

Non- specific effects of vaccines

Systematic Reviews Protocols

A Reingold --- PI , Epidemiology review

A Pollard -- PI, Immunological review

Two systematic reviews

EPIDEMIOLOGICAL STUDIES

Evidence available to document magnitude of any effect

IMMUNOLOGICAL STUDIES

Evidence available for non-specific immunological effects



EPIDEMIOLOGICAL STUDIES SYSTEMATIC REVIEW

Objective of the epidemiological studies systematic review

systematically identify, assemble, and critically appraise the evidence

(all published and grey literature)

“non-specific” effects of vaccines

on mortality unrelated to prevention of illness & deaths caused by the specific diseases against which the vaccines have been formulated

BCG, DTP & standard titre measles containing vaccines

Non-specific effects of vaccines

C = (A - B) =
deaths
from
infections
other
than...

A = All cause mortality

**B = Disease
specific
mortality**

Primary question = C ---- *this really documents the non-specific effects**
Secondary question = A ---- *this includes the disease specific and the potential non-specific effects*

** Vaccines may have “non-specific” effects on mortality unrelated to prevention of illness and deaths caused by the specific diseases against which the vaccines have been formulated*

Primary questions

- A. Is the administration of BCG in infancy associated with an effect on survival /deaths from conditions other than those conditions that the vaccine is designed to prevent in children up to five years of age?
- B. Is the administration of DTP in infancy associated with an effect on survival/deaths from conditions other than those conditions that the vaccine is designed to prevent in children up to five years of age?
- C. Is the administration of Measles in infancy associated with an effect on survival/ deaths from conditions other than those conditions that the vaccine is designed to prevent in children up to five years of age?

Secondary questions

- A. Is administration or non-administration of BCG vaccine in infancy associated with an effect on all-cause mortality/deaths from all causes in children up to five years of age?
- B. Is administration or non-administration of DTP-containing vaccine in infancy associated with an effect on all-cause mortality/deaths from all causes in children up to five years of age?
- C. Is administration or non-administration of measles-containing vaccine in infancy associated with an effect on all-cause mortality/deaths from all causes in children up to five years of age?

SECONDARY QUESTIONS

Vaccines

BCG

Measles

DTP

Is receipt or non-receipt of vaccine
X associated with an effect on
survival / all-cause mortality / deaths
from all causes in children up to five
years of age?

X

X

X

Is there a difference of the effect (e.g.)

between boys and girls

X

X

X

if the DTP vaccine is given after, with or, as the
last vaccine dose?

X

X

X

if the vaccine is co-administered with Vit A?

X

X

X

Inclusion criteria - study design

RCT or quasi-randomized controlled trials

Observational epidemiological studies

- case-control studies
- cohort studies

✗ Excluded: Ecological studies, Uncontrolled studies, animal or laboratory studies, studies including only individuals with the outcome of interest in the analyses (“case only” studies)

P children up to 5 years

I vaccination with BCG, DTP or measles
(as recommended by WHO)

C no vaccination (BCG, DTP or measles)
(or vaccination "out of sequence")

O death from all-causes, all-cause
mortality, child survival

Search Strategy

Article databases: Medline and Embase (in Embase.com), the Cochrane Library, African Index Medicus (AIM), the Indian Medlars Centre (IndMed), Latin American and Caribbean Health Sciences (LILACs), Current Controlled Trials metaRegister of Controlled Trials (mRCT, active and archived registers), UK Clinical Trials Gateway (UKCTG), US Food and Drug Administration (FDA), European Public Assessment Report (EPAR), listings of the European Medicines Agency (EMA), WHO International Clinical Trials Registry Platform Search Portal (includes: ClinicalTrials.gov, International Standard Randomized Controlled Trial Number Register (ISRCTN), and clinical trial registries of Australia, China, Germany, India, Iran, The Netherlands, New Zealand, Sri Lanka), GSK Clinical Study Register, and Clinicalstudyresults.org (includes Wyeth trial listings).

Grey Literature: unpublished study reports, conference proceedings (e.g. EMBASE and Scopus) and posters, dissertations and theses (if possible), Web search engines (i.e. Google Scholar)

Manual searches: bibliographies of relevant previous reviews and the reference lists of all articles found to identify studies not identified through the databases listed above.

We will also:

hand search content of www.indepth-network.org & www.optimunize.org

[contact experts in the field](#) and authors to ask for other publications or studies that might fit our selection criteria.

