KNOWLEDGE INFUSION:

FOCUS ON RISK-BASED DECISION-MAKING

Risk-Based Decision-Making Analysis of Babesia Microti Risk to the Canadian Blood Supply

Prepared by Canadian Blood Services Knowledge Mobilization Team
with special thanks to Margaret Fearon

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CENTRE FOR INNOVATION PRESENTS

Name: **Margaret Fearon**
Title: **Medical Director, Medical Microbiology**
Organization: **Canadian Blood Services**
Location: **Toronto, ON**

Presentation Objective:

- ✓ **Learn how Canadian Blood Services uses the Risk-Based Decision-Making Framework, developed by the Alliance of Blood Operators, to make informed decisions on strategies to deal with emerging and current risks to the blood supply.**

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Risk-Based Decision-Making Analysis of Babesia Microti Risk to the Canadian Blood Supply

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Knowledge Infusion: Focus on Risk-Based Decision-Making Case Studies
Dr. Margaret Fearon
February 27, 2017

The ABO Risk-Based Decision Making Framework for Blood Safety

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https://riskframework.allianceofbloodoperators.org/log-in/

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Policy foundations

1 Preparation

- Risk management principles
- Risk communication and stakeholder participation
- Assessment principles
- Risk tolerability

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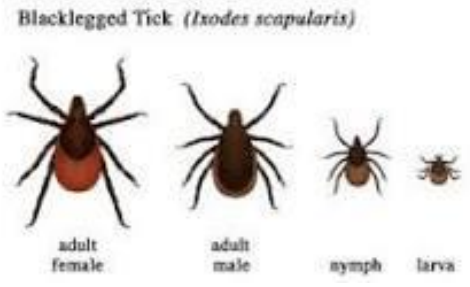
An emerging risk

2 Problem Formulation

Babesia microti (B. microti)

- An infection caused by a parasite transmitted by ticks.
- Endemic in parts of the United States with 96% of reported cases in Northeast and Midwest States.
- For some people (immunosuppressed, the elderly, and asplenics, symptoms can lead to severe complications that include death.



It can be transmitted by blood transfusion and is increasingly recognized as posing a risk to the US blood supply.

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Babesia microti – reported Cases of Transfusion Transmission

UNITED STATES	CANADA
160 transfusion transmissions[1]	1 transfusion transmission (1998)[2]
12 deaths	0 deaths

[1]Herwaldt BL, Linden JV, Bosserman E, et al. Transfusion-associated babesiosis in the United States: A description of cases. Ann Intern Med 2011;155:509-19.

[2]Kain KC, Jassoum SB, Fong IW, Hannach B. Transfusion-transmitted Babesiosis in Ontario: First reported case in Canada. CMAJ 2001;164:1721-3

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Evidence suggests B. microti is emerging as an endemic infection in Canada

- It is well established in the U.S. states bordering Canada.
- It has been identified (0.02 – 1.7% of ticks tested) in tick populations in Manitoba, Ontario, Quebec and New Brunswick, by passive and active surveillance.
- Incidence of Lyme disease, a reasonable surrogate for B. microti, appears to be slowly increasing.
- First confirmed human case of endemically acquired B. microti reported in Manitoba in 2013.

