement this new contraindication and selectively defer BCG vaccination with timely determination of the at-risk infant's HIV status, and if BCG remains scheduled soon after birth, both WHO[1] and IUATLD[54] recommend continuing routine BCG vaccination of asymptomatic newborns.

If implementation of selected deferred vaccination is feasible in certain resource-constrained settings with high tuberculosis burdens, immunization providers must consider the main objectives of a transition towards a selective BCG vaccination program. Most importantly, appropriate BCG vaccination of HIV-uninfected infants should continue undisrupted and other fundamental measures to protect HIV-infected (and HIV-exposed) infants from tuberculosis should be implemented, eg. improved screening for and management of maternal tuberculosis exposure.[55] In our algorithm (Figure 2), we outline the programmatic requirements for deferring BCG vaccination until infant HIV status has been determined. Effective coordination between maternal and child health programs is essential. Key questions for local policymakers considering implementation of a selective BCG vaccine policy include the following:

1. **Is routine early HIV testing in infants feasible?** A single HIV DNA PCR test has a sensitivity <40% for infants under 48 hours of age and reaches >90% at 2-4 weeks of age in non-breastfed infants.[56] New, simpler strategies using dried blood spot samples on filter paper have been applied in resource-limited settings.[46] In most prevention of mother-to-child transmission of HIV infection (PMTCT) programs in such settings, infant HIV PCR testing occurs at ≥6 weeks of age with additional delay for turnaround time of results. Although the infant's HIV exposure risk can be largely determined by maternal status, some pregnant women testing negative for HIV will seroconvert or acquire HIV before delivery in highly endemic areas.[57]

An additional consideration is the feasibility of repeated HIV testing in HIV-exposed infants who are breastfed by an HIV-infected mother, and who have ongoing risk of post-natal HIV infection. If HIV-infected mothers choose to breastfeed, exclusive breastfeeding is currently recommended for the first 6 months of life in settings where safe formula feeding is not feasible.[58] The effects of late postnatal HIV infection superimposed on earlier BCG administration are not known.

The main goals of universal HIV testing[57] are timely identification of HIV infection in pregnant women and infants, timely initiation of ART, and now, more appropriate tuberculosis preventive strategies.

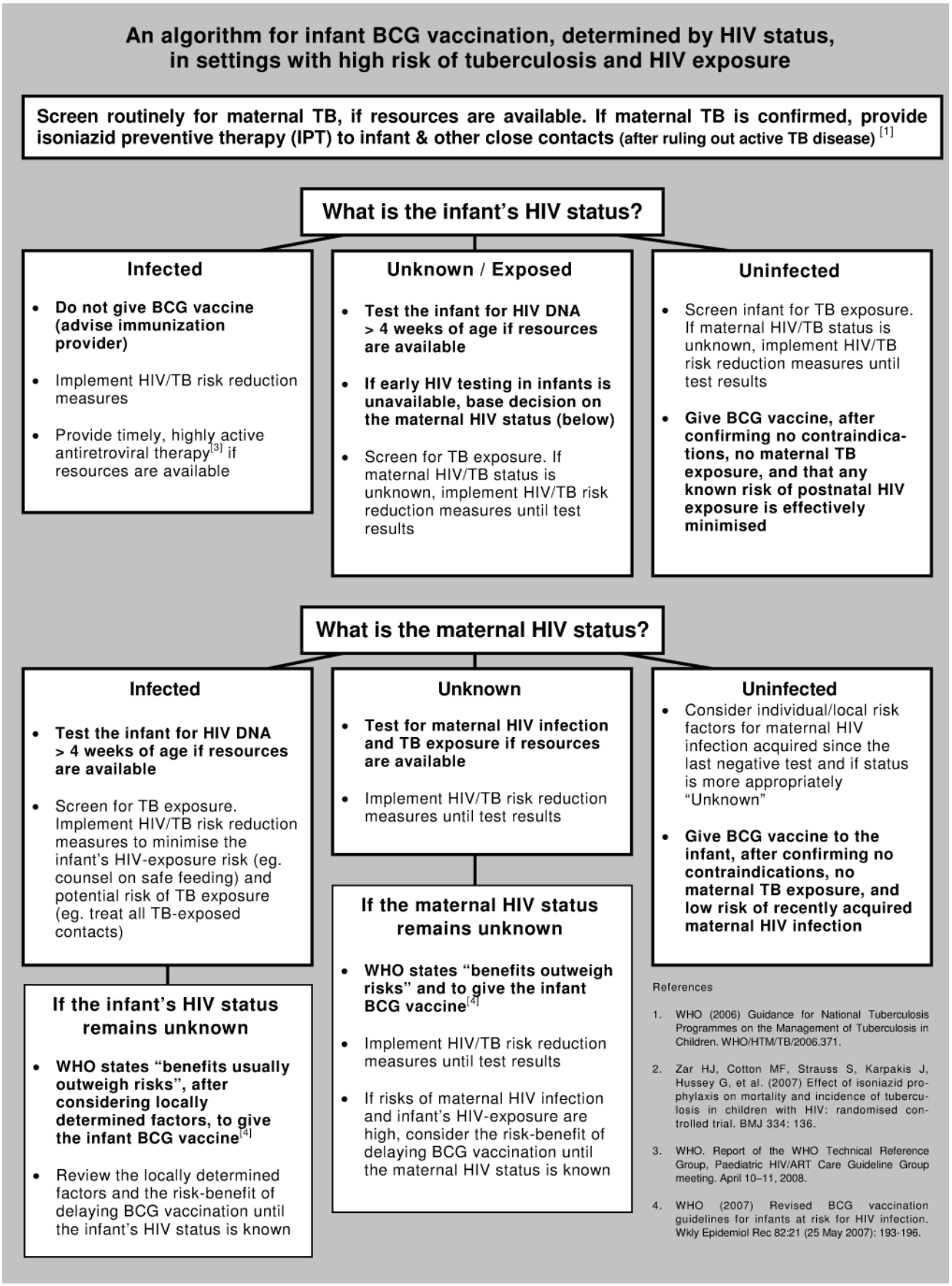
2. **Are PMTCT and other HIV programs effective?** Effectiveness includes full access to counseling, safe feeding options, and adequate antiretroviral therapy access in mothers and their infants. One of the main goals of PMTCT programs - to minimize the number of HIV-infected infants - will also then effectively minimize inadvertent BCG vaccination. In South Africa, an effective, well-integrated PMTCT clinic has lowered vertical transmission to just 2.9% in HIV-exposed infants who are tested at 6 weeks of age by HIV-DNA PCR.[59] However, long-term follow up of HIV-exposed infants remains a challenge. If access to infant HIV treatment is poor or available only in later clinical stages, the full benefits of early infant HIV screening may be limited.[60]

3. **Can the infant vaccination program be adequately coordinated with PMTCT programs?** A strategy where the infant's HIV exposure status directs the potential tuberculosis preventive measures requires confidential, integrated[42] management shared among local programs for immunization and HIV/tuberculosis prevention and treatment.

8a.11 Research priorities regarding alternative strategies to prevent tuberculosis in HIV-infected and HIV-exposed infants

In the current situation of unconfirmed benefit and confirmed increased risk of harm from BCG vaccination in HIV-infected infants, other effective and safe interventions to prevent tuberculosis should be investigated and prioritized. It is important not to overlook the need to strengthen existing HIV and tuberculosis control programs in high-

Figure 2


An algorithm for infant BCG vaccination, determined by HIV status, in settings with high risk of tuberculosis and HIV exposure
Screen routinely for maternal TB, if resources are available. If maternal TB is confirmed, provide isoniazid preventive therapy (IPT) to infant & other close contacts (after ruling out active TB disease) [1]
What is the infant's HIV status?
Infected
Do not give BCG vaccine (advise immunization provider)
Implement HIV/TB risk reduction measures
Provide timely, highly active antiretroviral therapy[3] if resources are available
Unknown / Exposed
Test the infant for HIV DNA > 4 weeks of age if resources are available
If early HIV testing in infants is unavailable, base decision on the maternal HIV status (below)
Screen for TB exposure. If maternal HIV/TB status is unknown, implement HIV/TB risk reduction measures until test results
Uninfected
Screen infant for TB exposure. If maternal HIV/TB status is unknown, implement HIV/TB risk reduction measures until test results
Give BCG vaccine, after confirming no contraindications, no maternal TB exposure, and that any known risk of postnatal HIV exposure is effectively minimised
What is the maternal HIV status?
Infected
Test the infant for HIV DNA > 4 weeks of age if resources are available
Screen for TB exposure. Implement HIV/TB risk reduction measures to minimise the infant's HIV-exposure risk (eg. counsel on safe feeding) and potential risk of TB exposure (eg. treat all TB-exposed contacts)
If the infant's HIV status remains unknown
WHO states "benefits usually outweigh risks", after considering locally determined factors, to give the infant BCG vaccine[4]
Review the locally determined factors and the risk-benefit of delaying BCG vaccination until the infant's HIV status is known
Unknown
Test for maternal HIV infection and TB exposure if resources are available
Implement HIV/TB risk reduction measures until test results
If the maternal HIV status remains unknown
WHO states "benefits outweigh risks" and to give the infant BCG vaccine[4]
Implement HIV/TB risk reduction measures until test results
If risks of maternal HIV infection and infant's HIV-exposure are high, consider the risk-benefit of delaying BCG vaccination until the maternal HIV status is known
Uninfected
Consider individual/local risk factors for maternal HIV infection acquired since the last negative test and if status is more appropriately "Unknown"
Give BCG vaccine to the infant, after confirming no contraindications, no maternal TB exposure, and low risk of recently acquired maternal HIV infection
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burden settings. Of key importance is improving maternal tuberculosis screening during the antenatal and postpartum period, which may reduce the risk of exposure and the incidence of tuberculosis in young children.

Isoniazid preventive therapy (IPT) is safe and effective in preventing tuberculosis and routinely recommended for infants having documented tuberculosis exposure.[61] However, the benefits of routine primary IPT are not clear in HIV-infected and HIV-exposed infants in the absence of reported tuberculosis exposure. The first randomized, controlled trial (RCT) of 263 South African HIV-infected children (median age 29.6 months) found that IPT in combination with co-trimoxazole was well-tolerated and reduced both all-cause mortality and tuberculosis incidence.[62] However, these results were not reproduced in a larger, phase II/III randomized controlled trial in southern Africa that enrolled more than 1350 HIV-infected or HIV-exposed uninfected infants at 3-4 months of age. Interim analysis demonstrated that IPT together with cotrimoxazole was safe but did not lower tuberculosis incidence or death in infants when a tuberculosis contact was excluded at enrolment.[63] The trial was recently discontinued early and full data analyses are ongoing. (personal communication, M.F. Cotton)

A landmark South African RCT has now shown that early ART in HIV-infected infants <12 weeks of age profoundly reduced all-cause mortality by 75% in the first year of life, compared with infants started on ART only when standard criteria based on CD4 depletion or severe clinical disease were met.[64] In April 2008, based on consistent findings from two RCTs,[64,65] the WHO Technical Reference Group has issued new guidance urging earlier initiation of ART in HIV-infected children.[66]

The available data therefore indicate a significant benefit of early ART initiation and a limited effect of routine IPT in reducing all-cause mortality in HIV-infected infants. It is not determined if timely ART will reduce tuberculosis incidence or alter BCG safety profile and enhance BCG immunogenicity and efficacy in HIV-infected children through improved cellular immunity and delayed HIV disease progression. dBCG can be viewed as a serious opportunistic disease in severely immunocompromised children. HIV-infected children inadvertently BCG-vaccinated but who receive early ART should be prospectively studied for rates of tuberculosis disease, BCG complications

and all-cause mortality. Another hypothesis is that timely ART may reduce the risk of dBCG and affect the risk of BCG Immune Reconstitution Syndrome (IRIS). BCG IRIS is a complication observed in some HIV-infected patients during cellular immune restoration with ART, but usually associated with a good prognosis.[67-69] Preliminary data from the early vs. deferred ART infant randomized trial indicate a significantly lower incidence of BCG IRIS in infants who received early ART.[70]

BCG efficacy data are not available for HIV-infected and HIV-exposed uninfected infants. There is currently no available vaccine against tuberculosis for HIV-infected infants that is proven effective and safe. As new vaccines against tuberculosis become available, they should be studied for safety, immunogenicity and efficacy in HIV-infected and HIV-exposed infants.

8a.12 Discussion

Based on the higher risk of dBCG, HIV infection has become a universal contraindication to BCG vaccination, including in settings with high tuberculosis burdens. We estimated a pooled risk of dBCG in HIV-infected infants of 979 per 100,000 (95% CI: 564 to 1506 per 100,000) based on cohort studies from tertiary centres, which was very close to the population-based estimate in South Africa of 992 per 100,000 (95% CI: 567 to 1495 per 100,000).[17] These findings indicate the generalisability of the risk of dBCG in vaccinated HIV-infected children in several different countries. The true incidence of dBCG in this subpopulation is likely under-reported as these represent cases detected at tertiary hospitals.

We have outlined the goals and prerequisites for a selective BCG vaccination program, and the benefits of early determination of HIV status. Countries with adequate resources and low HIV and tuberculosis burdens can offer selective and postponed BCG vaccination, with screening for immunodeficiency disorders. We believe that routine HIV testing and selective BCG vaccination based on the test result should also be made feasible in middle-income countries with established infant BCG vaccination and PMTCT programs. The timing of BCG in the immunization schedule should be carefully considered. Unfortunately, the programmatic requirements make this guidance less feasible and unlikely to be prioritized in most settings with severely limited re-

sources. HIV and tuberculosis burdens may be highest in these settings and routine BCG vaccination at birth currently continues irrespective of maternal HIV status. However, where resources for HIV and tuberculosis screening and treatment programs are now being scaled up, a selective infant BCG vaccination program should be incorporated when feasible. Programmatic research should closely monitor the effects of such potential transitions.

Other tuberculosis preventive strategies that are safe and effective should be prioritized in HIV-exposed and HIV-infected infants. Beyond the issues of decision making regarding BCG vaccination, it is now even more crucial to strengthen the existing capacities to screen for and manage HIV and tuberculosis infections, and to provide timely antiretroviral and anti-tuberculosis therapies to both mothers and infants. Improving antenatal tuberculosis screening and management will lower the risk of tuberculosis in the general infant population. Timely ART initiation in HIV-infected infants will delay HIV disease progression and reduce mortality. It remains to be determined whether HAART can lower the risk of tuberculosis[71] or the risk of dBCG in BCG-vaccinated HIV-infected infants and children, or both. The new awareness of dBCG risk in HIV-infected infants provides added incentive to ensure coordination of existing immunization, tuberculosis screening and PMTCT programs, and to investigate alternative effective and safe strategies in reducing tuberculosis in children, especially where HIV is highly prevalent.

