

Living systematic reviews

From theory to implementation: a story about Zika virus

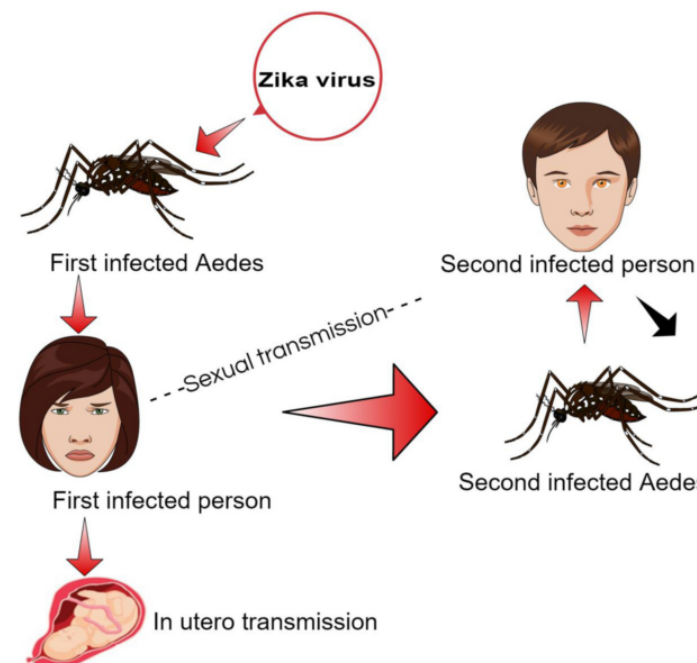
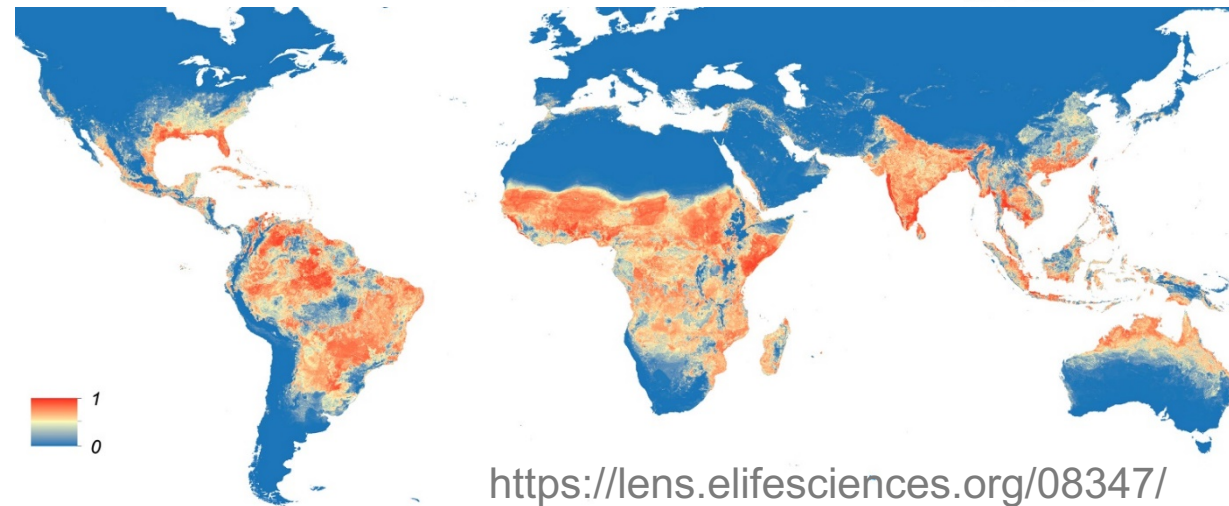
5th National Gathering of Swiss Medical Librarians
«Medical librarianship in the data age: transforming research data into clinical insight»
31.08.2017

Contents

- > Zika virus as example
 - Research questions
 - Emerging evidence
 - Need for speed, need for guidelines
- > The concept of living systematic reviews
- > Our practical implementation in three parts
 1. Automation of searching and deduplication
 2. Automation of screening/classification
 3. Automation of data output
- > Outlook/Discussion

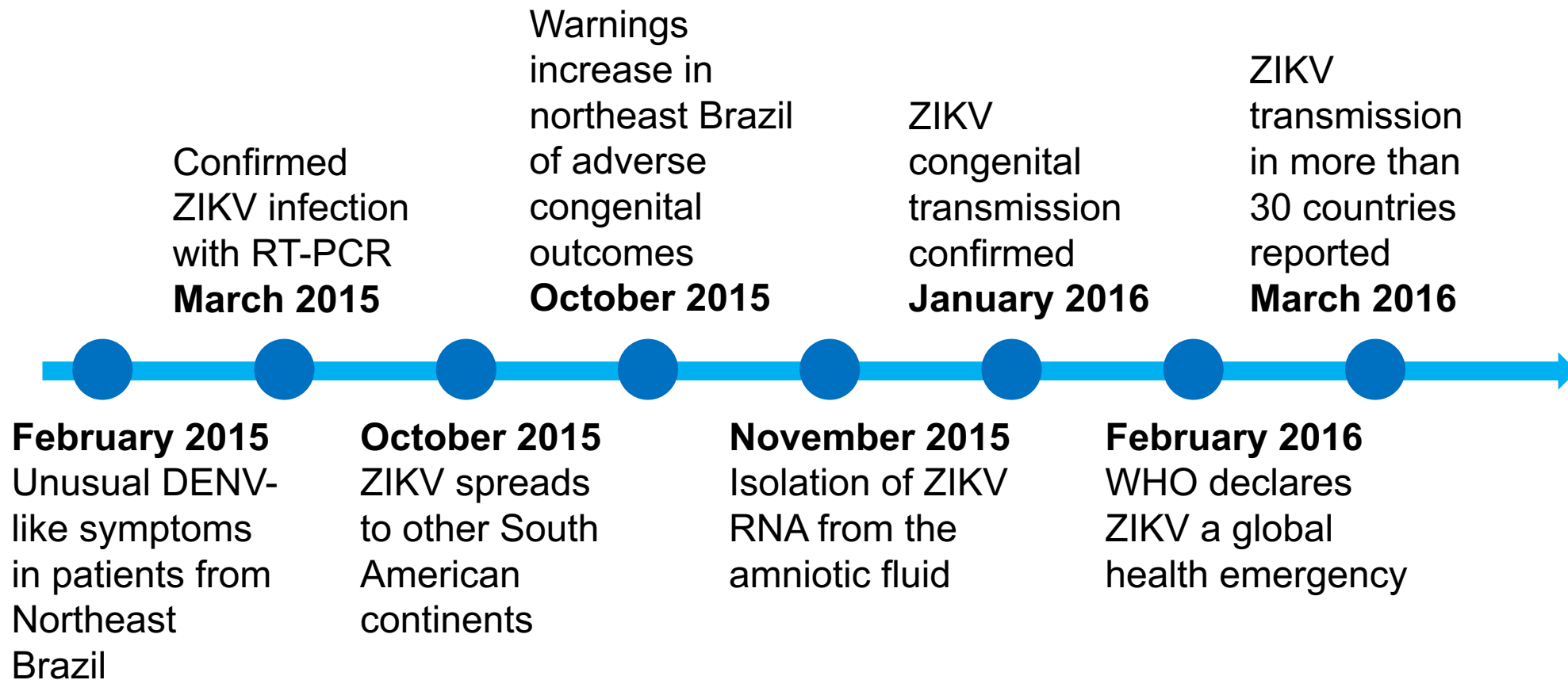
Zika virus outbreak on the American continent