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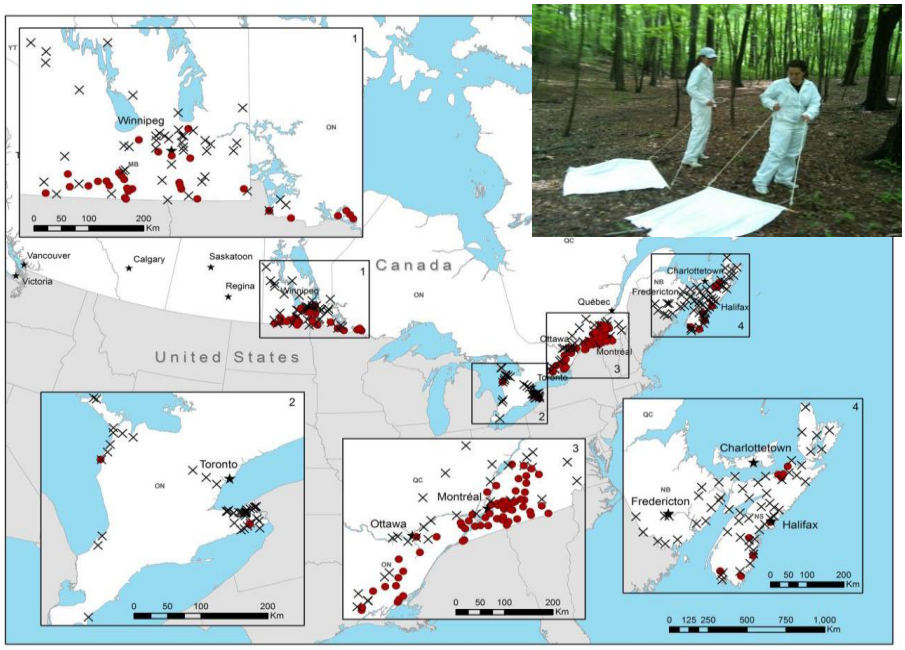
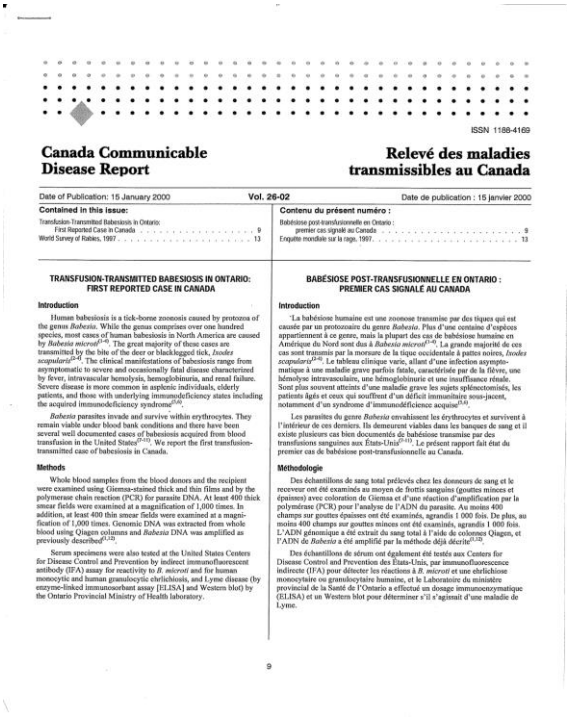
Results of Active Tick Surveillance 2008-2012



Ogden N. et al Environmental Risk from Lyme Disease in central and eastern Canada: a summary of recent surveillance information. CCDR 2014;40:58-67

Public Health Agency of Canada | Agence de la santé publique du Canada



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Contained in this issue:

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TRANSFUSION-TRANSMITTED BABESIOSIS IN ONTARIO: FIRST REPORTED CASE IN CANADA

Introduction

Human babesiosis is a tick-borne zoonosis caused by protozoa of the genus *Babesia*. While the genus comprises over one hundred species, most cases of human babesiosis in North America are caused by *Babesia microti*[1–6]. The great majority of these cases are transmitted by the bite of the deer or blacklegged tick, *Ixodes scapularis*[2–4]. The clinical manifestations of babesiosis range from asymptomatic to severe and occasionally fatal disease characterized by fever, intravascular hemolysis, hemoglobinuria, and renal failure. Severe disease is more common in asplenic individuals, elderly patients, and those with underlying immunodeficiency states including the acquired immunodeficiency syndrome[5,6].

Babesia parasites invade and survive within erythrocytes. They remain viable under blood bank conditions and there have been several well documented cases of babesiosis acquired from blood transfusion in the United States[7–10]. We report the first transfusion-transmitted case of babesiosis in Canada.

