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NOSOCOMIAL INFECTIONS AND THEIR MODELS: A NARRATIVE REVIEW

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ABSTRACT

Nosocomial infections also known as hospital acquired infections or healthcare associated infections pose significant burden on global healthcare system. These infections occur from interactions between patients, healthcare workers, the hospital environment and other users of the hospital. Mathematical modeling has proved to be an important tool for investigating the dynamics and assessing the impact of intervention strategies.

This narrative review focuses on deterministic and stochastic modeling of nosocomial infection transmission, with emphasis on variables and transmission pathways used in existing models. Relevant literatures were identified through search of major scientific database, using keywords related to models of nosocomial infections.

Although these modeling approaches contributed significantly to the study of the dynamics of nosocomial infections, they do have some limitations. This study reviewed existing models of nosocomial infections; highlighted key variables studied, and also identified gaps in the literature. The study revealed the need to include other contact patterns to enhance the understanding and control of nosocomial infections.

INTRODUCTION

Hospitals are primarily intended to be places of healing, where patients receive care that alleviates or cures their illnesses. Unfortunately, the hospital environment itself is often a significant source of infection. Patients, healthcare workers, visitors, and even family caregivers face risks of acquiring infections through various transmission pathways within healthcare settings.

In many cases, individuals admitted for one condition may develop additional infections unrelated to their initial illness; such infections are referred to as nosocomial infections, also known as hospital-acquired infections (HAIs) or healthcare-associated infections (HCAIs) [1].

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Common examples include urinary tract infections (UTIs), surgical site infections (SSIs), wound infections (WIs), and ventilator-associated pneumonia (VAP), etc. These infections are frequently caused by bacterial pathogens such as Staphylococcus aureus, Escherichia coli, and Enterococci etc.

Globally, nosocomial infections are among the major cause of morbidity and mortality among hospitalized patients [2]. According to World Health Organization Report [3], nearly 3.5 million people can lose their lives due to nosocomial infections every year up to 2050. This corresponds to 4.4 times the number of global deaths in 2021 due to human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) and sexually transmitted diseases combined. A global surveillance study across 204 countries and territories in 2019 reported that 4.95 million deaths were associated with various forms of nosocomial infections. The study further revealed that Western Sub-Saharan Africa had the highest mortality rate at 27.3 deaths per 100,000, while Australia recorded the lowest with 6.5 deaths per 100,000 [4]. In Nigeria, a recent review estimated that approximately 15.75% of hospitalized patients in Nigeria acquire nosocomial infection [5]. Also, in [6] a point-prevalence survey conducted across three acute care hospitals in Northern Nigeria, reporting 50 cases of HAIs among 321 patients, with an overall prevalence of 14.3%.

The transmission of nosocomial infections is complex, as it involves multiple interacting components within a healthcare environment. The basic transmission pathway for nosocomial infections is primarily the interactions between patients and healthcare workers, as well as contamination from the hospital environment ([7] and [8]). In many healthcare settings, especially low-income and middle-income countries, other actors such as informal caregivers and even visitors, play non-negligible but under estimated role in the transmission process. These additional pathways further influence the dynamics of the infection and highlight the need for more robust models.

Mathematical models have been used over centuries as a vital tool for understanding the transmission dynamics of infectious diseases ([9] and [10]) and have also been applied widely for modeling the spread of nosocomial infections ([7] and [8]). This is achieved by representing populations and their interactions through mathematical structures in order to identify key factors responsible for the spread of diseases and develop frameworks for evaluating intervention methods [11]. Deterministic models formulated using ordinary differential equations have been widely applied to describe the dynamics of infections within hospital settings ([12], [13] and [14]). These models are based on key variables and parameters necessary to capture the progression of disease within and between compartments. Through these variables and parameters, deterministic models give insights into threshold quantities, like the basic reproduction number, and equilibrium analysis.

Unlike deterministic models, stochastic models capture the inherent randomness in the transmission dynamics of nosocomial infections within the hospital. This approach is particularly suitable for hospital settings, where the population size is relatively small and chance events can significantly influence outcomes. According to [8], stochastic formulations often provide deeper insights into epidemic behavior in small populations compared to purely deterministic models. In general, stochastic epidemic models are developed as probabilistic counterparts of their deterministic analogues, by defining the rates at which transitions (or “jumps”) occur between compartments over infinitesimally small time intervals [15]. The stochastic framework also depends on variables and parameters governing the transmission process to define its transition probabilities. Though deterministic and stochastic models have been used extensively in modeling nosocomial infection's transmission, existing models have always concentrated on limited set of transition pathways, mostly the patient-healthcare worker's interaction ([7] and [8]). This has resulted in the underrepresentation of other viable transmission pathways. This narrative review will exhaustively examine the variables and transmission pathways in existing deterministic and stochastic models of nosocomial infections and emphasize the need to incorporate additional transmission pathways, to improve the accuracy of infection control strategies in a healthcare setting.

1.1 Eligibility Criteria

In developing this narrative review, relevant literature on mathematical modeling of nosocomial infections was identified through searches of major scientific databases, including PubMed, Scopus, Springer, and Google Scholar. The search was conducted using combinations of keywords such as nosocomial infections, hospital-acquired infections, healthcare-associated infections, deterministic models, and stochastic models. Emphasis was placed on studies published within the last two decades, while earlier works were also included to provide foundational context. Studies were included if they focused on mathematical or compartmental models of infection transmission within healthcare settings and provided explicit descriptions of model variables, parameters, or transmission pathways. Studies that did not involve modeling approaches, healthcare infections, or were not peer-reviewed were excluded. This study adopts a narrative review approach, but these criteria were applied to ensure the relevance and quality of the literature considered.