- > Transmitted by mosquitoes
- > (sexual transmission)
- > Size of the outbreak:
 - ~750,000 suspected or confirmed cases
 - 2767 confirmed microcephaly cases



[http://www2.paho.org/hq/index.php?option=com_content
&view=article&id=12390&Itemid=42090&lang=en](http://www2.paho.org/hq/index.php?option=com_content&view=article&id=12390&Itemid=42090&lang=en)

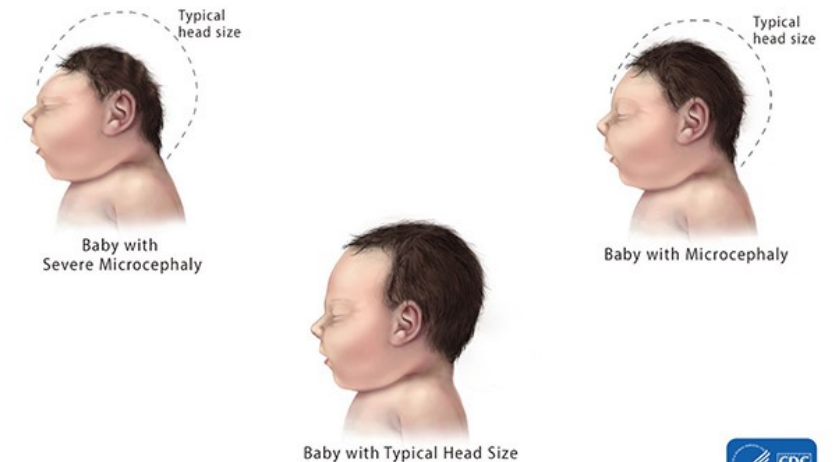
Timeline of the outbreak



Based on: dos Santos *et al.*, 2016
<http://dx.doi.org/10.1016/j.pt.2016.03.008>

Outcomes of interest

- > **Microcephaly/congenital adverse outcomes**
- > **Guillain Barré syndrome (GBS)**
- > NOT unique to Zika
- > Establish causality between Zika virus and the outcomes
- > Causality framework
 - 35 questions on microcephaly in 10 dimensions
 - 27 questions on GBS in 10 dimensions
- > **Sexual transmission of Zika virus**
 - Sexual transmission framework
 - 8 key parameters



Collecting evidence to answer questions

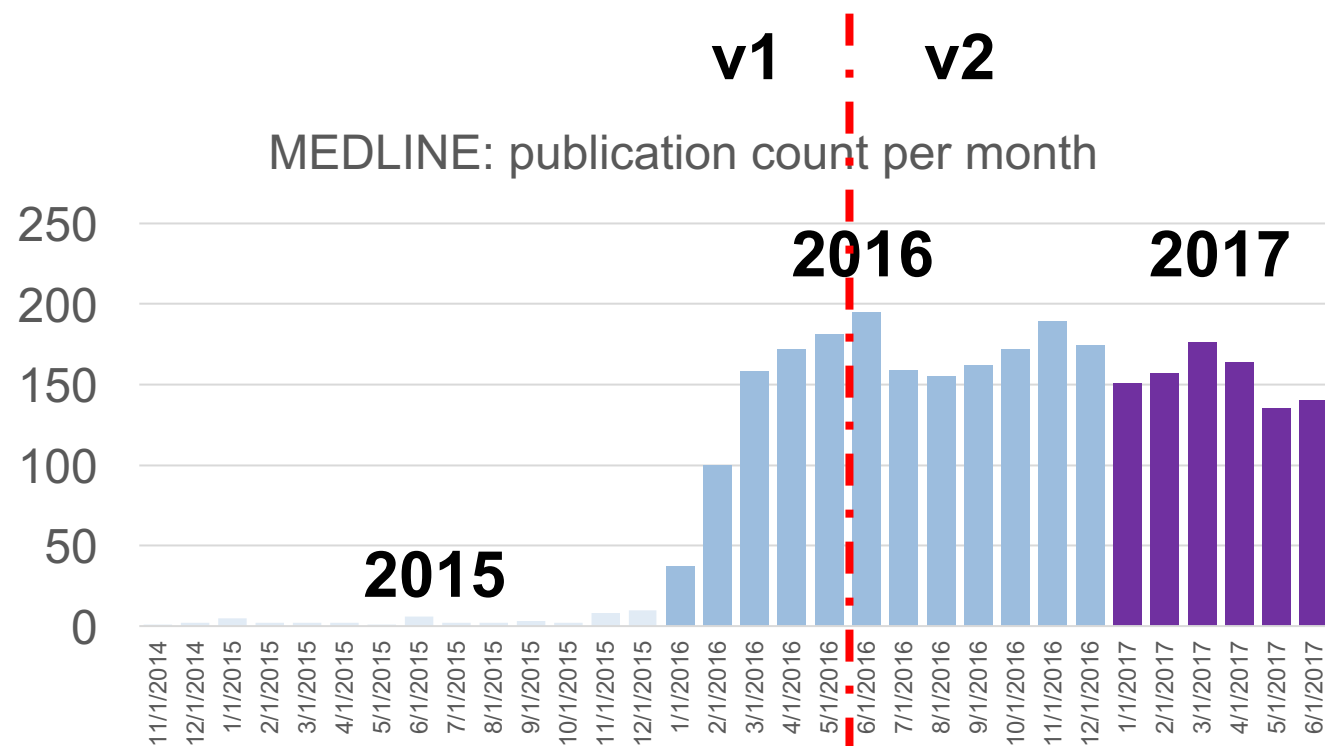
- > Whole body of evidence, published, unpublished, surveillance reports, etc.
- > Regardless of study type
- > “ZIKV OR zika virus”
- > **“Classic” systematic review**



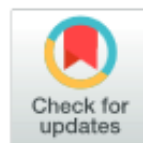
<http://www.cgiar.org/photos-videos/2009-cgap-photo-contest>

Evidence over time

- > Emerging evidence
- > Peer reviewed publications: MEDLINE, EMBASE, Lilacs
- > Preprint publications: BiorXiv, ArXiv, PeerJ
- > Weekly reports from CDC, ECDC, WHO, PAHO



> Evidence until 30-05-2016 assessed:



OPEN ACCESS

Citation: Krauer F, Riesen M, Reveiz L, Oladapo OT, Martínez-Vega R, Porgo TV, et al. (2017) Zika Virus Infection as a Cause of Congenital Brain Abnormalities and Guillain–Barré Syndrome: Systematic Review. *PLoS Med* 14(1): e1002203. doi:10.1371/journal.pmed.1002203

Academic Editor: Lorenz von Seidlein, Mahidol-Oxford Tropical Medicine Research Unit, THAILAND

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Published: January 3, 2017

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RESEARCH ARTICLE

Zika Virus Infection as a Cause of Congenital Brain Abnormalities and Guillain–Barré Syndrome: Systematic Review

Fabienne Krauer¹, Maurane Riesen¹, Ludovic Reveiz², Olufemi T. Oladapo³, Ruth Martínez-Vega⁴, Teegwendé V. Porgo^{3,5}, Anina Haeffliger¹, Nathalie J. Broutet³, Nicola Low^{1*}, WHO Zika Causality Working Group[¶]

1 Institute of Social and Preventive Medicine, University of Bern, Switzerland, **2** Pan American Health Organization, Washington DC, United States of America, **3** UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland, **4** Escuela de Microbiología, Universidad Industrial de Santander, Santander, Colombia, **5** Department of Social and Preventative Medicine, Laval University, Québec, Canada

¶ Membership of the WHO Zika Causality Working Group is provided in the Acknowledgments.
* nicola.low@ispm.unibe.ch

Abstract

Background

The World Health Organization (WHO) stated in March 2016 that there was scientific consensus that the mosquito-borne Zika virus was a cause of the neurological disorder Guillain–Barré syndrome (GBS) and of microcephaly and other congenital brain abnormalities based on rapid evidence assessments. Decisions about causality require systematic assessment to guide public health actions. The objectives of this study were to update and reassess the evidence for causality through a rapid and systematic review about links between Zika virus infection and (a) congenital brain abnormalities, including microcephaly, in the fetuses and offspring of pregnant women and (b) GBS in any population, and to describe the process and outcomes of an expert assessment of the evidence about causality.