Methods

Whole blood samples from the blood donors and the recipient were examined using Giemsa-stained thick and thin films and by the polymerase chain reaction (PCR) for parasite DNA. At least 400 thick smear fields were examined at a magnification of 1,000 times. In addition, at least 400 thin smear fields were examined at a magnification of 1,000 times. Genomic DNA was extracted from whole blood using Qiagen columns and *Babesia* DNA was amplified as previously described[11,12].

Serum specimens were also tested at the United States Centers for Disease Control and Prevention by indirect immunofluorescent antibody (IFA) assay for reactivity to *B. microti* and for human monocytic and human granulocytic ehrlichiosis, and Lyme disease (by enzyme-linked immunosorbant assay [ELISA] and Western blot) by the Ontario Provincial Ministry of Health laboratory.

BABÉSIOSE POST-TRANSFUSIONNELLE EN ONTARIO : PREMIER CAS SIGNALÉ AU CANADA

Introduction

La babésiose humaine est une zoonose transmise par des tiques qui est causée par un protozoaire du genre *Babesia*. Plus d'une centaine d'espèces appartiennent à ce genre, mais la plupart des cas de babésiose humaine en Amérique du Nord sont dus à *Babesia microti*[1–6]. La grande majorité de ces cas sont transmis par la morsure de la tique occidentale à pattes noires, *Ixodes scapularis*[2–4]. Le tableau clinique varie, allant d'une infection asymptomatique à une maladie grave parfois fatale, caractérisée par de la fièvre, une hémolyse intravasculaire, une hémoglobinurie et une insuffisance rénale. Sont plus souvent atteints d'une maladie grave les sujets splénectomisés, les patients âgés et ceux qui souffrent d'un déficit immunitaire sous-jacent, notamment d'un syndrome d'immunodéficience acquise[5,6].

Les parasites du genre *Babesia* envahissent les érythrocytes et survivent à l'intérieur de ces derniers. Ils demeurent viables dans les banques de sang et il existe plusieurs cas bien documentés de babésiose transmise par des transfusions sanguines aux États-Unis[7–10]. Le présent rapport fait état du premier cas de babésiose post-transfusionnelle au Canada.

Méthodologie

Des échantillons de sang total prélevés chez les donneurs de sang et le receveur ont été examinés au moyen de frottis sanguins (gouttes minces et épaisses) avec coloration de Giemsa et d'une réaction d'amplification par la polymérase (PCR) pour l'analyse de l'ADN du parasite. Au moins 400 champs sur gouttes épaisses ont été examinés, agrandis 1 000 fois. De plus, au moins 400 champs sur gouttes minces ont été examinés, agrandis 1 000 fois. L'ADN génomique a été extrait du sang total à l'aide de colonnes Qiagen, et l'ADN de *Babesia* a été amplifié par la méthode déjà décrite[11,12].

Des échantillons de sérum ont également été testés aux Centers for Disease Control and Prevention des États-Unis, par immunofluorescence indirecte (IFA) pour détecter les réactions à *B. microti* et une ehrlichiose monocytaire ou granulocytaire humaine, et le Laboratoire du ministère provincial de la Santé de l'Ontario a effectué un dosage immunoenzymatique (ELISA) et un Western blot pour déterminer s'il s'agissait d'une maladie de Lyme.

CASE REPORT

The first case of locally acquired tick-borne *Babesia microti* infection in Canada

Jared MP Bullard MD FRCPC[1,2,5], Arshad N Ahsanuddin MD[4], Anamarija M Perry MD[4], L Robbin Lindsay PhD[2,5], Mahmood Iranpour PhD[5], Antonia Dibernardo BSc[5], Paul G Van Caeseele MD FRCPC[1,2,3]

JMP Bullard, AN Ahsanuddin, AM Perry, et al. The first case of locally acquired tick-borne *Babesia microti* infection in Canada. Can J Infect Dis Med Microbiol 2014;25(6):e87–e89.