2.0 DETERMINISTIC AND STOCHASTIC MODELS OF NOSOCOMIAL INFECTIONS

Healthcare workers were recognized as key agents in the transmission of nosocomial infections [16], were they played a central role in infection dynamics. The host-vector malaria model originally developed by [17] and [18], where transmission occurs via a vector, the Anopheles mosquito has been adopted to model the transmission of nosocomial infections. This framework has since been adapted to describe hospital-acquired infections, with healthcare workers (HCW's) serving as transient "vectors" of transmission between patients.

In the nosocomial infection context, pathogens are assumed not to spread directly from patient to patient but through the contaminated hands of HCW's. Transmission occurs when a contaminated healthcare worker (H_c) comes in contact with an uncolonized patient(P_u), or when a colonized patient (P_c) interacts with an uncontaminated healthcare worker(H_u). Decontamination of H_c back to H_u takes place through intervention measures such as proper hand washing.

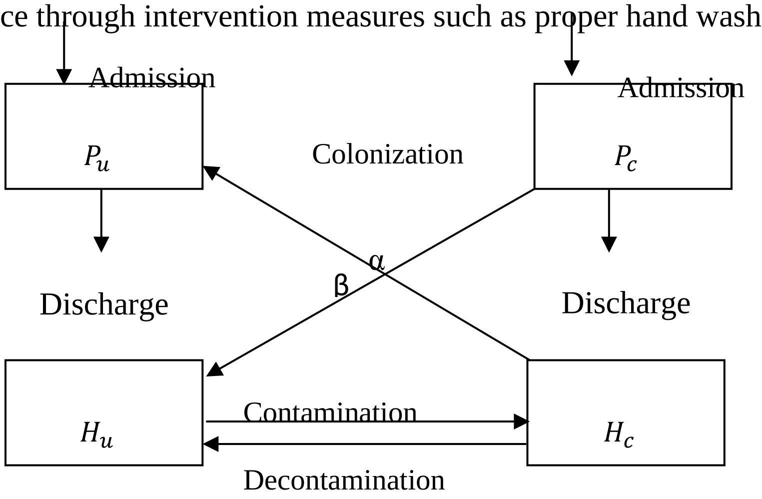

Figure 1: Compartmental flow diagram of the nosocomial infection transmission model

The key adjustment in Figure 1, compared with [17] and [18] host–vector model, is the inclusion of patient flow, that is, the admission and discharge of both colonized and uncolonized patients. This framework forms the foundation for developing more detailed models of nosocomial infection transmission.

Researchers have modeled the transmission of nosocomial infections using compartmental mathematical frameworks, often based on sporadic contact patterns between patients and healthcare workers ([19] and [7]). The foundational works in modeling hand-borne nosocomial infections are studies by [19] and [8]. These models studied the transmission of nosocomial pathogens using the basic nosocomial variables, the colonized and uncolonized patients, and the contaminated and uncontaminated healthcare workers. Subsequent models made some adjustments in the studied variables and considered incorporating, antimicrobial resistance, treatment dynamics, hospital and community reservoirs, professional volunteers, environmental contamination and bacteria load, exposed population, hospitalized population and community-infected populations as variables.

2.1 Foundational Deterministic and Stochastic Models of Nosocomial Infections

Early models of nosocomial infections as given by [19] gave a compartmental mathematical model of the nosocomial pathogen, Vancomycin-resistant enterococci (VRE) in intensive-care hospital settings. They studied the dynamics of this pathogen using the four basic compartmental variables, colonized (Y_p) and uncolonized (X_p) patients and contaminated (Y_h) and uncontaminated (X_p) HCW's and concluded that compliance to hand washing and cohorting of nursing staff are needed to prevent nosocomial transmission of VRE in endemic settings. . The model is given as

$$
\begin{aligned}
\frac{dX_p}{dt} &= \Lambda(1-\phi) - \gamma X_p - ab_p X_p Y_h \\
\frac{dY_p}{dt} &= \Lambda\phi - \gamma' Y_p + ab_p X_p Y_h \qquad (1) \\
\frac{dX_h}{dt} &= -ab_h X_h Y_p + \mu Y_h \\
\frac{dY_h}{dt} &= -\frac{dX_h}{dt}
\end{aligned}
$$

In [7] a mathematical model to describe the spread of hand-borne nosocomial pathogens such as Staphylococcus aureus, within a general medical–surgical ward was given. Unlike previous models, their work introduced a stochastic framework for studying nosocomial transmission. The basic model consisted of colonized patients(y), uncolonized patients(x), contaminated healthcare workers(y'), and uncontaminated healthcare workers (x'). From this deterministic structure, they derived a stochastic equivalent by converting rates into discrete variables with continuous time. Analysis of the stochastic model revealed that even small changes in pathogen transmissibility led to substantial differences in introduction rates, ward-level prevalence, and the number of colonized patient-days. The deterministic model is as follows:

$$
\begin{aligned}
\frac{dx}{dt} &= (1-\sigma)(\mu x + \mu y + \gamma y) - \beta x \frac{y'}{n'} + (1-\sigma)(\mu+\gamma)y \\
\frac{dy}{dt} &= \sigma(\mu x + \mu y + \gamma y) + \beta x \frac{y'}{n'} - (1-\sigma)(\mu+\gamma)y \qquad (2) \\
\frac{dx'}{dt} &= -\beta' y \frac{x'}{n'} + \mu' y'
\end{aligned}
$$