8a.13 Summary

- BCG vaccination is now a full contraindication in HIV-infected infants, including settings with high tuberculosis burdens.[1]

- The pooled estimated risk of disseminated BCG disease in HIV-infected infants is 979 per 100,000 (95% CI: 564 to 1495 per 100,000) vaccinations, or about one serious vaccine-related adverse event every 100 doses.

- For HIV-uninfected infants, effectiveness of BCG vaccination in preventing childhood disseminated tuberculosis is well established, and prevents about 40 cases of tuberculosis meningitis or miliary tuberculosis per 100,000 doses.[10]

- For HIV-infected infants, effectiveness of BCG vaccination is not established and is not adequately studied.

- A transition towards a selective BCG vaccination program based on HIV status in resource-limited settings requires accessible, effective and coordinated maternal and infant public health programs.

- An important goal is that established BCG vaccination programs should continue undisrupted for HIV-uninfected children who have no vaccine contraindications.

- Existing public health programs for HIV and tuberculosis need to be strengthened and other strategies considered, towards the goal of reducing these infections in high-risk children.

8a.14 Contributors & Acknowledgements

We are grateful to Adwoa Bentsi-Enchill (World Health Organization), Paul Fine and Punam Mangtani (London School of Hygiene and Tropical Medicine), Don de Savigny (Swiss Tropical Institute), and Meenakshi Dawar (Public Health Agency of Canada) for their helpful comments on an earlier version of this manuscript, and to Tom Smith (Swiss Tropical Institute) for his statistical advice.

TKM, ACH & GDH designed the paper. TKM wrote the first draft. All authors revised the manuscript and made substantial contributions to its intellectual content. The final version was approved by all authors.

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8b Making BCG vaccination programmes safer in the HIV era

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We declare that we have no conflicts of interest.

Keywords

BCG vaccines; infant, newborn; tuberculosis/prevention and control; HIV; AIDS-related opportunistic infections; immunization programs; risk assessment

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This manuscript was published in

The Lancet (2008): **372**:786-7

8b.1 Comment

Last year, WHO stopped recommending live, attenuated bacille Calmette-Guérin (BCG) vaccination at birth for asymptomatic HIV-infected infants, even where there is a risk of tuberculosis exposure early in life.[1] Data show that about 417 HIV-infected infants per 100 000 are affected by disseminated BCG disease,[2] a rate that is about 1000 times higher than in healthy HIV-uninfected infants (table). Disseminated BCG disease typically presents several months after vaccination in infants with rapid progression of HIV disease, and has an all-cause mortality of 75–86%.[2,6] Clinical features of disseminated BCG disease are similar to those of severe tuberculosis, and sophisticated laboratory facilities are needed to distinguish *Mycobacterium tuberculosis* from *M bovis BCG*.

Table

BCG vaccination: benefit versus risk in HIV-negative and HIV-positive infants

HIV status	Main benefit (miliary tuberculosis or tuberculous meningitis prevented,or both, worldwide)*	Most serious risk (disseminated BCG disease caused, worldwide)*
Negative	40 per 100 000 (40 000 cases)[3]	0.429 per 100 000 (429 cases)[4]
Positive	No available data	417 per 100 000 (1751 cases)[2]
*On the basis of annual estimates that BCG vaccine is given to 100 million[4] HIV-negative children and 0.42 million[5] children are newly infected with HIV.		

The Expanded Programme on Immunization (EPI) schedule recommends infant BCG vaccination soon after birth in countries with a high burden of tuberculosis, on the basis of evidence that vaccination averts 40 cases of miliary tuberculosis or tuberculous meningitis, or both, per 100 000 vaccinations in HIV-negative children.4 With 100 million BCG doses given every year worldwide, BCG is cost effective and prevents 40 000 cases of childhood tuberculosis (table).[4]

In 2007, about 420 000 new HIV infections occurred in children younger than 15 years of age.[5] Most were caused by perinatal transmission in sub-Saharan Africa, which is also the region with the highest burden of tuberculosis. If HIV-infected children continue to receive BCG vaccination, about 1700 HIV-infected infants will develop disseminated BCG disease every year. The effectiveness of BCG vaccination against disseminated tuberculosis in HIV-infected infants is unknown, but even if it is confirmed, the efficacy

rate would not be expected to approach that observed in immunocompetent children, and would still be exceeded by the risk of disseminated BCG disease. Concerns about the vaccine's safety coincide with the push for greater access to early HIV testing, and new guidance from WHO and UNAIDS[7] that urges prompt initiation of antiretroviral therapy in HIV-infected infants, which is shown to reduce their mortality.[8] The recommended test is HIV-DNA PCR between 4 and 6 weeks of age, but the cost of testing and turn around time for results can be considerable. In countries with HIV epidemics, universal antenatal HIV testing is recommended. To expand access, the health encounter rather than the type of health centre should be considered as a standard opportunity to test mothers for HIV, helped by an opt-out approach and rapid tests.[9]

The EPI can be expanded. In a Kenyan study, nearly all mothers (96%) who brought their children for vaccinations or acute care felt that provider-initiated HIV testing and counselling for mothers should be available onsite. Only rarely did mothers feel that the health centre for children was "the place for vaccines, not for testing".[10] The benefit and feasibility of routine HIV screening in infants have already been proven in immunisation clinics in South Africa.[11] EPI managers could link HIV-test information with the decision to provide BCG vaccination, if test results are well coordinated between EPI and other health programmes.

Safer BCG programmes are well established, but not where they are most needed. In most countries, BCG has been a routine public-health intervention since the inception of the EPI in 1974. Wealthy countries, such as the UK,[12] with a low burden of HIV and tuberculosis, have already established policies to exclude HIV before BCG is given.[13] Although a safe and selective policy for BCG vaccination on the basis of an infant's HIV status should be implemented in poor countries, action has not been forthcoming. This new understanding of BCG's risk-benefit has been described as a double-edged sword.[14] Delays in implementing the revised policy are mainly because of feasibility and the fear of losing the greater public-health good, if the overall immunisation programme is disrupted. There is a concern about potentially reduced BCG coverage for the vast majority of infants (ie, not HIV infected) if the public has less confidence in immunisation programmes or if selective vaccination is poorly implemented.

The HIV epidemic has changed the risk-benefit ratio of BCG, especially in settings with generalised HIV epidemics in which a considerable proportion of infants are exposed to or infected with HIV.

BCG vaccination remains an important and effective intervention. Introduction of selective BCG vaccination on the basis of HIV status should be done cautiously, to minimise the potential loss of BCG coverage in HIV-negative children. There are convincing examples of programmes that provide best-health practices even within poorly functioning health systems.[15]

Changes are now needed for what has been a routine childhood health practice for the past 30 years, because of the HIV epidemic. Many experts are concerned that an alarm raised over BCG safety in HIV-infected children could damage the uptake of all immunisations. The opposite might be true. If EPI managers lead and support responsible adaptations to make BCG vaccination selective and safer, public trust placed in childhood immunisations could grow even stronger.

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9 Review of the management of BCG-related adverse events following immunization

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Working manuscript

9.1 Introduction

In countries with high tuberculosis burden, WHO recommends vaccination with live attenuated *Mycobacterium bovis bacille Calmette-Guérin* (BCG) in all infants soon after birth, if there are no known contraindications.[1] BCG vaccines are proven effective against serious disseminated forms of tuberculosis in young children[2] and are offered routinely or in higher-risk selected populations in most countries. (see Figure 1) With over 80 years of experience and 3 billion[3] people worldwide having received BCG vaccines since 1921, a spectrum of BCG-related adverse events following immunization (AEFI) is known. BCG-related AEFI range from the common local reactions at the site of vaccination to the uncommon but serious, life-threatening disseminated infections. (see Figure 2)

Discussions within WHO and external expert bodies have recognised variations and inconsistency in the approach taken by different countries on the clinical management of BCG-related AEFI, particularly on management of the most common events of local reactions and regional lymphadenitis. The need was identified to synthesise available published literature and to form preliminary guidelines on appropriate management that would be helpful to health care providers.

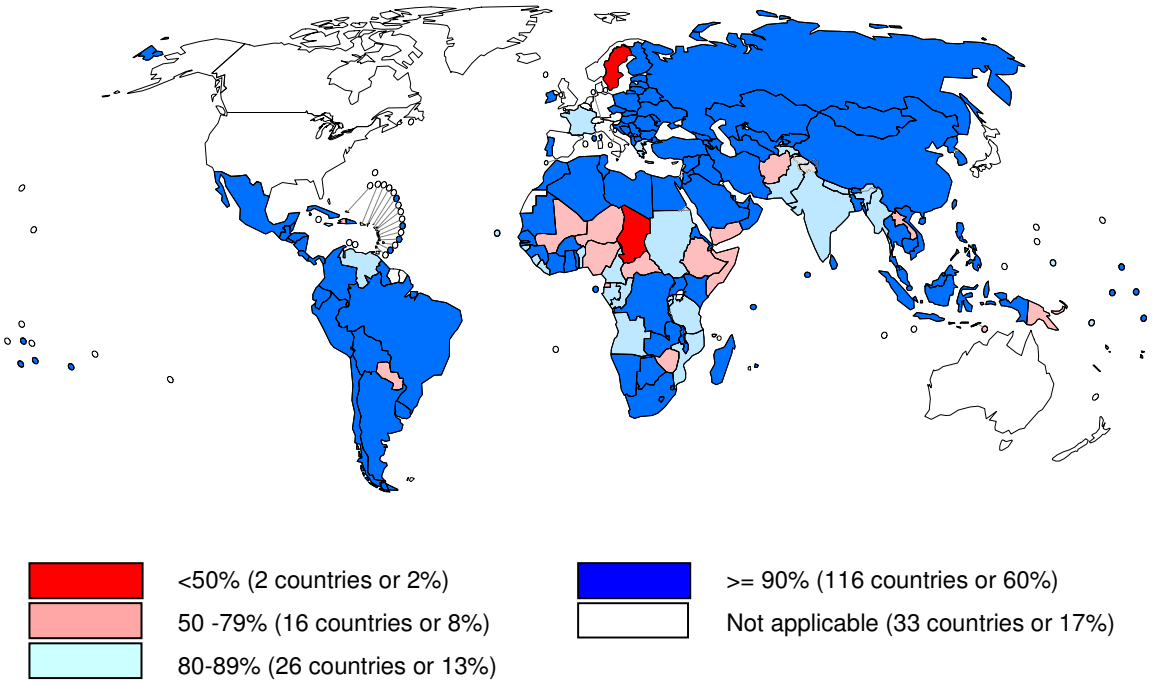
There has been no previous review on the management of the range of BCG-related adverse events, nor a review on the emerging phenomenon of BCG Immune Reconstitution Inflammatory Syndrome (IRIS). We thus conducted a systematic review on the available evidence for managing BCG-related AEFI. We also considered key issues in diagnosing *M bovis BCG* and potential BCG drug resistance. Our aim was to put forward evidence-based principles regarding BCG-related AEFI management for consideration by the global clinical and scientific community. We used the BCG adverse event framework established by Hesseling and colleagues[4] of Local, Regional, Distant, Disseminated, IRIS and Other BCG diseases (see Figure 2).

Hesseling and colleagues have recently published preliminary management guidelines for BCG AEFI in immunocompromised individuals, in particular their increased risk of dBCG, from a case series in HIV-infected children, while Juzi and colleagues described their early versus late surgical management.[4,5] Therefore this present review focuses on

management of BCG AEFI in the general pediatric population, i.e. immunocompetent children and BCG-related adverse events other than dBCG.

Figure 1

Global coverage of BCG vaccination at birth in 2007, World Health Organization



9.2 Materials and Methods

9.2.1 Identification of data

We conducted a systematic review of the published literature for studies examining BCG vaccine-related adverse events, in the following databases: PUBMED, COCHRANE CENTRAL, Uppsala Monitoring Centre Database (VIGIBASE), and technical guidelines from the WHO library database (WHOLIS) and all WHO regional databases. The defined strategy combined medical subject headings and keywords for additional articles up to 1 August 2008: “((adverse effect*) OR ("injurious effect*" OR "undesirable effect*" OR "side effect*" OR "adverse reaction*" OR "adverse event*")) AND (mycobacterium bovis OR BCG OR "Calmette*"), combined with “lymphadenitis”, “osteitis”, “randomized controlled trials”, and “epidemiological methods”. Internal WHO documents were reviewed and experts were consulted. For key articles we also examined bibliographies and citations through the Web of Science. Of articles ex-

amined by titles and then abstracts, those considered relevant were obtained for further assessment (TKM). Any uncertainties were discussed and resolved with other authors.

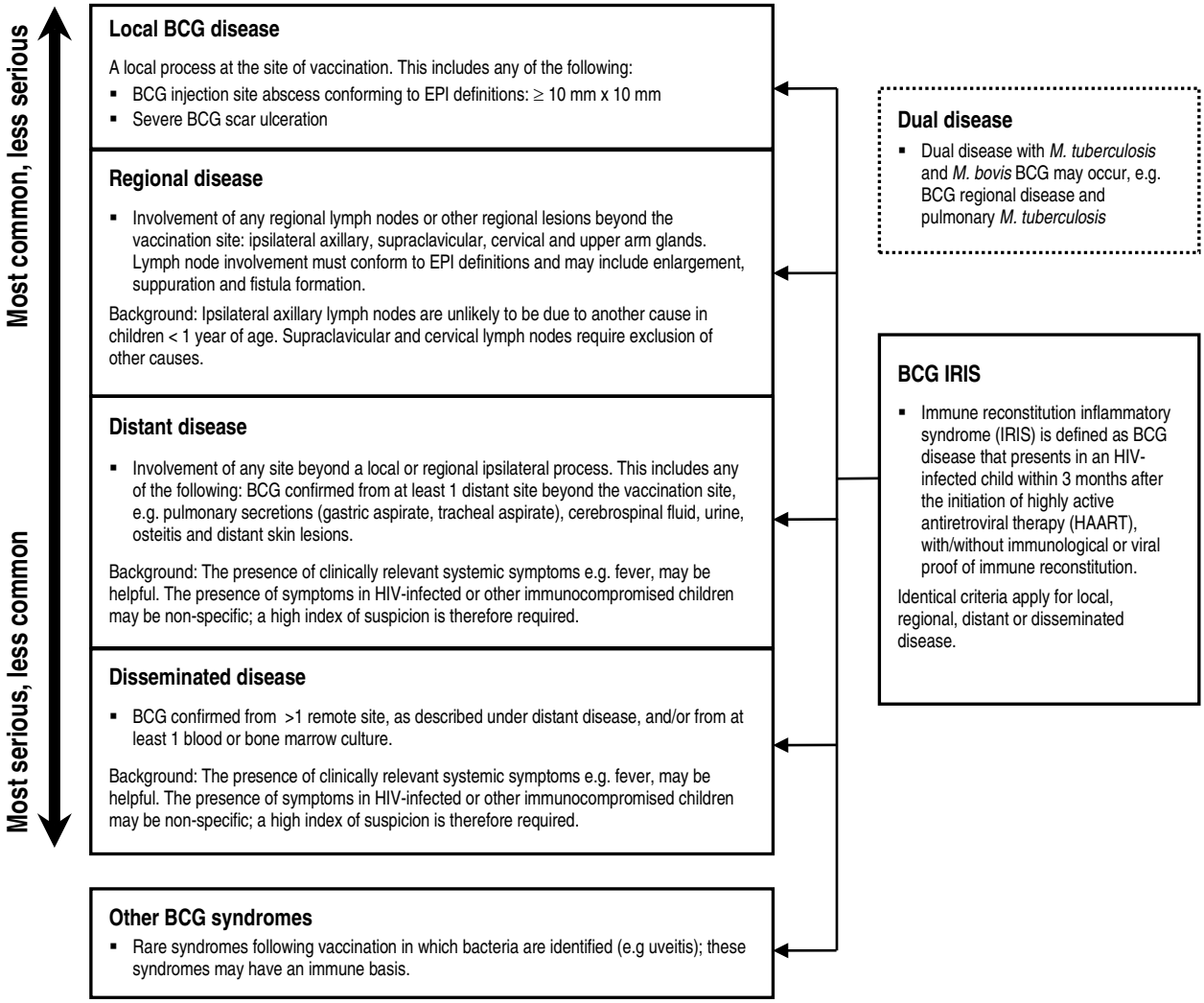
9.2.2 Inclusion and exclusion criteria

The criteria for inclusion were RCTs on the treatment of the range of BCG-related AEFI in immunocompetent vaccinees. For less common events, retrospective studies of BCG Distant Disease were included, as well as all case reports of the emerging phenomenon known as BCG IRIS, and case reports and reviews of a diverse group of other adverse events classified as Other BCG Syndromes. Studies were excluded if they described practices that were not recommended by WHO, such as repeat BCG vaccinations or percutaneous administration. Review of the management of dBCG was not conducted as these preliminary guidelines have recently been published.[4]

