



Monitoring Benefits and Risks of vaccines: the **ADVANCE/VAC4EU** ecosystem

Prof. Dr. Miriam CJM Sturkenboom, Julius Global Health

Vaccine preventable
diseases we have
almost forgotten



Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomsor, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associated by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12 children had intestinal abnormalities ranging from lymphoid nodular hyperplasia to pseudo-ulceration. Histology showed patchy chronic inflammation in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (two). There were no focal neurological abnormalities and EEG tests were normal. Amino-acid laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls (mean 1.3), low haemoglobin in four children, and low serum IgA in eight children.

Interpretation We identified associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time to possible environmental triggers.

Lancet 1998; **351**: 637–41

See Commentary page

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Introduction

We saw several children who, after a period of apparent normality, lost acquired skills, including communication. They all had gastrointestinal symptoms, including abdominal pain, diarrhoea, and vomiting and, in some cases, food intolerance. We describe the clinical findings, and gastrointestinal features of these children.

Patients and methods

12 children, consecutively referred to the department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms (abdominal pain, bloating and food intolerance) were investigated. All children were admitted to the ward for a week, accompanied by their parents.

Clinical investigations

Medical history, including details of immunisations and exposure to infectious diseases, and assessed the children. In 11 cases the history was obtained by the senior clinician (JW-S). Neurological and psychiatric assessments were done by consultant staff (PH, MB) with HMs-4 criteria.¹ Developmental records included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MA1 under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum, ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.² Chromatograms were scanned digitally on computers, to analyse the methylmalonic-acid zones from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample *t* test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for antidiomyces antibodies and boys were screened for fragile-X if this had not been done