$$\frac{dy'}{dt} = \beta' y \frac{x'}{n'} - \mu' y'$$

The equivalent stochastic process is,

$$\begin{aligned}
&\Pr\{[Y(t+\Delta t), Y'(t+\Delta t)] = [i+1, j] \parallel [Y(t), Y'(t)] = [i, j]\} \\
&\qquad\qquad = \frac{\beta(n-i)j\Delta t}{n'} + \sigma(\mu n + \gamma i)\Delta t + o(\Delta t) \\
&\Pr\{[Y(t+\Delta t), Y'(t+\Delta t)] = [i, j+1] \parallel [Y(t), Y'(t)] = [i, j]\} = \frac{\beta' i(n'-j)\Delta t}{n'} + o(\Delta t) \qquad (3) \\
&\Pr\{[Y(t+\Delta t), Y'(t+\Delta t)] = [i-1, j] \parallel [Y(t), Y'(t)] = [i, j]\} = (1-\sigma)(\mu+\gamma)i\Delta t + o(\Delta t) \\
&\Pr\{[Y(t+\Delta t), Y'(t+\Delta t)] = [i, j-1] \parallel [Y(t), Y'(t)] = [i, j]\} = \mu' j\Delta t + o(\Delta t)
\end{aligned}$$

These models, regardless their robustness, are limited by exclusion of other potential transmission routes, like environmental effect, and informal caregivers.

2.2 Models Incorporating Antimicrobial Resistance and Treatment Sites

A nosocomial infection on the effect of antimicrobial cycling was given in [12]. Here, when two or more antibiotic classes are alternated within a period of months to years to checkmate the spread of nosocomial infections in the hospital. They developed a mathematical model consisting of four compartments X, the uncolonized patients, S, the colonized patients, R_1, patients colonized by the strains resistant to drug1 , and R_2 , patients colonized by strains resistant to drug2. They concluded that cycling is unlikely to reduce either the incidence or spread of nosocomial infections but noticed that other strategies like mixing were each patient receives one of the drug classes simultaneously in the hospital yields better result.

The model is as follows,

$$\begin{aligned}
\frac{dS}{dt} &= (m-S)\mu - (\tau_1+\tau_2+\gamma)S + \beta SX + \sigma\beta(c_1R_1 + c_2R_2)S \\
\frac{dR_1}{dt} &= (m_1-R_1)\mu - (\tau_2+\gamma)R_1 + \beta(1-c_1)R_1X - \sigma\beta(c_1S + (c_1-c_2)R_2)R_1 \\
\frac{dR_2}{dt} &= (m_2-R_2)\mu - (\tau_1+\gamma)R_2 + \beta(1-c_2)R_2X - \sigma\beta(c_2S + (c_2-c_1)R_1)R_2 \qquad (4) \\
\frac{dX}{dt} &= (1-m-m_1-c_1-X)\mu + (\tau_1+\tau_2+\gamma)S + (\tau_2+\gamma)R_1 + (\tau_1+\gamma)R_2 - \beta X(S + \\
&\quad (1-c_1)R_1 + (1-c_2)R_2)
\end{aligned}$$

In [20], a deterministic model on nosocomial infection was formulated using a discrete time Markov chain model to describe the dynamics of Methicillin Resistant Staphylococcus Aureus (MRSA) in ICUs. They demonstrated that precautions through topical antibiotics application of nonabsorbable antibiotics, with the aim of reducing antibiotic resistance at the population level, can only be effective when (i) a high percentage of newly admitted patients are colonized and (ii) cross-transmission rates in the ward are low. Their findings claimed to represent a firm theoretical argument against the routine use of topical antimicrobial prophylaxis for infection control.

They described three different sites of colonization, that is, the skin (S), the gut (G) and the lungs (L). Hence they classified each patient in the ICU with these eight different labels: 0, G, S, L, GS, GL, SL and GSL, leading to eight-compartmental model.

$$\begin{aligned}
\dot{x}_0 &= \mu p_0 - (\sigma I + \mu)x_0 \\
\dot{x}_G &= \mu p_G - (\sigma I + \alpha_{GS} + \mu)x_G \\
\dot{x}_S &= \mu p_S + \sigma I x_0 - (\alpha_{SG} + \alpha_{SL} + \mu)x_S
\end{aligned}$$

$$
\begin{aligned}
\dot{x}_L &= \mu p_L - (\sigma I + \alpha_{LS} + \mu)x_L \\
\dot{x}_{GS} &= \mu p_{GS} + (\sigma I + \alpha_{GS})x_G + \alpha_{SG}x_S - (\alpha_{SL} + \mu)x_{GS} \\
\dot{x}_{GL} &= \mu p_{GL} - (\sigma I + \alpha_{GS} + \alpha_{LS} + \mu)x_{GL} \\
\dot{x}_{SL} &= \mu p_{SL} + (\sigma I + \alpha_{LS})x_L + \alpha_{SL}x_S - (\alpha_{SG} + \mu)x_{SL} \\
\dot{x}_{GSL} &= \mu p_{GSL} + (\sigma I + \alpha_{LS} + \alpha_{GS})x_{GL} + \alpha_{SL}x_{GS} + \alpha_{SG}x_{SL} - \mu x_{GSL}
\end{aligned}
\tag{5}
$$

These models included rotation of administration patterns of antimicrobial drugs and considered different sites of infection. They are largely patient-centered with no consideration of other transmission routes.