9.2.3 Case definitions and disease classification

WHO documents have not specified a classification of the range of BCG-related AEFI, highlighting mainly on country reports of "outbreaks" of BCG-related adverse events such as lymphadenitis or osteitis, as well as reports dBCG (also described as "BCGitis" or "BCGosis"). From the published literature, there have been three systems to classify and standardise reports covering the spectrum of BCG-related AEFI.[4,6-8]. The first classification by Lotte and colleagues,[6,7] from International Union Against Tuberculosis and Lung Disease (IUATLD), which covered international reports of all BCG-related AEFI between 1948-1982 and provided estimates of the adverse events incidence in general vaccinated populations in the pre-HIV era. With minimal overlap, Talbot et al reviewed the available literature on dBCG between 1980-1995 and adapted a BCG-related AEFI classification similar to the scheme used for opportunistic *M. avium complex* disease.[8] Hesseling and colleagues have recently proposed the first clinically based classification that is more relevant for differential diagnosis and management, which we use here (Figure 2).[4]

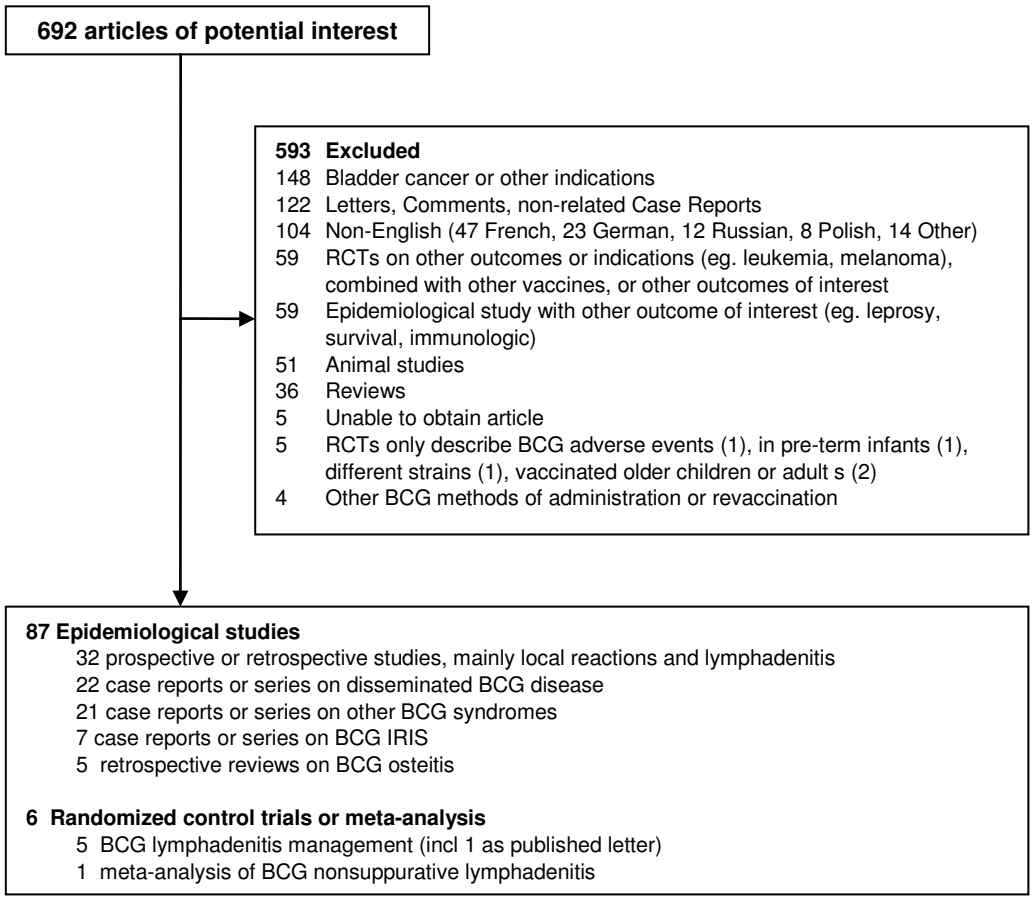
Figure 2
Framework for bacille Calmette-Guérin (BCG) disease in children
Adapted from Hesseling et al[4]



9.3 Results

A total of 692 potentially relevant articles were identified, of which 93 papers were examined further. Only 5 RCTs on lymphadenitis were identified. Most studies were small retrospective studies or case reports. Figure 3 below provides the search results.

Figure 3: Search results and inclusion and exclusion of identified studies



9.3.1 Normal BCG reactions

WHO recommends a single dose of intradermal BCG vaccine.[1] Proper administration is expected to lead to minor reactions of redness, induration and tenderness in > 90% of recipients.[9] A small papule usually develops and progresses to a nodule that may ulcerate or can have minor drainage for several months. The "primary complex" consists of a cutaneous nodule at the site of injection and a degree of swelling of the regional lymph nodes.[10] BCG is now the only commonly used vaccine that induces a local ulcer at the injection site.[11] Small abscesses are common, and have been reported to occur in 41% of recipients.[12] Usually only symptomatic, conservative management is required.[1] The natural course of BCG lymphadenitis is spontaneous regression of the

reaction usually within 9 months post-vaccination.[13,14] A 2-10 mm diameter scar will develop in most immunocompetent children.[12] Keloid scarring over the BCG administration site may be more common among Asian and African populations.[15]

The range of normal responses to BCG vaccination includes uncomplicated ipsilateral enlarged lymph nodes. The most commonly affected nodes are axillary followed by supraclavicular nodes, related to the lymphatic drainage from the recommended site of vaccination over the deltoid region. A rule of thumb from observational data is that lymph nodes less than 1 to 1.5 cm in diameter are more likely to spontaneously regress.[15,16]

9.3.2 Management of BCG adverse events by disease classification

Based on the evidence from this systematic review, a list of general and specific management considerations was formed for each classification of BCG-related AEFI. These preliminary guidelines are summarized below. Box 1 outlines general considerations, while specific management suggestions for immunocompetent children are listed in Box 2, and for immunocompromised children in Box 3. These preliminary guidelines need to be further evaluated by clinicians and other health care providers managing BCG-related AEFI.

There were insufficient reports on the disparate group of Other BCG Syndromes to formulate specific preliminary guidelines. These unusual syndromes include ophthalmic disease (eg. conjunctivitis, choroiditis, uveitis and optic neuritis) and dermatological manifestations such as lupus vulgaris following BCG vaccination. Most of the adverse events in this group are believed to represent systemic hypersensitivity phenomena.[4] It is important to note that reviews of cutaneous miliary tuberculosis were found to be associated with dBCG.[6,8,17] Disseminated cutaneous lesions are more common in immunodeficient individuals and should be a signal to screen for such an underlying condition. Inherent limitations of single case reports include the inability to make causal inferences of certain phenomenon, such as reports of basal cell carcinoma developing over a BCG vaccination scar. In general, these rare AEFI should be managed by specialist referral if available and decisions made on an individual basis.

9.3.2.1 Local disease

Local reactions such as ulcers and abscesses at or near the injection site are common. Abscesses following injection may be non-infected (sterile or "cold") and may be related to incorrect depth of the needle insertion for vaccination or from poorly-reconstituted vaccine.[18] Infected ("hot") abscesses may arise from nonsterile vaccine technique or secondary bacterial invasion.

There are no controlled studies on managing ulcerative lesions and abscesses at the injection site. Early small case series reported favourable results managing local abscesses with needle aspiration and a course of oral erythromycin,[19,20] however, the effect may have been explained by the benefit of aspiration alone or cases of erythromycin-sensitive secondary bacterial infection. Hanley and colleagues' non-controlled UK study randomized 18 adult vaccinees with BCG ulcers or abscesses (without regional disease) to one-month therapy of INH 6 mg/kg/day or erythromycin 250 mg four times daily. There was no difference in the blinded assessment of induration, erythema or time to resolution.[21] More recently, Jeena and colleagues reported an overall rate of 3.1% adverse events in a prospective study during the introduction of intradermal Danish 1331 BCG in South Africa.[12] Small injection-site abscesses were noted in 41% of AEFI reports. Regardless whether abscesses were untreated or aspirated, all resolved within 42 days.[12]

9.3.2.2 Regional disease eg. Lymphadenitis

BCG lymphadenitis is the most commonly reported adverse event. Regional disease is usually under 4% of BCG vaccinations,[6] but can be as high as 17.6%.[18] The reported incidence can depend on active case finding (eg. during a mass vaccination campaign), and the presence or absence of a case definition for reportable lymphadenitis. It is important to keep in mind that Regional disease may be a sentinel sign for distant or disseminated disease.

There are several non-controlled studies on BCG lymphadenitis, but only 5 randomized controlled trials (RCTs) on therapeutic interventions for BCG-related adverse events, all on regional lymphadenitis.[22-26] (Table 1) These RCTs were small, (total N=356), of varying quality, and examined different drugs or interventions. Only one trial considered and randomized needle aspiration as a therapeutic intervention, finding

a strong benefit in time to resolution at each interval of follow up at 2, 4, and 6 months (all p<0.002).[25] It is unclear whether a single dose of INH 50 mg[26] or streptomycin 20 mg/kg[24] instilled into the evacuated node had any additional benefit over aspiration. A review and meta-analysis[27] limited by the heterogeneity of these RCTs, found reasonable evidence, also well supported by observational studies, that prognosis and management could be sub-classified as "uncomplicated" or "complicated" lymphadenitis (see Box 2 for definitions).

The majority of cases of uncomplicated lymphadenitis appears to spontaneously regress and only requires watchful waiting over months. Of those progressing to suppuration, particularly early or rapid presenters (under 2 months post-vaccination), a stepwise approach to intervention appears appropriate in immunocompetent individuals with limited regional disease. Under sterile technique, needle aspiration of suppurative lymphadenitis is recommended, for shortened time to resolution,[25] reduced spontaneous drainage,[25,26] and the benefit of obtaining specimens to confirm the diagnosis. Banani & Alborzi empirically recommended inserting the needle 2-3 cm away from the enlarged node and not piercing overlying skin, with the intention of reducing the risk of sinus formation, and to apply mild compression over the suppurative area to facilitate aspiration; different aspiration techniques were not tested formally.[25] The aspirate should be tested for acid fast bacilli and culture and sensitivity to rule out secondary bacterial invasion.

In non-controlled surgical studies, incision and drainage or complete excision of affected lymph nodes were provided as early interventions.[14,28-30] In consideration of the reasonable likelihood of spontaneous resolution of lymphadenitis in immunocompetent individuals and from available RCTs, surgical intervention should be reserved for indications of progressive lymphadenitis, i.e. rapidly enlargening matted nodes, adherent to erythematous overlying skin or chronic fistulae.

9.3.2.3 Distant disease eg. Osteitis

Distant BCG disease (i.e. single organ involvement) has been reported mainly as infection of bone (osteitis) and bone marrow (osteomyelitis) that can affect both immunocompetent and immunodeficient vaccinees. Presentation may be delayed (> 12 months) following vaccination, with usually swelling and pain over the affected

limb.[31] BCG osteitis can affect many different bony sites, and particularly the epiphysis of long bones. BCG vertebral osteitis is documented but may be a less common presentation than due to *M. tuberculosis.*

Unusual BCG osteitis "outbreaks" occurred in Finland and in Sweden between 1971-1978, associated with a change of manufacturer of the BCG Göteburg strain[32,33] (becoming a chief reason for Sweden's discontinuation of their routine BCG vaccination program in 1975).[34] The change in BCG strain led to the highest ever reported incidence of BCG osteitis in Finland at 72.9 per 100,000. More than half of the osteitic lesions were in the lower extremity.[32] BCG osteitis outbreaks were also associated with a change in vaccine strain or manufacturer in former Czechoslovakia and in Chile.[124] (Table 2).

It is important to note the diagnosis of BCG osteitis in all reviews has not required laboratory-confirmation of a BCG isolate. Countries expressly used 4 main diagnostic criteria outlined by Foucard & Hjelmstedt: 1. positive BCG vaccination history; 2. no history of tuberculosis contact 3. radiographic changes and clinical picture typical of osteitis; and 4. a minimum of *one* of the following a) BCG strain isolated at the osteitic lesion, b) acid-fast bacteria demonstrated, c) histopathologic changes of tuberculosis process in the lesion.[35] BCG-attributed osteitis should be classified as a confirmed case only if a BCG strain is isolated at the site, or as a probable case if other causes of tubercular osteitis are not ruled out. The availability of PCR testing can improve the detection and confirmation of BCG ostetitis.[36]

There were no randomised or controlled studies on the management of BCG osteitis. These large retrospective studies are summarized in Table 2. Detailed management with drug dosages and durations were not fully described but in general, cases received long courses of multiple anti-tubercular drugs, usually for >6 months. Usual management was to treat with 3 anti-tubercular drugs that include isoniazid and rifampicin. The outcome was usually complete recovery, but there was a possible risk of bony deformities or growth plate disturbances. Patients on prolonged anti-tuberculosis chemotherapy should be monitored for drug toxicity.