A child with a complicated medical history that included asplenia acquired an infection with *Babesia microti* in the summer of 2013 and had not travelled outside of Manitoba. Although the clinical findings were subtle, astute laboratory work helped to reach a preliminary identification of *Babesia* species, while reference laboratory testing confirmed the diagnosis. Blacklegged ticks (*Ixodes scapularis*) are known to transmit *Borrelia burgdorferi* and *Anaplasma phagocytophilum* in the province; however, the present case represents the first known instance of tick-borne *B microti*, both in Manitoba and in Canada. The expanding territory of the blacklegged tick increases the relevance of this emerging infection. Clinicians, laboratory medical practitioners and public health officials should be aware of *B microti* as a potential locally acquired infection in Canada.

Key Words: *Babesia microti; Babesiosis; Blacklegged ticks; Canada; Emerging infection; Local acquisition*

Le premier cas d'infection à *Babesia microti* transmis par une tique à être contracté au Canada

Un enfant ayant des antécédents médicaux complexes, qui incluaient une asplénie, a contracté une infection à *Babesia microti* pendant l'été 2013, sans avoir quitté le Manitoba. Même si les résultats cliniques étaient discrets, un travail de laboratoire astucieux a contribué à l'identification préliminaire d'une espèce de *Babesia*. Le test du laboratoire de référence a confirmé le diagnostic. On sait que les tiques occidentales à pattes noires (*Ixodes scapularis*) transmettent le *Borrelia burgdorferi* et l'*Anaplasma phagocytophilum* dans la province. Le présent cas est toutefois la première occurrence connue de *B microti* à tique, tant au Manitoba qu'au Canada. L'expansion du territoire de la tique occidentale à pattes noires renforce la pertinence de cette infection émergente. Les cliniciens, les praticiens de laboratoires médicaux et les directeurs de la santé publique devraient savoir que le *B microti* peut être transmis localement au Canada.

CASE PRESENTATION

A seven-year-old boy presented to the emergency department at the Winnipeg Children's Hospital (Winnipeg, Manitoba) on August 7, 2013, with a five-day history of fever (up to 39.5°C) and a headache. He also complained of mild anorexia and malaise. He experienced no other meningeal or respiratory tract symptoms and there was no nausea, vomiting or diarrhea. His urine output was maintained, although urine was darker than normal. He did not complain of arthralgias, arthritis or myalgias. No rash, jaundice or icterus had been noted by his parents. His medical history consisted of multiple congenital anomalies related to a midline defect syndrome that had not been formally diagnosed. These consisted of hydrocephalus treated with a ventriculoperitoneal shunt; panhypopituitarism; partially corrected tetrology of Fallot and dextrocardia; and asplenia secondary to mid-gut malrotation, which was surgically corrected at two weeks of age. The patient had travelled with his relatives to the southeast corner of Manitoba to stay at a cabin four weeks before the onset of symptoms. He did not recall specific tick bites but had numerous mosquito bites during the 48 h he was there. He did not report any other animal exposures. The patient had received blood transfusions for his surgeries during his first month of life, but not after.

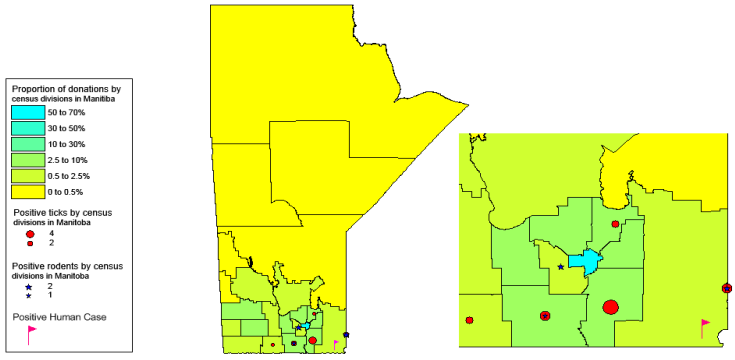
Screening blood tests, including electrolyte, urea and creatinine levels, were all within normal limits. His white blood cell count, hemoglobin and platelet levels were also normal. A manual slide review was performed due to abnormalities consistent with his asplenia, and a parasite believed to represent *Plasmodium falciparum* was noted. Blood smears were produced using the remaining blood sample. Numerous ring-form trophozoite parasites were observed within erythrocytes, and a lack of pigment and occasional tetrads/Maltese cross formations were noted (Figure 1). Based on these findings, and a lack of a significant travel history, identification was deemed to be consistent with *Babesia* species.

