Disclaimer:

What follows is a theoretical epidemiological investigation. It is not meant to be used directly for health-related decisions; if in need to take such a decision please seek professional medical advice.
1 Motivations
2 Modelization of the problem
3 Technical details: boundary condition
4 Results concerning the value function
5 Taking into account the individual decisions
   - Previous works
6 Individual cost function
7 Perspectives
Influenza A (H1N1) (flu) (2009-10)

- At 15/06/2010 flu (H1N1): 18,156 deads in 213 countries (WHO)
- France: 1334 severe forms (out of 7.7M-14.7M people infected)

Vaccination in France

- Adjuvant suspected of some neurological undesired effects; mass vaccination uncertainty (few previous studies for this size)
- Very costly campaign (500M EUR),
- Low efficiency (8% to 10% in France with respect to e.g., 24% US or 74% Canada).
**Example**: Influenza A in 2009 - 2010. Vaccination Coverage expected and realized in different countries on percentage of population: (See schedule 3 of the french parliamentary report number 2698)

<table>
<thead>
<tr>
<th>Countries</th>
<th>Target coverage</th>
<th>Effective rate of vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>100 %</td>
<td>10%</td>
</tr>
<tr>
<td>Belgium</td>
<td>100 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Spain</td>
<td>40 %</td>
<td>&lt; 4%</td>
</tr>
<tr>
<td>France</td>
<td>70 - 75 %</td>
<td>8.5 %</td>
</tr>
<tr>
<td>Italy</td>
<td>40 %</td>
<td>1.4 %</td>
</tr>
</tbody>
</table>
Vaccine scares

Previous vaccine scares (some have been disproved):
- France: hepatitis B vaccines cause multiple sclerosis
- US: mercury additives are responsible for the rise in autism
- UK: the whooping cough (1970s), the measles-mumps-rubella (MMR) (1990s).

Vaccine Scares: ”as cases of a disease decrease, people become complacent about their risk, and the threat of vaccines (imagined or real) seems greater than the threat of disease” (C. Bauch)

Question: individual decisions sum up to give a global response. How to model this?
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The SIR-V model

Figure: Graphical illustration of the SIR-V model. In this model all individuals are identical.

\[
\begin{align*}
\text{Susceptible} & \quad \rightarrow \quad \text{Infected} & \quad \rightarrow \quad \text{Recovered} \\
-\beta X_1 X_2 dt & \quad -\gamma X_2 dt \\
-dV & \\
\text{Vaccinated} &
\end{align*}
\]

Since \( X_1(t) + X_2(t) + X_3(t) + V(t) = cst = 1 \quad \forall t > 0 \), the variable \( X_3 \) is dependent on the others, we denote \( X = (X_1, X_2)^T \).

\[
\begin{align*}
\frac{dX_1}{dt} &= -\beta X_1 X_2 dt - dV(t) \\
\frac{dX_2}{dt} &= (\beta X_1 X_2 - \gamma X_2) dt \\
\frac{dX_3}{dt} &= \gamma X_2 dt \\
\frac{dV}{dt} &= dV.
\end{align*}
\]

**\( \beta \):** probability of contamination,

**\( \gamma \):** recovery rates,

**\( dV(t) \):** measure of vaccination
The vaccination model

Several possibilities to model vaccination:

⋆ $dV(t) = \lambda(t)X_1(t)dt$ : probability of individual vaccination in $[t, t + \Delta t]$ is $\lambda \Delta t$; $\lambda(t) \in [0, \lambda_{\text{max}}]$ or can also take value $\lambda \rightarrow \infty$ (for certain vaccination)

⋆ $dV(t) = u(t)dt$, a speed of vaccination model, $u(t) \in [0, u_{\text{max}}]$; then corresponding individual vaccination probability $\lambda(t)$ cannot be larger than $u(t)/X_1(t)$ (when this makes sense)

⋆ General case : $dV(t)$ is a (positive) measure on $[0, \infty]$; in particular $V$ can include (a countable set of) Dirac masses if vaccination of a non-negligible proportion of population can be instantaneous.