9.3.2.4 Disseminated BCG disease (dBCG)

Individuals at risk of disseminated BCG disease are almost exclusively those having underlying cellular immunodeficiency from primary disorders or acquired causes such as HIV. In light of mounting evidence, in 2007 WHO advised avoiding BCG vaccination if the recipient is HIV-positive, regardless of the local tuberculosis burden.[37] However inadvertent vaccination is expected to continue, particularly in low-resource HIV-endemic settings. Immunocompromised individuals face increased risk of BCG complications, in terms of incidence and severity, and the pooled estimated risk of dBCG from international studies is 979 per 100,000 HIV-infected vaccinees (95% CI: 564 to 1506 per 100,000), a rate that is more than 1000 times the risk in the general HIV-uninfected population.[38] dBCG has a high case fatality of about 75%, whether the underlying cause is PIDs or HIV, and the severity is related to the degree of immunodeficiency and concomitant illnesses.[4,8]

Management of dBCG is a medical emergency, requiring specialist care and aggressive multiple anti-tubercular drug therapy, considering the poor prognosis in the immunocompromised patient. Preliminary guidelines to manage dBCG are published, and indicate the need to conduct a full diagnostic workup in suspected cases of Distant BCG disease or dBCG (nodal aspirates, gastric washings, and bone marrow aspirate or blood cultures) and to provide multiple anti-tubercular drug therapy.[4] (see Box 3)

9.3.2.5 Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS is an important emerging adverse event that is not specific to HIV infection. The immunological and inflammatory mechanisms are not fully understood, but IRIS may occur when the presence of certain indolent opportunistic organisms in host tissues (subclinical or apparent infection) leads to a clinical exacerbation after improved immune function. Key factors are the temporal relationship and rapidity of the immune reconstitution. The syndrome is associated with a range of opportunistic pathogens including certain viruses and parasites, but in particular with mycobacteria; a possible reason is that mycobacterial organisms and antigenic particles can persist for extended periods in host tissues.[39]

BCG-related IRIS has been mainly reported in immunosuppressed children infected with HIV and recently initiating anti-retroviral therapy, and in those with primary

immune disorders (such as severe combined immunodeficiency syndrome) following curative therapy with bone marrow transplantation. Only 47 cases of BCG IRIS in HIV-infected children have been published in the literature.[4,40-45] An estimated 6% of BCG-vaccinated HIV-infected infants initiating highly active anti-retroviral therapy will develop BCG-related IRIS, with those younger (under 5 months of age) or with higher log viral loads at increased risk.[45] The syndrome should be suspected if the adverse event occurs, or is exacerbated, between 1 week[43] and up to 10 weeks[41] after the initiation of immune restorative therapy, if the immune restoration is effective (eg increasing CD4 count) and when there is no other plausible explanation.[39]

Management of BCG IRIS in HIV-infected infants available per case is summarized in Table 3. BCG IRIS may likely manifest in any class of BCG adverse events (see Figure 2), although the majority of cases are local reactions eg. site abscess, and regional lymphadenopathy which may lead to severe ulceration and drainage.[44] In the largest case series from South Africa, one case of Distant Disease[44] and one suspected but unconfirmed case of possible dBCG associated with IRIS were reported.[45] BCG-confirmed IRIS has presented in HIV-infected infants and children up to 9 years of age with a history of BCG vaccination at birth;[41] there have been no reports of IRIS in adults with a remote history of BCG vaccination in childhood.

The prognosis of BCG IRIS is generally good, assuming restorative immune therapy is achieved. As seen with the natural history of Local or Regional BCG disease in immunocompetent children, several cases of BCG IRIS in HIV-infected infants received watchful waiting, which led to drainage and spontaneous resolution of Local or Regional BCG disease after several months. The largest series from South Africa indicates that BCG IRIS management remains inconsistent.[44,45] A randomized controlled trial is warranted as there is sufficient clinical equipoise whether antitubercular therapy or surgery play any role in improving outcomes. At present, conservative management likely applies to children with IRIS as for immunocompetent children, provided Distant or dBCG disease is not suspected.

Table 1 Summary of randomized controlled trials on the management of BCG-related lymphadenitis (Regional disease)

1st Author Year SETTING	Study description, enrolment criteria	N	Placebo	Blind assessor	Control and intervention arms	Findings, Comments
Kuyucu[26] 1998 TURKEY	LA > 1.5 cm diameter, nonsuppurative	45	N	N	I: Control, observation (15) II: node aspiration + EM 40 mg/kg/day x 1 mo. (15) III: node aspiration + single dose SM 20 mg/kg instilled by needle puncture into node (15)	Outcome: average time to heal Control: 11.9 wks; of 12 (80%) led to fluctuance +spontaneous rupture, 6 (50%) developed a sinus. Arm II: 9.4 weeks (NS); Arm III: 7.1 weeks (significant). NS difference in risk of suppuration, but Arms II & III resolved earlier
Banani[25] 1994 IRAN	Suppurative LA. Nodal fluid confirmed with ultrasound if uncertain. BCG Pasteur Assessments unspecified if blinded, followed at 2, 4, 6 mos	77	N	?	I: Control, observation (34) II: aspiration, repeated as necessary (43)	Outcome: regression; spontaneous drainage, Arms II vs I 2 mos: 58 vs 9 %, p<0.0001; 7 vs 15%, NS 4 mos: 88 vs 26%, p<0.00001; 7% vs 38%, p<0.003 6 mos: 95 vs 65%, p<0.002; 7% vs 44%, p<0.002 The only RCT with aspiration as the therapeutic intervention. Size of nodes not given.
Noah[24] 1993 JAMAICA	LA +/- suppuration at presentation, classified by size: A: "simple" (69) B: LA > 2 cm (27) All in B received aspiration. A developing suppuration during course of study either continued in Arm II or given single INH instillation	96	Y	N	I: Placebo flavoured coloured syrup (34 from A) II: EM 50 mg/kg/day x 1 mo (35 A, 14 B) III: node aspiration + EM 50 mg/kg/day x 1 mo + saline placebo instilled in abscess (14 B) IV: node aspiration + EM 50 mg/kg/day x 1 mo + INH 50 mg single dose instilled in abscess (13 B)	Outcome: average time to heal Control = 5.7 mos, EM did not improve time to heal (A or C) Arms II vs I progress to suppuration (47% vs 60%, p=0.14) *Staphylococcus aureus* and gram-ve bacteria cultured from aspirate in some cases; authors interpreted as secondary infections. Suppuration criteria not clearly defined, and small sub-groups. Aspiration potential therapeutic confounder.
Caglayan[23] 1987 TURKEY	LA > 1.5 cm, nonsuppurative at presentation, classified by onset post-vaccination Early: presenting ≤ 2 months Late: presenting > 2 months Assessment at 6 mos	120	N	Y	I: Control, observation (19 early, 23 late) II: INH 10 mg/kg/day x 2mos (21) III: INH + RIF at 10 mg/kg daily x 2mos (21) IV: EM 30 mg/kg/day x 1 mo (36) Failures (progressing to drainage, change in skin colour or increased nodal size) led to complete surgical excision	Outcome of interest: resolution I: 28/42 (67%) resolved spontaneously. Late presenters were more likely to have spontaneous resolution (83% vs. 47%) NS between controls and other groups. 10 subjects did not complete study due to drug adverse effects
Close[22] 1985 DOMINICA	Criteria not provided. Some cases at enrolment had suppurative LA	18	N	?	I: Control, observation (10) II: INH 10 mg/kg/day x ?duration (8) Any abscesses were drained	States half the patients in both Arms I & II progressed to abscess, and healing time 2-7 months did not differ. States drainage hastened healing (technique and time interval). Published letter, missing some details.

LA = lymphadenitis; NS = non-significance; EM = erythromycin; INH = isoniazid; RIF = rifampicin; SM = streptomycin

Table 2 Summary of retrospective reviews of BCG Distant disease: osteitis

First author Yr, SETTING	Study years	Avg age at onset in mos (range)	BCG strain	No. of cases (girls)	Bones affected (# cases)	Estimated Incidence Per 100, 000	Management	Outcome
Kröger[32,33] 1994, 1995 FINLAND	1960-1978	18 (3 - 68)	Gothenburg Swedish Lab Gothenburg SSI from 1971-78	222 (106)	Many bony sites, majority femur (63), also tibia (44), sternum (36), humerus (19), clavicle, vertebrae, scapula, metacarpal, metatarsal.	15.3 - 72.9	Diagnosis on histopathologic results. 113/201 cultures positive for BCG. Strepto + ethio OR Strepto + INH OR Strepto + INH + RIF x 1 mo; INH + Ethio OR INH + RIF x 4 mos; INH alone x remaining mos. Dosages not provided.Chemotherapy 6 to 24 months, median duration of 12 months.	97% (216) cured without bony deformities. Serious sequelae: disturbances of growth (4), deformation of arm (1), keloid (1)
Bottiger 1982[31] SWEDEN	1973-1975	18 4 - 144	Gothenburg SSI from 1971-78	152 (70)	Femur (44), also tibia, fibula, foot, sternum, rib, forearms, vertebra, scapula. Multiple sites (11)	25 - 33	In 1971 changed manufacturer but used same Gothenburg strain Management not fully described	Surgical and prolonged anti-TB therapy > 12 months in 2 relapses.
Castro-Rodriguez[46] 1997 CHILE	1976-1995	11 (6.5 - 21)	Several BCG strains used	10 (4)	Proximal tibia (3), 1st metatarsal (3), hip, humerus	3.2	Followed guidelines for extra-pulmonary tuberculosis. INH 10/mg/kg/d + PZA 30 mg/kg/day daily x 2 months, followed by RIF+ INH twice weekly x 4.5 mos (total 6.5 mos).	All recovered, no bony deformities. Two had fistulous tracts and relapse and required longer therapy.
Vitkova[47] 1995 CZECH region	1981-1993	16 (7 - 45)	Moscow	46 (18)	Femur (10), tibia (9), humerus (7), sternum, foot, fibula, spinal	2.1 – 3.7	Unspecified anti-tubercular chemotherapy and in most cases surgical interventions. Dose of BCG Moscow was reduced to 0.025 mg at birth.	No deaths recorded.

INH = isoniazid; RIF = rifampin; E = ethambutol, Strepto = streptomycin, Ethio = ethionamide

Table 3 Management and outcomes of BCG-related Immune Restoration Inflammatory Syndrome (IRIS) in HIV-infected children: A total of 47 cases reported in the published literature.

						Management									
								Dose mg/kg/day					Outcome		
First author, Yr, SETTING	No of Cases	BCG strain	Adverse event	Age of onset, sex	BCG disease classification	Aspiration	Excisional Surgery	INH	RIF	EMB	PZA	Duration	Survived	Time to Resolution	Other Rx; Comments
Sharp[40] 1998 AUSTRALIA	1	Tokyo?	Suppurative axillary LA, Supraclavicular LA, fever	8 mo, M	Regional	--	biopsy	Y	Y	Y	Y	?	Y	time?	Doses not specified
Puthanakit[41] 2005 THAILAND	1	Tokyo	Axillary LA	9 yr, F	Regional	Y	--	10	15	--	--	36 wks	Y	by 24 wks	Improvement by 8 wks
	1	Tokyo	Site abscess + Axillary LA	8 yr, F	Local + Regional	Y	--	10	15	--	--	36 wks	Y	by 16 wks	Improvement by 8 wks
	1	Tokyo	Site abscess	8 yr, F	Local	Y	--	10	--	--	--	24 wks	Y	by 15 wks	Improvement by 4 wks
	1	Tokyo	Site abscess + Axillary LA	10 mo, F	Local + Regional	Y	--	--	--	--	--	--	Y	by 16 wks	Parents refused treatment
Hesseling[4] 2006 S. AFRICA	1	Danish	Suppurative axillary LA	5 mo, F	Regional	--	Y	25	25	10	30	12 wks	Y	?	
	1	Danish	Suppurative axillary LA	11 mo, F	Regional	Y	--	20	10	10	--	28 wks	N	?	Died (due to unrelated bacterial septicemia)
	1	Danish	Suppurative axillary LA + Multiple abscesses	5 mo, M	Regional	Y (IDx2)	--	20	10	15	20	28 wks	Y	?	+ Ethio 10 mg/kg/day + Oflox 15 mg/kg/day
	1	Danish	Site ulceration + Axillary LA	9 mo, M	Local + Regional	Y	--	20	15	25	15	>12 wks	Y	?	+ Cipro 15 mg/kg/day
Puthanakit[41] 2006 THAILAND	1	Tokyo	Site abscess	8 yr, F	Local	Y	?	?	?	?	?	?	Y	?	
	1	Tokyo	LA	8 yr, F	Regional	Y	?	?	?	?	?	?	Y	?	
Siberry[43] 2006 ETHIOPIA	1	?	Site abscess, drainage	9 mo, ?	Local	--	--	--	--			--	Y	by 3 wks	
Alexander[44] 2007 S. AFRICA	14	Danish	Not clearly described	?	Local & Regional (?)	?	?	?	?	?	?	?	Y (14)		Individual case management not described
Nuttall[45] 2008 S. AFRICA	21	Danish	5 Site abscess + Axillary LA 14 Axillary LA 2 Axillary LA + Supraclavicular LA	3.8-8.5 mo, 14 girls	Local & Regional (5) Regional (16)	?	?	?	?	?	?	?	Y (21)		Individual case management not described. One suspected case of disseminated disease

LA = lymphadenitis; ID = incision and drainage; INH = isoniazid; RIF = rifampicin; E = ethambutol, PZA = pyrazinamide; Ethio = ethionamide; Oflox = ofloxacin, Cipro = ciprofloxacin

Box 1

I. General considerations for management of BCG-related adverse events in children

1. The immune status of the affected individual determines the management
2. Rule out an immunocompromising condition; suspect if severe, unexpected, or prolonged disease
3. In many cases, cutaneous BCG disease indicates systemic BCG disease
4. Refer to specialist care for systemic and disseminated BCG disease (dBCG)
5. If HIV-positive, follow medical and surgical management and case reviews published elsewhere[4,5]
6. Systemic *M. bovis BCG* disease may have a non-specific presentation from tuberculosis, and that dual *M. bovis BCG* and *M. tuberculosis* disease has been demonstrated
7. Confirm the BCG infection. Under sterile technique, aspiration of abscesses or suppurative lymph nodes is both diagnostic and therapeutic (Ib). When indicated, take gastric aspirates and blood and/or bone marrow aspirates to rule out Distant Disease or dBCG
8. Test specimens and swabs for acid fast bacilli, and culture and sensitivity. *M bovis BCG* may be diagnosed by biochemical methods; DNA spoligotyping can speciate BCG strains
9. Test the BCG isolate's drug susceptibility. BCG strains have inherent drug resistance (ie pyrazinamide, cycloserine)
10. Acquired resistance to isoniazid and rifampin in BCG strains has been demonstrated
11. **Anti-tubercular monotherapy is never recommended**
12. Ensure corrective actions are taken, including investigation of apparent clusters, to reduce the risk of adverse events
13. Report the information to the appropriate surveillance system