MMR Vaccine safety scare based on false evidence, but with major impact

MMR uptake statistics

November 2012

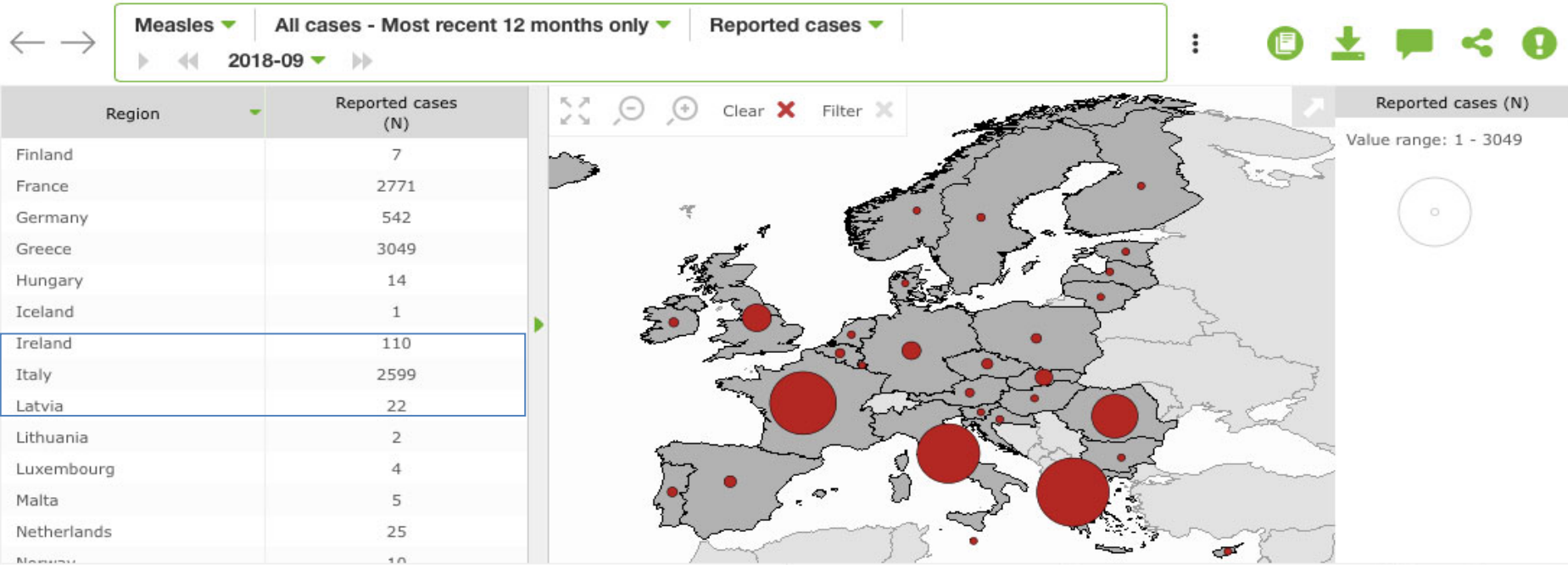


Above: MMR % coverage in England at 24 months, 1992-93 to 2011-12. Source: Health Protection Agency

Lack of proper evidence leads to hesitancy Impact of vaccine hesitancy: measles outbreaks



Surveillance Atlas of Infectious Diseases



How to increase coverage/trust

[Home](#) / [India news](#) / [Punjab government cracks down on rumour-mongers for spreading misinformation on](#)

Punjab government cracks down on rumour-mongers for spreading misinformation on Measles-Rubella vaccination campaign

The Government of Punjab is all set to act against the people who have allegedly been spreading false information against the ongoing vaccine drive in the state.

By: [FE Online](#) | New Delhi | Published: May 4, 2018 4:10 PM

[News](#) › [World](#) › [Europe](#)

France to make vaccination mandatory from 2018 as it is 'unacceptable children are still dying of measles'

Move follows similar initiative in Italy, where non-vaccinated children cannot attend state schools

[Katie Forster](#) Health Correspondent | [@katieforster](#) | Wednesday 5 July 2017 09:52 BST | [178 comments](#)

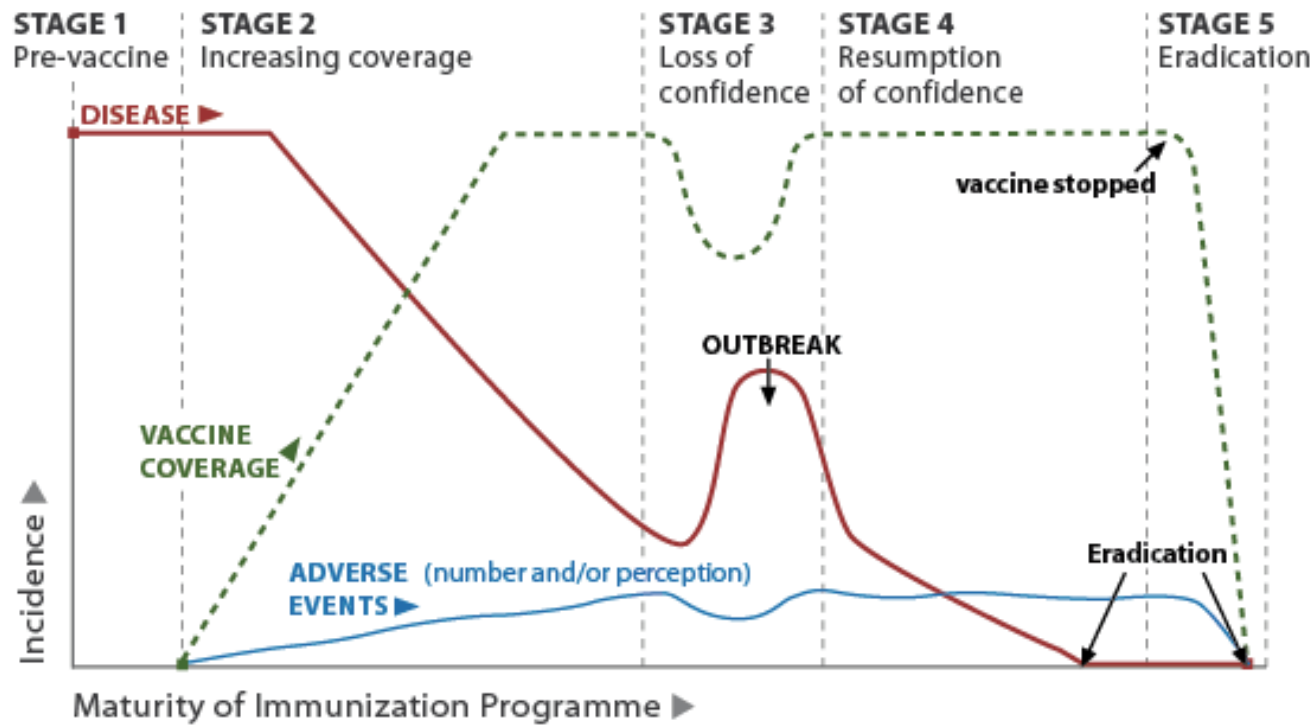
[News](#) › [World](#) › [Europe](#)