**"Observational
studies are vulnerable
to bias"**

Report of Systematic Review

Summary of the evidence

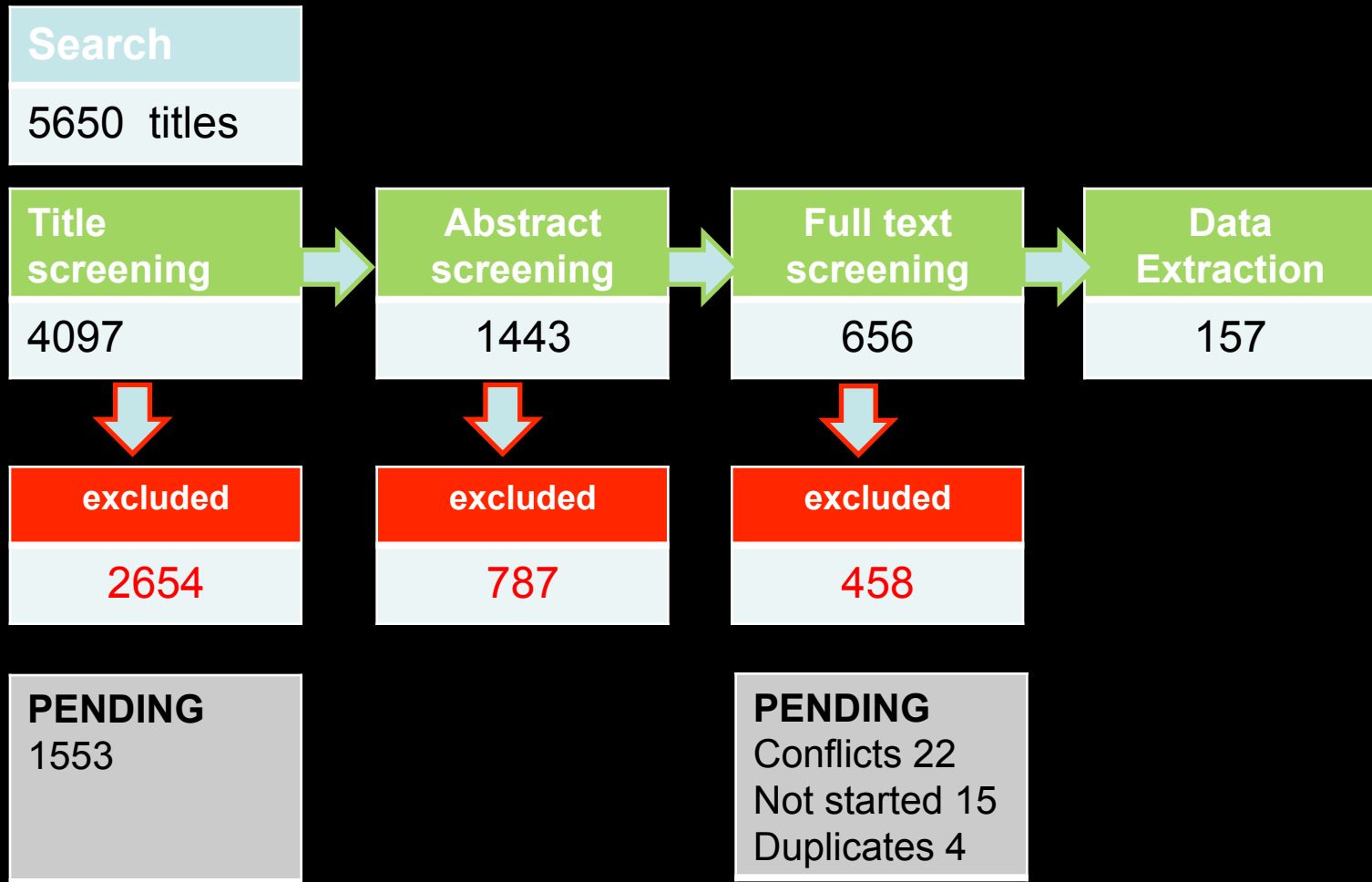
using SAGE guidelines,
tables, forest plots, figures

Assessment of risk of bias of included studies

RCTs – Cochrane tool

Observational studies – New tool

Screening process





IMMUNOLOGICAL STUDIES SYSTEMATIC REVIEW

Aim of the immunological studies review

- To systematically review available evidence
- To see if there is evidence of a biological mechanism to explain the proposed non-specific effects of vaccines on mortality
- To determine if current evidence is sufficiently compelling to warrant further investigation