Conclusion from that review:

- > “This systematic review found sufficient evidence to say that Zika virus is a cause of congenital abnormalities and is a trigger of GBS.”
- > “Rapid and systematic reviews with frequent updating and open dissemination are now needed both for appraisal of the evidence about Zika virus infection and for the next public health threats that will emerge.”



EPA

WHO has published its interim guidance on the prevention of sexual transmission of Zika virus using all available evidence. The recommendation for both men and women is to practice safer sex or abstinence for a period of six months, whether they show Zika symptoms or not.

[Read the guidance](#)

7 September 2016

Based on a systematic review of the science literature up to 30 May 2016, WHO concluded that Zika virus infection during pregnancy is a cause of congenital brain abnormalities, including microcephaly, and that Zika virus infection is a trigger of Guillain-Barré syndrome.

[Read the statement](#)

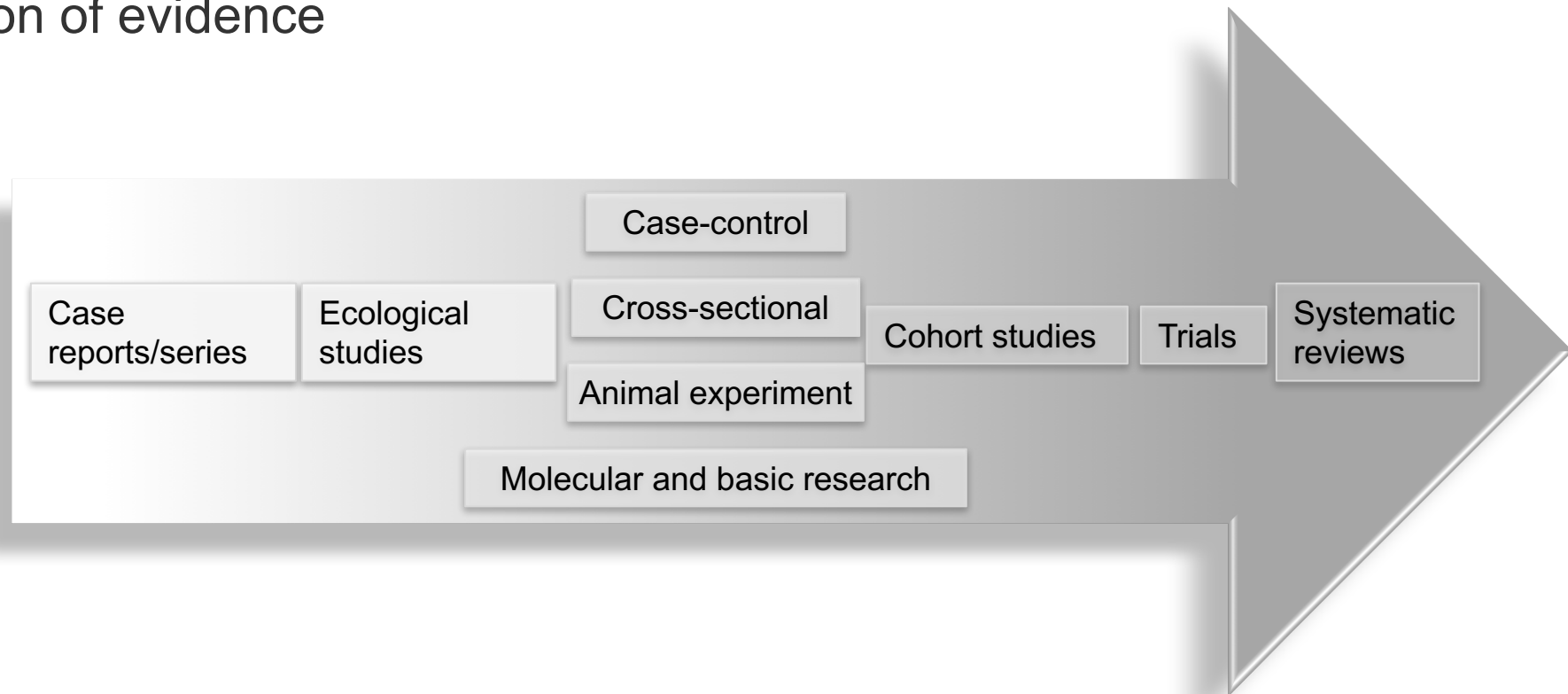


EPA/S. Mendoza

<http://www.who.int/emergencies/zika-virus/history/en/>

Interest from an epidemiological perspective

- > Evidence over time
- > Quality of evidence
- > Aggregation of evidence



Included for the congenital abnormalities

≤ 30-05-2016

31-05-2016 – 31-12-2016

	'v1'	'v2'
Type of study		
Case report	9	13
Case series	22	12
Case-control study	0	2
Cohort study	1	8
Cross-sectional study	2	1
Ecological study/outbreak report	5	3
Modelling study	2	0
Animal experiment/In vitro experiment	28	33
Sequencing and phylogenetics	3	3
	72	75

Zika, summarised

- > Keep on top of emerging evidence
 - See how evidence evolves
 - Interest in the whole evidence pyramid
 - Do conclusions change?
 - Can we quantify the causal relations (meta-analyses)?
- > Ready to answer new/updated questions
 - Sexual transmission of Zika

The concept living systematic review (1)

“Living systematic reviews are high quality, up-to-date online summaries of health research that are updated as new research becomes available, ...”

“There are four fundamental differences between conventional SR and living systematic review: **publication format**, **work processes**, author team management, and statistical methods.”

Elliott, J., Turner, T., Clavisi, O., Thomas, J., Higgins, J., Mavergames, C., & Gruen, R. (2014). Living Systematic Reviews: An Emerging Opportunity to Narrow the Evidence-Practice Gap. *Plos Medicine*, 11(2), e1001603.
<http://dx.doi.org/10.1371/journal.pmed.1001603>

The concept living systematic review (2)

“In the growing deluge of research the noble science of systematic review resembles **archaeology**: academic teams searching for buried artefacts and working tirelessly to reveal their true meaning.”