Italy makes 12 vaccines mandatory for school children in an attempt to combat 'anti-scientific theories'

New measures follow intense public debate sparked by measles outbreak

[Associated Press](#) | Saturday 20 May 2017 10:28 BST | [37 comments](#)

What can we expect in vaccination programs?



DOCTORS AND CITIZENS NEED TO RAPIDLY HAVE RELIABLE EVIDENCE ALSO ON SAFETY: EXAMPLE



**Lessons learned on H1N1 pandemic in 2009 led to
Accelerated Development of VAccine beNefit-risk
Collaboration in Europe**

www.advance-vaccines.eu
2012- March 2019





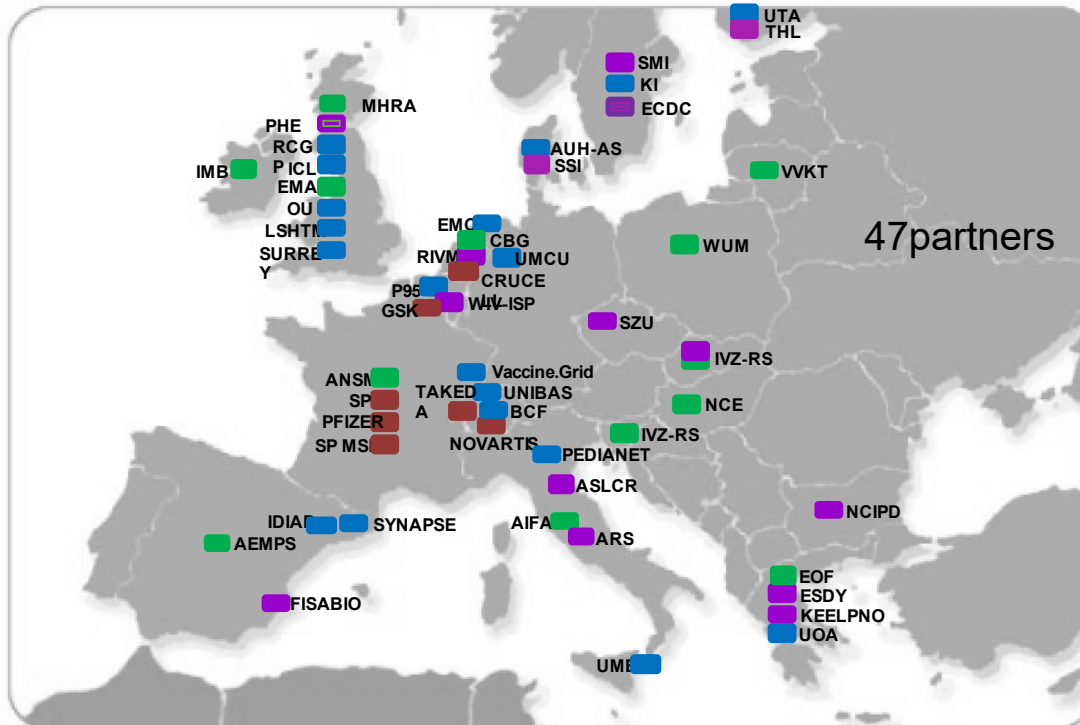
ADVANCE

VISION & MISSION

- “Best evidence at the right time to support decision-making on vaccination in Europe.”
- Based on secondary use of existing ‘big’ health data
- Stimulating collaboration between different stakeholders
- Requirements: Timely, Robust



ADVANCE ADVANCE is a European Partnership



47 partners across 19 European countries:

EMA and ECDC;
16 public research institutions;
9 national public health organisations;
8 national drug regulatory agencies,
7 vaccine manufacturers;
3 small medium enterprises
2 charities.