Vaccines under review: BCG, measles & DTP

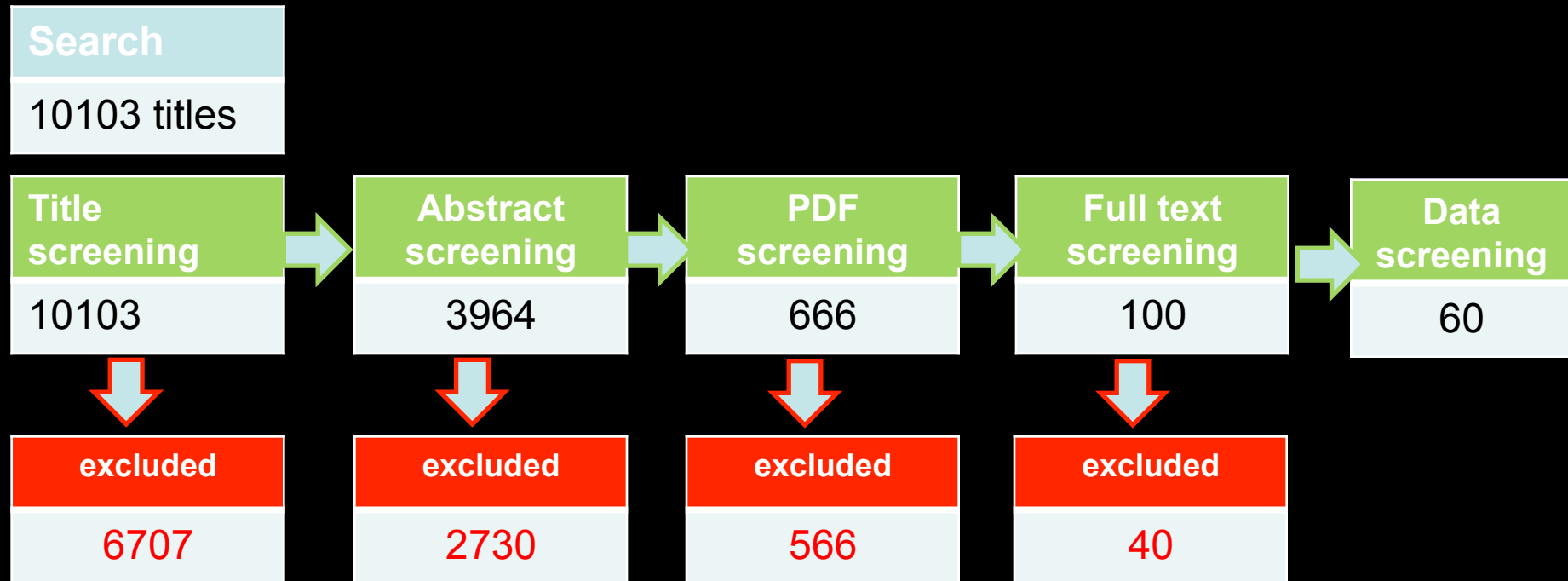
- Primary questions:
 - What is the effect of any of the vaccines under review given before 5 years of age on all available immune response markers in a non specific way?
 - If, in infancy, one of the vaccines under review is given first, does that effect the antibody response to a second different vaccine?

- Secondary questions:
 - Do the effects on immune response markers, if any, of any of the vaccines under review vary by sex of the child?
 - Do the effects on immune response markers, if any, of any of the vaccines under review vary by age at which they are delivered?
 - Do the effects on immune response markers, if any, of any of the vaccines under review vary by co-administration of Vitamin A?
 - Do the effects on immune response markers, if any, of any of the vaccines under review vary by co-administration of a second different vaccine?

Search strategy

- BCG vaccine OR measles vaccine OR DTP vaccine
- AND
- All available immune response markers
- Thorough search: Embase.com
- Complementary search: Pubmed, Cochrane and Trip database

Screening process



Comments by the WG to date

EPIDEMIOLOGY REVIEW

- Inclusion of high titer measles vaccine ?
- Review on non specific effects on morbidity outcomes ?
- Availability of data on effect on survival from conditions other than those conditions that the vaccine is designed to prevent vs all cause mortality ?
- Whether use of risk of bias assessment would "threaten" conclusions ?