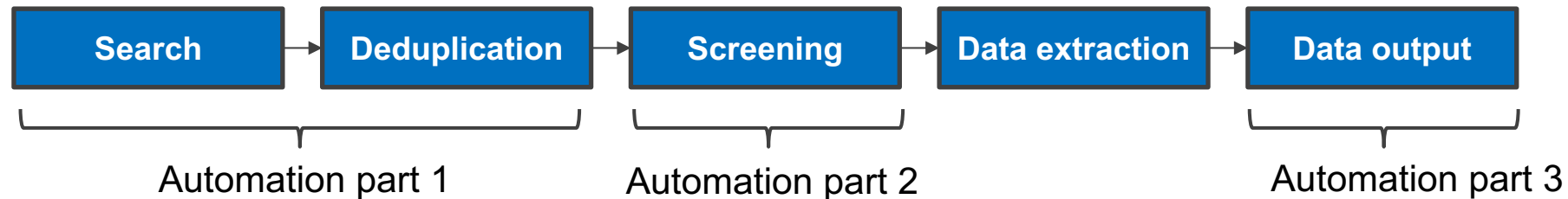
Elliott, J., Turner, T., Clavisi, O., Thomas, J., Higgins, J., Mavergames, C., & Gruen, R. (2014). Living Systematic Reviews: An Emerging Opportunity to Narrow the Evidence-Practice Gap. *Plos Medicine*, 11(2), e1001603.
<http://dx.doi.org/10.1371/journal.pmed.1001603>

The concept living systematic review (3)



The systematic review - components

- > PRISMA guidelines
- > Transparency
- > Workflow management

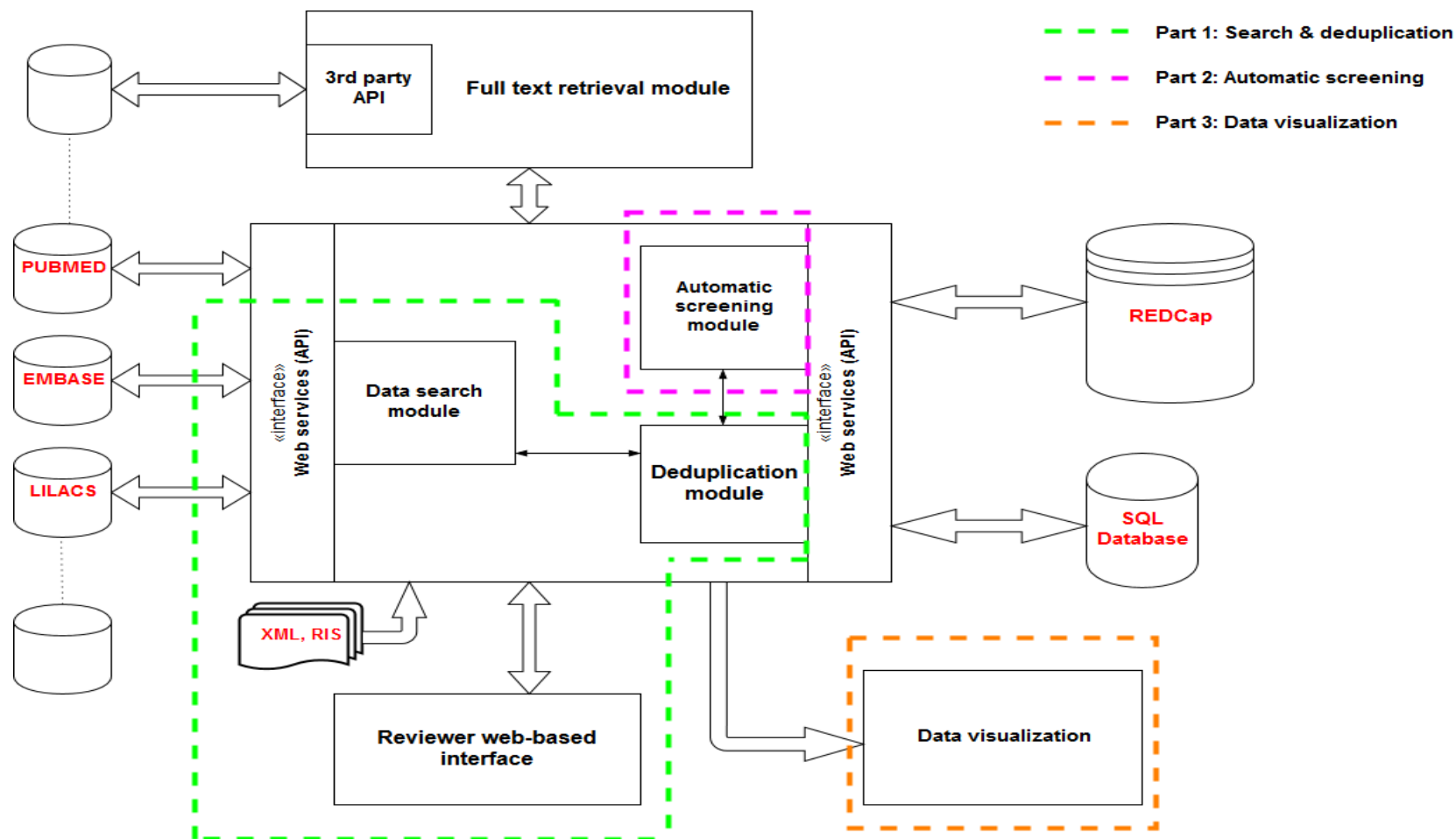


Why automation?

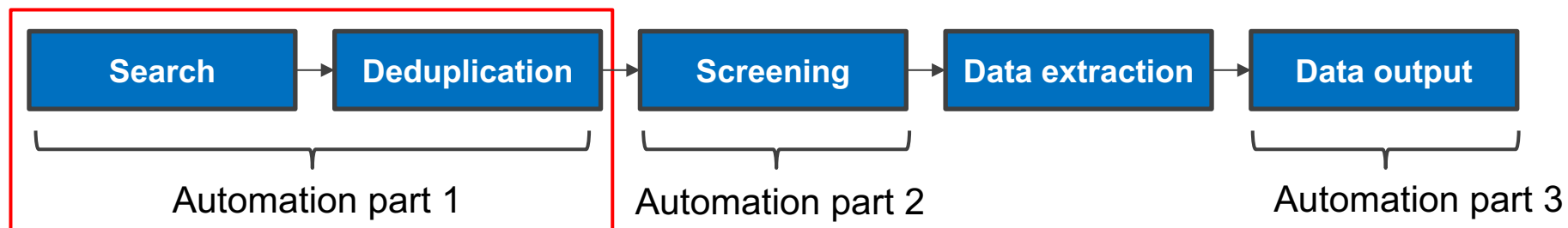
- > The amount of research is increasing considerably with very fast pace that makes the preparing for SRs very challenging.
A study in 2007¹ about the survival rate of SRs shows that 23% of SRs need to be updated within 2 years of publishing
- > The development of technologies (i.e Machine Learning) makes things easier and more possible.

¹Shojania, K. G., Sampson, M., Ansari, M. T., Ji, J., Doucette, S., & Moher, D. (2007). How quickly do systematic reviews go out of date? A survival analysis. *Annals of Internal Medicine*, 147(4), 224–233.

Automated system for SRs overview



Automation part 1



Automation part 1 – searching and deduplication

- > Data searching is implemented through user-defined queries based on search terms for specific bibliographic fields
- > Web services to different databases with different data structures
- > Import from external formats is possible (i.e. RIS, XML..).
- > Data is parsed in to formatted records, deduplicated before importing to local database (REDCap – Research Electronic Data Capture)
- > Involved reviewers will be notified by emails with new records.

Issues: Difference between databases

- > Different data structures or unstructured data
- > Availability of APIs to access the data sources
 - LILACS, WHO Reports do not officially provide APIs (LILACS is the most important and comprehensive index of scientific and technical literature of Latin America and the Caribbean)
- > Languages

Citations sometimes are provided in different languages.