Coordination team:

Miriam Sturkenboom, Vincent Bauchau, Patrick Mahy, Eva Molero

WP leaders:

WP1: Xavier Kurz, Vincent Bauchau
WP2 Jorgen Bauwens, Mendel Haag
WP3: Simon de Lusignan, Alena Khromava,
WP4: Kaatje Bollaerts, John Weil,
WP5: Miriam Sturkenboom, Lina Titievsky,
WP6: Eva Molero, Antonella Chiucchiuini,
WP7: Piotr Kramarz

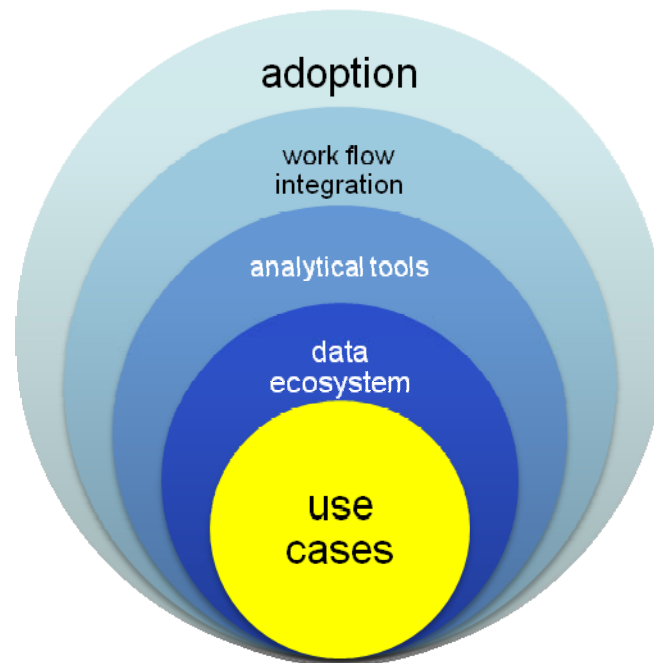


www.advance-vaccines.eu

Stepwise approach towards using Big Data



Universitair Medisch Centrum
Utrecht



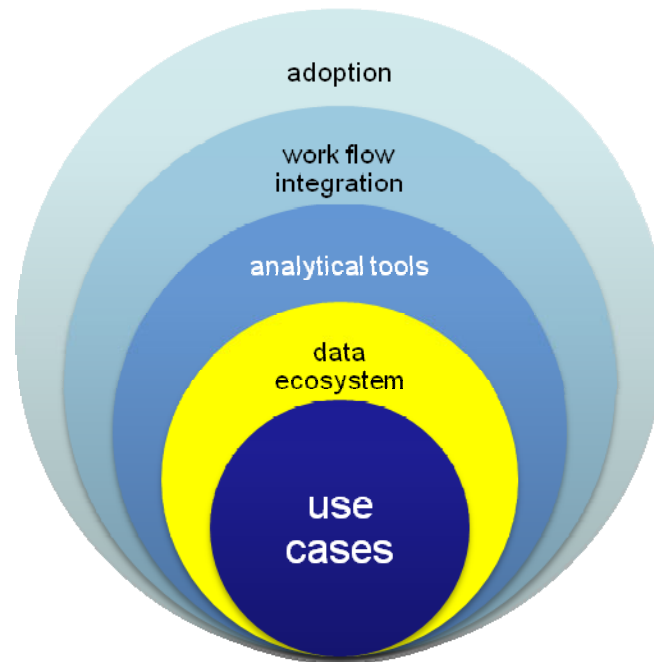


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WHAT EVIDENCE SHOULD THE ECOSYSTEM GENERATE?

Background rates
Vaccine coverage /exposures
Benefits of vaccination (effectiveness/impact)
Safety information
Benefit-risk monitoring

Stepwise approach to successful evidence generation from Big Data: the data ecosystem





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WHAT TYPE OF DATASOURCES ARE AVAILABLE?