Comments by the WG to date

IMMUNOLOGY REVIEW

- Inclusion of animal studies ?
- Broadening of immunological markers under assessment ?
- Inclusion of other vaccines ?
- Include other age groups?

POLICY QUESTION

Are the current data on
effect of vaccine X on
all-cause mortality
compelling enough to demand
further careful investigation?

PROCESS

**Systematic Review
process**

**SAGE
Working Group**

**Protocols + tools
development**

**Data extraction
(+ checking with PIs)**

**Quality + risk of
bias assessment**

Analysis

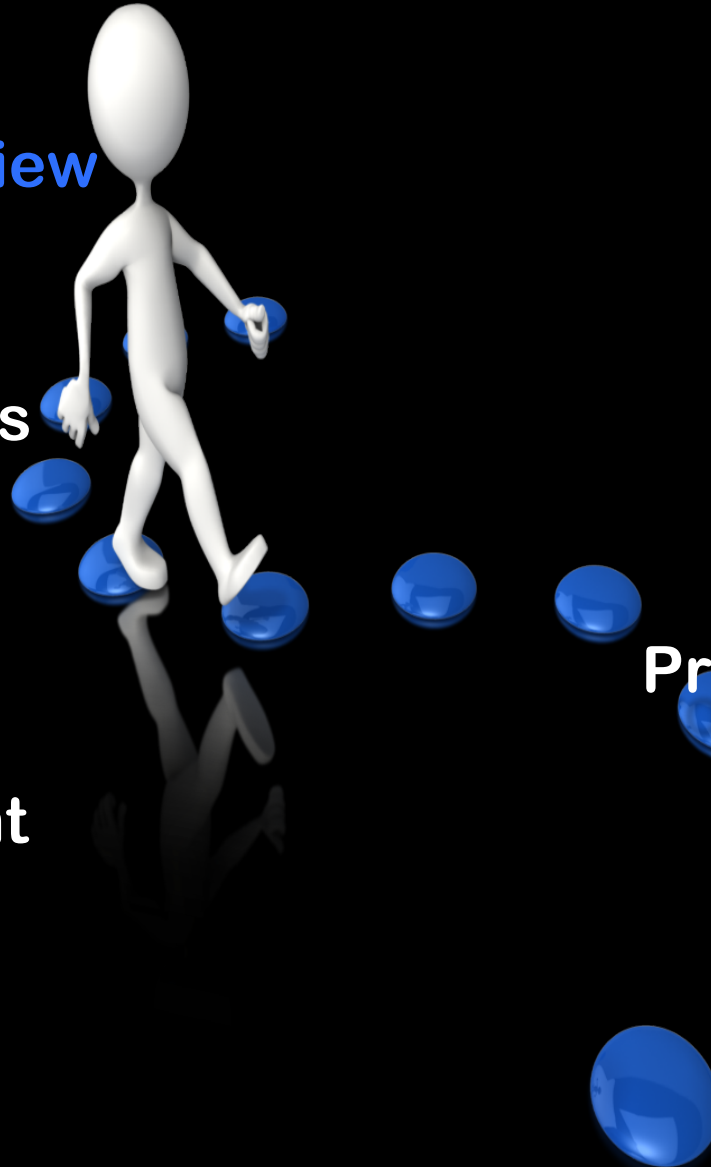