Number (proportion) of individuals vaccinated up to time $t$ is $\int_0^t dV(s)$; it is increasing which implies that $V$ is BV. This allows to give a meaning to the ODE (e.g., BV$^2$ functions would not be ok).
Vaccination cost functional

Cost for an infected person: \( r_I \).
Cost of the vaccine (including side-effects): \( r_V \).

Global cost for the society (from the initial state \( X_0 = (X_1(0), X_2(0))^T \)):

\[
J(X_0, V) = r_I \int_0^\infty \beta X_1 X_2 dt + r_V \int_0^\infty dV(t) \quad (1)
\]

It is an optimal control problem. The value function:

\[
\mathcal{V}(X) = \inf_{w \in \Omega} J(X, w)
\]

Here, \( \Omega \) is some set of admissible functions; e.g., measurable functions \( w: [0, \infty[ \to [0, u_{\text{max}}] \) and such as \( 0 \leq X_i(t) \leq 1, \forall t \geq 0, i \in \{1, 2\} \).
The value function $V$ must satisfy the HJB equation:

$$-\mathcal{H}(X, \nabla V) = 0$$

Let $X = (x_1; x_2)^T$ and $f(X, w) = (-\beta x_1 x_2 - w; \beta x_1 x_2 - \gamma x_2)$

$$\mathcal{H}(X, p) = \min_{w \in [0, u_{\text{max}}]} [f(X, w) \cdot p + r_l \beta x_1 x_2 + r_v w]$$

$$= -u_{\text{max}}(p_1 - r_v)_+ + \beta x_1 x_2(r_l + p_2 - p_1) - \gamma x_2 p_2.$$

But there is no a priori certainty that the solutions are $C^1$ (possible discontinuity introduced by $V$).
Existing literature

There has been a lot of work on this subject in the literature:

Abakuks, Andris, 1974 "Optimal immunisation policies for epidemics",
Behncke, Horst, 2000, "Optimal control of deterministic epidemics",
Funk, Sebastian and Salathé, Marcel and Jansen, Vincent A. A, "Modelling the influence of human behaviour on the spread of infectious diseases: a review"
C. T. Bauch, 2005, "Imitation dynamics predict vaccinating behaviour"
Hethcote, Herbert W. and Waltman, Paul, 1973, "Optimal vaccination schedules in a deterministic epidemic model"
Sethi, Suresh P. and Staats, Preston W., 1978, "Optimal control of some simple deterministic epidemic models",
Ledzewicz, Urszula and Schättler, Heinz, 2011, "On optimal singular controls for a general SIR-model with vaccination and treatment"
Andris Abakuks, 1972, "Some optimal isolation and immunisation policies for epidemics"

but none shows any regularity of the value function
Previous works show that optimal strategy is of the form: maximum intensity vaccination on $[0, \theta(X)]$. Thus $\mathcal{V}(X) = \mathcal{F}(X, \theta(X))$ with $\mathcal{F}$ regular.

The question is: Is $\theta(X)$ regular? Let us plot $\theta(X)$. 

Regularity issues

**Left image**: (zoom) vaccination time $\theta(X)$ for a particular choice of parameters.

**Right image**: multiple solutions exist on the frontier where $\theta(X)$ is not regular. The solid region is the vaccination region ($\theta(X) \geq 0$). The figure illustrates two strategies that are equivalent: the solid path corresponds to a no vaccination strategy, the dashed path to a partial vaccination strategy; both have same cost, i.e., non-uniqueness of the optimal strategy.

Generic results suggest that the solution will not be $C^1$. The derivation under $C^1$ hypothesis has to be checked under weaker assumptions (or hypothesis to be proved).

We use the concept of **viscosity solution** introduced by Pierre-Louis Lions and Michael Crandall (1992, 1997). Widely used for the optimal control problem.
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On red boundary there is no natural boundary condition to use. If the system starts e.g., with $X_2 = 0$ on the red boundary it will remain with $X_2 = 0$ at all times but this behavior is unstable. As soon as $X_2(0) > 0$ (even very very small) and $X_1(0) > \gamma/\beta$ the value function takes large values (larger than $\min(r_i, r_V)(X_1(0) - \gamma/\beta)$) and do not converge to zero when $X_2(0)$ tends to 0.