**Survey of databases:
25 databases response
100 M source population**

**ADVANCE system testing
19 databases, 8 countries
60 M source population**

**ADVANCE proof of concept
10 databases, 5 countries
40 M source population**



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ADVANCE DATA SOURCES N=19
IN CONSORTIUM

Type	Names	Countries	Outcomes
Disease surveillance	pediatric surveillance, GP surveillance, lab surveillance, OSIRIS	Belgium, Netherlands	Reported cases
Trial cohorts	HPV trial cohort Tampere	Finland	linkage to in-outpatient registries
General Practice	RCGP, THIN, BIFAP, SIDIAP, ARIANNA, IPCI, PEDIANET	UK, Spain, Italy, Netherlands	outpatient and reported inpatient Dx
Claims record linkage	Aarhus, SSI, ASL Cremona, ARS, Sweden	Denmark, Italy, Sweden	hospital discharge/ER

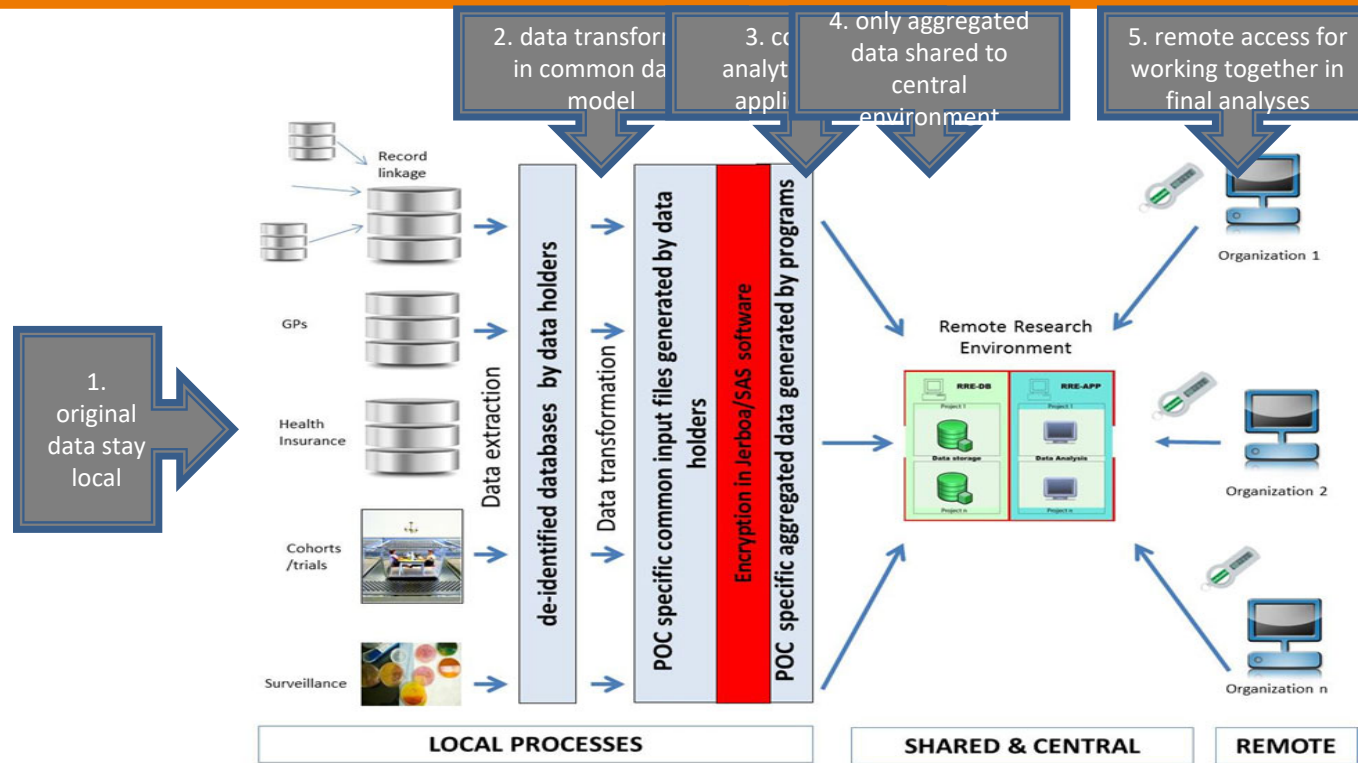


From Sturkenboom M. et al. *The ADVANCE distributed network system for evidence generation on vaccines coverage, benefits and risks based on electronic health care data*