2.3 Models Linking Hospital and Community Reservoirs

A nosocomial infection model by [21] considered both hospital and community reservoirs of MRSA colonization. They used mathematical models to describe the dynamics of MRSA in seven compartments, the colonized patients in the hospital (y) , the uncolonized patients in the hospital (x), the isolated patients in the hospital (z) , the colonized patients in the community with high readmission rate (y_c) , the uncolonised patients in the community with high readmission rate (x_c) , the colonized patients in the community with low readmission rate (y_c') , and the uncolonized patients in the community with low readmission rate (x_c') .

They showed that prompt and effective patient isolation can contribute to control by reducing transmission. The model is given below.

$$
\begin{aligned}
\frac{dy}{dt} &= \beta xy - \lambda y + v y_c + \xi y_c' - \mu y - \Phi(y,z) \\
\frac{dx}{dt} &= -\beta xy + \lambda y + v x_c + \xi x_c' \\
\frac{dz}{dt} &= \Phi(y,z) - pz \\
\frac{dy_c}{dt} &= \mu y + p(1-\pi)z - (v + \lambda + \gamma)y_c \\
\frac{dx_c}{dt} &= \mu x + \lambda y_c + p\pi z - (v + \gamma)x_c \\
\frac{dy_c'}{dt} &= \gamma y_c - (\xi + \lambda)y_c' \\
\frac{dx_c'}{dt} &= \gamma x_c + \lambda y_c' - (\xi + \lambda)x_c'
\end{aligned}
\tag{6}
$$

This model studied the colonization of patient's both in the hospital and community with their readmission rates and isolation effect. Though it gave an important extension beyond hospital-based models but did not address the role of the environment and informal caregivers in the transmission dynamics of nosocomial infections.

2.4 Stochastic Models for the Transmission of Nosocomial Infections in ICU

A stochastic model developed by [22] estimated the transmission rate of MRSA in an intensive care unit (ICU). They formulated a mathematical method consisting of four compartments, the colonized patients(Y_p), uncolonized patients(X_p), contaminated HCW's (Y_h) and uncontaminated HCW's (X_h).

The hand hygiene compliance was dictated to be the most effective intervention method. Declonization was predicted to be somewhat infective and increasing the number of HCW's was seen to increase the transmission of MRSA, in the absence of patient cohorting.

The model is as follows,

$$
\frac{dX_p}{dt} = (1-\sigma)\Omega + dY_p - cp_{hp}X_pY_h - \mu X_p
$$

$$\frac{dY_p}{dt} = \sigma\Omega + cp_{hp}X_pY_h - \mu'Y_p - dY_p \tag{7}$$
$$\frac{dX_h}{dt} = -cp_{ph}X_hY_p + \kappa Y_h$$
$$\frac{dY_h}{dt} = cp_{ph}X_hY_p - \kappa Y_h$$

The stochastic model constructed as,

$$\begin{aligned}
&\Pr\big(Y_p(t+\delta) = i+1\big|Y_p(t) = i\big) = cp_{hp}\big(n_p - i\big)\overline{Y_h}\delta + \mu\sigma\big(n_p - i\big)\delta + o(\delta)\\
&\Pr\big(Y_p(t+\delta) = i-1\big|Y_p(t) = i\big) = \big(d + \mu'(1-\sigma)\big)i\delta + o(\delta)\\
&\Pr\big(Y_p(t+\delta) = i\big|Y_p(t) = i\big) = 1 - cp_{hp}\big(n_p - i\big)\overline{Y_h}\delta - \mu\sigma\big(n_p - i\big)\delta - \big(d + \mu'(1-\sigma)\big)i\delta + o(\delta)\,,
\end{aligned} \tag{8}$$

which are the probabilities during a small time interval(δ) of transiting from one state to another.

Also in [23], a structured continuous-time hidden Markov chain was used to model the acquisition of nosocomial pathogens and compared their results with that obtained from genotyping. They found that hidden Markov models can be applied to serial prevalence data to estimate the characteristics of acquisition of nosocomial pathogens and distinguished between epidemic and sporadic acquisition. This model was able to estimate transmission parameters despite imperfect detection of the organism.

$$\frac{d(N-C)}{dt} = \mu C - \beta C(N-C) - \nu(N-C)$$
$$\frac{dC}{dt} = \beta C(N-C) + \nu(N-C) - \mu C \tag{9}$$

To apply the HMM they constructed an equivalent stochastic model as

$$\begin{aligned}
&\Pr[C(t+h) = i+1|C(t) = i] = \beta i(N-i)h + \nu(N-i)h\\
&\Pr[C(t+h) = i-1|C(t) = i] = \mu ih\\
&\Pr[C(t+h) = i|C(t) = i] = 1 - \beta i(N-i)h + \nu(N-i)h - \mu ih\\
&\Pr[C(t+h) = j(j \neq i, i+1, i-1)|C(t) = i] = 0
\end{aligned} \tag{10}$$

These models incorporated randomness in the modeling scheme and evaluated transmission probabilities and uncertainty in small populations, relevant for ICU's. Despite this, the models were also restricted to the basic variables (patient-HCW's pathway) in modeling the spread of nosocomial infections.