The black arrow indicates the typical evolution of the SIR system; all trajectories converge to points on the green boundary.
The cost function $J(X_0, V) = \int_0^\infty \beta X_1 X_2 r_1 dt + \int_0^\infty r \cdot dV(t)$ has no dumping term, need to work in infinite horizon. This is a problem when trying to obtain Lipschitz regularity for the value function.

In general, a convenient hypothesis (cf. also Crandall, Ishii, Lions [1992]) for the uniqueness of $F(x, V, DV) = 0$ is that $F$ be strictly monotone in the second argument. Here $H$ does not depend on this argument.
Other technicalities : solutions

- The boundary problem : prove uniqueness on increasing domains $D_\alpha$ converging to full domain :

  $\begin{align*}
  X_2 &
  \downarrow \\
  1 &
  \\
  A &=(\gamma/\beta,0) \\
  0 &
  \\
  B_\alpha &=(1-\alpha,\alpha) \\
  D_\alpha &
  \end{align*}$

- No dumping term : note that the vaccination time is less than $T_{\text{max}} = 1/u_{\text{max}}$ and vaccination occurs at the beginning. Thus on $[0, T_{\text{max}}]$ obtain Lipschitz estimates for the value function and then use properties of $J(X,0)$ (because control is null after $T_{\text{max}}$);

- Non-monotonicity of $F$ : change of variables (Kružkov) $\nu \mapsto 1 - e^{-\nu}$. 
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Results obtained:

⋆ the HJB equation admits a unique solution; furthermore the solution is $C^1$ for $r_V < r_V^{crit}$, otherwise it is Lipschitz.

⋆ explicit construction for the solution and the optimal vaccination strategy;

⋆ rigorous justification of the limit $u_{max} \to \infty$;

Global optimal vaccination strategy: decomposition in vaccination and non-vaccination region. The non vaccination is attractive.
Results for $\gamma/\beta = 0.5$

Optimal strategy for $r_V = 0.5r_I$.

Optimal strategy for $r_V = 1.1r_I$.

This calls for asking the nature of optimality: how can be optimal to vaccinate someone when $r_V > r_I$?
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Taking into account the individual decisions: previous literature

Bauch & Earn (PNAS 2004) consider the SIR-V model with births and deaths:

\[
\begin{align*}
  dS &= \mu(1 - p) - \beta SI dt - \mu S \\
  dI &= (\beta SI - \gamma I) dt - \mu I \\
  dR &= \gamma I dt - \mu R \\
  dV &= \mu p.
\end{align*}
\]

- \( \beta \): probability of contamination,
- \( \gamma \): recovery rates,
- \( dV(t) \): measure of vaccination
- \( \mu \): the birth / death rate
- \( p \): the probability to vaccinate at birth

★ the vaccination is at birth only (probability \( p \)); at equilibrium vaccination occurs when the probability to be infected \( \geq r_V/r_I \).
★ no time dependence; individual strategies are rather simple.
★ equilibrium ok if everybody does the same
★ no eradication possible through voluntary vaccination, endemic state (coherent with literature)
★ “vaccine scare behavior” : let other vaccinate (when perceived risk differs from that of majority)
Taking into account the individual decisions: previous literature

Galvani & Reluga & Champan (PNAS 2006) consider a double SIR-V periodic model of flu with two age groups (break at 65yrs). Vaccination is separated from dynamics, once at the beginning of each season.

Results: show that actual vaccine coverage is consistent with individual optimum; explain impact of age-targetted campaigns (children).
Bauch (2005):

- time dependent vaccination rate $p(t)$;

- probability to be infected is approximated by a “rule of thumb” (proportional to $I(t)$);

- the corresponding dynamics is a phenomenological proposal ($m$ a parameter):

$$\frac{dp(t)}{dt} = kp(1 - p)(mrI(t) - rV)$$
Remarks on the individual vaccination strategy:

- the simplest one: vaccinate now or never; simple but is it always optimal? stable equilibrium?
  Equilibrium vision: all individuals are the same if one vaccinates everybody does (100% coverage!!!) ... free ride effect.