Automated deduplication

- > Duplicates are visible in the new search data with the existing one
- > Duplicates can be seen within the data sources themselves. E.g. PUBMED, EMBASE or PUBMED with EMBASE
- > The deduplication involves in comparing two citations based on their bibliographic data → Not quite a trivial task due to some issues in different data formats, incomplete data, missing or even errors
- > The deduplication was done manually using EndNote Wichor¹ procedure → Time-consuming

¹Bramer, W., Giustini, D., de Jonge, G., Holland, L., & Bekhuis, T. (2016). De-duplication of database search results for systematic reviews in EndNote. *Journal Of The Medical Library Association : JMLA*, 104(3), 240-243.
<http://dx.doi.org/10.3163/1536-5050.104.3.014>

[Pediatr Infect Dis J.](#) 2017 May;36(5):500-501. doi: 10.1097/INF.0000000000001482.

Zika Virus Infection Associated With Congenital Birth Defects in a HIV-infected Pregnant Woman.

[João EC¹](#), [Gouvea MI](#), [Teixeira ML](#), [Mendes-Silva W](#), [Esteves JS](#), [Santos EM](#), [Ledesma LA](#), [Gomes AP](#), [Cruz ML](#).

Author information

- 1 From the *Infectious Diseases Department, Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil; †Instituto Nacional de Infectologia Evandro Chagas - Fiocruz, Rio de Janeiro, Brazil; and ‡Hospital Maternidade Maria Amelia Buarque de Hollanda, Rio de Janeiro, Brazil.

Abstract

We describe a case of Zika virus infection acquired during the first trimester in a HIV-infected pregnant woman that led to multiple fetal malformations and fetal demise in Rio de Janeiro, Brazil.

PMID: 28403053 DOI: 10.1097/INF.0000000000001482

[Pediatr Infect Dis J.](#) 2016 Dec 15. doi: 10.1097/INF.0000000000001482. [Epub ahead of print]

Zika Virus Infection Associated with Congenital Birth Defects in a HIV-Infected Pregnant Woman.

[João EC¹](#), [da Silveira Gouvea MI](#), [de Lourdes Benamor Teixeira M](#), [Mendes-Silva W](#), [Esteves JS](#), [Santos EM](#), [Ledesma LA](#), [Cruz ML](#).

Author information

- 1 1Infectious Diseases Department, Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil 2Instituto Nacional de Infectologia Evandro Chagas - Fiocruz, Rio de Janeiro, Brazil 3Hospital Maternidade Maria Amelia Buarque de Hollanda, Ana Paula Gomes, MD, Infectious Diseases Department, Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil.

Abstract

We describe a case of Zika Virus infection acquired during the first trimester in a HIV-infected pregnant woman that led to multiple fetal malformations and fetal demise in Rio de Janeiro, Brazil.

PMID: 27997515 DOI: 10.1097/INF.0000000000001482

Issues: Unique identifiers?

> No universal identifier

Different DOI's or missing DOIs

- BioRxiv publication
- Final publication

Miller, J. (2016). Mathematical models of SIR disease spread with combined non-sexual and sexual transmission routes. *bioRxiv*. doi:10.1101/087189



Miller, J. C. (2017). Mathematical models of SIR disease spread with combined non-sexual and sexual transmission routes. *Infectious Disease Modelling*, 2(1), 35-55. doi:10.1016/j.idm.2016.12.003

Issues: Data in different formats or incomplete

- > E-pub, Indexing Date, Publication Date
2016-06-04 or *04 June 2016* or *04/06/2016* or *06/2016* or **Summer 2016**
Pages: 212 – 219 or *212-19* or *212*
- > Journal name
Pediatr Infect Dis J vs **Pediatric Infectious Disease Journal**
- > Authors
Delaine M, Weingertner AS, Nougairède A, Lepiller Q, Fafi-Kremer S, Favre R, Charrel R

or

Maia Delaine, Anne-Sophie Weingertner, Antoine Nougairède, Quentin Lepiller, Samira Fafi-Kremer, Romain Favre, and Rémi Charrel

Deduplication tools and algorithms

- > EndNote, Mendeley or some Reference Manager packages
 - Automated but low sensitivity
 - Integration is not easy
- > Rule-based algorithm from Yu Jiang¹ show good results in terms sensitivity and specificity
 - Publication year and PMID should not be used as unique identifiers
- > EndNote with Wichor's protocol
 - Manual and time-consuming

¹Jiang, Y., Lin, C., Meng, W., Yu, C., Cohen, A., & Smalheiser, N. (2014). Rule-based deduplication of article records from bibliographic databases. *Database*, bat086, <http://dx.doi.org/10.1093/database/bat086>

Our algorithm

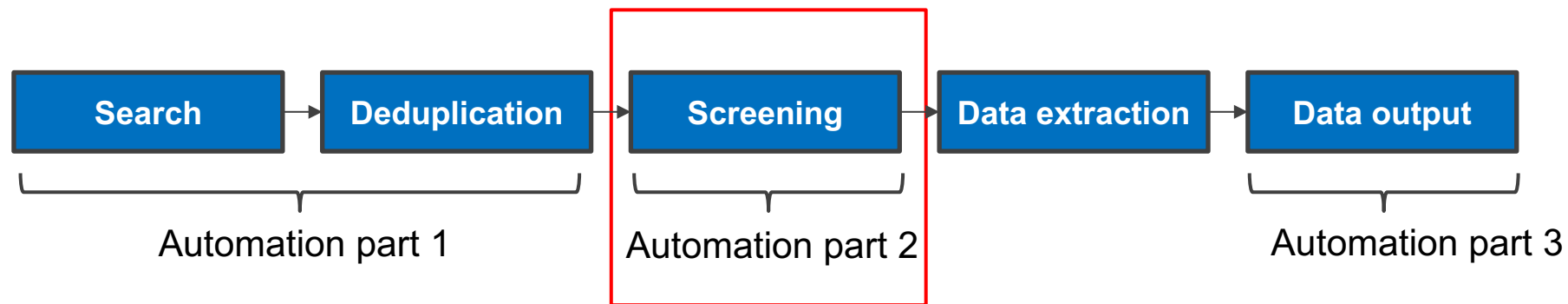
- > Optimized rule-based deduplication of Yu Jiang
Rule-based approach: combination of different bibliographic data to get the reasonable accuracy
- > Journal titles are compared using prefix matching and length similarity.
- > Titles and text fields (pagination, volume, issue) are compared using the Longest Common Subsequence (LCS) algorithm and combined with the length similarity.
- > DOI comparison for non-arXiv, non-bioRxiv citations
- > Combination of other bibliographic values: matched titles, matched authors, matched paginations, etc.,.

Performance of the algorithm

- > Total records: 1471 (840 Pubmed + 631 Embase)
- > True duplicates: 562
- > True unique: 909

	Endnote simple	Endnote partly wichor	Endnote full wichor	Our method
True positive (n) (correctly identified)	356	409	551	555
False negative (n) (duplicates missed)	206	153	11	7
Sensitivity (%) (95% CI)	63.3 (59.3-67.2)	72.8 (69.0-76.3)	98.0 (96.5-98.9)	98.8 (97.5-99.4)
True negative (n) (unique records)	909	909	907	908
False negative (n)(incorrectly identified as duplicate)	0	0	2	1
Specificity (%) (95% CI)	100.0 (99.6-100.0)	100.0 (95% CI: 99.6-100.0)	99.8 (99.2-99.9)	99.9 (99.4-100.0)