Box 2

II. Specific management considerations for BCG-related adverse events in <u>immunocompetent</u> children

A. Local disease: abscesses and ulcers

1. Local abscesses and ulcers at the site of injection are common in immunocompetent individuals
2. Conservative management is recommended with watchful waiting to ensure resolution
3. Cleanse and cover oozing lesions
4. Healing and scarring is expected to occur over several months
5. Most abscesses resolve spontaneously. Large abscesses may be aspirated and contents should be sent for culture
6. If an infected abscess is suspected or pathogenic bacteria cultured (eg. *S. aureus*), provide appropriate antibiotic therapy

Box 2 (continued)

II. Specific management considerations for BCG-related adverse events in immunocompetent children

B. Regional disease: lymphadenitis

1. Lymphadenitis occurs in immunocompetent and immunocompromised individuals
2. Immunocompromised individuals are more likely to have severe disease and systemic or disseminated complications associated with lymphadenitis, and management should be based on most severe classification
3. If immunocompromsed, refer to management algorithm for HIV-infected children[4]
4. Classify lymphadenitis as
   - Uncomplicated (firm or small nodes < 1.5 cm, afebrile, no systemic signs), or
   - Complicated (suppurative, abscess formation, drainage, sinus formation, adherent overlying skin)
5. Lymphadenitis is more likely to progress to complicated in individuals with early or rapid presentation < 2 months post- vaccination
6. Uncomplicated nodes should be left untreated and reassurance provided
7. Advise that normal resolution takes 2 - 9 months. Monitor for complications and progression to systemic disease
8. If complicated lymphadenitis develops, the 1st line management should be aspiration and culture or swab of fluid contents
9. Sterile aspiration of nodes that are suppurative is diagnostic, therapeutic, and hastens resolution
10. In immunocompetent patients, anti-tubercular or other antibiotics do not hasten resolution
11. Anti-tubercular therapy or surgery is not indicated in the majority of cases
12. An appropriate antibiotic may be indicated if an infected abscess is suspected or pathogenic bacteria are cultured (eg. *S. aureus*)
13. Seek a surgical opinion if multinodal and progressive disease, i.e. matted nodes and adherence to overlying skin
14. **Anti-tubercular monotherapy is never recommended**

C. Distant disease: eg. osteitis

1. Occurs in immunocompetent and immunocompromised individuals, the latter may have dBCG
2. Refer to proposed management algorithm if an immunocompromsing condition is confirmed[4]
3. Cases should be considered confirmed or probable with a bone aspiration biopsy prior to therapy. A confirmed case has isolated a BCG strain. A case is probable if there is a history of BCG vaccination, compatible clinical + histopathological picture of tubercular osteitis + no history of tuberculosis contact
4. Most cases are managed with medical therapy: usually≥ 3 anti -tubercular drugs for a min of 6 months
5. Monitor for drug toxicity
6. Follow closely with imaging and to watch for progression i.e. disseminated disease
7. Generally a good prognosis in immunocompetent individuals, though disruption to the bony growth plate can occur
8. Seek a surgical opinion if medical therapy appears ineffective

Box 3

III. Specific management considerations for BCG-related adverse events in <u>immunocompromised</u> children

D. Disseminated BCG disease – general comments

1. Occurs almost exclusively in patients with an underlying immunocompromising condition
2. Medical emergency and specialist management and aggressive multi-drug therapy are warranted
3. Prognosis is generally poor, with a high case mortality rate

Management of BCG disease in HIV-infected or immunocompromised children:
reproduced from Hesseling et al.[4]

I. Local or regional disease

- **Treat medically:**
  - Isoniazid 15-20mg/kg/day
  - Rifampicin 20mg/kg/day
  - Pyrazinamide 20-25 mg/kg/day (2 months, or until tuberculosis excluded)
  - Ethambutol 20-25mg/kg/day
  - Ofloxacin 15mg/kg/day or Ciprofloxacin 30mg/kg/day
- Consider therapeutic aspiration if node fluctuant
- 2-4 weekly follow-up; if no improvement, or deterioration of adenitis after 6 weeks antituberculosis therapy, consider excision biopsy
- If on anti-retroviral therapy (ART), ensure ART is compatible with tuberculosis drugs
- Refer to infectious disease service
- Monitor for drug toxicity
- Report as vaccine-related adverse event to EPI

II. Suspected or confirmed distant or disseminated disease

- Treat medically as above
- Consider expedited initiation of ART if HIV-infected
- Monitor for drug toxicity
- Report as vaccine-related adverse event to EPI

E. Immune reconstitution inflammatory syndrome (IRIS)

1. BCG IRIS is an emerging phenomenon seen with other diseases in immunocompromised individuals receiving effective immune restoration therapy (i.e. highly active anti-retrovirals in HIV-infection or bone marrow transplantation in severe combined immunodeficiency)
2. All classifications of BCG adverse events are possible (Local, Regional, Distant, Disseminated, Other)
3. Diagnosis is made when cases present usually 1-10 weeks of initiating immune restorative therapy, immune function improvement is proven, and there is no other plausible cause.
4. IRIS has a good prognosis with low mortality
5. Usually, BCG IRIS will present as Local or Regional exacerbations. One suspected though unconfirmed case of disseminated BCG IRIS was reported
6. It is unclear whether antibiotics or surgery play any role in managing Local or Regional BCG disease (similar to management for immunocompetent children)
7. Cases may be carefully followed without anti-tubercular therapy and observed for progressive disease
8. Controlled studies on the clinical management are encouraged

9.3.3 Further key issues on managing BCG-related AEFI

9.3.3.1 Transmission of BCG disease

Ulceration of the vaccination site is common and even expected in normal reactions. Viable BCG shed from the ulcer has been found in adult volunteers at least one month post-vaccination.[48] It is prudent to cover oozing sites and dispose of bandages appropriately.[48] WHO commented on the theoretical possibility that individuals recently BCG-vaccinated with draining ulcers could potentially infect unvaccinated contacts, particularly those who are immunocompromised.[49] There have been no reported cases of adverse events from person-to-person spread and infection from BCG vaccination.

Nosocomial transmission of BCG strains used in chemotherapy has, however, been molecularly proven in two hospitals. Two cases initially attributed to a history of BCG exposure from vaccination and endogenous BCG reactivation were later found to be from nosocomial exposure to another patient's immunotherapy with BCG strain Tice.[50,51] Similarly, a second centre reported 3 serious nosocomial infections from exposure to a BCG immunotherapy strain that infected immunocompromised patients admitted on the same ward, leading to permanent changes in hospital biosafety practices.[52] This highlighted the importance of careful diagnosis of *M. bovis BCG* strain before attributing the disease to latent BCG vaccine strain reactivation, as there can be more than one source of exposure to BCG, particularly on a cancer ward.

9.3.3.2 Laboratory diagnosis

It is crucial to obtain appropriate and adequate fluid and tissue specimens for testing. *M. bovis BCG* infection is under-diagnosed and under-reported for several reasons. At minimum, specimens should be tested for acid fast bacilli, culture and sensitivity and if available, recommended biochemical markers to speciate any cultured isolates identified up to *M. tuberculosis* complex (mycobacteria pathogenic to humans that includes *M. bovis).*[53] Definitive confirmation of the *Mycobacterium bovis BCG* vaccine strain by molecular methods should be performed where available.[54,55] The superiority of molecular testing has been shown by the test's ability to correct misdiagnosed cases (eg. erroneously diagnosed as *M. tuberculosis* infection[56] or *M. bovis* infection[57]), cases that otherwise would have remained undetected,[4] or the cases noted above which depended upon PCR tests to confirm the source was a chemotherapeutic BCG strain.[50-52] Furthermore, dual disease of *M.bovis BCG* and *M. tuberculosis* has been demonstrated.[4]

9.3.3.3 Anti-tubercular drug resistance

Health care providers should be aware that all *M. bovis BCG* strains are inherently resistant to pyrazinamide. Several BCG strains used in immunotherapy have been shown to have distinct antibiotic susceptibility profiles, and resistance to cycloserine.[58]

There is evidence that BCG strains have a potential to acquire resistance to anti-tubercular drugs, particularly following monotherapy, and this has important implications for management. This potential was first recognised as early as the 1950's, when BCG Göteburg strain acquired a degree of isoniazid resistance, likely from selection of resistant "mutants" from serial cultures.[59]

In 2004, a single case report in the UK and another in Brazil indicated possible reduced isoniazid sensitivity and reduced multi-drug sensitivity following monotherapy and multidrug therapy, respectively for BCG-related lymphadenopathy in children. Minimum inhibitory concentrations (MICs) were not provided.[60,61] In 2005, the Netherlands notified WHO of mycobacterial isolates identified molecularly as BCG Danish 1331 having low or intermediate level isoniazid resistance (MIC = 0.5mcg/mL) following isoniazid monotherapy for BCG-related lymphadenitis in 5 children (unpublished data). Also in 2005, a South African HIV-infected infant with disseminated BCG disease had a PCR-proven BCG Danish 1331 strain that acquired both isoniazid and rifampicin resistance (MIC $\geq$ 0.3 mcg/mL and MIC $\geq$ 32 mcg/mL, respectively) during multiple anti-tubercular drug therapy.[62]

Acquired resistance has also been reported following treatment of BCG immunotherapy-related adverse events. In 2006, the BCG isolate acquired rifampicin resistance (MIC $\geq$ 32 mcg/mL) after a course of isoniazid monotherapy followed by rifampicin monotherapy in an elderly Canadian woman with bladder cancer.[63]

The Global Advisory Committee for Vaccine Safety, an independent scientific advisory for WHO, reviewed the reports of drug resistance in the Dutch cases, and concluded that the few cases of resistance did not warrant a change in vaccination policy.[64] The information does however, have implications for BCG-related AEFI management. If the decision is to provide anti-tubercular drugs, monotherapy should be avoided. Where available, susceptibility testing should be performed and repeated, for potential acquired resistance, and the appropriate authorities notified.

9.4 Discussion

BCG is the only currently available vaccine against tuberculosis and part of childhood immunization programs worldwide because of reliable protection against pediatric tuberculosis. Although BCG vaccines are considered very safe in immunocompetent recipients, they are some of the most reactogenic vaccines in current use, with injection-site ulcers and scarring considered normal.[11] This review was conducted because there was no previous review to guide management of BCG-related adverse events, and because widely different clinical practices are being followed. Our aim was to develop evidence-based, preliminary guidelines for further evaluation by clinicians and immunisation providers. Key general and specific considerations on the management of Local, Regional, Distant, IRIS, and Disseminated BCG adverse events have been summarised in Boxes 1-3. An early key point in management is determining the individual's immune status. Clinical suspicion must remain high if the presentation is unusually severe, which may signal an underlying immunodeficiency. It is important to note our proposed guidelines are not intended to replace local expertise and clinical judgement in individual cases.

Despite longstanding use of BCG vaccines and the frequency of Regional disease outbreaks, there were surprisingly few controlled studies on BCG-related AEFI. The controlled studies available had inconsistent definitions and interventions which limited comparisons. We did not review non-English studies or the literature on the clinical and surgical management of dBCG disease in HIV-infected children, as large case series and discussion of management on this issue were recently published.[4,5] BCG is also the only vaccine used as a chemotherapeutic agent.[65] There is a body of literature on adverse events from BCG immunotherapy against certain cancers, as BCG has been given as an intravesical instillation against superficial bladder cancers for decades. The spectrum of adverse events following chemotherapy includes disseminated infections and a definitive urological review on the management of BCG immunotherapy-related adverse events would be valuable.[66]

Community health care providers usually encounter the most common BCG-related AEFI - Local or Regional BCG disease. The limited evidence indicates that neither anti-tubercular drugs nor surgery have been effective in hastening resolution in immunocompetent individuals. Medical and surgical interventions also have additional risks and complica-

tions. Furthermore, it is not known if anti-tubercular treatment reduces or negate any protection against *M. tuberculosis* disease induced by vaccination. From the available evidence, we suggest that clinicians have a low threshold to perform needle aspiration of enlarged abscesses or suppurative, fluctuant lymph nodes, using sterile technique. This is a minimally invasive procedure and has the advantages of obtaining specimens to confirm the diagnosis, evacuate caseous inflammatory debris, and hasten resolution. Molecular techniques now provide a sensitive tool to detect BCG disease, however many settings may not have these resources. Importantly, anti-tubercular monotherapy is not recommended as the potential for BCG acquired drug resistance has been demonstrated.

There are other factors affecting the incidence of BCG-related AEFI. BCG vaccines are a group of different attenuated live strains. During the 1920s, samples of the original BCG strain were distributed to several laboratories worldwide where propagation continued by serial cultures for >30 years, before preservation by freeze-drying (lyophilization) became standard. Genetic drift before lyophilization resulted in several live attenuated BCG daughter strains (eg. Pasteur, Copenhagen, Tokyo, Moreau) now manufactured,[67] each having a unique genotype.[3] It is not fully clear whether certain BCG vaccines have better efficacy and safety profiles[49] but there is evidence that certain strains such as BCG Pasteur and Danish 1331 are more reactogenic[12,18] and Moreau, Tokyo and Glaxo are more attenuated strains.[68] Milstein and Gibson reviewed countries' reports of BCG lymphadenitis outbreaks, finding that in addition to the type of BCG strain, the AEFI reports were affected by manufacturing methods, bacillary dose, repeated dosing, route of administration, age at vaccination, administration technique, and artefactually from changes to adverse events reporting systems.[1,18]

This review focussed on the management of BCG-related AEFI. It is important to remember that many adverse events are not related to the vaccine (i.e. unrelated to the intrinsic properties of the vaccine). One mandate of immunization programs is to provide effective surveillance, with investigation of serious or unusual cases and clusters of AEFI. Other causes of AEFI include programmatic errors such as improper administration, coincidences, and reactions from an injection per se. AEFI management requires reporting to appropriate local health authorities. Full efforts should be made in identifying programmatic issues that may reduce its incidence, such as improved screening for immunocom-

promising conditions or refresher training on proper intradermal and sterile injection technique.

We also encourage more information by publication of rare syndromes or serious diseases related to BCG vaccination. A clinical classification system of BCG-related adverse events is now available (Figure 2)[4] as well as consensus AEFI definitions of induration, redness, swelling, abscess, nodule and cellulitis at the injection site, developed by the Brighton Collaboration.[69] These standard systems should be used to improve the quality and comparability in newer studies.

In conclusion, preventive vaccines provide enormous health benefits against death and disability from infectious diseases, and are given safely in the vast majority of the population. Like any medical intervention, vaccines can unfortunately cause adverse events. One aspect of a responsible and responsive immunization program includes the availability of evidence-based guidelines based on reviews such as this, to provide optimal clinical management of adverse events arising from recommended vaccinations. Our hope is that these management considerations will be useful for immunization providers and clinicians to improve patient outcomes and enhance investigation and reporting of BCG-related adverse events.