Report to WG

Questions for SAGE

**Protocol + tools review
Review of first draft**

Final report review

Report to SAGE

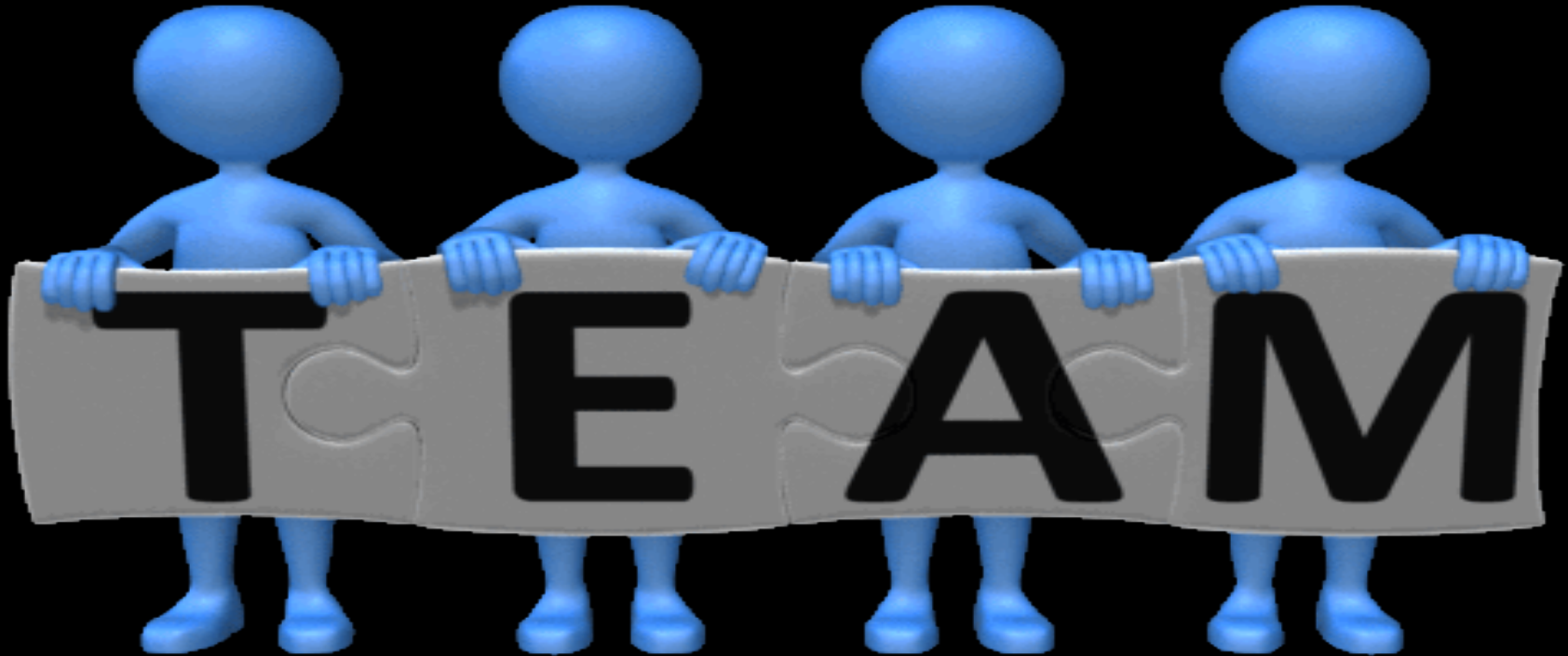


**Content
experts**

**Methods
experts**

**Systematic
Review experts**

**SAGE WG
Secretariat**



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Dr K Soares, Enhanced Reviews

SAGE WG on NSE
WHO Secretariat,
AM Henao & Ximena Laurie



Suggestions regarding the systematic review ?

Other analysis that could be relevant to NSE?

Advice on data/info that could be useful?

Backup slides (1/2)