- a naive one: “vaccinate with certainty at some given instant in the future, instant that can be computed now”: naive because the individual level equations are RANDOM processes. Suppose optimal vaccination time is \( t \), one is not sure to not be infected by time \( t \).

- more realistic: mixed probabilistic strategies: the individual has a probability \( \lambda_I(t)\delta t \) to vaccinate in the time interval \([t, t + \delta t]\)
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Individual cost functional

\[
\begin{align*}
    dX_1 &= -\beta X_1 X_2 dt - u_G(t) dt \\
    dX_2 &= (\beta X_1 X_2 - \gamma X_2) dt \\
    dX_3 &= \gamma X_2 dt \\
    dV &= u_G(t) dt.
\end{align*}
\]

vaccination at the society level with rate \(u_G(t)\).

Individual decision: the strategy \(\lambda_I\) (truncated at \(\frac{u_{\text{max}}}{X_1(t)}\) cf. above).

\[
dU(t) = (-\beta X_2 - \lambda_I) U(t) dt.
\]

\(U(t) = \) survival rate of the susceptibles (the "probability" to not be infected neither vaccinate up to time \(t\), i.e., percentage still in class \(X_1\)).

\[
J_I(\lambda_I) = \int_0^\infty U(t) [r_1 \beta X_2 + r_V \lambda_I] dt.
\]

\(J_I = \) the cost functional for the individual

Equilibrium condition for the global strategy to arise from individual decisions: \(u_G(t) = \lambda_I(t) X_1(t)\). (when this operation makes sense) (Mean Field Games, cf. Lasry, Lions!).
Theoretical results:

★ the individual vaccination is at the beginning
\[ \lambda_I = \frac{u_{max}(t)}{X_1(t)} \cdot 1_{[0,\theta_I(X)]}(t); \]

★ to optimize for equilibrium \( t \mapsto J_I(X, \frac{u_{max}(\cdot)}{X_1(\cdot)} \cdot 1_{[0,t]}(\cdot)); \) non-smooth (not \( C^1 \));

★ technical remark: the overall infection risk \( \int_t^\infty \beta X_1(\tau) X_2(\tau) d\tau \)
  (depending on \( u_G \)) is decreasing with respect to time (convexity for \( t \mapsto J_I(\ldots) \)).

★ a stable equilibrium exists, no free-ride effect

★ at equilibrium the optimal switch point is also \( \int_t^\infty \beta X_1(\tau) X_2(\tau) d\tau \)
  \[ \frac{X_1(t)}{X_1} = \frac{r_v}{r_I} \]

★ the frontier of the vaccination region is the surface \( \zeta(X_1, X_2) = \frac{r_v}{r_I} \).

Here \( \zeta(X) \) is the size of a non-controlled epidemic starting from \( X \).
Remark: vaccination region independent of $u_{max}$ (!), can pass easily to the limit $u_{max} \to \infty$.

Mean cost for an individual in the stable individual-global equilibrium is larger than the cost for the, non stable, societal (non-individual) equilibrium. The stable strategy will be preferred even if it is more costly for everyone.

Red: vaccination in the first model and in the individual model, green: vaccination for the first model but not for the individual, blue: no vaccination in both models.
The SIR model was fit to the observed vaccination coverage (J.P. Guthman et al. BEH 2010); the other parameters were chosen consistent with ranges from the literature (large CIs!). Time axis = weeks starting from W19Y2009; peak = W49Y2009 (30), vaccination peak = W51Y2009 (31-32), vaccination end W05Y2010 (40).
The results indicate that the first ones to stop vaccination were people in a group with $r_V/r_I \approx 10\% - 15\%$ (week 32). The last one correspond to $r_V/r_I < 1\%$ (week 40; model cannot be more precise with available data).
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Work in progress and perspectives

- More general strategies,
- Birth / deaths taken into account,
- Structured population models: age, geographical location,
- Stochastic dynamics,
- Impact of the societal penalty for non-vaccination; do we obtain the (societal, non individual) solution even for $r_V \geq r_I$?
- ...

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