Twenty-four hours after initial evaluation, the patient was notified to return to the emergency department and the Pediatric Infectious Diseases Service was consulted. At this point, the patient was asymptomatic and the parasitemia level was determined to be 1%. He was diagnosed with mild babesiosis and prescribed a six-week course of atovaquone and azithromycin. Serology testing for *Borrelia burgdorferi* was ordered and found to be negative. Follow-up bloodwork was performed one week into his treatment course. At that time, the patient continued to have headache and intermittent, nonspecific abdominal pain. A mild anemia and slightly increased transaminase levels and bilirubin were noted. A blood specimen was collected and sent to the National Microbiology Laboratory for confirmation of *Babesia microti* infection, and to rule out infection with *B burgdorferi* and/or *Anaplasma phagocytophilum*. While polymerase chain reaction (PCR) was negative for the latter two organisms, real-time PCR was performed using primers that target the chaperonin-containing t-complex rna (CCTζ) (1) and subsequently confirmed using a second real-time PCR assay targeting the 18S ribosomal RNA gene (in-house/Applied Biosystems,

[1]*Cadham Provincial Laboratory, Manitoba Health;* [2]*Department of Medical Microbiology;* [3]*Department of Paediatrics and Child Health;* [4]*Department of Pathology, University of Manitoba;* [5]*Zoonotic Diseases and Special Pathogens, National Microbiology Laboratory, Winnipeg, Manitoba*

Correspondence: Dr Jared Bullard, 750 William Avenue, Winnipeg, Manitoba R3C 3Y1. Telephone 204-945-1306, fax 204-786-4770, e-mail jared.bullard@gov.mb.ca

Positive ticks and rodents with proportion of CBS donations by census divisions in Manitoba*



*Map courtesy of Robbin Lindsay, National Microbiology Laboratory, Public Health Agency of Canada

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What level of risk does Babesia microti pose to the blood supply in Canada?

- 2013 study conducted by Canadian Blood Services and Héma Quebec revealed:
  - Seroprevalence testing of 13,993 blood donors in affected regions indicated no positive donors

Conclusion: Current risk to blood supply is very low.

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Assessment team

Dr. Margaret Fearon, Director, Medical Microbiology

Dr. Sheila O'Brien, Associate Director, Epidemiology & Surveillance

Judie Leach Bennett, Director, Centre for Innovation

Sheila Ward, Partner, Industry Knowledge Integration

Stephanie Kelly, Senior Manager, Stakeholder Relations

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Assessment question

What are the **current** and **future** risks of babesia microti to Canadian blood donors and transfusion recipients and what are the **options** to address the risks to the Canadian blood supply?

What are **reasonable** short and long term **risk reduction strategies**, including surveillance and triggers for future action?

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Risk scenarios

Scenario 1 - Current state:
The risk of babesia is low. The risk is being managed through public health and tick surveillance coupled with periodic blood donor seroprevalence studies.

Scenario 2 - Potential future state:
The risk of babesiosis to the blood supply escalates and requires a more substantial mitigation response, over and above the ongoing prevalence surveillance.

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Risk Management Options

Scenario 1	Low risk: manage through public health and tick surveillance coupled with periodic blood donor seroprevalence studies
Option A	When risk is low, maintain surveillance (i.e. monitor public health surveillance for disease such as Lyme disease, ticks and human cases, in Canada and U.S.) and undertake enhanced surveillance in the form of a blood donor seroprevalence study every 3-5 years. Timing of the study will be guided by data emerging from ongoing surveillance such as increased babesiosis in U.S. states or human cases in Canada.