Immunological terms included in the Embase search

Activins OR 'cytokine'/exp OR activin OR 'adipocytokines' OR 'adipokine' OR 'adipokines' OR 'adipose tissue derived cytokine' OR 'Acrp 30' OR 'Acrp30' OR 'adipocyte complement related protein 30' OR 'adipocyte most abundant protein 1' OR 'adipoq' OR 'APM 1' OR 'APM1' OR 'GBP 28' OR 'GBP28' OR 'gelatin binding protein 28' OR 'AIF 1' OR 'AIF1' OR 'cytokine AIF 1' OR 'cytokine AIF1' OR 'daintain' OR 'a proliferation inducing ligand' OR 'a proliferation inducing ligand protein' OR 'antigen CD256' OR 'CD256 antigen' OR 'protein APRIL' OR 'protein TALL2' OR 'protein TNFSF 13' OR 'protein TNFSF13' OR 'TALL 2 protein' OR 'TALL2 protein' OR 'TNF and ApoL related leukocyte expressed ligand 2' OR 'TNF related death ligand 1' OR 'TNFSF 13 protein' OR 'TNFSF13 protein' OR 'tumor necrosis factor and apolipoprotein related leukocyte expressed ligand 2' OR 'tumor necrosis factor ligand superfamily member 13' OR 'tumor necrosis factor related death ligand 1' OR 'tumor necrosis factor SF13' OR 'tumor necrosis factor superfamily member 13' OR 'B lymphocyte activating factor [134-285]' OR 'B lymphocyte stimulator [134-285]' OR 'ATX protein' OR 'ectonucleotide pyrophosphatase phosphodiesterase 2' OR 'ENPP2 protein' OR 'PDNP2 protein' OR 'protein ATX' OR 'protein ENPP2' OR 'protein PDNP2' OR 'antigen CD257' OR 'B-cell activating factor' OR 'B cell activation factor' OR 'B lymphocyte activating factor' OR 'B lymphocyte stimulator' OR 'B lymphocyte stimulator protein' OR 'BAFF' OR 'BLyS protein' OR 'CD257 antigen' OR 'protein BLyS' OR 'protein TALL 1' OR 'protein TALL1' OR 'protein TNFSF13B' OR 'TALL 1 protein' OR 'TALL1 protein' OR 'TNF and ApoL related leukocyte expressed ligand 1' OR 'TNFSF13B protein' OR 'tumor necrosis factor and apolipoprotein related leukocyte expressed ligand 1' OR 'tumor necrosis factor ligand superfamily member 13B' OR 'B cell differentiation factor' OR 'bcd' OR 'B cell growth factor' OR 'bcgf' OR 'growth factor, b cell' OR 'bone morphogenetic proteins' OR 'bone morphogenic protein' OR 'BMP 12' OR 'BMP12' OR 'cartilage derived morphogenetic protein 3' OR 'CDMP 3' OR 'CDMP3' OR 'GDF 7' OR 'GDF7' OR 'growth and differentiation factor 7' OR 'growth differentiation factor 7' OR 'BMP 15' OR 'BMP15' OR 'GDF 9B' OR 'GDF9B' OR 'growth and differentiation factor 9B' OR 'growth differentiation factor 9B' OR 'BMP 2' OR 'BMP2' OR 'BMP 4' OR 'BMP4' OR 'BMP 5' OR 'BMP5' OR 'BMP 6' OR 'BMP6' OR 'BMP 9' OR 'BMP9' OR 'GDF 2' OR 'GDF2' OR 'growth and differentiation factor 2' OR 'growth differentiation factor 2' OR '4-1BB ligand' OR '4 1BB ligand' OR '4 1BBL protein' OR 'CD137L' OR 'ligand 4 1BB' OR 'protein 4 1BBL' OR 'antigen CD153' OR 'CD153 antigen' OR 'CD153 antigens' OR 'CD30L' OR 'protein TNFSF 8' OR 'protein TNFSF8' OR 'TNFSF 8 protein' OR 'TNFSF8 protein' OR 'tumor necrosis factor ligand superfamily member 8' OR 'tumor necrosis factor superfamily member 8' OR 'antigen CD154' OR 'CD154 antigen' OR 'CD40L' OR 'CD40L antigen' OR 'protein TNFSF 5' OR 'protein TNFSF5' OR 'TNFSF 5 protein' OR 'TNFSF5 protein' OR 'tumor necrosis factor ligand superfamily member 5' OR 'tumor necrosis factor superfamily member 5' OR 'antigen cd70' OR 'antigens, CD70' OR 'CD27 ligand' OR 'CD27L' OR 'CD70 antigens' OR 'colony-stimulating factors' OR 'colony stimulating activity' OR

Backup slides (2/2)