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10 Discussion and Conclusions

The aim of this dissertation was to synthesise and contribute to knowledge and scientific discussion on the clinical, epidemiological and public health issues surrounding influenza vaccination in pregnant women and BCG vaccination in HIV-infected infants.

A narrative review of influenza vaccination in pregnancy was conducted, with consideration of theoretical risks of vaccination unique in pregnancy. The review was limited by the heterogeneity of retrospective cohort studies that measured different outcomes over different time periods (and influenza strains). A summary excess rate of influenza-related hospitalisation per trimester was inappropriate. The systematic review of dBCG in HIV-infected infants is the first to gather all available international evidence and to calculate a pooled estimate of the incidence from hospital studies. The final review gathers and evaluates all available evidence on the management of BCG-related adverse events, although the quality of studies was generally poor.

Vaccines have been responsible for tremendous achievements in global public health. Each year immunisations prevent 3 million paediatric deaths and 750,000 disabilities (Ehreth 2003). However vaccines are still underused, inequitably distributed, poorly understood, and viewed with suspicion by some members of the public (Breiman 2001). It is also recognised that the very act of enhancing safety surveillance and vaccine safety research can heighten public doubts about vaccines rather than offer reassurance of good monitoring (Francois *et al.* 2005).

Safety concerns are heightened in particular with preventive medicines such as vaccines. It is important to recognise the high level of societal expectation. In general, if per dose comparisons were made, the safety profiles of vaccines are superior to commonly used chemical drugs. It is understandable, however, that the medical imperative of *primum non nocere* is set far higher for preventive drugs in healthy populations, as compared with those given to treat ill populations. Vaccines, as with other public health interventions, can expose millions of individuals, and often in combinations or series of doses. Several vaccines are targeted to vulnerable subpopulations such as infants, for whom a serious AEFI could impact all potential years of life. As a vaccine

succeeds in disease prevention, the expectations and focus on the vaccine's safety profile increase.

Vaccine risk communication and public perception are discussed below, but it is important to note there also remains substantial room to improve communication of safety reporting within the scientific community, and to raise adverse events analysis to the level of efficacy analysis in studies (O'Neill 2001). This is a particular opportunity in large phase III trials which can provide rigorously controlled data on vaccine effectiveness and more common adverse events. Subgroup analyses can provide cautious hypotheses on concerns or benefits in subpopulations that can lead to formal investigation.

Statements such as "There were no serious adverse events." or "The vaccine was found to be safe." are often seen in published trials, and can lead to misinterpretation that may affect risk perception and management. It may be less well understood that vaccine safety itself cannot be "proven" and instead, is indirectly inferred by the absence of serious adverse events (Clements 2004).

The Consolidated Standards of Reporting Trials (CONSORT, www.consort-statement.org) is the authoritative guide recommended by all major journals. The guide recommends reporting of all important adverse events as well as reasons for subjects discontinuing the trial. It provides an example that compares frequencies of adverse events between trial arms. CONSORT recommends a statement on how sample size was determined, and the power to detect a certain effect size. However, there is no current recommendation or example of a prefacing statement that describes the limits of assessing safety. This is an overlooked issue that could be addressed.

It would be valuable if CONSORT recommended that a contextual, post hoc statement be consistently reported about zero-numerator serious adverse events in trials. As described in the Introduction, Hanley's Rule of Three approximates with 95% certainty the upper limit of a probability of an event, were it to exist, based on the number of independent observations (Hanley & Lippman-Hand 1983; Eypasch *et al.* 1995; Jacobson *et al.* 2001; Fritzell 2002). This approximation is not well-known or reported by trialists (Jovanovic & Levy 1997). There are other full statistical methods that can be used to estimate the probability from zero numerators (Chen & McGee 2008). This would provide a worst-case estimate of the incidence for a potential serious adverse

event within the trial period. An example of a more meaningful statement on safety reporting in a trial would be: "This trial found no serious adverse events in a sample size of N, followed for X days, with approximately 95% certainty that if any serious AEFI existed, the risk would be less than Y times per 100,000 doses".

Safety reporting that included the sample size or approximation of the non-incidence rate of a potential serious adverse event would serve as a reminder to the scientific community that all studies have limits in *not* detecting an event. Fuller contextual descriptions of adverse events should also be provided on the drug labelling and on-line websites of manufacturers.

10.1 Influenza and inactivated influenza vaccines in pregnancy

There are several considerations from the review in Chapter 7 (Mak *et al.* 2008a). What was highlighted is the substantial evidence indicating that pregnant women were disproportionately harmed during two of the past three pandemics in the last century. One historical review of the 1918/9 pandemic found estimates of fatal influenza in pregnancy from death certificates to be 530 to 570 per 100,000, compared with deaths in non-pregnant women of childbearing age of 490 per 100,000. Maternal deaths were likely underestimated as pregnancy status is not always known or recorded on the certificates (Reid 2005). During the pandemic, a report from one Parisian hospital described 70% of pregnant women having pulmonary complications with early abortion in 6%, preterm delivery in 17%, and a case fatality of 60%. The common impression in 1918/9 was described in the journal, The Lancet: "'Woe unto them that are with child,' might have been written of this influenza epidemic" (Anon 1919). There were similar case fatality rates during the 1957/8 pandemic. Possible factors that may have increased the vulnerability of pregnant women were underlying comorbidities and normal immunological or physiologic changes in pregnancy (Crapo 1996).

Another influenza pandemic is expected. Considerable effort has been made to prepare for what is expected to be a true global health emergency. Emergent influenza strains are being closely monitored for one that may produce the next pandemic. Since 1997, several new subtypes have been documented (H5N1, H9N2, H1N2, H7N7) (Nicholson *et al.* 2003). Of particular concern was zoonotic outbreaks of H5N1 avian influenza causing fatalities in poultry handlers (Shu *et al.* 2006)). WHO pandemic

planning is based on the best-case scenario of a pandemic with 20% of the global population ill, 28 million hospitalised and 7 million dying (Stohr & Esveld 2004). In the worst-case scenario, based on an impact similar to the 1918/9 pandemic, the upper limit is as high as 81 million dying, with 96% of deaths occurring in the developing world (Murray *et al.* 2006).

The next influenza pandemic will mobilise the first concerted public health effort to interrupt the impact and global spread through timely mass vaccination. Countries are urged to establish pandemic preparedness plans that include vaccine stockpiles and policies that outline the subpopulations given immunisation priority (WHO 2005). For these reasons, among others, an in-depth review of the risk-benefit surrounding maternal influenza vaccination was timely. The evidence from past pandemics clearly indicates pregnant women may need to be prioritised as one of the more vulnerable group for vaccination during a pandemic. Of course exact disease patterns of the pandemic influenza should be analysed in real time as data become available, to identify all subpopulations excessively affected by that specific strain.

For interpandemic influenza, there are several factors that add complexity to the risk-benefit assessment for vaccination in pregnancy. It is important to note that in general, cumulative mortality from inter-pandemic years is still higher than in a pandemic (Simonsen *et al.* 1997). The review found the evidence of influenza-related burden in pregnancy was based mainly on retrospective electronic databases, the largest consistently finding excess influenza-attributed hospital admissions in pregnant women in the second and third trimesters and in those having co-morbid conditions. However, there is concern with imprecision, biases and residual confounding even with carefully adjusted observational data (Jackson *et al.* 2006; Belongia & Shay 2008).

There are several variables that limit conclusions on vaccine effectiveness and influenza-attributed morbidity, based on the evidence summed across influenza seasons from retrospective database studies. Influenza morbidity varies year to year, depending on factors including virulence, strain geographic distribution, and level of cross-protection from past immunisation (from natural infection or vaccination). The composition of inactivated influenza vaccines is determined and manufactured each year, and the level that the vaccine strains correspond to circulating wildtype strains can be a determinant of that year's vaccine effectiveness.

Currently a substantial amount of available safety data on influenza vaccination in pregnancy is based on a large US maternal cohort established in the 1950s. Although providing reassuring evidence, the data reflect the safety of 1950s inactivated influenza vaccines (arguably even higher reassurance, as these were less purified) in a study where enrolled pregnant women received combinations of other vaccines.

Ethical reasons preclude the conduct of a vaccine trial with pregnant controls in settings that have already established policies to provide that vaccine in pregnancy. At present, there is only one RCT conducted in Bangladesh on maternal vaccination in the third trimester that measured influenza-confirmed illness in the infants, with encouraging vaccine effectiveness of 61% (95% CI: 9 to 84%) against febrile laboratory-confirmed influenza in infants and 28% (95% CI: 4 to 46%) against non-specific febrile respiratory illness in mothers (Zaman *et al.* 2008). The RCT was small, indicated by the wide confidence intervals surrounding the estimates. More data are needed as the current evidence base for the effectiveness of maternal influenza vaccination using laboratory-confirmed outcome measures is based on a few hundred subjects.

For these above reasons, more vaccine safety data on modern influenza vaccines are needed. A carefully designed, large prospective cohort study would be highly valuable in addressing any remaining scepticism about the true burden of seasonal influenza and vaccine effectiveness in pregnant women and their young infants. Such a study should measure both effectiveness by laboratory-confirmed influenza and influenza-like clinical illnesses in mothers and infants. Terminology should be clear in identifying "laboratory-confirmed" illness as opposed to less specific measures of influenza-associated (or -attributed or -related) illness or respiratory infections during the influenza season, as previous terms were not always clear (Bhat N. *et al.* 2005). Virologic surveillance of circulating wildtype strains in the study setting should be actively undertaken. Laboratory investigations would preferably include a combination of clinic rapid diagnostic tests for influenza and as well as laboratory confirmation (Effler *et al.* 2002). It would be ideal if a study year included a severe influenza season. Although severity is not fully known prior to the onset of the season, a greater burden of disease is expected when a major drift is predicted in the circulating influenza viruses.

There is in general, a paucity of new vaccines and other drugs in the pipeline being developed specifically for maternal health. The fallout from teratogenic effects of thalidomide in pregnancy in the 1960s has led to understandable caution with medicines given to pregnant women, particularly in the first trimester during organogenesis (White *et al.* 2008). Furthermore, there is minimal market or legal incentive for the pharmaceutical industry to conduct the necessary pre-licensing investigations to determine if use in pregnancy can be an additional on-label indication. The result is that reproductive and developmental toxicology studies in animals are not performed during the pre-clinical stages of most drugs in development, and the pregnant subpopulation are actively excluded from pre-licensing trials. Most currently used vaccines were licensed without pre-licensing data on safety in pregnancy (Gruber 2003).

Vaccination in pregnancy entails the highest level of societal and ethical expectations for safety, and especially for new medicines in pregnancy. For the first time, there are vaccine candidates in advancing stages of clinical trials that are against neglected tropical diseases. There are several tropical parasitic diseases causing enormous disease burdens and all currently lack vaccines. Some are known to have major adverse impacts on maternal and fetal health, such as malaria, hookworm, schistosomiasis, and Chagas disease (Hotez & Ferris 2006). When considering the consequences of malaria in pregnancy alone, the risks include maternal anaemia, intrauterine growth retardation, fetal infection and infant deaths related to increased prematurity and low birth weight. About 50 million pregnant women live in malaria-endemic regions, and each year 75,000 to 200,000 infant deaths are associated with maternal malaria (Steketee *et al.* 2001).

It is important to consider the global perspective that 99% of all maternal deaths occur in low-income countries. There are many neglected areas of research on the pathogenesis, immunology, epidemiology and public health consequences of several infectious diseases in pregnancy (Greenwood *et al.* 2007). If the hope for new poverty-related vaccines (and other medicines) is realised, it is expected that these vaccines will be used almost exclusively in poorly resourced countries, where infrastructure to support pharmacovigilance is weak. (Travelers may also receive these vaccines, and travel medicine linked databases can be another potential source for safety surveillance of new vaccines in more resourced settings). This is particularly a

critical issue if new vaccines are given in pregnancy and rigorous, long-term follow up is essential. An existing collaboration like the INDEPTH network of 38 demographic surveillance sites in 19 non-industrialised countries (http://indepth-network.org) would be an ideal platform for long-term longitudinal studies on drug safety and effectiveness against poverty-related diseases. Building upon this established research network would strongly address the recognised need to improve pharmacovigilance in less resourced countries (Bentsi-Enchill 2007). There are several relevant areas for potential research in vaccine pharmacovigilance in low-resource countries. Despite decades of providing thiomersal-containing tetanus toxoid vaccine in pregnancy in many countries, there are only two published, reassuring case-control studies on tetanus toxoid exposure in pregnancy and congenital abnormalities (Silveira *et al.* 1995; Czeizel & Rockenbauer 1999). Another neglected area of research is specific vaccine effects in malnourished or preterm infant subpopulations.

In countries where vaccination in pregnancy is routinely given, there are several reasons why improved AEFI surveillance of vaccination in pregnancy should be augmented by establishing a long-term active registry (Gruber 2003). Pregnancy status is not consistently recorded, nor is additional important information usually captured in general registries, such as timing of exposure(s) in gestational weeks (EMEA 2005). Although epidemiological studies and passive surveillance systems have not indicated harm, lingering public concerns in industrialised countries over thiomersal in vaccines given in pregnancy and childhood have increased the market for thiomersal-free vaccines in single-dose vials (Mak *et al.* 2008b). This change was based on precautionary grounds and to maintain public confidence in immunisations in these countries. An active registry in these better-resourced settings would be valuable for long-term evaluation of thiomersal-free vaccinations in pregnancy and in childhood, to follow up pregnancy outcomes and the incidence of childhood development disorders.

If only thiomersal-containing influenza vaccine is available, as in many countries, the benefit of vaccination is expected to greatly exceed any theoretical risks in pregnancy. In the event of a pandemic, large multi-dose vials may be used for maximally efficient vaccine production, and a preservative such as thiomersal will be required (Cox 1997; Celis 2005). Such a scenario also provides an important opportunity for AEFI surveil-

lance during mass vaccination in a pandemic, particularly as the vaccine is being rapidly manufactured and given in mass campaigns.

AEFI surveillance of pregnant women inadvertently vaccinated, especially during mass vaccination can provide important information that could not be collected in intervention studies. Health care workers and military workers are often targeted groups for vaccination, and many are women of child-bearing age. Even with history-taking and screening, an estimated rate of unknown pregnancy up to 4 weeks gestation was 6 per 1000 women in the United States (CDC 2003). An example is from the United States, where smallpox vaccination has been reintroduced for mainly military personnel. As routine smallpox vaccination was discontinued a generation ago, familiarity with the vaccine had faded. However, fetal vaccinia is a known serious AEFI from vaccination in pregnancy. For these and other reasons, the United States enhanced passive surveillance as well as an active national smallpox vaccine registry for inadvertent vaccination in pregnancy (CDC 2003).