2.5 Models Incorporating additional Contact Groups

A model that considered the impact of semi-professional volunteer workers on the transmission of MRSA in a tertiary hospital in China was given in [13]. They developed a compartmental model to describe the transmission of MRSA. The model has six compartments, that is, colonized patients (P_c) and uncolonized patients (P_u) , contaminated HCW's (H_c) and uncontaminated HCW's (H_u), and contaminated volunteers (V_c) and uncontaminated volunteers (V_u). Analysis of the model showed that increase in the handwashing compliance of both HCW's and volunteers will reduce transmission of MRSA drastically. Also, since volunteers care for patients on one-to-one basics, they showed that replacing volunteers with HCW's will increase the transmission of MRSA.
The model is as follows

$$\frac{dP_u}{dt} = \lambda(1-\phi) - [\frac{(1-\eta)}{N}\beta_{PH}H_c(t) + \frac{(1-\xi)}{N}\beta_{PV}V_c(t)]P_u(t) - \delta_u P_u(t)$$

$$
\begin{aligned}
\frac{dP_c}{dt} &= \lambda\phi + [\frac{(1-\eta)}{N}\beta_{PH}H_c(t) + \frac{(1-\xi)}{N}\beta_{PV}V_c(t)]P_u(t) - \delta_c P_c(t)\\
\frac{dH_u}{dt} &= -\frac{(1-\eta)}{N}\beta_{PH}P_c(t)H_u(t) + \gamma_H H_c(t)\\
\frac{dH_c}{dt} &= \frac{(1-\eta)}{N}\beta_{PH}P_c(t)H_u(t) - \gamma_H H_c(t)\\
\frac{dV_u}{dt} &= -\frac{(1-\xi)}{N}\beta_{PV}P_c(t)V_u(t) + \gamma_V V_c(t)\\
\frac{dV_c}{dt} &= \frac{(1-\xi)}{N}\beta_{PV}P_c(t)V_u(t) - \gamma_V V_c(t)
\end{aligned}
\qquad (11)
$$

Also, the transmission of MRSA in a nursing home for the elderly was considered by [24]. They constructed a deterministic model consisting of four different compartments; colonized (C) and uncolonized (U) residents, and contaminated (H_c) and uncontaminated (H) healthcare workers. They also developed an equivalent stochastic model to elucidate the behavior of the model by understanding the prevalence of MRSA, its persistence and possible control measures for the pathogen in the nursing home.

They concluded that MRSA may persist without strict screening and decolonization at admission.

The deterministic model is:

$$
\begin{aligned}
\dot{U} &= (1-\lambda)\Lambda + \omega C - \frac{\beta_r}{N_r}UC - \frac{\beta_h}{N_h}UH_c - \gamma_u U\\
\dot{C} &= \lambda\Lambda + \frac{\beta_r}{N_r}UC + \frac{\beta_h}{N_h}UH_c - (\omega + \gamma_c)C\\
\dot{H} &= -\frac{\alpha_h}{N}HC + \mu H_c\\
\dot{H}_c &= \frac{\alpha_h}{N}HC - \mu H_c
\end{aligned}
\qquad (12)
$$

Similarly, the equivalent stochastic model stating the transition probabilities of various events occurring in (t+dt) is as follows:

$$
\begin{array}{ll}
P(H_c, 1) = \lambda[\gamma_u N_r - (\gamma_u - \gamma_c)C]dt & C \to C + 1\\
P(H_c, 1) = \frac{\beta_r}{N_r}(N_r - C)Cdt & C \to C + 1\\
P(H_c, 1) = \frac{\beta_h}{N_h}(N_r - C)H_c dt & C \to C + 1\\
P(H_c, -1) = \omega C dt & C \to C - 1\\
P(H_c, -1) = \gamma_c C dt & C \to C - 1\\
P(1, C) = \frac{\alpha_h}{N_h}(N_h - H_c)Cdt & H_c \to H_c + 1\\
P(-1, C) = \mu H_c dt & H_c \to H_c - 1
\end{array}
\qquad (13)
$$

Similarly, in [25] deterministic and stochastic mathematical models to investigate the impact of environmental contamination and presence of volunteers in the transmission of MRSA were formulated. The model comprises of susceptible HCW’s (H^s), contaminated HCW’s (H^c), susceptible patients (P^s), infectious patients (P^c), the density of bacteria in the ward (W), and the number of volunteers (V).

The analysis of the models showed that the magnitude of treat posed by environmental contamination is high and free-living bacteria in hospital environment enhances the transmission of the infection and may initiate an outbreak even when the HCW’s and patients are all free from infection. The model is as follows,

$$
\begin{aligned}
\frac{dH^s}{dt} &= -(\beta_1 P^c + v_1 W)H^s + \gamma H^c \\
\frac{dH^c}{dt} &= (\beta_1 P^c + v_1 W)H^s - \gamma H^c \\
\frac{dP^s}{dt} &= (1-\bar{\phi})\Lambda - (1-q)\overline{\beta_2} H^c - ((1-p)\overline{v_2} W)P^s - d_1 P^s \\
\frac{dP^c}{dt} &= (1-r)\bar{\phi}\Lambda + (1-q)\overline{\beta_2} H^c + \big((1-p)\overline{v_2} W\big)P^s - d_2 P^c \\
\frac{dW}{dt} &= \lambda P^c - (\mu + \xi V + v_1 H)W
\end{aligned}
\tag{14}
$$

The stochastic equivalent was given by stating the transition states and rates (probabilities) at which they occur.

