Epidemics 8 (2014) 28–40

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

Speed versus coverage trade off in targeted interventions during an outbreak

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ARTICLE INFO

Article history:
Received 23 September 2013
Received in revised form 1 April 2014
Accepted 14 May 2014
Available online 15 August 2014

Keywords:
Outbreak control
Influenza
Timeliness
Coverage
Sensitivity
Diagnostic

ABSTRACT

Which case-based intervention measures should be applied during an epidemic outbreak depends on how timely they can be applied and how effective they are. During the course of each individual's infection, the earlier control measures are applied on him/her the more effectively further disease spread can be prevented. However, quick implementation can lead to loss of efficacy or coverage, e.g., when individuals are targeted based on rapid but poorly sensitive diagnostic tests in place of slower but accurate PCR tests. To analyse this trade off between speed and coverage we used stochastic models considering how the individual reproduction density is modified by interventions. We took as example the case-based intervention strategy employed in the Netherlands during the beginning of the H1N1 pandemic. Suspected cases were isolated and samples were collected for PCR diagnosis. In case of positive diagnosis, antiviral drugs were provided to contacts as post-exposure prophylaxis. At the time there were also rapid influenza diagnostic tests (RIDTs) available which provided results within an hour after sample collection compared to a median of 2.7 days for PCR tests, but they were less sensitive. We studied how interventions based on RIDTs with various sensitivities affect the outbreak size and how these compare to PCR diagnosis based interventions. Using an intervention based on a bedside RIDT with 60% detection ratio or a laboratory RIDT with 70% detection ratio is as effective as the most effective PCR-diagnosis based intervention. Relative performances of interventions are not dependent on the basic reproduction number R_0 but only on distributions of individual reproduction density and of delay periods. The individual reproduction density combines R_0 and infection time distribution, both crucial in determining the impact of case-based interventions during epidemic outbreaks.

Introduction

Different types of intervention can be applied during epidemic outbreaks in an attempt to reduce outbreak effects, such as final size, incidence, prevalence, morbidity and mortality. Case-based interventions are focused around infected individuals. They are applied at a time which is specific for each individual, depending on when he/she is identified (or suspected) as infected, and reduce the individual's infectious potential from then on. For example, isolation, quarantine, post-exposure prophylaxis of infected and traced contacts would be case-based interventions.

Success of a case-based intervention in reducing the number of subsequent infections is directly linked with how timely it is implemented and how complete the implementation coverage is: the earlier the implementation and the higher its coverage, the more effective the intervention is. But there are situations where a quicker intervention implementation is only possible at the cost of coverage loss and vice versa, e.g., when the intervention is based on a quicker but less sensitive diagnostic test versus a slower but more

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http://dx.doi.org/10.1016/j.epidem.2014.05.003

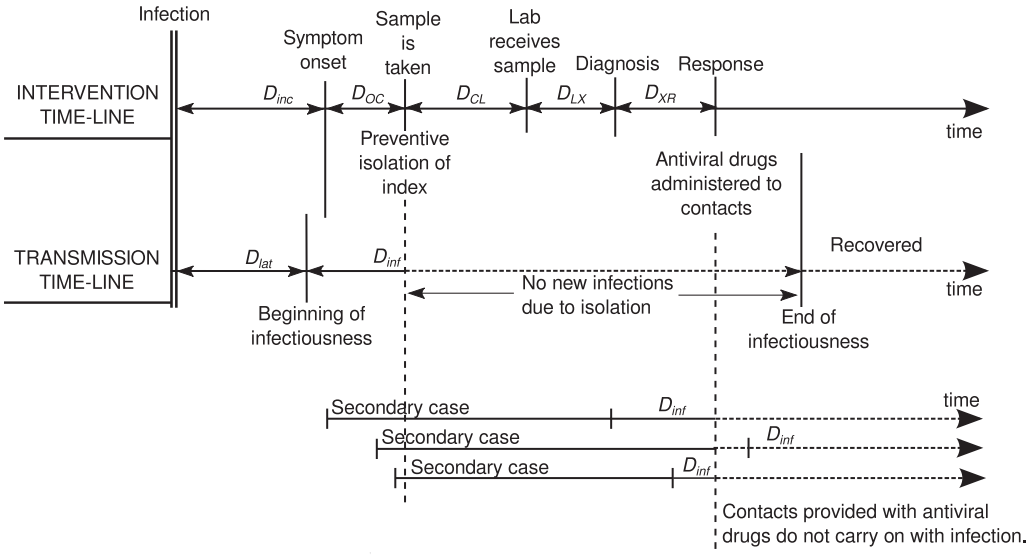

Fig. 1. Schematic time-line of the intervention applied to positively diagnosed individuals and to their high risk contacts from the moment of infection of the index case. Durations of different periods are indicated as D_{lat} for latency (individual infected but not yet infectious), D_{inf} for infectious, D_{inc} for incubation (time to symptom onset), D_{OC} for period between symptom onset and consulting the general practitioner (which coincides with the collection of samples for diagnosis), D_{CL} time for transporting samples to the laboratory, and D_{LX} time between arrival to laboratory and diagnosis result, D_{XR} time to apply response on contacts after a diagnosis is positive.