Automation part 2



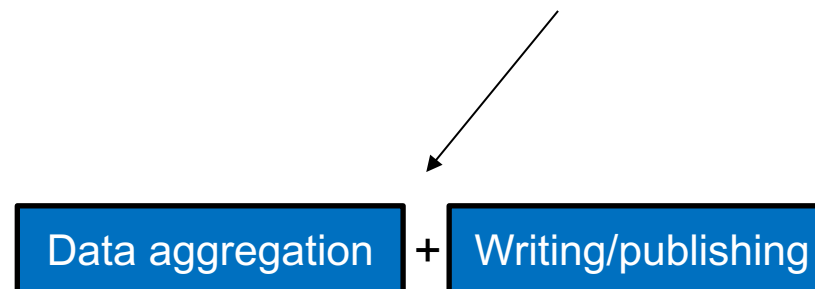
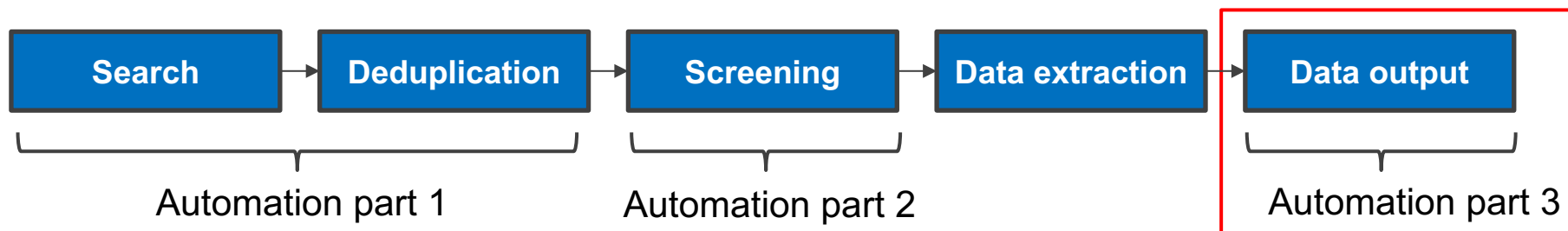
Automation part 2 – Assisted screening

- > ML is employed in assisting with screening which substantially reduces the workload.
- > Stimulated by the results from previous studies:
 - Khabsa et al (Rayyan tool for SRs) with recall > 95%, Wallace et al (Semi-automated screening) reduces 40% - 50% workload
- > We aim to build up an automated screening for inclusion prediction of title/abstract and inclusion prediction of full-text.
- > Ongoing models will focus on: Random Forest, SVM and Naïve Bayes classifications.

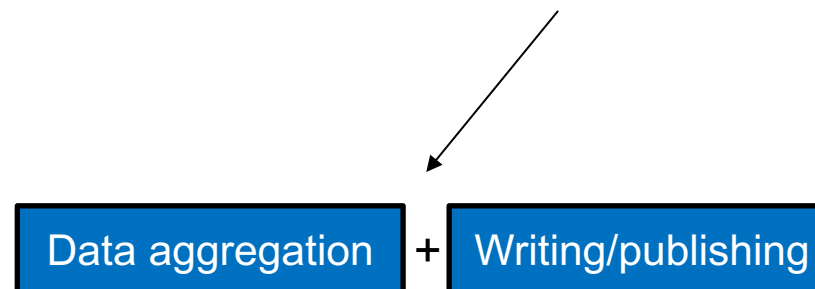
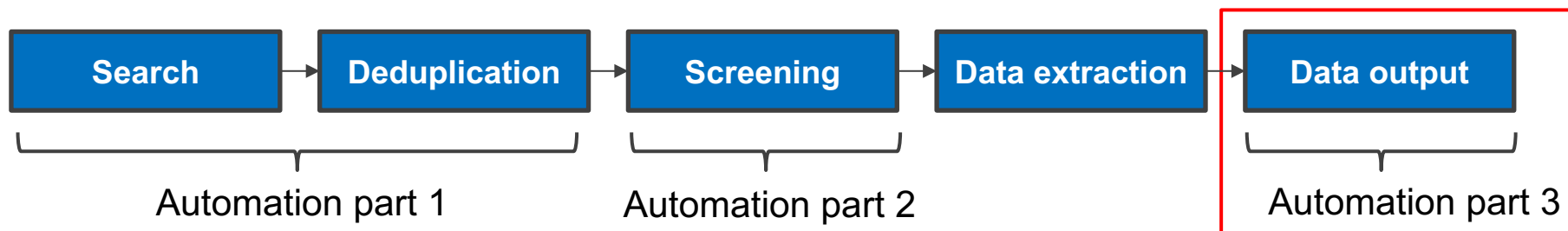
Khabsa, M., Elmagarmid, A., Ilyas, I., Hammady, H., & Ouzzani, M. (2015). Learning to identify relevant studies for systematic reviews using random forest and external information. *Machine Learning*, 102(3), 465-482. <http://dx.doi.org/10.1007/s10994-015-5535-7>

Wallace, B., Trikalinos, T., Lau, J., Brodley, C., & Schmid, C. (2010). Semi-automated screening of biomedical citations for systematic reviews. *BMC Bioinformatics*, 11(1), 55. <http://dx.doi.org/10.1186/1471-2105-11-55>