Table 1: State Transitions and their Rates

State Transitions	Rates
$(H^s, H^c, P^s, P^c, W) \rightarrow (H^s - 1, H^c + 1, P^s, P^c, W)$	$\beta_1 P^c H^s$
$(H^s, H^c, P^s, P^c, W) \rightarrow (H^s - 1, H^c + 1, P^s, P^c, W - 1)$	$v_1 W H^s$
$(H^s, H^c, P^s, P^c, W) \rightarrow (H^s + 1, H^c - 1, P^s, P^c, W)$	γH^c
$(H^s, H^c, P^s, P^c, W) \rightarrow (H^s, H^c, P^s + 1, P^c, W)$	$(1-\bar{\phi})\Lambda$
$(H^s, H^c, P^s, P^c, W) \rightarrow (H^s, H^c, P^s, P^c + 1, W)$	$\phi\Lambda$
$(H^s, H^c, P^s, P^c, W) \rightarrow (H^s, H^c, P^s - 1, P^c + 1, W)$	$\beta_2 H^c P^s$
$(H^s, H^c, P^s, P^c, W) \rightarrow (H^s, H^c, P^s - 1, P^c + 1, W - 1)$	$v_2 W P^s$
$(H^s, H^c, P^s, P^c, W) \rightarrow (H^s, H^c, P^s - 1, P^c, W)$	$d_1 P^s$
$(H^s, H^c, P^s, P^c, W) \rightarrow (H^s, H^c, P^s, P^c - 1, W)$	$d_2 P^c$
$(H^s, H^c, P^s, P^c, W) \rightarrow (H^s, H^c, P^s, P^c, W + 1)$	λP^c
$(H^s, H^c, P^s, P^c, W) \rightarrow (H^s, H^c, P^s, P^c, W - 1)$	μW

These models are particularly important because they went beyond the patient-HCW's centered transmission and included professional volunteers and environmental contamination. While in [13], professional volunteers were incorporated, in [23] the effect of environmental contamination was included, and this was implicitly modeled with the presence of volunteers. Unlike models by [13] and [23], the model by [24] accessed the spread of nosocomial infections in a nursing home for the elderly, showing possible transmissions in care homes. These models demonstrated that non-HCW's pathway can significantly influence the infection dynamics, hence the need to consider other transmission pathways like informal caregivers (patient's family caregivers).

2.6 Models Incorporating Environmental Contamination

A study on the additional effect of environmental factor in the transmission dynamics of nosocomial infections by [26] cited the case of an outbreak of Klebsiella pneumoniae carbapenemase (KPC) infections in the Clinical Center at the National Institute of Health in Bethesda Maryland (CCNIH) USA. This was to show in addition the importance of the inclusion of environmental effect in the transmission of Nosocomial infections. As such, they classified two levels of room contaminations, level 0 (uncontaminated or contaminated at low levels) and level 1 (contaminated at significantly high level).

They described the model using six compartments, that is, the uninfected patients susceptible to acquiring the infection in level 0 contaminated rooms (S_0), uninfected patients susceptible to acquiring the infection in level 1 contaminated rooms (S_1), infected patients in level 0 contaminated rooms (I_0), infected patients in level 1 contaminated rooms (I_1), uncontaminated HCW (H_u), and contaminated HCW (H_c).

Their model showed the importance of small ward populations and transfer structures (movement between wards) in the transmission and persistence of nosocomial infections.

$$\begin{aligned}
\frac{dS_0(t)}{dt} &= \frac{1-\alpha_0}{T_0}I_0(t) + \frac{1-\alpha_1}{T_1}I_1(t) - \frac{\pi_0\rho}{T_v}H_c(t)S_0(t) + v_1S_1(t)\\
\frac{dS_1(t)}{dt} &= \frac{\alpha_0}{T_0}I_0(t) + \frac{\alpha_1}{T_1}I_1(t) - \frac{\pi_1\rho}{T_v}H_c(t)S_1(t) - t_1S_1(t) + v_1S_1(t)\\
\frac{dI_0(t)}{dt} &= \frac{-1}{T_0}I_0(t) + \frac{\pi_0\rho}{T_v}H_c(t)S_0(t) + \delta_1I_1(t) - \delta_0I_0(t)\\
\frac{dI_1(t)}{dt} &= \frac{-1}{T_1}I_1(t) + \frac{\pi_1\rho}{T_v}H_c(t)S_1(t) + \epsilon_1S_1(t) - \delta_1I_1(t) + \delta_0I_0(t)\\
\frac{dH_u(t)}{dt} &= \frac{1}{T_v}H_c(t) - \frac{1}{T_v}(\omega_0I_0(t) + \omega_1I_1(t) + \xi_1S_1(t))H_u(t)\\
\frac{dH_c(t)}{dt} &= -\frac{1}{T_v}H_c(t) + \frac{1}{T_v}(\omega_0I_0(t) + \omega_1I_1(t) + \xi_1S_1(t))H_u(t)
\end{aligned} \tag{15}$$