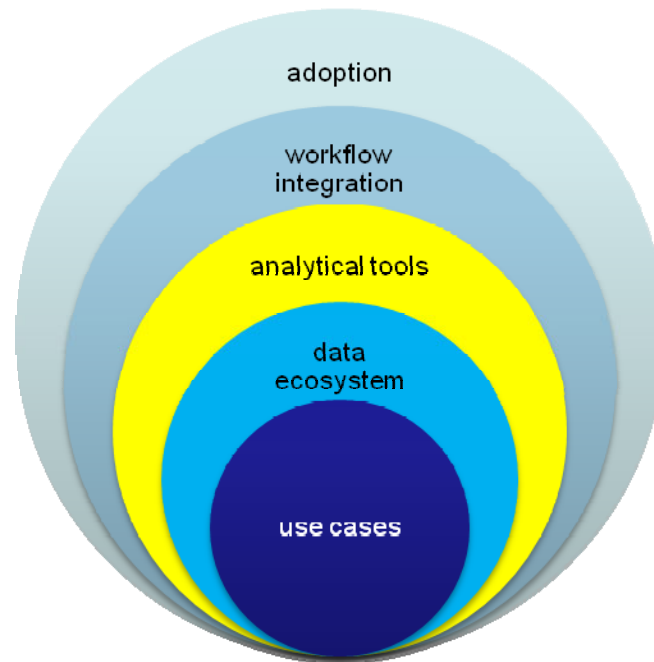


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HOW TO OPERATE THE ECOSYSTEM DISTRIBUTED DATASOURCES: 5 KEY PRINCIPLES



Stepwise approach to successful Big Data and Analytics integration- step 3; analytical tools





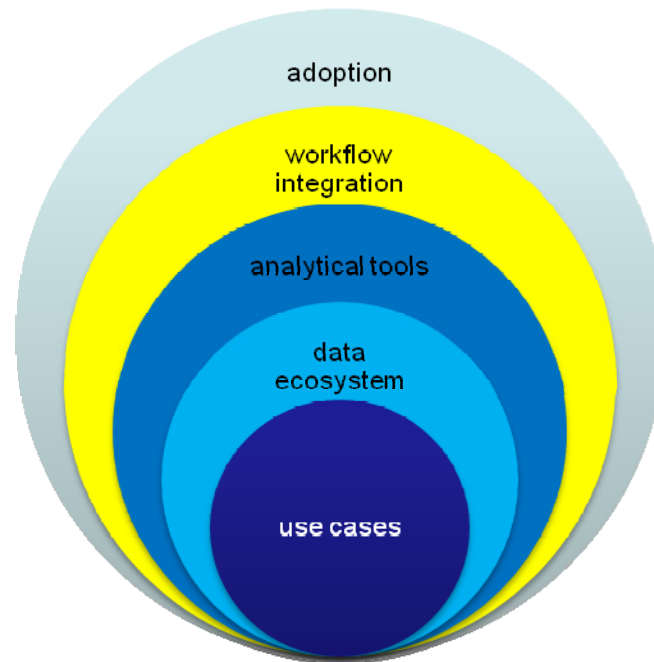
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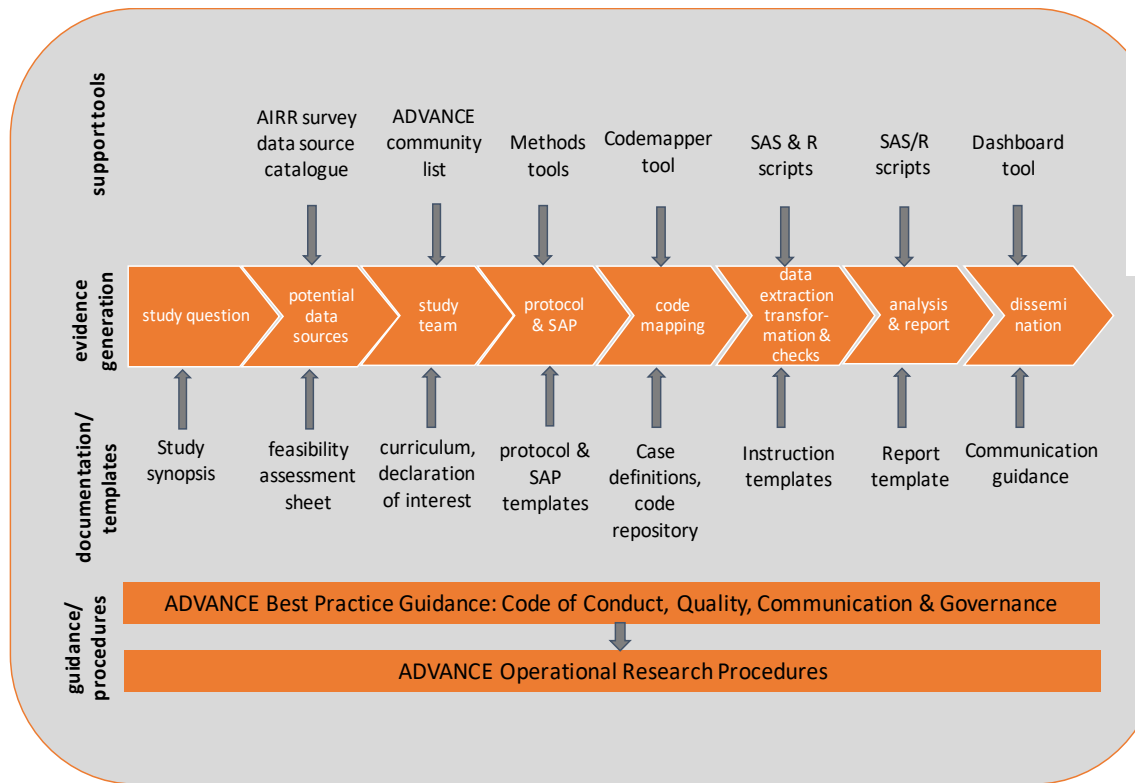
ANALYTICAL TOOLS OPEN SOURCE