sensitive diagnosis. Because of this trade-off it is not directly clear which kind of diagnostic test would render a case-based intervention more effective.

We analysed the case-based intervention strategy implemented in the Netherlands during the beginning of the H1N1 pandemic. In combination with providing general hygiene advice when novel influenza A (H1N1) was detected in the Netherlands, a case-based intervention plan was put in place to contain the spreading of the new influenza virus (Hahné et al., 2009). Fig. 1 shows a schematic time-line of the intervention. Suspected cases were isolated while samples were transported to specialised laboratories for diagnosis by polymerase chain reaction (PCR) tests (Meijer et al., 2009; van Asten et al., 2009). High risk contacts of suspected cases were located and in case of a positive diagnosis anti-viral drugs were administered to them as post-exposure prophylaxis (PEP). PCR diagnostics sensitivity is less than ideal given that the viral load content of field collected samples is highly variable and dependent on the infection-age at which it is collected [e.g., van Boven et al., 2010]. But given appropriate influenza viral RNA samples, the typing of novel influenza A (H1N1) based on PCR has a high sensitivity [e.g., Vinikoor et al., 2009, Bouscambert Duchamp et al., 2010]. Therefore, PCR diagnostic tests are considered the gold standard method to evaluate sensitivity of other diagnostic techniques. However, besides the need for specifically dedicated personnel, laboratory and equipment, PCR tests are time consuming: Although one PCR diagnostic test can take up to 8 h in the laboratory (from receiving the sample to reporting the test result), the time between sample collection and reporting the result is considerably extended due to transport, queueing, working schedules and other logistics. At the time there were also commercially available, widely used, rapid influenza diagnostic tests (RIDTs). These tests are portable, have no need of specialised resources or personnel, and provide a result within the hour. RIDTs can be performed at the bedside or as quick tests at laboratory locations [e.g, Crawford et al., 2010]. However, despite their speed and ease of use, RIDTs were discarded as reliable diagnostic tests in the Netherlands because their overall sensitivity to novel influenza A (H1N1) viral antigens was between 40% and 69% when compared to the PCR gold standard technique (Balish et al., 2009; Jernigan et al., 2011).

The question arises whether and when using RIDTs in place of PCR tests for diagnosis of the novel influenza A (H1N1) would have rendered the applied interventions more effective. To answer this question we used stochastic models of H1N1 influenza outbreaks that follow each infector individually, from the moment he/she has been infected. The models include the concept of individual reproduction density, which is the rate of infections produced per unit time by an infector at any given infection-age (the time passed since becoming infected). This provides flexibility to follow the new cases each infector will generate as his/her individual reproduction density can be modified depending on whether and how late after infection an intervention is applied onto him/her. We analysed the results of our models to determine which diagnostic test would have rendered the intervention more effective in reducing the growth of the epidemic, depending on diagnostic test speed and sensitivity.

Methods

We modelled the Dutch situation at the introduction of the novel influenza A (H1N1) in 2009 by assuming implementation of intervention measures based on RIDTs performed at the bedside and based on RIDTs performed at laboratory locations with varying sensitivities. We compared these results to those from models assuming implementation of intervention measures based on the standard PCR diagnosis. To evaluate the performance of the different interventions we focused on the attack rate: the lower it is the better the performance of the intervention is.

Individual reproduction density and interventions

The basic reproduction number, R_0, indicates the average number of new infectees that a random infector produces during his infectious period in a completely susceptible population, in the absence of any intervention. If $R_0 < 1$ an outbreak will die out without becoming large, but if $R_0 > 1$ it is likely that the outbreak becomes large, i.e., affects a significant fraction of the population. The individual reproduction number corresponds to the expected number of new infectees that a particular infector produces during his infectious period (Lloyd-Smith et al., 2005). We write the individual reproduction number of a particular infector as R_j. We denote with a subscript j all quantities corresponding to a particular subject j, meaning that these quantities tend to vary among