A model by [8] considered the impact of bacteria load within the hospital environment in the transmission of MRSA. They developed a deterministic model of five compartments, that is, colonized patients, the uncolonized patients, the contaminated HCW's, the uncontaminated HCW's and the bacteria load in the hospital environment. They also developed an equivalent stochastic model using a Continuous Time Markov Chain (CTMC) approach, to better understand the model behavior. The analysis of both the deterministic and stochastic models gave some key control measures, such as increasing the hand hygiene compliance of HCWs, enhancing environmental disinfection, and lowering transmission between patients, HCWs, and the environment. The model is,

$$\begin{aligned}
\frac{dP_u(t)}{dt} &= (1-\theta)[\gamma_uP_u(t) + \gamma_cP_c(t)] - \alpha_p\beta_p(1-\eta)P_u(t)H_c(t) - k_pP_u(t)B_e(t) - \gamma_uP_u(t)\\
\frac{dP_c(t)}{dt} &= \theta[\gamma_uP_u(t) + \gamma_cP_c(t)] + \alpha_p\beta_p(1-\eta)P_u(t)H_c(t) + k_pP_u(t)B_e(t) - \gamma_cP_c(t)\\
\frac{dH_u(t)}{dt} &= -\alpha_p\beta_h(1-\eta)P_c(t)H_u(t) + \mu_cH_c(t) - k_hH_u(t)B_e(t)\\
\frac{dH_c(t)}{dt} &= \alpha_p\beta_h(1-\eta)P_c(t)H_u(t) - \mu_cH_c(t) + k_hH_u(t)B_e(t)\\
\frac{dB_e(t)}{dt} &= \nu_pP_c(t) + \nu_hH_c(t) - \gamma_bB_e(t)
\end{aligned} \tag{16}$$

To construct the equivalent stochastic model, they adopted the Continuous Time Markov Chain process (CTMC) and stated that since, $P_c(t) + P_u(t) = N_p\ and\ H_c(t) + H_u(t) = N_h$, then $P_u(t) = N_p - P_c(t)\ and\ H_u(t) = N_h - H_c(t)\ \forall\ t \geq 0$ making the process trivariate. These three variables have a joint probability given by $p_{(s,j,k)}(t) = Prob\{P_c(t) = s, H_c(t) = j, B_e(t) = k\}$, where $s = 0,1,\dots,N_p;\ j = 0,1,\dots,N_h;\ and\ k \geq 0$.

The transition probabilities are written as follows:

$$p_{(s+i_1,j+i_2,k+i_3);(s,j,k)}(\Delta t) = \begin{cases}
[\theta[\gamma_u(N_p-s) + \gamma_cs] + \alpha_p\beta_p(1-\eta)(N_p-s)j + k_p(N_p-s)k]\Delta t & (i_1,i_2,i_3) = (1,0,0)\\
\gamma_cs\Delta t & (i_1,i_2,i_3) = (-1,0,0)\\
[\alpha_p\beta_h(1-\eta)s(N_h-j) + k_h(N_h-j)k]\Delta t & (i_1,i_2,i_3) = (0,1,0)\\
\mu_cj\Delta t & (i_1,i_2,i_3) = (0,-1,0)\\
[\nu_ps + \nu_hj]\Delta t & (i_1,i_2,i_3) = (0,0,1)\\
\gamma_bk\Delta t & (i_1,i_2,i_3) = (0,0,-1)\\
1 - [\theta[\gamma_u(N_p-s) + \gamma_cs] + \alpha_p\beta_p(1-\eta)(N_p-s)j + k_p(N_p-s)k]\Delta t & \\
\quad -\gamma_cs\Delta t - [\alpha_p\beta_h(1-\eta)s(N_h-j) + k_h(N_h-j)k]\Delta t - \mu_cj\Delta t & \\
\quad -[\nu_ps + \nu_hj]\Delta t - \gamma_bk\Delta t & (i_1,i_2,i_3) = (0,0,0)\\
0 & elsewhere
\end{cases} \tag{17}$$

A compartmental mathematical model by [14] was formulated to investigate the effect of environmental contamination on the spread of MRSA in hospitals, using Caputo fractional derivative. He created a fractional counterpart of the model by [8], in order to model the memory-dependent behaviour of the system, using the Caputo fractional derivative operator. The model examined has five compartments, the uncolonized patients Pu(t), the colonized patients Pc(t), the uncontaminated healthcare workers Hu(t), the contaminated healthcare workers Hc(t), and the bacteria load in the environment B(t). The Caputo fractional derivative is denoted as ${}_{C}D^{\chi}\omega(t)$ and defined as, ${}_{C}D^{\chi}\omega(t) = \frac{1}{\Gamma(1-\chi)}\int_0^t \frac{\omega'(\tau)}{(t-\tau)}d\tau$.

He gave the system of fractional derivative as,

$$\begin{aligned}
{}_{C}D^{\chi}P_u(t) &= (1-\alpha^{\chi})\left[\beta_u^{\chi}P_u(t) + \beta_c^{\chi}P_c(t)\right] - \gamma_p^{\chi}\kappa_p^{\chi}(1-\theta^{\chi})P_u(t)H_c(t) - \sigma_p^{\chi}P_u(t)B(t) - \beta_u^{\chi}P_u(t)\\
{}_{C}D^{\chi}P_c(t) &= \alpha^{\chi}\left[\beta_u^{\chi}P_u(t) + \beta_c^{\chi}P_c(t)\right] + \gamma_p^{\chi}\kappa_p^{\chi}(1-\theta^{\chi})P_u(t)H_c(t) + \sigma_p^{\chi}P_u(t)B(t) - \beta_c^{\chi}P_c(t)\\
{}_{C}D^{\chi}H_u(t) &= -\gamma_p^{\chi}\kappa_h^{\chi}(1-\theta^{\chi})P_c(t)H_u(t) + \nu_c^{\chi}H_c(t) - \sigma_h^{\chi}H_u(t)B(t) \qquad (18)\\
{}_{C}D^{\chi}H_c(t) &= \gamma_p^{\chi}\kappa_h^{\chi}(1-\theta^{\chi})P_c(t)H_u(t) - \nu_c^{\chi}H_c(t) + \sigma_h^{\chi}H_u(t)B(t)\\
{}_{C}D^{\chi}B(t) &= \mu_p^{\chi}P_c(t) + \mu_h^{\chi}H_c(t) - \beta_b^{\chi}B(t)
\end{aligned}$$