- **Design tools**
 - Misclassification of benefit studies
- **Mapping disease codes & vaccines**
 - Codemapper
 - VaccO: vaccine ontology
- **Quality control**
 - Jerboa software (JAVA) for population & events
 - R package for vaccines
- **Data transformation for specific studies**
 - benefit, risk, coverage: double coded R & SAS
- **Dissemination**
 - Dashboard
 - reports

Tools and
deliverables available
on [www.advance-
vaccines.eu](http://www.advance-vaccines.eu)

Stepwise approach to successful Big Data and Analytics integration- step 4 workflow integration





Review
The ADVANCE Code of Conduct for collaborative vaccine studies
 Xavier Kurz ^{a,*,}, Vincent Bauchau ^{b,}, Patrick Mahy ^{c,}, Steffen Glismann ^{d,}, Lieke Maria van der Aa ^{e,}, François Simondon ^{e,}, for the ADVANCE consortium ¹

Best practice guidance required



ADVANCE

EXAMPLE RESULTS BENEFIT RISK MONITORING: DASHBOARD

- Near real-time monitoring of vaccination coverage, benefits, and risks using **electronic healthcare records through the ADVANCE workflow**
- <http://apps.p-95.com/pertussis-dev/>
 - May support health care professionals & regulators with vaccine monitoring

[dashboard](#)