Automation part 3



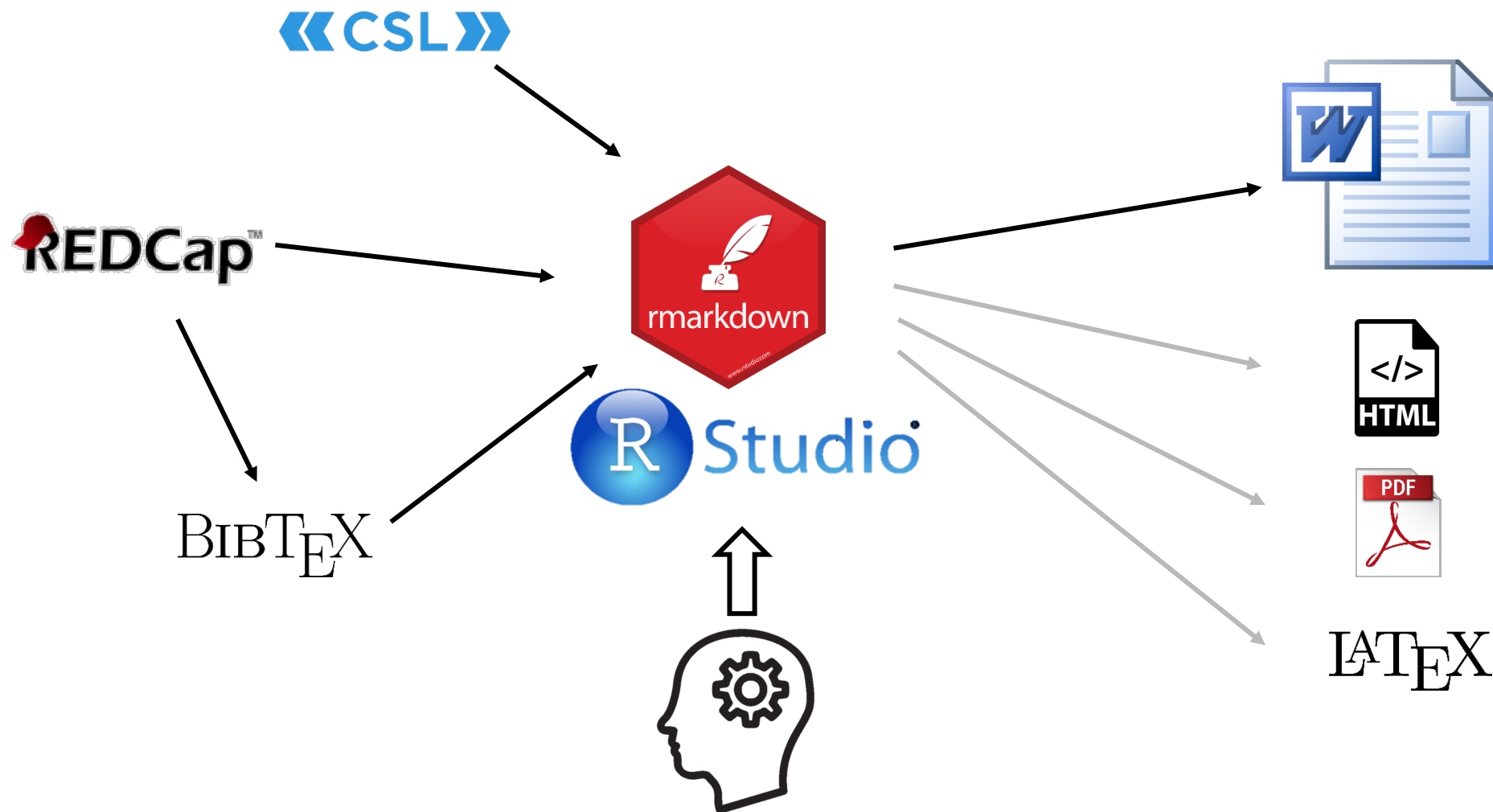
Automation part 3



Automation part 3 - Requirements

- > Get the data from REDCap
- > Perform predefined analyses: counts, summary statistics, meta-analysis
- > Output tables and figures
- > Integrate in 'human' written text
- > Handle citations/references
- > Integrated publication possibilities - Versioning

Information flow: Creating a document



Example

- > We included ``r nrow(dbv)`` in vivo and in vitro studies of which ``r nrow(subset(dbv, male==1))`` hold information on the male reproductive tract and ``r nrow(subset(dbv, female==1))`` on the female reproductive tract ``r insertref(dbv[,1])``.
- > We included 21 in vivo and in vitro studies of which 14 hold information on the male reproductive tract and 11 on the female reproductive tract [75–95].

Rmarkdown

- > Simple syntax
- > Use of programming code within document (R, Python, SQL, Bash, JavaScript)
- > Flexible output styles
- > Easy citation [`@bibtexkey`] or [`@bibtexkey1;@bibtexkey2`]

>



Bibtex

- > Simple syntax
- > Stable citation keys (self-defined)
- > Import-export reference managers

```
@ARTICLE {REDCAP1976,  
  author = {Nicastri, E. and Castilletti,  
            C. and Balestra, P. and Galgani, S. and  
            Ippolito, G.},  
  title = {Zika Virus Infection in the  
            Central Nervous System and Female  
            Genital Tract},  
  journal = {Emerg Infect Dis},  
  volume = {22},  
  number = {12},  
  year = {2016},  
  pages = {2228-2230},  
  doi = {10.3201/eid2212.161280}  
}
```


Item Type: Journal Article
Citation Key: REDCAP1976
Title: Zika Virus Infection in the Central Nervous System and Female Genital Tract

- ▼ Author: Nicastri, E.
- ▼ Author: Castilletti, C.
- ▼ Author: Balestra, P.
- ▼ Author: Galgani, S.
- ▼ Author: Ippolito, G.

Abstract:
Publication: Emerg Infect Dis
Volume: 22
Issue: 12
Pages: 2228-2230
Date: 2016
Series:
Series Title:
Series Text:
Journal Abbr:
Language:
DOI: 10.3201/eid2212.161280

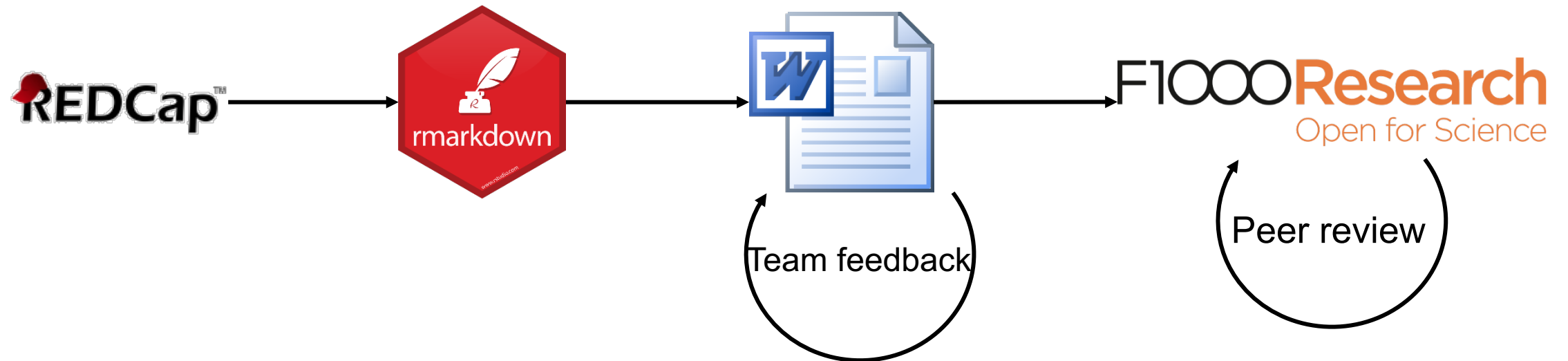
Limitations

- > Feedback/commenting issue
 - Manual implementation of changes, from word back to markdown file
- > References in Word in plain text

<p>We included 21 in vivo and in vitro studies of which 14 hold information-details on the male reproductive tract and 11 on the female reproductive tract [75–95].</p>	<p> Counotte, Michel Jacques (ISPM) How many in vivo studies?</p>
---	---

Publishing workflow

> Version x:



Open Peer Review

Referee Status:   

Invited Referees

	1	2	3
REVISED version 3 published 14 Nov 2013		 report	 report
		↑	↑
REVISED version 2 published 01 Nov 2013	 report	 report	 report
	↑		
version 1 published 25 Sep 2013	 report		

- 1 Maximiliano Gutierrez, MRC National Institute for Medical Research, UK
- 2 Yoshiko Takahashi, Kyoto University, Japan
- 3 Tom Gillis, Louisiana State University School of Medicine, USA

Read the reports (6), Responses (1)

Dynamic Citation

Reprogramming diminishes retention of *Mycobacterium leprae* in *Schwann* cells and elevates bacterial transfer property to fibroblasts [v3; ref status: indexed, <http://f1000r.es/2ae>]


Reprogramming diminishes retention of *Mycobacterium leprae* in *Schwann* cells and elevates bacterial transfer property to fibroblasts [v2; ref status: indexed, <http://f1000r.es/280>]

Reprogramming diminishes retention of *Mycobacterium leprae* in *Schwann* cells and elevates bacterial transfer property to fibroblasts [v1; ref status: approved with reservations 1, <http://f1000r.es/1u5>]


F1000Research

Versioning and traceability

CrossMark


Updates are available
New version dated 2013-11-01

Click to view New version:
<https://doi.org/10.12688/f1000research.2-198.v2>


Updates are available
New version dated 2013-11-14

Click to view New version:
<https://doi.org/10.12688/f1000research.2-198.v3>

Reprogramming diminishes retention of Mycobacterium leprae in Schwann cells and elevates bacterial transfer property to fibroblasts
Crossref DOI link: <https://doi.org/10.12688/f1000research.2-198.v1>
Published:
Update policy: <https://doi.org/10.12688/f1000research.crossmark-policy>

> Authors

> More Information

All comments (0)

Changes over time

- > Methodological changes over time
 - Versioning of methodology/PROSPERO
- > Search strategies that can be improved
- > Questions that need modification
- > New questions that may arise

Comments/discussion

- > Where/how can time be gained?
- > “Identifying studies for inclusion is one of the most labour-intensive and time-consuming tasks of the systematic review process.”¹
- > Peer review, publication process
 - Preprint availability?