He observed that Caputo fractional derivative can change the course of spread of MRSA by understanding the model system in depth and examining the effects of different parameters in making predictions about the system behavior. This offers a comprehensive analysis in predicting and comparing infection control methods.

These models explicitly incorporated the effect of environmental variables in the dynamics of the infection, showing the importance of studying other variables.

2.7 Multi-Compartment Models

A model on community-acquired MRSA and hospital-acquired MRSA was considered by [27], using eight-compartmental model and assessed the effect of some intervention methods in preventing the spread of the disease. Their work suggested an increase in the level of awareness concerning the transmission of MRSA is extremely significant in preventing the further spread of both CA-MRSA and HA-MRSA.

The eight compartments consists of susceptible individuals (S), individuals who are infected with CA-s.aureus (C_c), individuals who are infected with CA-MRSA (C_I), individuals who are infected with HA- s.aureus (H_c), individuals who are infected with HA-MRSA (H_I), antibiotic group Oxazolidinones (O),antibiotic group Glycopeptides (G), antibiotic group Trimethoprim-derivatives (T) as below:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda(1-k_1-k_2-k_3-k_4) - \beta_1 C_c S - \beta_2 C_I S - \beta_3 H_c S - \beta_4 H_I S + \gamma_1 O + \gamma_2 G + \gamma_3 T + a\delta_1 C_c +\\
&\quad b\delta_3 H_c - \mu S\\
\frac{dC_c}{dt} &= \Lambda k_1 + \beta_1 C_c S - [a\delta_1 + (1-a)\delta_2]C_c - \mu C_c\\
\frac{dC_I}{dt} &= \Lambda k_2 + \beta_2 C_I S + (1-a)\delta_2 C_c - (o_1 + g_1 + r_1)C_I - \mu C_I\\
\frac{dH_c}{dt} &= \Lambda k_3 + \beta_3 H_c S - [b\delta_3 + (1-b)\delta_4]H_c - \mu H_c \qquad (19)\\
\frac{dH_I}{dt} &= \Lambda k_4 + \beta_4 H_I S + (1-b)\delta_4 H_c - (o_2 + g_2 + r_2)H_I - (\mu + d)H_I\\
\frac{dO}{dt} &= o_1 C_I + o_2 H_I - \gamma_1 O\\
\frac{dG}{dt} &= g_1 C_I + g_2 H_I - \gamma_2 G\\
\frac{dT}{dt} &= r_1 C_I + r_2 H_I - \gamma_3 T
\end{aligned}$$

While this model improved on capturing realistic infection states and intervention effects by aggregating contact patterns, it did not explore the caregivers' role.

DISCUSSION

This narrative review examined both deterministic and stochastic models of nosocomial infections, with emphasis on the variables used and transmission pathways considered in the existing models. Most of the reviewed literature focused on interactions between patients and healthcare workers and in some cases the contaminated hospital environment. These models have significantly improved the understanding of nosocomial infection transmission and gave valuable insights for designing effective control strategies.

Despite these advancements in modeling the dynamics of nosocomial infections, limitation still exist in the current literature. Most existing models are centered on the interaction between patients and HCW's with little attention given to other viable pathways, especially the Informal Caregivers (like, patients family caregivers). These caregivers provide informal care to the patient, and indulge in numerous activities like, feeding, bathing, administering drugs to the patient etc. Their frequent and close contacts with patients give opportunity for possible transmission. As a result, the exclusion of caregiver's-mediated pathway can lead to underestimation of infection risks and inefficient prevention strategy, especially for low-income and middle-income countries (like Nigeria) where family caregivers provide extensive care.

While some existing models attempted to include other transmission pathways, such as volunteers or environmental reservoirs, none of these captured the nature of caregivers' interactions. Incorporating informal caregivers into the modeling framework of nosocomial infections will be essential to capturing the real interactions within hospitals and improve the applicability of deterministic and stochastic models. The caregiver-mediated pathway when incorporated will also improve the strategies for infection prevention and control methods.

CONCLUSION

Nosocomial infections remain a global challenge in public health management, hence requires being studied elaborately using robust models to adequately understand and control its transmission. Existing deterministic and stochastic models on nosocomial infections have made substantial contributions in understanding the transmission dynamics of hospital acquired infections. Despite these advances the scope is still inadequate to completely describe various pathways in the transmission dynamics of nosocomial infections. Extending the scope of these models to explicitly incorporate patient's family caregivers as a distinct transmission pathway in nosocomial infection modeling is essential for achieving a more comprehensive model. Future strides in modeling the transmission of nosocomial infections should include informal caregivers using empirical data, in order to improve the accuracy of the model and enhance the effectiveness of infection prevention and control strategies in healthcare settings, most especially in low-income and middle-income countries, like Nigeria were family caregivers are predominant.

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