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Risk Management Options

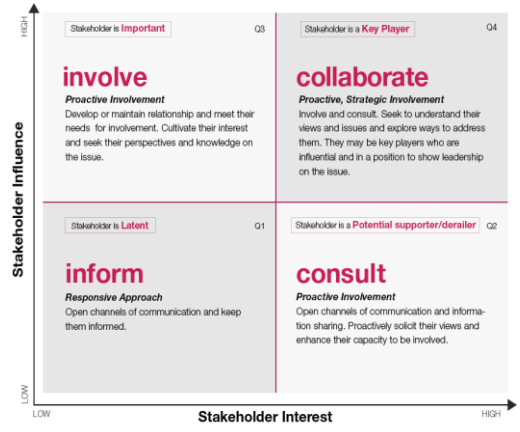
Scenario 2	Risk escalates: requires a more substantial mitigation response, over and above the ongoing prevalence surveillance.
Option B	If risk increases based on information from Options A, stop collecting blood from the risk area.
Option C	If risk increases based on information from A, undertake selective testing for babesiosis of a) donors living in high risk areas and b) travellers to US or Canadian risk areas.
Option D	Maintain a small inventory of babesia tested units for selected patients, e.g. neonates.
Option E	Implement universal testing for babesiosis.
Option F	Implement pathogen reduction technology.

Participation Strategy

3 Participation Strategy

Feedback from stakeholder consultation with National Liaison Committee, March 2016:

- Vector-borne threats becoming more common
- Good test run for this and future disease threats
- Response must be appropriate to threat level posed
- Regular communication with stakeholders will reduce fear around emerging threats
- Requires consistent funding and routine collection of surveillance data; support for investment for a proactive response
- Obtain donor consent for future tests to enable research and quick response



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What the analysis revealed - Scenario 1:

4 Assessments

- Risk to blood supply from babesia is very low; zero antibody positives amongst ~14,000 donors.
- Monitoring for increase in babesia should continue, including blood donor seroprevalence monitoring.
- Donor travel to endemic areas of the U.S. is currently the key risk factor for Canadian blood supply.
- Trigger to reassess risk level will be observed increase in level of babesia in general or donor population.

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What the analysis revealed - Scenario 2:

- Reasonable to assume experience in U.S. will be similar in Canada (transfusion transmissions, fatalities).
- There is no licensed universal test for babesia in Canada or the U.S.
- There is no pathogen reduction technology available to treat all fresh blood components.
- Donor travel questions, to prompt deferral, have not been very effective due to complexity/depth of questioning required.

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Mitigation option for Scenario 1

5 Evaluation

When the risk of B. microti is low, the risk mitigation provided by a Option A is considered tolerable:

- ongoing passive and active tick monitoring,
- blood donor seroprevalence studies every 3-5 years
- revisit the 3-5 year study timetable depending on developments with the tick data.

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Mitigation option for Scenario 2

The risk mitigation provided by Option C is the proposed option:

Introduce selective testing of donors living in high risk areas and travelers to the U.S. or Canadian risk areas.

- A reliable investigational test is available.
- Focus on regional risk balances effective mitigation against cost.
- More manageable operationally than ceasing collections in certain areas.
- Distributes a small risk across all inventory (i.e. that an infected donor may donate outside a high risk area).

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Decision

6 Decision

- EMT endorsed the recommendation of the assessment team
- They directed that a donor seroprevalence study should be conducted no later than 2918 to
  - Reassess the level of risk
  - Serve as a basis for developing a trigger to escalate migration efforts in accordance with Scenario 2
- EMT requested some knowledge mobilization about the application of the RBDM framework at CBS. Please follow the link below for more information on this case study. https://blood.ca/en/blog/2016-12/making-decisions-right-way-global-endeavour-part-1

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