10.2 Tuberculosis and BCG vaccines in HIV-infected children

Early on in the HIV epidemic, there were concerns and calls for research on the safety of BCG vaccination in HIV-infected infants (Wright 1987; Reichman 1989; Athale *et al.* 1992; Weltman & Rose 1993). The review in Chapter 8a systematically gathered cohort studies in the HIV-infected infant subpopulation. Signals of an increased dBCG risk in HIV-infected children were reported as early as 1993 (Besnard *et al.* 1993).

A lack of studies still remains, however, on BCG effectiveness specifically in the HIV-positive infant subpopulation. A small case-control study of 116 pediatric tuberculosis cases in Zambia found that the presence of a BCG scar in HIV-infected children did not provide lower odds of tuberculosis (OR 1.0, 95% CI: 0.2 to 4.6) while HIV-uninfected children had lower odds (OR 0.41, 95% CI: 0.18 to 0.92) (Bhat G. J. *et al.* 1993). A retrospective study in Argentina found that 12.5% (51/374) of hospitalised HIV-infected children had tuberculosis disease and there was no significant difference between tuberculosis rates in BCG vaccinated (10.9%, 95% CI: 4.5% to 21.2%) and non-vaccinated children (14.2 %, 95% CI: 10.5% to 18.6%) (Fallo *et*

al. 2005). Prevention of childhood tuberculosis and vertical HIV transmission currently rests on non-vaccine strategies.

There are many issues raised with WHO's revised policy to contraindicate BCG in this subpopulation. One is the need to reexamine the recommended EPI immunisation schedule to provide BCG at birth or soon postnatally in countries having a substantial proportion of immunodeficient infants, as the current earliest determination of infant HIV status by PCR is 4-6 weeks of age. The standard EPI schedule with BCG at birth has not changed since the original outline for 6 vaccines established in the 1970s; diphtheria/pertussis/tetanus vaccines, however, first began at 3 months of age but EPI later recommended starting at 6 weeks of age (Halsey & Galazka 1985). It is important to note the EPI schedule was intended to serve as a general guide for countries to establish their own vaccine policies, and the schedule was not expected to be universally appropriate for all epidemiological and cultural settings (WHO 1980; Galazka *et al.* 1984). There are several variations in BCG vaccine policies among countries that do not conform with the suggested EPI schedule (Fine *et al.* 1999), (www.bcgatlas.org). Formal decision analyses and modeling of the different risk-benefit parameters and BCG strategies in settings with high HIV and tuberculosis settings would be valuable.

The risk of dBCG is estimated to be about 1% of vaccinated HIV-infected infants and efforts should be directed at addressing the root causes to decrease the subpopulation at risk (Mak *et al.* 2008d). Even in highly HIV-endemic settings, if maternal HIV prevalence can be reduced, or vertical transmission minimised by well functioning PMTCT programmes providing access to ART and safe breastfeeding, the absolute number of dBCG cases from inadvertent vaccination would be minimised even if BCG coverage continued routinely. For example, in one South African province, the estimated annual number of infants newly infected by HIV has decreased by nearly half in three years, from 1573 infants in 2004 to 806 infants in 2006. The improvement is mainly due to lower vertical transmission rather than change in the maternal HIV rate (Hesseling *et al.* 2008). In KwaZulu-Natal, vertical transmission rates as low as 2.9% have been reached (Geddes *et al.* 2008).

There is now strong evidence that ART initiated by 6-12 weeks of age will reduce early mortality (Violari *et al.* 2008) and may possibly reduce tuberculosis in HIV-in-

fected infants (Kouakoussui *et al.* 2004). Timely ART requires timely HIV diagnosis, and one possibility is to integrate early infant HIV testing with the 6-week EPI visit (Mak *et al.* 2008c). Another question raised is the appropriate frequency of HIV tests and the trade-off of delaying BCG vaccination in HIV-exposed uninfected infants, as there is no information on BCG's profile in this subpopulation. Assuming some protection would be afforded from BCG, postponing BCG vaccination in HIV-exposed uninfected infants could increase their risk of progressive tuberculosis disease in settings highly endemic for tuberculosis.

As access to ART expands, an important question is raised if there is now a safer time period to give BCG vaccination in HIV-infected infants stabilised on ART. BCG would not be contraindicated if the vaccine's long-term risk-benefit approached a similar ratio as immunocompetent children. There is sufficient clinical equipoise on the effect of delaying BCG vaccination in HIV-infected infants on ART to warrant a controlled trial of BCG vaccine in this subpopulation. *M. tuberculosis* IRIS and ART-associated tuberculosis are serious diseases (Meintjes *et al.* 2008), particularly when compared with BCG IRIS. Furthermore, having to treat tuberculosis infection first can delay ART initiation. The lack of reliable correlates of immune protection against tuberculosis make study endpoints more challenging (Fine 1995). Such a trial would require long-term follow up to examine all-cause mortality, culture-positive tuberculosis, and all BCG AEFI.

There is an interesting corollary in BCG vaccine policy for HIV-infected infants and those with PIDs. Concern has centred around SCID, the most common congenital immune deficiency disorder. Suggestions have been made in industrialised settings with low tuberculosis burdens to postpone BCG vaccination to avoid complicating the prognosis of infants later diagnosed with HIV or PIDs (Romanus *et al.* 1992; Dawar *et al.* 2004). Some policies in industrialised countries postpone BCG for 6 months or more (Infuso *et al.* 2006).

As discussed in Chapter 8a, risk-benefits weights in industrialised settings with low tuberculosis and HIV burdens are different. Industrialised settings have more resources, lower disease endemicity and hence higher risk intolerance. The incidence of SCID can be about 1-20 per 100,000 which can be a more common cause of immunodeficiency than HIV in infants in certain settings (Dawar *et al.* 2004). Some

subpopulations targeted for BCG vaccination may have a higher genetic predisposition for PIDs and potential BCG AEFI can interfere with life-saving treatment. SCID is not usually detected until 6 months of age and not regularly included in newborn screening, although routine screening is under consideration because a panel to test for SCID exists (Lindegren *et al.* 2004). If an infant with SCID is diagnosed early and receives prompt bone marrow transplantation (which has the potential of full, permanent immune restoration) survival is as high as 97%. Survival decreases to 69% if transplantation occurs after 3.5 months of age. The difference is mainly due to serious opportunistic infections developing after the first few months of life, including dBCG (Skinner *et al.* 1996; Buckley 2002; Ikinciogullari *et al.* 2002).

As the current situation stands, there is no licensed vaccine against tuberculosis recommended in HIV-infected individuals, for whom tuberculosis is the leading cause of death. Non-vaccine strategies are the current mainstay; WHO recommends intensive early case detection and management by Directly Observed Therapy, Shortcourse (DOTS), which can have some effect in reducing disease transmission (Corbett *et al.* 2007). However, diagnosis and management strategies are complicated, drug-resistant tuberculosis is an increasing concern, and global tuberculosis incidence continues to climb. There is an urgent need for highly effective new tools to reduce transmission by preventing primary latent tuberculosis and reactivated tuberculosis disease, both which are major stumbling blocks for control.

As described earlier, BCG remains clinically relevant in immunocompetent recipients for reliable vaccine safety and effectiveness against childhood disseminated tuberculosis (Trunz *et al.* 2006) as well as against leprosy (Fine 1995). However with the contraindication in immunocompromised vaccinees and limited effects against adult pulmonary tuberculosis and disease transmission, some have called BCG an outdated vaccine (Gudmundsdotter & Hallengard 2008). There are several new tuberculosis vaccine candidates under clinical trials that either boost upon or replace current BCG vaccines (Kamath *et al.* 2005; Brennan *et al.* 2007). Potential new strategies are generating great interest, as these are the first tuberculosis vaccine candidates in 80 years (Hoag 2004).

Two vaccine candidates based on boosting prior BCG vaccination are noted. There is considerable interest in maintaining BCG as an established EPI childhood vaccination

for its potential as a live vector for recombinant antigens of diseases (tuberculosis and potentially others). This strategy known as a heterologous prime-boost combination provides a prime vaccination such as BCG to increase Th-1 cellular immune responses, followed later by a booster using a different type of vaccine against the same antigen (McShane & Hill 2005). The advantage of maintaining BCG vaccination is that the majority of the world's populations in current need of a new tuberculosis vaccine are already primed, having received childhood BCG vaccination.

MVA85A is an example of a recombinant boost vaccine and a leading candidate under clinical trials, but is not yet tested in immunocompromised recipients (Ibanga *et al.* 2006; Hawkridge *et al.* 2008). BCG-killed *M. vaccae* vaccine is a nonrecombinant boost candidate that was selected specifically for testing in HIV-infected recipients. After promising early trials (Waddell *et al.* 2000; Vuola *et al.* 2003), a placebo-controlled phase III RCT (ClinicalTrials.gov NCT00052195) was conducted of a killed whole-cell *M. vaccae* tuberculosis vaccine as a five-dose series booster. Over 2300 BCG-vaccinated, HIV-infected Tanzanian adults with childhood BCG vaccination scars and CD4 counts > 200 cells/mm^3 were enrolled (Hoag 2004). The seven-year trial is completed and preliminary results confirms effectiveness against laboratory-confirmed tuberculosis; full analyses are awaited (IUATLD 2008). The vaccine has not been tested in children. Safety concerns in immunodeficient recipients remain, however, if BCG is maintained as a potential antigen-delivery system and priming vaccine.

There is encouraging animal research into a new recombinant BCG vaccine strain, rBCG30 which has shown greater protective immunity against tuberculosis in the guinea pig model, and could eventually replace current BCG strains (Horwitz *et al.* 2000). The strain was further engineered to reduce the risk of overwhelming infection in the immunodeficient host. rBCG(mbtB)30 continues to overexpress the major secretory protein of *M. tuberculosis* but also limits the number of replications of the BCG organism. When compared with BCG, this recombinant BCG strain was shown to be more attenuated in the SCID mouse model (Tullius *et al.* 2008). This is a promising step towards development of an improved BCG vaccine strain that is safe and effective in both immunocompetent and immunodeficient populations.

The safety and effectiveness of live, attenuated vaccines in immunocompromised sub-populations is poorly studied in general. One corollary is the policy that live attenuated measles vaccination be given in HIV-infected children who are asymptomatic or have early signs of immunosuppression, and to avoid vaccination only if there are signs of severe immunosuppression (WHO 2004). A study on active surveillance for serious measles-related AEFI in children born to HIV-infected mothers with adequate laboratory investigations would be valuable. Results are awaited from a Cochrane systematic review on the current available evidence on this issue (Unnikrishnan *et al.* 2007).

10.3 Management of BCG-related adverse events

The review of management of BCG-related AEFI in Chapter 9 was part of a larger ongoing initiative by WHO to update a guide on the incidence and management of serious AEFI of vaccines. The original document provided only brief clinical management on serious adverse events related to EPI vaccines (WPRO 1999).

Practical considerations on investigation and management of AEFI for each vaccine should be made readily available to EPI mangers and health care providers, as appropriate reporting mechanisms and a standard response are emphasised. This is especially relevant during National Immunisation Days (NID) where the absolute number of AEFI will increase as an expected proportion of doses administered in an intense and short campaign period when AEFI surveillance may also be heightened. Demonstration of timely AEFI investigation and guidance on the clinical management of confirmed vaccine-related AEFI also provides assurance to the public that the immunisation programme is actively managed and monitored.

Management guidelines may also help reduce the unnecessary use of antitubercular drugs for BCG local or regional disease in immunocompetent individuals. The review identified the issue of the potential of acquired, anti-tubercular drug resistance in *M. bovis BCG*, but it appears that distant or disseminated BCG disease is not likely to lead to infectious pulmonary disease. This may be due to the ancestral species *M. bovis* having a predilection for extrapulmonary tuberculosis. Human-to-human transmission of BCG disease has not been demonstrated.

One of the main issues impeding adequate surveillance of BCG AEFI is the lack of adequate screening for serious BCG disease. BCG is closely related to *M. tuberculosis,* and as described in Chapter 9, misdiagnoses and non-specific diagnoses have occurred. Over the past 10 years, emerging availability of multiplex real-time PCR assays can now rapidly speciate MTBC members (Talbot *et al.* 1997; Pinsky & Banaei 2008). However, surveillance requires adequate laboratory facilities and resources. The majority of serious BCG-related AEFI is expected to occur undetected in poorly-resourced sub-Saharan African countries where the global HIV burden in children is concentrated. There is an approximate 1% risk of dBCG with resulting 75% all-cause mortality from inadvertent vaccinations in the HIV-infected infant subpopulation without access to timely antiretroviral therapy. dBCG is iatrogenic and potentially avoidable, raising considerable ethical issues.

10.4 Immunisation programmes

Rychetnik noted that "public health interventions tend to be complex, programmatic, and context dependent" (Rychetnik *et al.* 2002). Decision-making in public health programmes balances the tensions among utilitarian, egalitarian and communitarian ethical principles (Roberts & Reich 2002). Immunisation policy is based on many considerations, but in general the ethical principle emphasised is utilitarian for maximising the overall population benefit and herd immunity against a disease. Furthermore, operational factors are taken into account, based on the feasibility, logistics and availability of resources to conduct and sustain the large-scale public effort.

Issues facing immunisation programmes and decision making are substantially different in industrialised and non-industrialised countries. Although immunisation programmes seek to reduce global health inequity by reducing vaccine-preventable diseases, vaccines are unequally distributed within and among countries. This is especially reflected by newly licensed vaccines which are first introduced in industrialised countries, although poor countries have the populations that would benefit the most (Franco 2007). Organisations such as GAVI must play a role in providing leadership to develop new market strategies that sustain and expand access to vaccines in poorly resourced countries.

Clearly, screening for vaccine contraindications is more feasible in industrialised countries and there are classic policy criteria in determining whether to screen populations (Andermann *et al.* 2008). Beyond screening for subpopulations at increased risk from vaccination, the possibility of individualised genetic screening before vaccination has been put forward. "Vaccinomics", is the area of pharmacogenomics that aims to investigate for underlying immunogenetic mechanisms of vaccine-related adverse events (Poland *et al.* 2008). For example, genetic differences were compared in the 94/428 (22%) individuals who developed fever after smallpox vaccination against afebrile vaccinees (Stanley *et al.* 2007; Reif *et al.* 2008). Vaccinomics is a potentially broad area of research, but highly at odds with feasibility of screening in large-scale programmes, especially when considering that currently available screening tests for known contraindications such as HIV and SCID are not optimally performed.

10.5 Public perception and risk communication

Immunisation has been called a social contract and responsibility, as most current preventive vaccines are against human-to-human infections. There is an impressive number of potential vaccine candidates against infectious diseases, chronic diseases and cancer, but societal understanding and value of these developments have not kept pace (Breiman 2001).