Received: August 25, 2016

Accepted: November 16, 2016

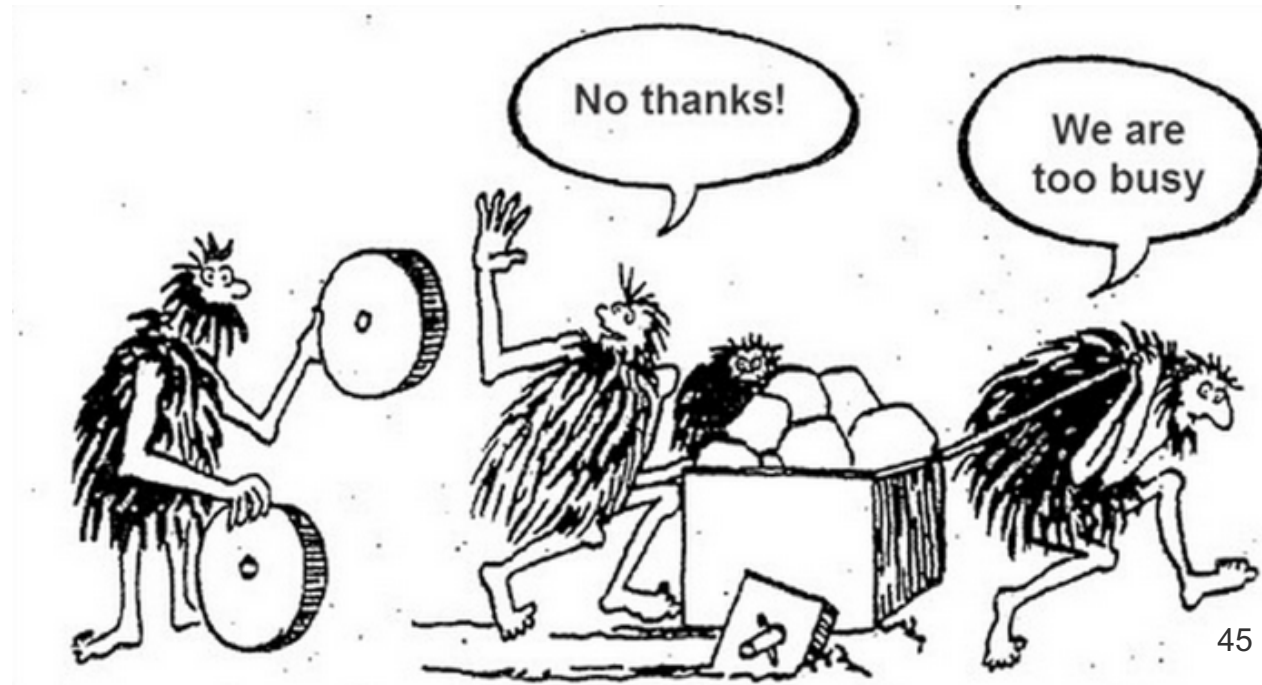
Published: January 3, 2017



¹O'Mara-Eves, A., Thomas, J., McNaught, J., Miwa, M., & Ananiadou, S. (2015). Using text mining for study identification in systematic reviews: a systematic review of current approaches. *Systematic Reviews*, 4(1). <http://dx.doi.org/10.1186/2046-4053-4-5>

Outlook

- > Combining the right tools, not reinventing the wheel.
- > Enabling reviewers to move from being archeologists to something more contemporary?
- > Have a system that notifies and supports the reviewer
- > Generalizability
- > Set up for outbreak response



Acknowledgements

- > ISPM Review team:
 - Maurane Riesen
 - Million Abraha
 - Dianne Egli-Gany
 - Jingying Wang
 - Valerie Porgo
 - Anina Häfliger
- > Nicola Low
- > WHO
- > SNF

Blank slide

Estimated Zika virus importations to Europe by travellers from Brazil.

Massad E^{1,2}, Tan SH³, Khan K⁴, Wilder-Smith A^{5,6,7}.

⊕ Author information

Abstract

BACKGROUND: Given the interconnectivity of Brazil with the rest of the world, Zika virus (ZIKV) infections have the potential to spread rapidly around the world via viremic travellers. The extent of spread depends on the travel volume and the endemicity in the exporting country. In the absence of reliable surveillance data, we did mathematical modelling to estimate the number of importations of ZIKV from Brazil into Europe.

DESIGN: We applied a previously developed mathematical model on importations of dengue to estimate the number of ZIKV importations into Europe, based on the travel volume, the probability of being infected at the time of travel, the population size of Brazil, and the estimated incidence of ZIKV infections.

RESULTS: Our model estimated between 508 and 1,778 imported infections into Europe in 2016, of which we would expect between 116 and 355 symptomatic Zika infections; with the highest number of importations being into France, Portugal and Italy.

CONCLUSIONS: Our model identified high-risk countries in Europe. Such data can assist policymakers and public health professionals in estimating the extent of importations in order to prepare for the scale up of laboratory diagnostic assays and estimate the occurrence of Guillain-Barré Syndrome, potential sexual transmission, and infants with congenital ZIKV syndrome.

KEYWORDS: Brazil; Europe; Zika virus; importations; travel

PMID: 27193266 PMCID: PMC4871896

Estimated Zika virus importations to Europe by travellers from Brazil.

Massad E^{1,2}, Tan SH³, Khan K⁴, Wilder-Smith A^{5,6,7}.

⊕ Author information

Abstract

Background Given the interconnectivity of Brazil with the rest of the world, Zika virus (ZIKV) infections have the potential to spread rapidly around the world via viremic travellers. The extent of spread depends on the travel volume and the endemicity in the exporting country. In the absence of reliable surveillance data, we did mathematical modelling to estimate the number of importations of ZIKV from Brazil into Europe. **Design** We applied a previously developed mathematical model on importations of dengue to estimate the number of ZIKV importations into Europe, based on the travel volume, the probability of being infected at the time of travel, the population size of Brazil, and the estimated incidence of ZIKV infections. **Results** Our model estimated between 508 and 1,778 imported infections into Europe in 2016, of which we would expect between 116 and 355 symptomatic Zika infections; with the highest number of importations being into France, Portugal and Italy. **Conclusions** Our model identified high-risk countries in Europe. Such data can assist policymakers and public health professionals in estimating the extent of importations in order to prepare for the scale up of laboratory diagnostic assays and estimate the occurrence of Guillain-Barré Syndrome, potential sexual transmission, and infants with congenital ZIKV syndrome.

KEYWORDS: Brazil; Europe; Zika virus; importations; travel

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Microcephaly Case Fatality Rate Associated with Zika Virus Infection in Brazil: Current Estimates.

[da Cunha AJ](#)¹, [de Maqalhães-Barbosa MC](#), [Setta FL](#), [de Andrade Medronho R](#), [Prata-Barbosa A](#).

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Abstract

Considering the currently confirmed cases of microcephaly and related deaths associated with Zika virus in Brazil, the estimated case fatality rate (CFR) is 8.3% [95%CI:7.2-9.6]. However, a third of the reported cases remains under investigation. If the confirmation rates of cases and deaths are the same in the future, the estimated CFR will be as high as 10.5% (95%CI:9.5-11.7).

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[Cunha AJ](#)¹, [de Maqalhães-Barbosa MC](#), [Lima-Setta F](#), [Medronho RA](#), [Prata-Barbosa A](#).

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