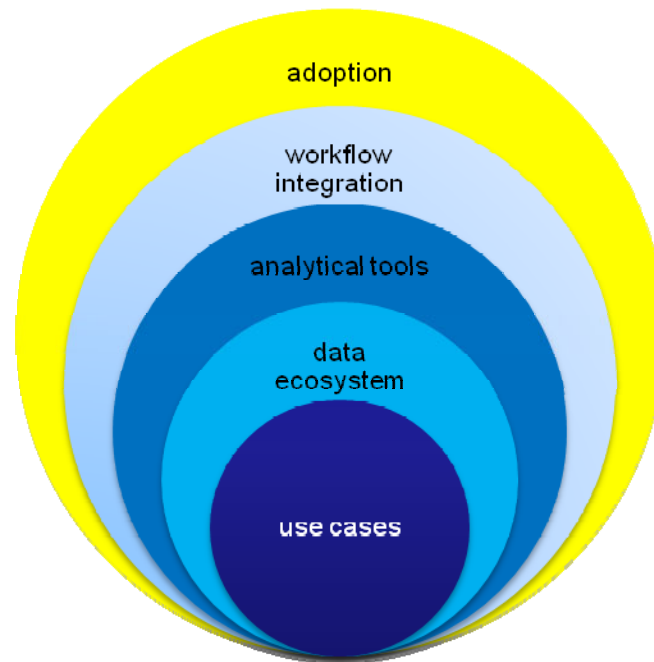
efpia



Stepwise approach to successful Big Data and Analytics integration: adoption



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ADVANCE Will ADVANCE ecosystem be adopted?

ADVANCE Project demonstrated successfully the feasibility to generate timely and robust evidence and generated a Blueprint for implementation (www.advance-vaccines.eu)

D7.7 Blueprint of a framework to rapidly provide scientific evidence on post-marketing vaccination benefits and risks for informed decisions

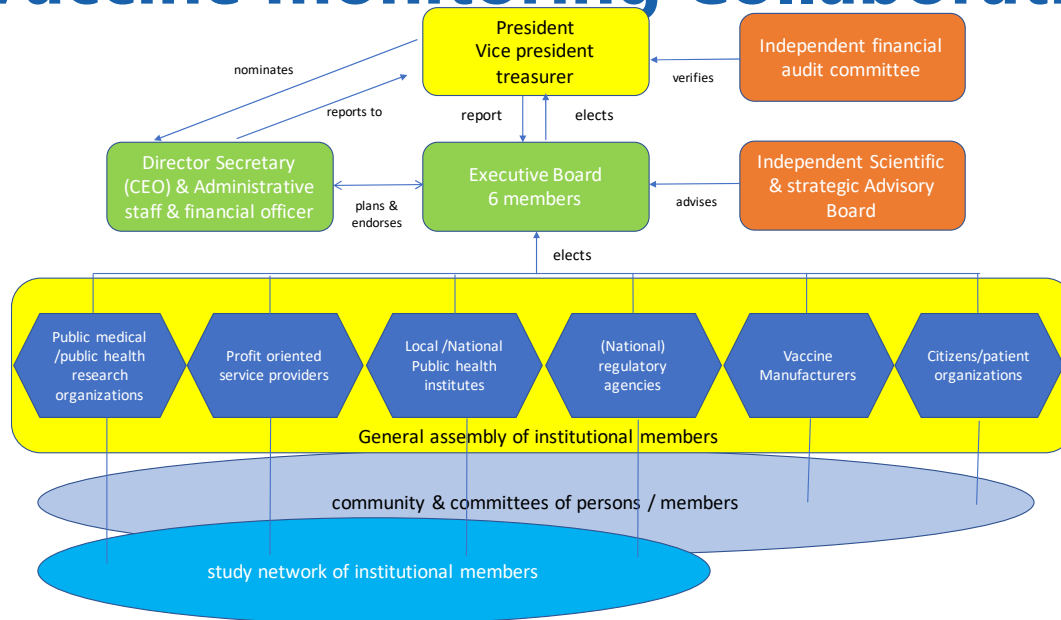
WP7 – Implementability analysis

V1.0
[Final]

Lead beneficiary: ECDC
Date: September 30, 2018
Nature: PU
Dissemination level: PU

All stakeholders agree that we should maintain the platform & hub to generate timely & robust vaccine evidence in Europe

Non-for profit international association in development: Vaccine monitoring Collaboration for Europe



VAC4EU

Legal status: VAC4EU will be a non-for profit international association.

Vision: Best actionable evidence on vaccine coverage, benefits and risks.

Mission: To provide the European largest possible trusted platform, a community and a study network to support timely actionable evidence generation on post-licensure vaccine coverage, benefit and/or risk as well as disease rates/burden

Governance: VAC4EU will have institutional and personal members.

Membership: VAC4EU will be an open association, organizations and people can join at any time



ADVANCE THANK YOU TO ALL PARTNERS!



Final event March 6, 2019, Royal Academy of Science, Brussels