' colony stimulating factors' OR 'fibroblast derived differentiation inducing factor' OR 'ectodermal dysplasia protein' OR 'ectodysplasin 1' OR 'ectodysplasins' OR 'EDA A protein' OR 'EDA protein' OR 'protein EDA' OR 'protein EDA A' OR 'am 424' OR 'am424' OR 'recombinant human leukemia inhibitory factor' OR 'recombinant leukemia inhibitory factor' OR 'EMAP II' OR 'endothelial monocyte activating polypeptide 2' OR 'antigen CD178' OR 'CD178 antigen' OR 'CD95 ligand' OR 'CD95L' OR 'CD95L protein' OR 'Fas antigen ligand' OR 'Fas ligand protein' OR 'FasL protein' OR 'protein CD95L' OR 'protein FasL' OR 'protein TNFSF 6' OR 'protein TNFSF6' OR 'TNF superfamily member 6' OR 'TNFSF 6 protein' OR 'TNFSF6 protein' OR 'tumor necrosis factor ligand superfamily member 6' OR 'fibroblast growth factors' OR 'fibroblast stimulating factor' OR 'heparin binding growth factor' OR 'fgf 1' OR 'FGF1' OR 'fgf 10' OR 'FGF10' OR 'fgf 14' OR 'FGF14' OR 'fgf 16' OR 'FGF16' OR 'fgf 18' OR 'FGF18' OR 'fgf 19' OR 'FGF19' OR 'fgf2' OR 'FGF 2' OR 'fgf21' OR 'FGF 21' OR 'fgf23' OR 'FGF 23' OR 'fgf3' OR 'FGF 3' OR 'fgf4' OR 'FGF 4' OR 'fgf5' OR 'FGF 5' OR 'fgf6' OR 'FGF 6' OR 'fgf8' OR 'FGF 8' OR 'fgf9' OR 'FGF 9' OR 'interleukin' OR 'interleukins' OR 'il 1' OR 'il 2' OR 'il 4' OR 'il 5' OR 'il 6' OR 'il 9' OR 'il 10' OR 'il 12' OR 'il 13' OR 'il 17' OR 'il 23' OR 'interferon' OR 'helper cell type 1' OR 'T helper 1' OR 'T helper type 1' OR 'Th1 cells' OR 'helper cell type 2' OR 'T helper 2' OR 'T helper type 2' OR 'Th2 cells' OR 'helper cell/exp OR 't helper' OR 'B lymphocyte/exp OR 'B-lymphocyte subsets' OR 'B-lymphocytes' OR 'b-lymphocytes, regulatory' OR 'B cell' OR 'bone marrow derived lymphocyte' OR 'bone marrow lymphocyte' OR 'bursa derived lymphocyte' OR 'lymphocyte, b' OR 'lymphocyte, bone marrow derived' OR 'lymphocyte, bursa derived' OR 'regulatory B lymphocyte' OR 'antibody-producing cells' OR 'antibody forming cell' OR 'antibody producing cell' OR 'immunoglobulin forming cell' OR 'B memory cell' OR 'B memory cells' OR 'B memory lymphocyte' OR 'B memory lymphocytes' OR 'memory B cell' OR 'memory B cells' OR 'memory B lymphocyte' OR 'memory B lymphocytes' OR 'cell, plasma' OR 'flamed plasma cell' OR 'flamed plasmacell' OR 'plasma cells' OR 'plasmacyte' OR 'plasmatocyte' OR 'plasmocyte' OR 'plasmocyte, flamed' OR 'B cell precursor' OR 'B cell precursors' OR 'B cell progenitor' OR 'B cell progenitors' OR 'B lineage precursor' OR 'B lineage precursors' OR 'B lineage progenitor' OR 'B lineage progenitors' OR 'B lymphocyte precursor' OR 'B lymphocyte progenitor' OR 'B lymphocyte progenitors' OR 'B lymphoid precursor cell' OR 'B lymphoid precursor cells' OR 'B lymphoid progenitor' OR 'B lymphoid progenitors' OR 'B precursor' OR 'B precursors' OR 'B progenitor' OR 'B progenitors' OR 'cell, pre B' OR 'immature B cell' OR 'immature B cells' OR 'pre B cell' OR 'pre B cells' OR 'precursor B cell' OR 'precursor B cells' OR 'precursor B lymphocyte' OR 'precursor B lymphocytes' OR 'precursor cells, B-lymphoid' OR 'precursor cells, B lymphoid' OR 'pro-B cell' OR 'pro-B cells' OR 'progenitor B cell' OR 'progenitor B cells' OR 'transitional B cell' OR 'transitional B cells' OR " tumor necrosis factor receptor 1"/exp OR " tumor necrosis factor receptor 1 " OR " CD120a antigen" OR " receptors, tumor necrosis factor, type I" OR " tumor necrosis factor receptor type 1" OR " tumor necrosis factor receptor type I" OR 'dendritic cell/exp OR 'dendritic cells' OR 'dendritic cell' OR 'langerhans cell' OR 'langerhans cells' OR 'T lymphocyte/exp OR 'amplifier t lymphocyte' OR 'lymphocyte, thymus' OR 'T-lymphocytes' OR 't-lymphocytes, suppressor-inducer' OR 'T cell' OR 'T cells' OR 'thymic lymphocyte' OR 'thymus dependant lymphocyte' OR 'thymus dependent cell' OR 'thymus dependent lymphocyte' OR 'thymus derived cell' OR 'thymus derived lymphocyte' OR 'thymus lymphocyte'