As the immunisation programme succeeds and cases of vaccine-preventable diseases sharply decline, so does the public consciousness of the disease and its consequences. In particular in industrialised countries, public focus has shifted towards issues of vaccine safety and the risk of rare but serious adverse events. Cases of AEFI temporally associated with vaccination can be compelling and emotive. Vaccine safety issues are raised more frequently when the vaccine-preventable disease has become less common or is less likely to be fatal or cause permanent damage (Neuzil & Griffin 2005). An example is with influenza. For most cases, seasonal influenza is a self-limited illness, and influenza is an example that may encourage complacency, partly due to familiarity with seasonal occurrence, the perception that influenza is a benign or inconsequential illness, and the misnomer of attributing any mild respiratory illness as the "flu".

A secure climate to report safety is required to reduce repercussions and indemnity. This is needed in particular for vaccination in pregnancy where a societal, political, legal and financial framework must be established by government, academia and industry to address the barriers (Brent 2003). Some countries have already acted from earlier pressures. Vaccine safety issues were prominent in the 1970s, with legal damages awarded to injuries attributed to immunisation from diphtheria toxoid, whole-cell pertussis and tetanus toxoid vaccines. This led to the US National Childhood Vaccine Injury Act in 1986 which established a compensation program on a "no-fault" basis (CDC 2008).

True "outbreaks" of BCG-related adverse events have led to public outcry and cessation of BCG immunisation programmes in Austria (Hengster *et al.* 1992) and Sweden (Romanus 1990). Some have estimated that an incidence of more than 1% in reported BCG-related lymphadenitis can lead to disruption of the immunisation programme (Milstien & Gibson 1990).

More often, serious claims against vaccines are later shown to be unfounded, but the immediate effects can severely undermine vaccine uptake, from which the valid immunisation programme more slowly recovers. This has been seen in many settings worldwide, such as the concern of measles vaccine and autism in the United Kingdom (Burgess *et al.* 2006), of hepatitis B vaccine and multiple sclerosis in France (Ascherio *et al.* 2001), of polio vaccine and temporally related deaths during a severe malaria epidemic in Uganda (Nuwaha F *et al.* 2000), or of polio vaccine inducing infertility in northern Nigeria (Jegede 2007). Lessons learnt from past vaccine scares can be used as an opportunity to improve responses to future crises (Francois *et al.* 2005).

Uncertainty from incomplete scientific information pervades many levels of medical decision-making for interventions in general, not just for vaccine safety and effectiveness (Politi *et al.* 2007). The challenge lies in providing precise scientific communication and imparting a balanced perspective to health care providers and to the public regarding risks, particularly of small-probability events and uncertainty. Presenting the risks and benefits of vaccines in a balanced manner is essential. Near zero risks, though small, should not be simply dismissed.

Research on methods to improve the precision of risk communication have taken into account the general public's abilities with numeracy, charts and varying perceptions of terminology for frequency. Public risk perception has been shown to have a ratio bias, where a ratio using smaller numbers (i.e. 1 in 10) is perceived as being a lower risk than the equivalent mathematical ratio with bigger numbers (i.e. 10 in 100). Suggestions for communicating small probabilities include stating the absolute value of an increased risk above the baseline risk, and not just the relative magnitude. Perspective about a low risk event has been presented graphically by a sliver in a pie chart, or by the use of a magnifying glass over a low probability event along an arithmetic scale of frequencies (Lipkus 2007).

The Erice Declaration of 1997 and the Manifesto in 2007 were two international statements developed by a group of pharmacovigilance experts (The Erice Declaration 1997; Anon 2007). The declaration emphasised that effective communication on safety of medicines was needed, and that pharmacovigilance was a collective responsibility among society, health providers, researchers, media, and industry and government representatives. The manifesto called for global reform of the science of pharmacovigilance, toward proactively developing new methods to collect, monitor and study the risks and benefits of drugs, with core involvement of the public. These mandates apply to all medicines, but have particular relevance for vaccines.

10.6 Conclusions

The focus of this dissertation was on vaccine safety and effectiveness in subpopulations. First, a narrative review examined the evidence for the risk from maternal influenza in pandemics and epidemics and the safety and effectiveness of maternal vaccination with inactivated influenza vaccines. Second, a systematic review was conducted on the risk of disseminated BCG disease in HIV-infected infants and the implications of revised BCG vaccine policy in low-income settings. A third review synthesised the evidence-based management of BCG-related adverse events. Based on these studies and the discussion, the following main conclusions were drawn:

1. From historical reports and epidemiological studies, pregnant women were at increased risk of death during influenza pandemics and of excess hospitalisations with increasing length of gestation in epidemic years, when compared with non-

pregnant peers. Based on a limited number of vaccine safety studies conducted in pregnant women (largest being N=2291), serious adverse events have not been detected. Several countries now formally recommend seasonal influenza vaccination in pregnancy. Enhanced safety surveillance and long-term follow up of vaccinated cohorts are recommended.

2. HIV-infected children face a much higher risk of *M. tuberculosis* disease, however BCG effectiveness in preventing tuberculosis in this subpopulation has not been shown or adequately investigated. The summary risk of disseminated BCG disease in HIV-infected infants was 979 per 100,000 (95% CI: 564 to 1506) vaccinees, indicating a risk more than a thousandfold higher than in the baseline HIV-negative population. Further research includes studying the impacts from delaying BCG, potential ameliorating effects of ART that may improve BCG's risk-benefit profile, operational research for integration of early infant HIV testing with EPI, and new tuberculosis vaccine candidates that are safe and effective in the immunocompromised subpopulation.

3. Guidelines on the management of BCG-related adverse events are an important component of a well prepared, actively managed and monitored immunisation programme. The first point in management is determination of the affected individual's immune status, as local and regional BCG disease in immunocompetent children usually can be managed conservatively. If the decision is made to provide antitubercular drug therapy, monotherapy should be avoided because of the demonstrated potential of BCG to acquire drug resistance.

4. Vaccine pharmacovigilance is an increasingly important area of active research for various reasons in industrialised and non-industrialised countries. Several different database platforms are now available to evaluate safety. The collection, analysis and reporting of adverse events in trials need to be improved. Phase III and IV studies can provide valuable opportunities to investigate vaccine safety and effectiveness in subpopulations. In poorly resourced countries, current and future vaccines, especially those targeting poverty-related diseases, would be ideally investigated through large cohort studies within established surveillance networks.

10.7 References

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11 Appendix: A closer look at influenza vaccination during pregnancy - Authors' reply

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All authors declare that we have no conflicts of interest. JL has retired from the Department of Health.

This manuscript was published in:

The Lancet Infectious Diseases (2008): **8**:662-3

Authors' reply

We thank David Ayoub and Edward Yazbak for their interest in our Review. We do not agree, however, with their view that we presented selective findings, or that evidence supporting influenza immunisation in pregnancy is inconsistent with available vaccine safety data.

We systematically searched the current available literature on the risk of influenza infection and the risk-benefit of influenza vaccination in pregnancy.[1] We considered the studies' methodology, sample size, settings, influenza periods, outcome measures, whether adjustments were made for confounders, and the study years (since the type, spread, and virulence of influenza viruses vary across seasons[2]). The largest and longest historical cohort studies,[3,4] which compared rates in defined influenza seasons with peri-influenza seasons stratified by trimester and adjusted for comorbidities, did find excess hospital admissions in pregnant women. Risk of hospital admission increased with length of gestation and with comorbidities. Another large cohort study published since our Review also supports these findings.[5]

By contrast with hospital admission, we noted that maternal mortality from seasonal influenza is rarely reported (though well documented in past pandemics). Without routine laboratory testing, excess all-cause mortality is a longstanding epidemiological marker of the severity of seasonal influenza.[2] Ashley and colleagues,[6] from the UK's Office for Population Censuses and Surveys (now the Office for National Statistics), published in a peer-reviewed journal. They listed the main causes of death from random sampling one in 15 death certificates during the severe 1989-90 influenza epidemic. Eight deaths in pregnancy were found, compared with two in a similar 1985-86 sample, suggesting an excess 90 maternal deaths (8×15-2×15). Ács and colleagues[7] used records and patient recall to classify maternal influenza-like illness. It is important to note that this study, as well as others investigating prevalence of serological infection[8] or hospital admission rates,[3,4,9,10] were insufficiently powered to examine maternal mortality rates during seasonal influenza. Database cohorts are limited to easily measured outcomes usually without virological confirmation. We commented on two 5-6-year observational studies,[9,10] one having low influenza-attributed admission rates,[10] showing no benefit from maternal vaccination against medically attended in-

fluenza-like illness in infants. The study authors noted limitations including insufficient power,[9,10] residual confounding, non-specific outcomes, and study years including mild influenza seasons.[9] Randomised controlled trials (RCTs) provide evidence robust to both known and unknown confounders. Zaman and colleagues'[11] RCT published in *The New England Journal of Medicine* indicated a vaccine effectiveness in the third trimester of 63% (95% CI: 5-85%) against laboratory-confirmed febrile influenza illness in infants, and 36% (95% CI: 4-57%) against maternal febrile respiratory illness. The control arm appropriately received polysaccharide pneumococcal vaccine, which might even have reduced their risk of pneumonia. Influenza-related morbidity rates in this trial are not unique to low-income settings.[12]

Munoz and co-workers[13] found no increased risk of hospital admission for respiratory illness in infants of vaccinated mothers. The higher antenatal proportions of transient hypertension (not pre-eclampsia), abnormal glucose tolerance tests, and infections (mostly streptococcal B) were not related to timing of maternal vaccination. Pregnancy outcomes did not differ between non-vaccinated and vaccinated women. From table 5,[13] based on one infant case in non-vaccinated, and two cases in vaccinated mothers, Ayoub and Yazbak calculated a 7.3-fold risk for pyloric stenosis, but without adjustment for confounders or providing 95% CI (0.68-81.86) indicating compatibility with chance.

From Heinonen and colleagues' study,[14] Ayoub and Yazbak cited relative risks of specific malformations standardised for hospital (ie, unadjusted for confounding), whereas Heinonen and colleagues provided adjusted relative risks (ARRs) for confounders indicating no association between influenza vaccination in the first 4 months of pregnancy and any malformation (ARR 0.89, 95% CI: 0.61-1.32) or organ-system specific malformations.[14] As multiple comparisons were made and based on few cases, chance findings can occur. Heinonen and co-workers considered statistical testing inappropriate, noting "the positive associations, even when striking, are uninterpretable without independent confirmatory evidence".[14] Heinonen and co-workers examined topical thiomersal antimicrobial, not a vaccine preservative, based on 60 exposed pregnant women and found no association with malformations in any trimester when ARRs were adjusted for confounding (ARR 3.13, 0.87-7.60).[14]

Newer evidence included in three comprehensive reviews[15-17] does not support a causal link between thiomersal in childhood vaccines and developmental toxicity. Furthermore, thiomersal-free inactivated influenza vaccines are now available in North America and Europe specifically for pregnant women and children, as a precautionary measure.[18] Ayoub and Yazbak cited a literature review prepared to support nomination to the National Toxicology Program (NTP) of the US Department of Health and Human Services.[19] The NTP made no classifications or conclusions regarding teratogenicity of thiomersal. Information on denominators, confounders, and levels of ascertainment are needed to assess data from passive reporting systems such as the US Vaccine Adverse Event Reporting System.[20]

The current evidence base does not indicate any serious risk from maternal influenza vaccination. We have recommended robust surveillance and research that includes virologically confirmed outcomes, to monitor safety and effectiveness where influenza immunisation is routinely recommended in pregnancy.

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12 Acknowledgements

Unwavering support from my partner and friends sustained and reminded me at crucial moments the basic "why" for practising medicine and then later pursuing research in international health with a base in Switzerland. It is possible to return stronger from the bourn of an undiscover'd country if one does not travel alone.

The dissertation was completed under the aegis of Marcel Tanner, whom I sincerely thank for his academic provision and sharing many insights from his boundless views. My gratitude is also to Don and Jenny de Savigny for their kind hospitality and wide-ranging discussions and to Jennifer Keiser for her steady support and collegiality. Many thanks to Jürg Utzinger, Penelope Vounatsou, Ingrid Felger, Christoph Hatz, Thomas Smith, Jakob Zinsstag, and Hanspeter Marti for fruitful discussions. Christine Mensch gave me tremendous support, as well as Christine Walliser, Marianne Hess, and Margrit Slaoui, considering personal welfare well beyond administrative issues.

There are many roads one might take in academia and I drew inspiration from certain paths. My thanks to Punam Mangtani for scientific rigour and integrity, Dina Pfeifer and Meenakshi Dawar for ideals and straight shooting, Anneke Hesseling for motivation and collaboration. *Sine qua non.* This applies also to fine memories and proofs of concept with Melissa Penny, Lena Fiebig, Leonore Lovis and Eric Grüter. Hearty thanks to Laura and Dominic Gosoniu, Joshua Yukich, Bianca Plüss, Mwifadhi Mrisho, Susan Rumisha, Andri Christen, Gonzalo Durán Pacheco, Jan Hattendorf, Amanda Ross, Ricarda Windisch, Claudia Sauerborn, Nafomon Sogoba, Daniel Weibel, Stefan Dongus, Constanze Pfeiffer, Karin Gross, Ellen Stamhuis, and Jennifer Saurina for their camaraderie. I am sure to have missed officemates unintentionally. P.S. long live WIB co-inspirators.

In addition I thank all collaborators for the opportunity in 2006 and 2007 to design and conduct community-based studies first hand in a new north-south collaboration with Lao PDR on the clinical epidemiology of helminth infections, providing me strong insights into a wide range of research practices. In Switzerland the project was under Peter Odermatt and supported by Jürg Utzinger, Jennifer Keiser, Christoph Hatz, and Penelope Vounatsou. Leonore Lovis joined the field in 2007 and my sincerest thanks to her for

robust scientific methods and surmounting many challenges. Barbara Matthys, Peter Steinmann, Julie Balen, Stefanie Knopp and Guojing Yang kindly shared tips with me on running field studies. In Lao PDR, the project was under Kongsap Akkhavong and ultrasonography by Oroth Rasphone. Many memorable months were spent in rural villages with them and physicians who started dissertations at the institute: Khampheng Phongluxa, Somphou Sayasone, Phonepasong Soukhathammavong, Monely Vanmany, and Youthanavanh Vonghachack. Lasting memories include the patients who presented at our open medical clinic, the sinh-ful baths daily in the Mekong, generator repairs and potholes, the visit of Susie and Marcel Tanner with members of the Swiss Rotary Club, and the many festivals. My final word of thanks must go to the hundreds of Laotians who agreed to participate in these studies. Their trust and hospitality during our stays are not forgotten.

The PhD commenced on 3 January 2006. The dissertation was submitted on 24 November 2008 and defended on 2 February 2009.

Members of the PhD Committee: Marcel Tanner (supervisor), Paul-Henri Lambert, Punam Mangtani, Dina Pfeifer, and David Schellenberg; Chaired by Gerd Pluschke.

Funding

Financial support is gratefully acknowledged. Funding was provided by the Swiss National Science Foundation and the Swiss Agency for Development and Cooperation (Project No. 110020), the University of Basel and the Swiss School of Public Health+.